Guidance on Radiation Dose Limits for the Lens of the Eye

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National Council on Radiation Protection and Measurements
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Preface

This Commentary has been prepared in order to provide guidance on whether existing dose limits to the lens of the eye should be changed in the United States. The guidance is based on a detailed evaluation of recent studies on the radiation dose response for the development of cataracts.

A number of NCRP publications have addressed the issues of risk and dose limitation in radiation protection that have included specific organs and the lens of the eye:

- Report No. 91, Recommendations on Limits for Exposure to Ionizing Radiation (NCRP, 1987);
- Report No. 98, Guidance on Radiation Received in Space Activities (NCRP, 1989a);
- Report No. 115, Risk Estimates for Radiation Protection (NCRP, 1993a);
- Report No. 116, Limitation of Exposure to Ionizing Radiation (NCRP 1993b);
- Commentary No. 12, Radiation Exposure and High-Altitude Flight (NCRP, 1995);
- Report No. 132, Radiation Protection Guidance for Activities in Low-Earth Orbit (NCRP, 2000);
- Report No. 136, Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation (NCRP, 2001);
- Report No. 167, Potential Impact of Individual Genetic Susceptibility and Previous Radiation Exposure on Radiation Risk for Astronauts (NCRP, 2010a);
- Report No. 168, Radiation Dose Management for Fluoroscopically-guided Interventional Medical Procedures (NCRP, 2010b); and,
- Report No. 174, Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance (NCRP, 2013).

The Commentary evaluates recent studies that have provided information regarding the dose response curve for the development of cataracts, including: considerations for cataract severity; addressing possible differences in cataract induction by dose rate; commenting on the issue of severity of disease in the context of radiation detriment; opening discussion about the appropriate dose limits for protection of the lens of the eye from developing cataracts; determining the effectiveness of protective measures for the eye; and, identifying future research needs.

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1. Executive Summary

The major radiation damage response of the clear crystalline lens of the eye is the loss of lens clarity resulting in clouding or opacification known as a cataract that in an extreme case (usually after high doses > 5 Gy in a single exposure) can cause blindness (e.g., significant visual impairment). However, exposure to low doses of radiation can lead to minor opacifications many years later. The impact of cataract outcomes on vision following either high- or low-doses are highly dependent on the type of radiation, how the exposure of the lens was delivered with respect to dose fraction and time, the genetic susceptibilities of the individual exposed, and also the actual location of the opacity within the lens that may form relative to the visual axis of the individual. The International Commission on Radiological Protection (ICRP) has recently recommended a reduced equivalent dose limit for occupational exposure of the lens of the eye to 20 mSv y^{-1}, averaged over 5 y, with no single y > 50 mSv, based on an evaluation of the epidemiological evidence of cataracts in radiation-exposed human populations. Consideration of these recommendations for lower dose limits, and the cost-benefit consequences associated with adopting them, is taking place worldwide by countries including the United States. This NCRP Commentary was requested by the U.S. Nuclear Regulatory Commission to evaluate clinical and experimental evidence for the risk of radiation-induced cataract, to consider cataract types and dose and dose-rate dependence of cataract formation, to provide guidance on whether existing dose limits to the eye should be changed in the United States, and to identify whether any research gaps exist in our understanding of radiation effects on the lens of the eye.

This Commentary addresses radiation protection principles with respect to the lens of the eye, summarizes the current understanding of eye biology and lens effects (including ionizing radiation effects), reviews and evaluates the current epidemiology related to ionizing radiation and cataracts, assesses exposed populations with the potential for significant radiation exposures to the lens, and makes several conclusions and recommendations.

Further, this Commentary takes into account the most current information regarding the epidemiologic and mechanistic understanding of the development of cataracts and specifically addresses four core questions:

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

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. The review of mechanistic studies by several authors as summarized in this Commentary suggests that radiation-induced opacities could be stochastic in nature and perhaps not deterministic (i.e., tissue reactions), as long thought. However, the link between the induction of any, even minor, opacities in animal models and the occurrence of clinically-relevant, vision-impairing cataracts (VICs) in humans is still far from clear. Because of the incoherence of the mechanistic and epidemiologic evidence, it is not yet known if radiation cataractogenesis can be classified as strictly stochastic or deterministic in nature. The epidemiological evidence to date indicates a threshold model, and NCRP has determined that this model should continue to be used for radiation protection purposes at this time.

The value of the threshold for detectable opacities or vision-impairing cataracts is less clear, with the epidemiological evidence currently pointing to a threshold for vision-impairing cataracts for doses in the region of 1 to 2 Gy. However, NCRP has concluded that it is not possible to make a specific quantitative estimate of lens effect thresholds at this time.

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

The epidemiological evidence presented in Section 5 of this Commentary demonstrates that, although different studies have looked at many of these factors independently, there is still

very little evidence upon which to base an answer to this question. The mechanistic evidence is clearer in some instances (e.g., in terms of a differential effect of increased ionizing radiation qualities enhancing the induction and progression of opacities) but, as noted above, the relationship between the results from animal models and risks of vision-impairing cataracts in humans is still not clear. The 'normal' lens loses clarity with attained age due to a number of physiological aging processes. As such, NCRP has determined that further, 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. Improvements in methods to determine lens doses in the clinic and the workplace, and in technical approaches to score the different types of lens opacifications arising in different anatomical regions of the lens will strengthen the quality of the new dose-dependent cataract data obtained. Advancement of more basic research on the exact biological target for species-specific differences in radiation-induced cataract formation could lead to the development of biochemical countermeasures that may be applied to attenuate or prevent cataract formation.

How should detriment be measured and/or evaluated for cataracts?

Vision-impairing cataracts 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). ICRP Publication 118 (2012) noted that acute doses up to about 0.1 Gy produce no functional impairment of tissues, that detectable lens changes can be identified as low as between 0.2 and 0.5 Gy, and concluded that a nominal threshold of 0.5 Gy for acute or protracted exposure for lens tissue effects is an appropriate method for evaluating lens detriment. While NCRP recognizes that the mechanisms underlying the transition of minor lens opacifications to clinically significant vision-impairing cataracts 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 that there is an association between exposure to ionizing radiation and initiation or development of post-subcapsular cataracts, mixed and/or cortical vision-impairing cataracts in humans for various exposure situations. The systematic review of the current eye epidemiology data has shown that the probable risks for cataracts (i.e., specifically post-subcapsular, mixed, and/or cortical cataracts) are likely increased at an exposure level that is somewhat less than the earlier estimates by ICRP or NCRP. Both ICRP and NCRP had earlier assumed threshold values for vision-impairing cataracts of 2 to 10 Sv for single brief exposures and > 8 Sv for protracted exposures (NCRP, 1989a; ICRP, 2007). ICRP has also noted that ophthalmologically-detectable opacities might result from lower doses of 0.5 to 2 Sv for acute exposures (ICRP, 1991; 2012).

NCRP acknowledges that most of the available data on lens effects have large associated uncertainties and limitations that do not yet support a quantitative estimate of a specific threshold value for effects from either acute or chronic lens exposures. However, the preponderance of evidence appears to suggest the possibility that effects (e.g., lens opacities and/or cataracts) could occur at lower doses than previously considered when developing occupational lens of the eye dose limit recommendations based on the potential for worker lens doses over time. Therefore, NCRP has determined that it is 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 effective dose limit of 50 mSv (NCRP, 1993b). No new annual dose limit is recommended for members of the public lens of the eye exposure as NCRP judges the existing annual limit of 15 mSv (NCRP, 1993b) to be adequately protective.

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). If it is necessary 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,' Gy-Eq). This may then be compared to the limit expressed in gray (Gy).

NCRP recommends that the annual dose limit for occupational exposures for the lens of the eye be reduced to 50 mGy.

While the currently available information for the effects of ionizing radiation on the lens has provided input on appropriate guidance with regard to radiation protection, much more work is needed to develop a complete understanding of such detriments. NCRP recommends ongoing evaluation and additional research in the following areas: comprehensive evaluation of the overall effects of ionizing radiation on the eye, dosimetry methodology and dose-sparing optimization techniques, additional high quality epidemiology studies, and a basic understanding of the mechanisms of cataract development.

2. Introduction

The cornea and the crystalline lens of the eye are our windows to the world. The opacification of the lens that we call 'cataract' prevents light from reaching the retina at the back of the eye, and is the major cause of blindness worldwide, despite being curable by lens replacement surgery. Cataracts can form in different anatomical locations within the lens, perhaps due to different etiologies. The posterior subcapsular cataract has long been associated with the radiation-induced etiology, although it might be prevalent in patients with diabetes or after steroid treatments.

Prevention of cataracts is an important goal requiring an understanding of the various and diverse causes of lens opacification. Significant epidemiological differences in cataract prevalence have been reported in different countries depending on genetics, pathologies or environmental exposures. Since early clinical evidence from radiotherapy (Merriam and Focht, 1957; Merriam et al., 1972) indicated an apparent dose threshold below which radiation cataracts had not been reported, it was thought that radiation cataract could be prevented by limiting the dose of ionizing radiation to the lens of the eye. However, the radiation etiology is complex because cataracts also can be produced by exposure to a variety of wavelengths throughout the electromagnetic spectrum from x rays to microwaves (Harding and Crabbe, 1984); causation also has been linked to exposures to sunlight, infrared, and ultraviolet light; and, it is now understood that cataracts occurring as a result of exposure to very low doses are likely to have extremely long latency periods. Thus, prevention of cataracts appears to be more complex than by simply limiting exposure of the lens to ionizing radiation.

Recent epidemiological evidence has suggested that the threshold dose of ionizing radiation for specific tissue reaction effects with late manifestation (including the lens) may be lower than previously thought (EPRI, 2014; ICRP, 2012), and that radiation cataractogenesis may even be a stochastic effect. In April of 2011, ICRP issued a "Statement on Tissue Reactions" (ICRP, 2011) that was followed by ICRP Publication 118 "ICRP Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold

Doses for Tissue Reactions in a Radiation Protection Context" (ICRP, 2012). The key issues addressed in ICRP Publication 118 are the following:

- ICRP has defined a 'practical' threshold dose that is required to cause a particular tissue injury effect in at least 1 % of exposed individuals.
- The threshold for lens of eye effects (cataracts and other opacities) is now considered to be 0.5 Gy. Previous dose limits were based on a much higher threshold, in the range of ~ 2 to > 5 Gy (ICRP, 2012).
- ICRP recommended a reduced equivalent dose limit for occupational exposure of the lens of the eye to 20 mSv y^{-1}, averaged over 5 y, and no single y > 50 mSv. This is the same value as the ICRP recommended for occupational effective dose limit, which is applicable to the whole body (ICRP, 2012).
- The new recommended equivalent dose limit for occupational exposure of the lens of the eye is based on prevention of radiogenic cataracts with an ICRP underlying assumption of a nominal threshold at 0.5 Gy for acute, protracted or chronic exposure. ICRP recognized that there was less evidence for protracted or chronic exposure results and that the available evidence mainly refers to opacities rather than cataracts impairing vision (ICRP, 2012).
- ICRP noted that these new recommendations (ICRP, 2012) were consistent with their basic framework of radiological protection: "…to prevent the occurrence of deterministic effects, by keeping doses below the relevant thresholds, and to ensure that all reasonable steps are taken to reduce the induction of stochastic effects…" (ICRP, 1991).

This represents a significant change from previous recommendations of an annual occupational limit of 150 mSv equivalent dose for protection of the lens of the eye. These changes, and the ramifications of implementing them, are under consideration by several countries, including the United States.

This Commentary was requested by the U.S. Nuclear Regulatory Commission (NRC) to evaluate recent studies on the radiation dose response for the development of cataracts; to consider the type and severity of the cataracts and their dose rate dependence; to provide guidance on whether existing dose limits to the lens of the eye should be changed in the United States; and, to suggest research needs regarding radiation effects on and dose limits to the lens of the eye. This Commentary is intended to supplement the previous recommendations from NCRP provided in Report No. 116 (1993b).

This Commentary takes into account the most current information regarding the epidemiologic and mechanistic understanding of the development of cataracts and addresses four core questions:

- Should radiation-induced cataracts be characterized as stochastic or deterministic (or tissue reactions) effects?
- What effects do LET, dose rate, acute and/or protracted dose delivery have on cataract induction and progression?
- How should detriment be measured and/or evaluated for cataracts?
- Based on current evidence, should NCRP change the recommended limit for the lens of the eye?

2.1 Background

Constantine in the 11th century coined the term cataract to describe the changes in transparency of the lens that impair vision, and that may occur in perhaps 20 diseases (Potts, 1979). The role of radiation in the induction of cataract was recognized soon after the discovery of x rays (see historical review in Bendel et al., 1978). The early estimate of risk of induction of cataract in humans by exposure to low-Linear Energy Transfer (LET) radiation was heavily based on the radiotherapy studies of Merriam and co-workers (Merriam and Focht, 1957; Merriam et al., 1972). Cataracts arising in patients treated for head and neck cancers with various doses and dose fractions of photons were scored. Four observations were made:

1. The threshold of x-ray irradiation for the induction of minimally detectable lens opacities for single exposures was 2 Gy, and 5.5 Gy with exposures fractionated over 3 months or longer,
2. The threshold dose to cause a progressive cataract was about 5 Gy,
3. All patients developed cataracts after a single dose of 7.5 Gy or 14 Gy fractionated exposures, and
4. The time between exposure and detection of the cataracts was inversely related to dose.

These observations, together with additional information from other reports involving whole-body human radiation exposures for bone marrow transplantation or cancer treatments (Britten et al., 1966; Henk et al., 1993; Morita and Kawabe, 1979) led to the establishment of acute and protracted ionizing radiation dose limits for the lens of the eye. Another major source of information on radiation-induced cataracts came from the study of the atomic bomb survivors (Choshi et al., 1983, Miller et al., 1967; 1968; Otake and Schull, 1982). Primarily using these cataract data from human exposures, ICRP Publication 14 (1969), ICRP Publication 26 (1977) and ICRP Publication 60 (1991a) have provided previous radiation protection recommendations.

2.1.1 Purpose

The purpose of this Commentary is to make a detailed re-evaluation of the available literature on the radiation dose response for the development of cataracts, to evaluate the quality of the quantitative measurements, to understand the underlying susceptibility of the lens to radiation exposure, and to consider the interaction of confounding factors such as normal aging. Despite advances in technology that have helped to reduce radiation doses in the clinic to patients and staff, occupational radiation exposures of the lens of the eye have increased in certain aspects of medical practice (e.g., interventional radiologists and cardiologists) likely because of the application of interventional techniques to additional pathologies and the

consequent increase of workload (Abe et al., 2013; Dauer, 2014; Dauer et al., 2010; Vano et al., 1998).

2.1.2 Evaluation Methodologies

This Commentary was written by multi-disciplinary experts based on a comprehensive review of all prior radiation lens dose limits from national and international regulatory or advisory bodies. The key epidemiological and radiobiological literature upon which the previous guidance on dose limits was based was carefully evaluated with a focus on understanding the statistical significance of each of the study populations, and where possible, the identification of the underlying dose response-dependent variables and mechanisms of action. Low-LET radiation was the predominant radiation source scrutinized. The methodology used in assessing cataracts in the background of the aging lens was carefully noted in each study. Cataract prevention strategies have been evaluated in terms of their potential impact on radiation protection practices and the recommended dose limits. Science gaps and research needs were identified.

2.2 Core Questions

Four core questions were defined as important to address in this Commentary.

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

Radiation effects are frequently identified as either stochastic or deterministic for radiation protection purposes. Stochastic effects are defined as random events leading to effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) is a direct function of radiation dose. Stochastic effects are commonly regarded as having no threshold. Hereditary effects and some somatic effects, especially cancer, are regarded as being stochastic. Deterministic (tissue reaction) effects may appear early or late after irradiation. These effects occur above a threshold dose, and increase in both incidence and severity with increasing dose. Radiation-induced cataracts have long been assumed to be a deterministic effect due to the reported threshold effect, a dose below which cataracts are not

identified. Recent evaluation of cataracts after low doses of radiation has revealed that the lower the dose, the longer the latency before a frank opacity appears (Blakely, 2012). The availability of new technologies to digitally detect cataracts has highlighted the fact that more sensitive methods to detect and score cataracts that impact vision have been improving and contributing to quantitative and qualitative evaluations of cataract grades. However, comparisons with results acquired with older technologies are difficult. ICRP has noted that more recent epidemiology appears to support a nominal low threshold of about 0.5 Gy for opacities and/or cataract induction (ICRP, 2012).

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

Merriam and Focht (1957; 1962) were early pioneers in the study of the relationship between radiation dose and human cataract formation. They studied patients exposed to orthovoltage radiation for head and neck cancers with ophthalmologic examinations every 3 y after treatment. They concluded that single doses of 200 rad (2 Gy) or cumulative doses of 550 rad (5.5 Gy) were adequate to induce cataracts. Their work also suggested that the amount of radiation delivered in a single exposure might be as important as the total dose. They demonstrated that higher doses were related to earlier onset and more severe cataract formation, but that fractionating the total dose lengthened the latent period and resulted in less severe cataract formation (Gragoudas et al., 1995; Merriam, 1957). Ferrufino-Ponce and Henderson (2006) have pointed out that Henk et al. (1993) and Gragoudas et. al. (1995) described a slightly higher threshold for cataract formation after fractionated radiotherapy (5 Gy) and highlighted the tendency for lower cataract rates with lower dose fraction sizes. This dose threshold was confirmed by Esik (1996) and similar thresholds increased the risk of cataract formation with other radiation modalities (Fife et al., 1994).

2.2.3 How should detriment be evaluated for cataracts?

A cataract is defined as a clouding of the normally transparent crystalline lens that can lead to a decrease in vision depending on the anatomical location of the opacity relative to the

visual axis. Vision-impairing cataracts (VICs) could be considered to be the endpoint of greatest concern in terms of lens radiation protection. However, the mechanisms underlying the transition from minor lens opacifications to clinically significant VICs are still not well understood, and this is likely to be an extremely relevant radiation protection issue requiring further investigation. Some have suggested using specific tests to evaluate loss in visual contrast sensitivity (Vano et al., 2013a). If a cataract impairs visual function, lens replacement surgery, although an invasive procedure, is usually highly successful.

2.2.4 Based on current evidence should NCRP change the recommended limit for the lens of the eye?

Many questions remain unanswered regarding the current evidence for a dose threshold for radiation-induced cataract. Despite the high prevalence of cataract formation after elevated doses of radiation, a percentage of patients still do not develop clinically-significant cataracts (Ferrufino-Ponce and Henderson, 2006). The underlying mechanisms of radiation-induced cataract are not yet completely understood. The Commentary addresses the available data and makes specific recommendations on the limit for the lens of the eye.

3. Radiation Protection Principles

NCRP in its 1993 recommendations (NCRP, 1993b) established a framework for radiation protection composed of three main elements:

- **Justification** – the need to justify any activity which involves radiation exposure on the basis that the expected benefits to society exceed the overall societal costs.
- **ALARA** – the need to ensure that the total societal detriment from such justifiable activities or practices is maintained as low as is reasonably achievable (ALARA), economic and social factors being taken into account.
- **Limitation** – the need to apply individual dose limits to ensure that the procedures of justification and ALARA do not result in individuals or groups of individuals exceeding levels of acceptable risk.

It was recognized that the use of the term ALARA was analogous to the term optimization used by ICRP (1989a). However, it should be kept in mind that the expression ALARA is only part of the concept of optimization when dealing with medical exposures of patients, recognizing that the radiation protection framework applies in a different way to occupational and medical exposures. The ICRP concept of optimization implies, more precisely, keeping patient exposure to the minimum necessary to achieve the required medical objective (diagnostic or therapeutic). In diagnostic imaging and x-ray guided interventions, it means the number and quality of images are sufficient to obtain the information needed for diagnosis or intervention. The focus of the effort in NCRP Report No. 116 (NCRP, 1993b) was to relate their recommendations, and any adjustments, to ICRP Publication 60 (1991a) to form guidance for the U.S. Nuclear Regulatory Commission (NRC) for use in the formulation of rulemaking leading to possible changes in the regulatory dose limits for occupational workers. The dose limits previously recommended by NCRP are discussed below (Section 3.3).

551
552 ## 3.1 Issue of Radiation Risks
553
554 Risk estimates provided by NCRP (1993a) were primarily focused on stochastic risk for
555 two major potential outcomes following ionizing radiation exposures: cancer and genetic
556 (inheritable) effects. However, annual equivalent dose limits to the lens to prevent deterministic
557 effects for occupational workers and the public were recommended.
558
559 ### 3.1.1 BEIR V Report
560
561 The National Research Council of the National Academies updated their findings on the
562 effects of low-levels of ionizing radiation on populations (NA/NRC, 1980) in a new report in
563 1990 (NA/NRC, 1990), known as the BEIR (Biological Effects of Ionizing Radiation) V report.
564 That report stated: "…it is clear from the foregoing that detectable injury of the lens can result
565 from a dose of as low as 1 Gy, depending on the dose rate and LET of the radiation, the threshold
566 for a vision-impairing cataract under conditions of highly fractionated or protracted exposure is
567 thought to be no less than 8 Sv…" (NA/NRC, 1990). The conclusion from this review was that
568 such doses would exceed the amount received from occupational exposure under normal
569 working conditions and also greatly exceeded the exposures to members of the general
570 population from non-occupational types of exposure. Because the belief at the time was that
571 radiation-induced cataracts were strictly deterministic effects (i.e., there were dose thresholds),
572 no stochastic risk estimate was provided and that was reflected in NCRP (1993a) not providing
573 specific risk factors for radiation-induced cataracts.
574
575 ### 3.1.2 UNSCEAR
576
577 The principal issues of risk referred to by NCRP in establishing the recommendations in
578 1993 (NCRP, 1993b) besides BEIR V were a set of United Nations Scientific Committee on the
579 Effects of Atomic Radiation (UNSCEAR) reports available at the time (UNSCEAR, 1972; 1977;
580 1986; 1988). All of these reports focused on stochastic effects (i.e., cancer or genetic effects) and
581 the limited amount of information on somatic effects was largely focused on the human embryo

and fetus. UNSCEAR (1986) did provide information regarding malformations of the eye during periods of major organogenesis, but not on effects on the adult lens of the eye. Although UNSCEAR (1988) did consider the acute effects of exposures from the Chernobyl nuclear power plant accident, lens of the eye effects were not identified. Hence, the risk factors provided by NCRP (1993a; 1993b) for the lens of the eye were largely based on BEIR V alone.

3.2 Foundation of Dose Limits

The goal of radiation protection is to prevent the occurrence of serious radiation-induced conditions (acute and chronic deterministic effects) in exposed persons and to reduce stochastic effects in exposed persons to a degree that is acceptable in relation to the benefits to the individual and to society from the activities that generate such exposures (NCRP, 1993b). As such, the foundations of dose limits are the specific objectives of radiation protection, namely: 1) to prevent the occurrence of clinically significant radiation-induced deterministic effects by adhering to dose limits that are below the apparent threshold levels, and 2) to limit the risk of stochastic effects (i.e., cancer and genetic effects) to a reasonable level in relation to societal needs, values, benefits gained and economic factors (NCRP, 1993b). These objectives can be achieved by ensuring that all exposures are 'As Low As Reasonably Achievable' (ALARA) in relation to benefits to be obtained and by applying dose limits for controlling occupational and general public exposures (NCRP, 1993b).

3.3 Previous NCRP Recommendation on the Lens of the Eye

NCRP provides scientific guidance and advice regarding radiation protection issues. A number of NCRP reports explicitly address issues relevant to this Commentary's focus on the lens of the eye. A brief summary of the key points on lens of the eye protection from each of these reports is included in Table 3.1. Additional detailed summaries of each of the relevant NCRP reports have also been collated recently by EPRI (EPRI, 2014).

612

613 **Table 3.1**–Previous NCRP guidance on lens of the eye protection.

NCRP Report	Key Points
No. 91 (1987)	• Lens opacification identified as a nonstochastic effect • Dose thresholds depend heavily on the biological endpoints considered and their precise definition • 150 mSv annual dose equivalent to the lens of the eye occupational limit • 50 mSv annual dose equivalent to the lens of the eye public limit
No. 115 (1993a)	• Noted a consideration of late and non-cancer somatic effects, including effects of ionizing radiation on inducing cataracts in the lens of the eye
No. 116 (1993b)	• Lens of the eye limits expressly based on prevention of deterministic effects • 150 mSv annual equivalent dose to the lens of the eye occupational limit • 15 mSv annual equivalent dose to the lens of the eye member of the public limit

614

615

616 **Table 3.1**–(continued).

NCRP Report	Key Points
No. 132 (2000a)	• Radiation protection limits for occupationally exposed persons were recommended to prevent clinically significant deterministic effects • For deterministic effects, organ doses should be multiplied by an appropriate relative biological effectiveness (RBE) to adjust for radiation quality (Gy-Eq) • For activities in low-earth orbit, limits of 4.0, 2.0, and 1.0 Gy-Eq for career, 1 y, and 30 d respectively to prevent deterministic effects on the eyes • Noted that limiting the scattered dose to the lens of the eye to a range of 1 to 3 Gy prevented major clinical effects on the eye based on work showing thresholds ranging from 2 to 10 Gy acute doses and 4 Gy for fractionated doses

617

618

619 **Table 3.1**–(continued).

NCRP Report	Key Points
No. 153 (2006a)	• Definition of a clinically significant cataract is obscured by the unidirectional nature of cataracts • Relatively low doses of space radiation are correlated with an increased incidence and earlier appearance of cataract
No. 167 (2010a)	• Noted that some recent research suggested that there may not be a definite threshold for radiation effects on the lens of the eye
No. 168 (2010b)	• Noted that until current dose-limit values are reassessed, it is prudent to regard eye exposures in much the same way as whole-body exposure (i.e., ensure exposures are consistent with the ALARA principle)

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627 **3.4 Previous ICRP Recommendations**
628
629 The predecessor of ICRP was established in 1928 in order to provide scientific guidance
630 on the growing use of ionizing radiation in the medical community. ICRP has expanded its
631 efforts to include many other aspects of radiation protection, including astronauts exposed to
632 space radiation and the wide-spread use of radiation sources in the field of nuclear energy.
633 Recent recommendations by the ICRP (2012) on significantly lowering the lens of the eye dose
634 limits have led to much discussion in the radiation protection community. A brief summary of
635 the key points on lens of the eye protection from each of these reports is included in Table 3.2.
636 Additional detailed summaries of each of the relevant ICRP publications have also been recently
637 collated by EPRI (EPRI, 2014).
638
639 **3.5 Other International Reviews**
640
641 UNSCEAR eventually reviewed lens of the eye health effects in several later reports
642 (UNSCEAR, 2008; 2011b; 2013b) typically noting that cataracts are deterministic effects.
643 UNSCEAR (2008) acknowledged that several newer studies suggested that pre-clinical lens
644 opacity lesions may form after dose to the lens < 1 Gy and noted that additional follow-up of the
645 major cohorts was necessary to better characterize the risk to the lens. UNSCEAR (2013b)
646 suggested that childhood exposures result in an approximately two-fold increase in sensitivity
647 compared to adulthood exposures for cataracts, although the levels of evidence were
648 characterized as ‘weak.’
649
650

651

652 **Table 3.2**–Previous ICRP recommendations on threshold values for lens injuries and lens
653 dose limits.

ICRP Publication	Key Points
No. 41 (1984)	• Threshold dose denotes the amount of radiation that is required to cause a particular effect in at least 1 to 5 % of exposed individuals • Threshold dose equivalent of protracted low-level occupational radiation for vision-impairing cataracts is estimated to exceed 8 Sv, although detectable opacities might result from smaller doses • 150 mSv dose equivalent occupational limit each year for 50 y would not cause a vision-impairing cataract (ICRP, 1984)
No. 60 (1991a)	• Severe effects are not likely in most tissues at annual doses of less than about 0.5 Gy • Lens of the eye shows higher sensitivities • Pathogenesis of lens opacification not well understood

654

655

656 **Table 3.2**–(continued).

ICRP Publication	Key Points
No. 85 (2000)	• Noted that work suggests a 2 Gy threshold for cataract with 5 Gy being necessary to produce progressive disease • There is evidence that lens opacification, without loss of vision, can result from exposure to doses as low as 0.2 Gy • 2 Gy acute radiation dose may cause cataract • 4 Gy protracted exposures may cause cataract if received in less than 3 months • 5 Gy protracted exposures may cause cataract in periods exceeding 3 months
No. 103 (2007)	• 150 mSv annual equivalent dose to the lens of the eye occupational limit • 15 mSv annual equivalent dose to the lens of the eye public limit • Because of uncertainty concerning lens of the eye risk, there should be particular emphasis on optimization in situations of exposure of the eye • Noted that cataracts took several years to develop after an absorbed dose of ~ 1.5 Gy • Recognized uncertainties in the assignment of dose thresholds for cataracts

657

658

659 **Table 3.2**–(continued).

ICRP Publication	Key Points
No. 118 & Tissue Effects Statement (2011; 2012)	• Underlying assumption of a nominal threshold of 0.5 Gy for acute or protracted exposure • Detectable lens changes noted at doses of between 0.2 and 0.5 Gy • Acute doses up to ~ 0.1 Gy produce no functional impairment of tissues • Occupational lens of the eye limit of 20 mSv y^{-1}, averaged over defined periods of 5 y, with no single year exceeding 50 mSv • No new limit recommended for public exposures to the lens of the eye (i.e., public lens of the eye limit to remain at 15 mSv y^{-1})

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The International Atomic Energy Agency (IAEA) incorporated ICRP revised dose limits to the lens of the eye (ICRP, 2011; 2012) into the most recent version of the International Basic Safety Standards on radiation protection and safety of radiation sources (IAEA, 2011) and held several technical meetings on the subject (IAEA, 2012; 2013) emphasizing medical facilities, industrial radiographers/facilities, veterinary radiology, and nuclear facilities as work areas that should be assessed for the potential for risk of elevated doses to the lens of the eye. The European Commission has adopted the new limit suggested by ICRP in the recent Directive 2013/59/Euratom. The former U.K. Health Protection Agency [HPA, now Public Health England (PHE)] endorsed the conclusion reached by ICRP (Bouffler et al., 2012) and noted that further work is required to establish the magnitude of risk at low doses and following protracted exposure. The Canadian Nuclear Safety Commission (CNSC) proposed new recommendations in alignment with the recommendations of ICRP (CNSC, 2013). Based on member surveys (Broughton et al., 2013), the International Radiation Protection Association (IRPA) noted that the relationship between dose and cataract formation is not well understood and the causality should be clarified. They also noted concerns with considering fatal and non-fatal effects in a similar fashion, as well as inconsistency in the lens of the eye literature and tenuous results therein. The Health Physics Society (HPS) recommended that the scientific basis for cataract development (and not minor lens opacities that do not impair vision) be clearly delineated for chronic radiation exposures before changing the annual eye dose limit (Pryor, 2011). Additional detailed summaries of the epidemiological literature and these international reviews have been collated by EPRI (EPRI, 2014).

3.6 Practical Radiation Protection of the Eye

3.6.1 Monitoring Eye Doses

The annual dose limit for the lens of the eye is given in terms of the equivalent dose (H_t) and by definition this value is based on the mean absorbed dose ($D_{t,r}$) averaged over the volume of the lens. Wording provided in ICRP Publication 103 (2007) states: “The operational quantity

for individual monitoring is the personal dose equivalent, $H_p(d)$, which is the dose equivalent in ICRU (soft) tissue at an appropriate depth, d, below a specified point on the human body. The specified point is normally taken to be where the individual dosimeter is worn. For the assessment of effective dose, $H_p(10)$ (i.e., a depth d = 10 mm) is chosen, and for the assessment of the dose to the skin and to the hands and feet the personal dose equivalent, $H_p(0.07)$, with a depth d = 0.07 mm, is used. A depth of d = 3 mm has been proposed for the rare case of monitoring the dose to the lens of the eye. In practice, however, $H_p(3)$ has rarely been monitored and $H_p(0.07)$ can be used for the same monitoring purpose. Operational quantities are measurable, and instruments for radiation monitoring are calibrated in terms of these quantities. In routine monitoring of low-LET radiation types, the values of these operational quantities are typically taken as a sufficiently precise assessment of effective dose and skin dose, respectively, in particular, if their values are below the protection limits." While this Commentary did not specifically evaluate the accuracy or adequacy of the quantity personal dose equivalent for assessing the radiation exposure of the lens of the eye, Table 3.3 summarizes information related to the issue of measuring the lens of the eye dose equivalent (LDE) with different low-LET radiation types and at different depths in the eye related to the 'true' LDE. For non-low LET exposure situations, such as in neutron exposures, $H_p(0.07)$ and $H_p(10)$ are probably not appropriate surrogates for $H_p(3)$ because of buildup of charged secondaries from high-energy neutrons as well as scattering and attenuation of low-energy neutrons. Uncertainties in radiation weighting factors should be viewed as a source of dosimetric uncertainty (i.e., contributing to uncertainty in equivalent dose to the lens) (NCRP, 2011; 2012).

For medical workers exposed as part of fluoroscopically-guided interventional (FGI) procedures (e.g., those associated with interventional radiology or cardiology), NCRP has provided specific guidance on monitoring lens of the eye exposures in Report No. 168 (NCRP, 2010b). In addition, the European Union Basic Safety Standard (EU BSS) recommends adequate individual monitoring for all workers receiving equivalent lens doses > 6 mSv (BSS, 2014). Various types of radiation monitors are available. NCRP (2000a) provides detailed descriptions of several types of dose-monitoring devices. The radiation monitors and monitoring services should comply with the National Voluntary Laboratory Accreditation Program (NIST, 2008).

NOT TO BE DISSEMINATED OR REFERENCED

Table 3.3–How to measure LDE[a] for low-LET radiation (adapted from Behrens and Dietze, 2011).

Radiation Field	$H_p(0.07)^b/H_{lens}$	$H_p(3)^c/H_{lens}$	$H_p(10)^d/H_{lens}$
Photons < 30 keV	0.9 – 5	0.6 – 1	0.01 – 0.9
Photons > 30 keV	0.8 – 1.1	1 – 1.2	0.9 – 1.2
Electrons	1 – 500	~ 1	<< 1 – 1.2
Implementation	Adequate for photon radiation	Adequate for photons, necessary for beta	Not appropriate for low E photons or beta

[a]LDE = lens of the eye dose equivalent.
[b]Measurement by an extremity dosimeter.
[c]Measurement by a proposed dosimeter dedicated to LDE.
[d]Measurement by a whole-body dosimeter.

731
732 A worker in the FGI procedure environment may wear as many as three personal
733 dosimeters (i.e., on the torso, at the neck, on the hand). However, these devices indicate only the
734 radiation level received by the device. None of these dosimeters directly measure the value of the
735 equivalent dose (E or H_E) received by the worker. The actual values require adjustments for the
736 attenuation of the radiation due to the use of protective equipment by individual workers. Two
737 different methods for positioning personal dosimeters on staff wearing protective aprons are used
738 at present in the United States. These are a single dosimeter worn at the neck outside and above
739 the protective apron; and, dual dosimeters, one worn under the protective apron at the waist or on
740 the chest and the other worn outside and above the apron at the neck (NCRP, 2010b). ICRP
741 (2000a) recommended that staff performing FGI procedures wear two dosimeters, one under the
742 apron and one at collar level above the protective apron.
743
744 Equivalent dose to the lens of the eye is usually inferred from a personal dosimeter
745 placed elsewhere on the worker's body. The preferred locations are either at the collar level
746 outside any radiation protection garments or near the eyes. In general, the reading on a collar
747 dosimeter is likely to be somewhat higher than the actual dose to the lens of the eye (Kim et al.,
748 2008). Measurements can be performed to define a correction factor if needed (Farah et al.,
749 2013). The collar dosimeter reading should be directly used in the absence of such a measured
750 correction. Over-table x-ray systems result in more scattered radiation to the upper body of
751 workers performing FGI procedures than do under-table x-ray systems (NCRP, 2010b).
752 Opacities in the lens of the eye have been reported with over-table x-ray systems (Farah et al.,
753 2013; Vano et al., 1998b). When protective eyewear is worn it reduces exposure to the lens of
754 the eye. Useful attenuation depends on the size and shape of the device as well as on the working
755 conditions of the wearer. The actual attenuation is seldom as high as the nominal attenuation of
756 the protective eyewear (Moore et al., 1980; Schueler et al., 2009).
757
758 When specific lens of the eye dosimetry has not been used (as has been the case for many
759 professional workers in the medical sector), it may be possible to make an indirect estimation of
760 lens dose. Vano and colleagues (2013b) tested such an approach and noted that: "…the

experimental results of such a methodology allow for realistic estimations of the dose to the lenses of the eyes from the workload of the cardiologists and from the level of use of radiation protection tools when personal dosimeters have not been regularly used."

Investigations should occur if personal-dosimeter readings for an individual are substantially above or below the expected range for that individual's duties (NCRP, 2010b). As an example, NCRP Report No. 168 (2010b) noted: "Too low a dosimeter reading should prompt a formal investigation … collar-dosimeter readings that are < 25 % of the average reading for that worker or worker group should be investigated to determine if the assigned dosimeter is being worn appropriately."

3.6.1.1 ICRP External Dose Factors for Lens of the Eye. ICRP recently published recommendations on special considerations for assessing absorbed dose in the lens of the eye (ICRP, 2010). ICRP acknowledged strong differences in sensitivity to ionizing radiation exposure with respect to cataract induction among the tissues of the lens of the eye (Charles and Brown, 1975; ICRP, 1955) and suggested that in such cases it is necessary to consider a local volume within the organ in which the dose is highest (ICRP, 2010). Since ICRP referenced computational phantoms that represented the lens of the eye at a relatively low level of resolution, an ICRP Task Group decided to adopt stylized models of the eye and lens for electrons, photons and neutrons for estimating the dose conversion coefficients for irradiations resulting in a steep dose gradient (ICRP, 2010). The eye model of Behrens et al. (2009), based on the recommended data given in Charles and Brown (1975), was adopted for photon, electron and neutron radiations. For electron irradiation, the bare eye model was assumed to be exposed (Figure 3.1). For photon and neutron irradiation calculations, the eye model was incorporated into the head of a mathematical model averaged from Adam and Eva (ICRP, 2010) (Figure 3.2).

Dose conversion coefficients for these more refined lens geometries in the stylized phantoms were calculated for several irradiation conditions and geometries. These are provided in Appendix F, ICRP Publication 116 (ICRP, 2010) and can be utilized for assessing absorbed dose in the lens of the eye.

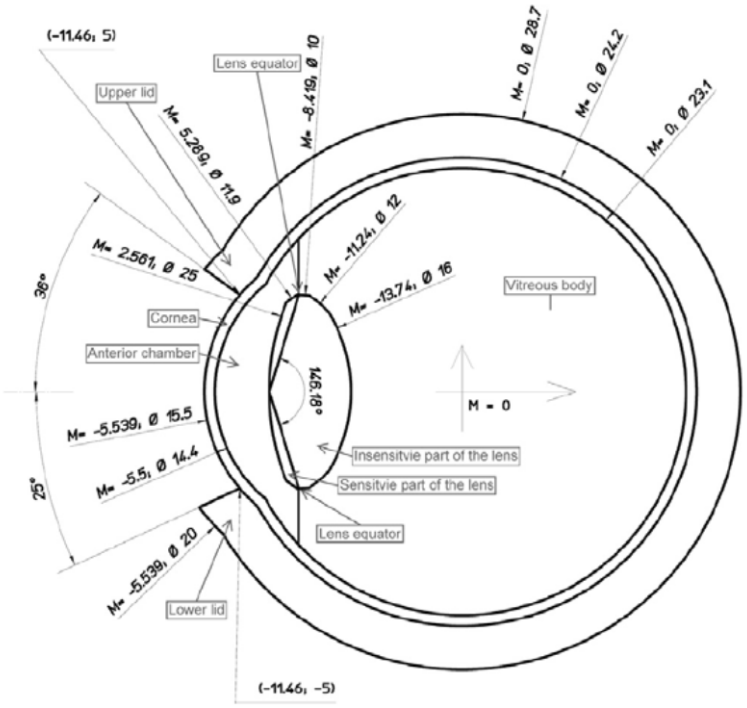


Fig. 3.1. The detailed stylized eye model by Behrens et al. (2009) as it was simulated in ICRP Monte Carlo calculations. All dimensions are given in mm. M denotes the x-position of the centers of the spheres and ϕ denotes the corresponding diameters (ICRP, 2010).

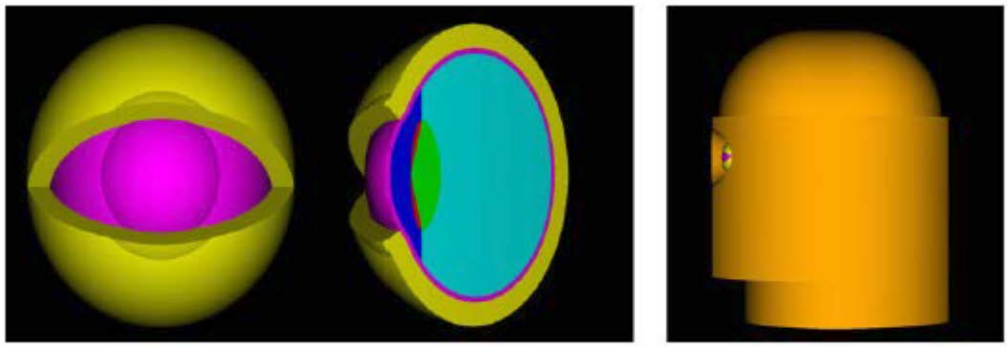


Fig. 3.2. Three-dimensional views of the eye as simulated in ICRP Monte Carlo calculations. Left shows a side view of the eye model implemented in the stylized head phantom shown at the right (ICRP, 2010).

3.6.1.2 EURADOS and ORAMED European Projects. EURADOS is a non-profit organization promoting research and development as well as European cooperation in the field of ionizing radiation dosimetry. In a recent EURADOS report (2014), it was stated that the challenge is to provide reliable, accurate and on-line personal dosimetry information for occupationally exposed workers. This requires monitoring workers in real time for all limiting dose quantities (i.e., whole body, lens of the eye, extremities, etc.) regardless of the protection methods used and to provide input for the optimal application of the ALARA principle. There is still much work to be done regarding lens of the eye dosimetry. For example, standardization of methods to measure lens of the eye dose, development of practical lens of the eye dosimeters, and testing and comparing different lens of the eye dosimeters are needed. There is also a lack of data for lens of the eye doses of workers in different industries. For example, in medical applications, correlations of lens of the eye doses with other dose quantities, determination of reference lens of the eye doses for different procedures, as well as testing and improvement of the efficiency of different protection measures (such as leaded glasses) need to be explored. The development of a dosimetry protocol to assess all of these factors is particularly required.

The main objective of the European Optimization of Radiation Protection for Medical (ORAMED) staff (Domienik et al., 2011) project was to obtain a set of standardized data on extremity and lens of the eye doses for staff in interventional radiology and cardiology. A coordinated measurement program in different hospitals in Europe was carried out. The highest doses were found for procedures involving implants of pacemakers, renal angioplasties and embolizations. The highest lens of the eye doses were measured during embolizations. It was concluded that it is difficult to find a general correlation between kerma area product and extremity or lens of the eye doses, although other studies have suggested this association (Dauer et al., 2010).

3.6.2 Methodologies for Protecting the Eye

The practical problems for protection of the lens depend on the type of radiation, its energy and the operational exposure scenario (i.e., the geometry relative to radiation source and shielding), chiefly concerning the use of appropriate radiation and general eye safety tools (e.g., screens or goggles) that are compatible with the work to be performed. In FGI procedures, the use of adequate eye protection is clearly a necessity, especially for high-volume practices (Dauer et al., 2010; NCRP, 2010b). Several guidance documents for the medical industry have been developed that suggest means of comprehensive lens protection for occupational exposures (e.g., Chambers et al., 2011; ICRP, 2000; Miller et al., 2010; NCRP, 2010b; Stecker et al., 2009). Leaded glasses have been shown to reduce lens doses by a factor of about three (or higher), shielded sterile drapes by a factor of about 25, and suspended ceiling shields by a factor > 100 (Thornton et al., 2010). Additional optimization suggestions for patient protection are needed [e.g., Prins et al. (2011)]. In the nuclear industry, it is common to utilize respirator face shields, bubble suit masks, and/or goggles in order to reduce beta doses to the lens.

3.6.3 Health Surveillance Programs

Few (if any) detailed protocols on health surveillance programs for lens opacities have been issued. Some of the published papers with results of the IAEA Retrospective Evaluation of Lens Injuries and Dose (RELID) program recommend that (Vano et al., 2013a): Periodically obtain a comprehensive ophthalmologic examination, including a detailed dilated slit lamp examination of the posterior lens region, as part of regular medical evaluations recommended by regional or national regulations.

The RELID international study was initiated by the IAEA in 2008. RELID had two components, namely, 1) evaluation of dose and 2) evaluation of radiation injury. A number of eye testing examinations were carried out. The evaluation of radiation dose to the eye is not a straightforward issue. The current measurement techniques are not adequately developed and are

not available for routine use to inform radiation dose to the lens of the eye. Thus retrospective estimations have become necessary, for instance using RELID forms for retrospective evaluation of doses filled in by the exposed individuals. Each participant was asked to provide information on the number of years of work in interventional laboratories, use of protective screens and eye wear, work load with fluoroscopy time and cine (digital or filmed dynamic records of fluoroscopic examinations) details, as well as other information pertaining to techniques that may have had bearing on the radiation dose to the lens of the eye. Based on this information, the radiation dose was estimated. Availability of personal monitoring badge data assisted in correlation. The location of the individual in relation to the radiation source was also taken into account. An ophthalmologist then tested the participants' eyes and scored the PSC opacities using Merriam-Focht scores (0.5, 1.0, 1.5, etc.) separately for each eye. The quantification of opacity score also contributed to the comparison with the estimated radiation dose and established correlation (IAEA, 2014a; 2014b). Other surveillance programs have been suggested (McCarty et al., 2000).

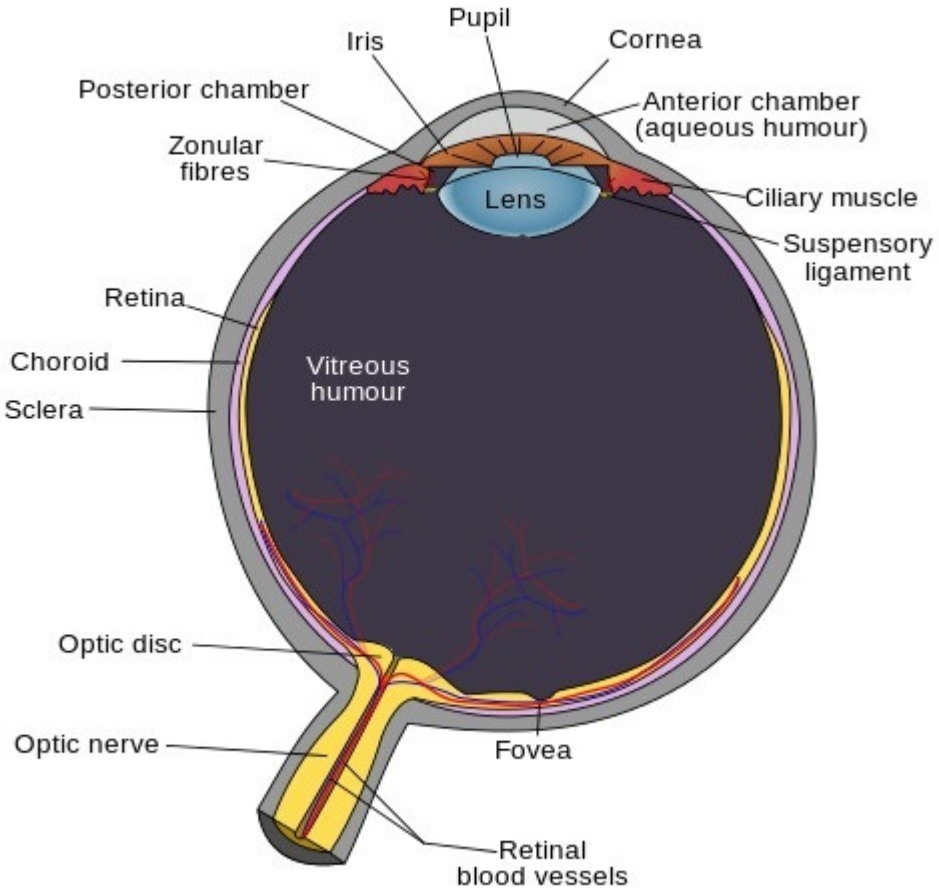
4. Eye Biology and Lens Effects

A brief description of the anatomy of the eye with an emphasis on the lens is provided here to facilitate identification of each of the ocular structures pertinent to the discussion that follows.

4.1 Eye Biology

The size of the normal human eye is remarkably similar among adults. The axial length of the globe along the visual axis averages 24 mm (ranging from 21 to 27 mm), and the vertical diameter averages 23.5 mm. The full size of the eye is attained by age 13. The globe has three major layers, enclosing three transparent structures. The outmost layer is composed of the cornea and sclera. The middle layer is known as the uvea, and consists of the choroid, ciliary body and iris. The choroid is the vascular layer of the eye, containing connective tissue, and lying between the retina and the sclera. The innermost layer is the retina. The three transparent structures within the layers are the aqueous humor, the lens, and the vitreous body. The anterior chamber is the region between the cornea and the iris, and the posterior chamber lies between the iris and the lens. The lens is suspended from the ciliary body by the suspensory ligaments. The vitreous humor is a clear jelly that occupies a greater volume than the aqueous humor present behind the lens. Since the adult lens is avascular, oxygen and nutrients diffuse to the lens through both the aqueous and vitreous humors. The trabecular meshwork is an area of tissue in the eye located around the base of the cornea, near the ciliary body, and is responsible for draining the aqueous humor from the eye via the anterior chamber (the chamber on the front of the eye covered by the cornea). The conjunctiva is the transparent membrane that lines the eyelid and covers the sclera (white part of the eyeball). The macula is a very small oval yellowish area surrounding the fovea at the center of the retina (a thin layer of light-sensitive tissue that lines the back of the eye). The fovea is the region of the retina responsible for fine vision. The macula is the region of greatest visual acuity. Light rays are focused onto the retina, where they are transmitted to the brain and interpreted as the images seen (Figure 4.1).

907



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909

910 **Fig. 4.1.** Schematic diagram of the human eye (adapted from Wiki, 2014).

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912

913
914 **4.1.1** Lens Anatomical Features
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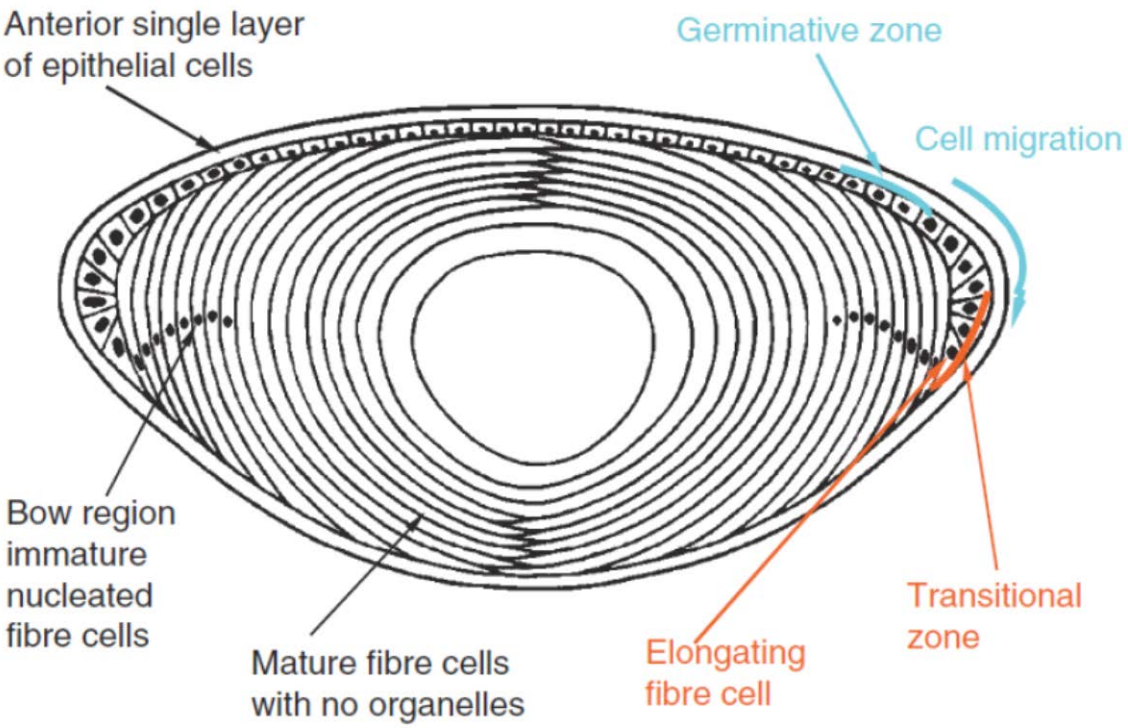
916 The adult lens is a transparent organ located behind the cornea and the iris with an
917 average horizontal diameter of 9 to 10 mm, and an anterior-posterior thickness of 4.5 mm. The
918 outer edge of the light-facing side of the lens consists of a single layer of epithelial cells, and a
919 membrane that covers the entire organ (Kuszak et al., 1994). The lens germinal epithelium is
920 located around the circumference of the lens at its most peripheral extent, termed the 'bow' of
921 the lens. Here fibroblast growth factor 2 (FGF-2) triggers differentiation of the lens epithelial
922 cells into the second cell type in the lens, the lens fiber cell. As the lens fiber cells migrate
923 inwards, all intracellular organelles including the nucleus, mitochondria, Golgi, etc. disappear
924 (Bassnett and Mataic, 1997). The lens fiber cells remain attached anteriorly within the lens
925 beneath the single layer of lens epithelium, and posteriorly to the posterior capsule, until they
926 detach from the capsule and attach to the fiber cells on the other side and form a suture (Figure
927 4.2). It is at this location that PSC cataracts associated with exposure to ionizing radiation may
928 form. The lens fiber cells can be described as "bags of crystalline proteins" as they approach the
929 nucleus of the lens. Since there is little protein turnover in the lens fiber cells, damage to the lens
930 proteins accumulates throughout life (Roberts, 2011). The oxygen tension in the lens is very low,
931 but is sufficient for photo-oxidation to occur (Mclaren et al., 1999). Lens cells have several
932 defense systems against light and radiation damage, including antioxidant enzymes [e.g.,
933 superoxide dismutase (SOD) and catalase], and antioxidants (e.g., vitamin E, vitamin C, lutein,
934 and glutathione) (Roberts, 2001). However, these defense systems become diminished after 40 y
935 of age (Lyle et al., 1999). The lens of the adult eye does not have a vascular supply, and as a
936 consequence all necessary materials must be supplied to the eye by the surrounding ocular fluid
937 (the aqueous humor) and all toxic materials must be removed by normal turnover of the aqueous
938 humor (Beebe, 2008).
939
940

941



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943

944 **Fig. 4.2.** Anatomy of the human lens, a diagrammatic representation of the lens and
945 formation of secondary fiber ('fibre' in figure) cells is shown. Epithelial cells in the anterior
946 germinative zone proliferate in response to FGF stimulation and migrate to the transitional zone
947 posterior to the equator, where upon exposure to higher concentrations of FGF, they differentiate
948 and elongate to form the secondary fiber cells. The fiber cells are gradually packed into the
949 center of the lens, losing organelles as they mature (Augusteyn, 2008).

950
951

952
953 **4.1.2** Lens Proliferative Organization
954
955 The human lens is reported to grow in a biphasic manner throughout life (first
956 asymptotically from conception until early in a newborn's life followed by linear growth) and
957 shows no evidence of slowing of growth with age (Augusteyn, 2008). Similar observations have
958 been made for lens growth in African elephants, American minks, hippopotami, Spanish ibexes,
959 and woodchucks, but approximately 126 other species studied (including rodents commonly used
960 for laboratory studies of radiation effects on the lens) demonstrated asymptotic lens growth
961 throughout life (Augusteyn, 2014). Normal lens development and growth are dependent on the
962 precise spatial and temporal regulation of lens cell proliferation and fiber cell differentiation.
963
964 **4.2 Cataracts**
965
966 A number of causative factors have been identified for the formation of opacifications
967 (cataracts) in the lens of the eye. This section of the Commentary focuses on cataract
968 characteristics, evaluation and etiology.
969
970 **4.2.1** Cataracts and Opacifications
971
972 A cataract is a clouding or opacification that occurs in the normally clear lens of the eye.
973 Some cataracts are clinically unimportant, not impairing vision in any way. Nevertheless,
974 cataracts remain the most common cause of severe visual impairment, with visual loss occurring
975 because the opacification prevents light from passing through and being focused on the retina
976 (Yanoff, 2008).
977
978 Most cataracts are associated with aging, but there are a variety of other etiologic factors
979 including: exposure to ionizing and nonionizing radiation, medications, and trauma (Michael and
980 Bron, 2011). In a review of 4,425 persons aged 55 to 80 y at baseline that were followed for an
981 average of 9.8 y, Chang et al. (2011) reported the following associations: increasing age with
982 increased risk of all types of cataract and cataract surgery; males with increased risk of PSC

cataracts and decreased risk of cortical cataracts; non-whites with increased risk of cortical cataract; hyperopia with decreased risk of PSC cataract, nuclear cataract, and cataract surgery; vitamin use with decreased risk of nuclear cataract; diabetes with increased risk of cortical cataract, PSC cataract, and cataract surgery; higher educational level with decreased risk of cortical cataract; and, smoking with increased risk of cortical cataract and cataract surgery. Cataracts can reduce the sharpness of vision and can contribute a colored tint to vision. Most cataracts lead to difficulty in observing contrasts in lighting and colors, driving, and reading due to the scattering of light by the opacifications.

Cataracts are usually corrected with surgical removal followed by implantation of an intraocular lens of appropriate optical power as an out-patient procedure (Vasarada et al., 2012). While 90 % of patients acquire totally corrected vision, there are some complications that can occur in a low percentage of patients including retinal detachment, edema, formation of secondary cataracts on the replaced lens, and others. Stein (2012) reviewed the available literature on serious adverse events after cataract surgery and noted that the risks varied. PSC rupture occurred in 1.9 to 3.5 % of patients, retinal detachment in 0.4 to 3.6 % of patients, endophthalmitis in 0.05 to 0.3 % (with a collective rate of 0.128 %) of patients, and suprachoroidal hemorrhage in 0.03 to 0.13 % of patients (Stein, 2012). It should be noted that while this surgery is routine, it is not available throughout the world in developing nations, and thus cataract development can have significant consequences in those areas.

There is active research in preventing and potentially reversing lens opacities in experimental laboratory models of cataract. Two recent reports indicate that specific sterols administered as eye drops can reverse cataract and improve lens transparency in different animal models, and also when administered to human ex vivo lens in experiments (Makley et al., 2015; Zhao et al., 2015). Clearly more work needs to be done to determine whether these treatments reduce all types of cataracts, and whether or not they can be adapted for use in humans.

4.2.2 Cataract Types, Severity and Impact on Vision

Cataracts are usually classified in a somewhat qualitative manner, based on the location of the opacity. Nuclear sclerosis is the most common type of cataract located in the central nuclear part (or central zone) of the lens. Sclerotic changes indicate a change in hardness, and there is often a deposition of brown pigment within the lens. It is linked to smoking as a major causal factor, possibly due to the related inhibition of antioxidant action (Sulochana et al., 2002). Cortical cataracts result from opacities in the cortex of the lens usually beginning in the peripheral part of the lens and spreading into the center of the lens (Richter-Meuksch et al., 2011). Cortical cataracts are associated with diabetes, and exposure to both ultraviolet (Javadi and Zarei-Ghanavati, 2008) and ionizing (Chylack et al., 2009) radiations. PSC cataracts begin in the back of the lens, adjacent to the capsule in which the lens is situated, and are linked to steroids, diabetes and ionizing radiation as causal sources. Supranuclear cataracts are located above the nuclear region of the lens, and are reported to occur in patients with Alzheimer's disease and Down syndrome (Goldstein et al., 2003; Hockwin, 1994-1995; Moncaster et al., 2010).

It is also worth noting that aging has been linked to all types of cataracts (Beebe et al., 2008) and that more than one type of cataract can be observed in a single lens. Examples of age-related cataracts are shown in Figure 4.3.

Cataracts are also classified as immature, mature and hyper-mature types depending on the degree of opacity vs transparent protein that is present in the lens. In a mature cataract, all of the lens protein is opaque, while in an immature cataract, some of the lens proteins are transparent. For hyper-mature cataracts, proteins in the lens have become liquid (Chylack et al., 1988; 1989; 1993). Cataracts may also be classified as hard or soft depending on the color of the opacity. Light (white) colored opacities are considered soft and dark colored (yellow or darker) are considered as hard (Chew et al., 2010).

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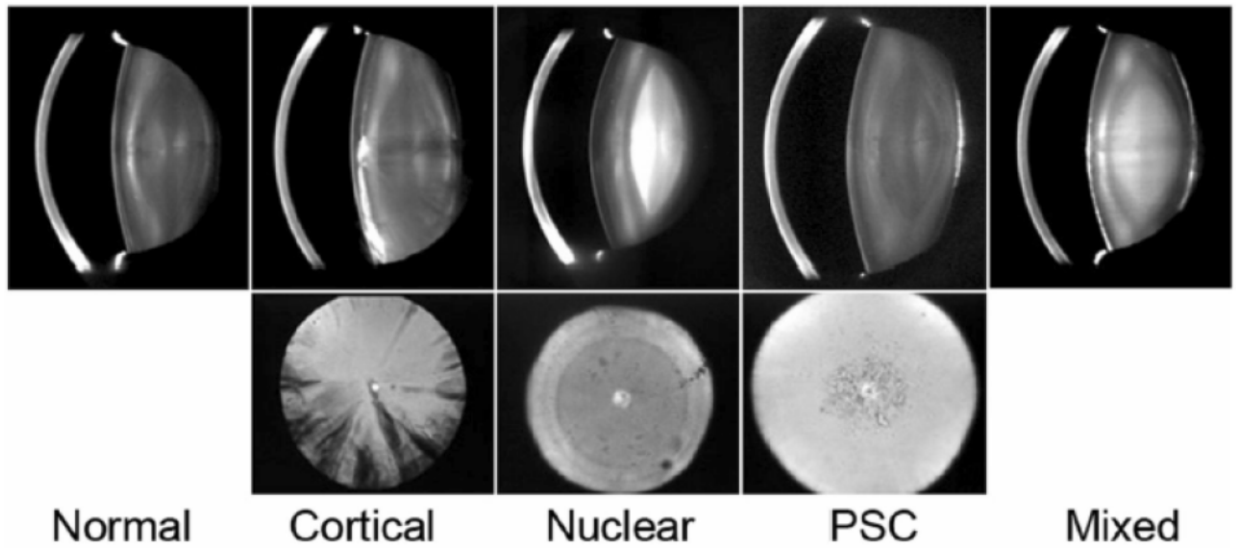

Fig. 4.3. Examples of the common types of age-related cataracts are shown here. The upper row of images shows Scheimpflug camera views of the normal lens and four types of age-related cataracts. The images show (from left to right) the cross-section of the cornea, the dark gap of the aqueous humor and then the area of the lens from anterior to posterior. Note the bright anterior spokes of the cortical cataract, the bright midline nuclear cataract, and the bright PSC cataract in the middle of the visual axis at the extreme posterior position. Frequently lenses have several cataract types, designated mixed cataracts. The lower row of photographs represents retroillumination images of the three common types of age-related cataracts looking down along the visual axis (Beebe, 2008).

Cataracts can also be delineated as either partial or total, based on the extent of the opacity. For total cataracts, the whole lens has lost transparency, while for partial cataracts, only certain portions of the lens are opaque. A partial cataract may remain stationary or it may later extend, becoming progressive. The most common partial cataracts are the anterior and posterior polar cataracts, both of which are stationary. Anterior and posterior cortical cataracts are progressive partial cataracts. They may be stationary for years, and/or progress with time after their initial appearance.

Clinical studies in humans have shown that depending on the radiation dose and duration of exposure, a radiation-induced opacity could remain stationary in the early stages, develop to an intermediate stage and remain stationary, or cross a threshold for clinical significance and progress to a fully mature cataract (Merriam and Focht, 1957). Clearly, VICs could be considered the endpoint of greatest concern in terms of lens radiation protection. However, the mechanisms underlying the transition to clinically significant VICs are still not well understood, and this is likely to be an extremely relevant radiation protection issue requiring further investigation.

4.2.3 Cataract Causes

Age is the most common cause of cataract, with small cataracts that do not significantly impair vision first evident usually at age 40 but not impacting vision significantly until one to two decades later. With time, environmental factors (such as sunlight exposure, exposure to chemicals, etc.) will cause proteins in the lens to aggregate and cloud a small portion of the lens. As the cataract grows larger with age, vision becomes more impaired (Michael and Bron, 2011; Wiekel et al., 2013).

Blunt trauma to the lens can cause thickening and swelling of the lens fibers; in some cases, the capsule can be damaged as well. Electrical injuries (such as lightning injury, high- and

low-voltage injury) also have been reported to cause cataracts in a small percentage of patients (Hashemi et al., 2008; Korn and Kikkawa, 2014).

Patients with metabolic disorders (such as diabetes and galactosemia) and skin disorders (such as atopic dermatitis and eczema) have a higher incidence of developing cataracts than the general population. There appears to be a genetic component to the origin that may be important in these patients as well (Hamada and Fujimichi, 2015). A variety of infections (e.g., leprosy, varicella, and toxoplasmosis) predispose to the development of cataracts, and rubella in utero can lead to cataracts in infants (Thompson et al., 2014). Some medications such as corticosteroids can induce cataracts, particularly PSC cataracts (Dynlacht, 2013).

Epidemiological studies and experiments in animal systems have demonstrated that exposures to ultraviolet radiation can induce cataracts. Both UV-A and UV–B have been implicated. While UV-B is associated with shorter wavelengths and has less penetration than UV-A, it is very damaging and has been heavily implicated in cataract induction. UV-A penetrates through the inner skin layers of the eyelid and the other protective parts of the eye and also can damage the lens. Ocular protection reduces the incidence, and increased dose and exposure time increase the incidence. Individuals who work outdoors or spend much time exposed to sunlight are more likely to develop opacities, and there is concern with reductions in the ozone cover around the earth that cataract incidence may increase (Collman et al., 1988).

Of most importance to this Commentary is the association of cataract induction with exposure to ionizing radiation, which is discussed in Section 4.3.2.

4.2.4 Cataract Mechanisms

The mechanisms of cataract induction are not fully understood. Opacifications can occur due to the misfolding of lens crystalline proteins or due to dysregulation of lens cell morphologies. The underlying cause of these changes is unclear, although some have considered that oxidative stress may be an initiating factor that leads to lipid peroxidation, DNA and/or

protein damage and thus results in later changes in the lens and onset of cataractogenesis. Most of the agents associated with cataract development are agents that lead to the production of reactive oxygen species and oxidative stress in cells. Moreau and King (2012) review the mechanisms of cataract disease associated with protein aggregation.

Deregulation of normal lens proliferation and differentiation that results in disorderly arrangement of protein fibers leads to a loss of transparency and cataracts (Benedek, 1971). Using a transgenic mouse model, Lovicu et al. (2004) demonstrated that during the formation and growth of transforming growth factor beta (TGFβ) induced subcapsular plaques, lens epithelial cells lose key phenotypic markers including E-cadherin and connexins 43, they multilayer and subsequently differentiate into myofibroblastic and/or fiber-like cells. They propose that other growth factors in the eye, namely fibroblast growth factor, may also play a role in the establishment and regulation of the key cellular processes leading to lens pathology (Lovicu et al., 2004). Understanding the effects of this cytokine and other molecular aspects and cellular dynamics of cataract formation and growth is essential to devising strategies for slowing or preventing cataracts.

Recent studies have also examined a possible role of protein folding functions in cataractogenesis; much work has shown that mutations in lens connexins, proteins associated with maintaining lens cell gap junctions and cell chaperone function (which refolds misfolded proteins) are associated with the development of congenital cataracts in humans. It is thought that somatic defects in these pathways may also be associated with onset of cataracts from oxidative damage causes (Berthoud and Beyer, 2009; Beyer et al., 2013). Similarly, genetic polymorphisms of another chaperone protein, HSP70, also have been found to be associated with cataract induction (Hamada and Fujimichi, 2015; Zhang et al., 2013).

Many have discussed a possible role for DNA damage in the induction of cataracts, although not all cells of the lens have DNA. Several reports have noted that damaged nuclei, mitochondria, and DNA can be found in subcapsular and cortical cataracts, possibly due to the

failure of lens fiber cells in the bow region of the lens to differentiate properly (Pendergrass et al., 2005; Pendergrass et al., 2010).

It is unclear whether cataracts of different morphologies have different pathologies. The focus of this commentary is on ionizing radiation-induced cataracts, and by necessity, reference to studies of cataracts of other causes will be limited.

4.2.5 Examination and Quantification of Lens Changes

Although visual acuity and functional impairment tests are modern methods to evaluate visual decrements, the evaluation of radiation effects on the crystalline lens has primarily been limited to clinical examination and documentation of physical changes in the anatomy of the lens. Since different types of cataract are associated with opacities in various different parts of the lens, it is appropriate to classify cataracts according to their location within the lens.

The development of biomicroscopy instrumentation to noninvasively observe the eye has progressed from the original ophthalmoscope that Babbage designed in 1846 (Duke-Elder, 1962) to the use of oblique illumination and microscopic examination with a slit lamp (Berliner, 1966; Tate and Safir, 1991), and the specular microscope (Bourne and Enoch, 1976). Two approaches have been used: (1) subjective methods of lens observation based largely on slit lamp microscopy, and (2) objective methods of determining lens transparency or lens opacity, also based on slit lamp documentation, but according to the Scheimpflug principle combined with the retroillumination technique (Hockwin, 1994-1995) (Table 4.1).

Due to age-related changes in the transparency of the lens, early lenticular changes due to cataract formation cannot be discerned by subjective methods. The densitometric analysis of Scheimpflug slit images, however, allows the exact measurement of the light scatter in the single lens layers, and enables the early recognition of disturbances in transparency crucially important

Table 4.1—Comparison of methods used to score lenticular cataracts in vivo.

Method	Provides	Advantages	Disadvantages	Reference
Slit-lamp biomicroscopy exam with photography or video	• Slit of light is projected onto the lens and detected by a long working distance microscope focused on the lens – first developed by Gullstrand in 1911	• Provides visual display	• Subjective evaluation	Duke-Elder, 1962
Scheimpflug slit-lamp exam with camera optics	• Scheimpflug imaging initially provided photographic images for comparison with standard photographs of different cataract features	• Rapid • Easy to perform • Fast to learn	• Geometric optical limitations and imaging through the cornea leads to high-order image distortion • Requires pupil dilation • Posterior cortex or capsule lesion difficult to score	Brown, 1974; Cook and Koretz, 1998

Table 4.1—(continued).

Method	Provides	Advantages	Disadvantages	Reference
Scheimpflug rotating photo-slit-lamp camera exam Pentacam image analysis and assays lens density	• Cross-sectional lens image from anterior to posterior to evaluate lens density • Image of lens nucleus and PSCs located in the center of the posterior lens aspect • New optical technologies, such as Pentacam acquire 50 images in ~ 2 sec by a rotating Scheimpflug camera measurement and offer built-in Pentacam Nucleus Staging software for objective classification • Camera captures images in different meridians and creates a 3D image of the crystalline lens • Scheimpflug images allow for a continuous measure, whereas the LOCS III which has grading systems in steps, permit the detection of more subtle amounts of progression	• Permits scaling of the lens density from less to more sclerotic by visual inspection or densitometric planimetry • Best imaging of nuclear sclerosis or nuclear cataract • Provides objective measure of lens density compared to LOCS III	• No standardized screening evaluation of cataracts published yet	Datiles et al., 1995; Gupta et al., 2013; Hockwin et al., 1982; Kirkwood et al., 2009; Lim et al., 2014; Sasaki and Nakamura, 1978; Sasaki et al., 1979

Table 4.1—(continued).

Method	Provides	Advantages	Disadvantages	Reference
"Thrifty" Scheimpflug retro-illuminated slit-lamp exam	• Retro-imaging the lens with a flash reflected off the retinal surface resulting in an orange color "disc" against which lens opacities appear as areas of darkness	• Used in population-based studies • Can be used to detect non-central PSC that could be missed or inadequately imaged with the Scheimpflug techniques	• More cost effective	Klein and Klein, 1992
MRI refractive index	• Non-optical imaging technique that provides novel information on lens shape, including asphericity of lens surface and ciliary body position and anatomy	• Does not require information on lens optical properties	• Time consuming technique • Low resolution	Jones et al., 2005; Kasthuriragan et al., 2011; Strenk et al., 2004
Scheimpflug 3D-microscopic tomography	• 3D microscopic imaging of the cataract in a human lens in vivo		• Not yet used for large population-based studies • No data on radiation-induced cataracts with this method	Masters, 1998

in cataract epidemiology (Hockwin, 1994-1995; Jain and Grewal, 2009; Wegener and Junga, 2009). Prevalence and/or incidence studies involving a single examination of a cohort have severe limitations in assessing multifactorial cataract processes which require repeated examinations for objective classification before visible opacifications appear (Datiles and Ansari, 2006).

Quantification of cataracts has commonly been done using the Merriam-Focht Cataract Scoring System (Figures 4.4.a-d). The Merriam-Focht system has been described as: "…taking into account the frequency of observed posterior and anterior opacities, sutural changes, vacuoles and other lens defects, and the percent opacity as a function of lens anterior and posterior surface area…" (Merriam and Focht, 1962). Figure 4.5 illustrates the tendency of human radiation-induced cataracts to develop in the PSC region of the lens.

A Lens Opacities Classification System (LOCS) III also has been developed to facilitate scoring of the severity of cataracts. This system includes slit-lamp images for grading nuclear color and nuclear opalescence as well as retroillumination images for grading cortical cataracts and PSC cataracts. Severity is graded on a decimal scale (Figure 4.6) (Chylack et al., 1993).

Several standardized clinical grading and photographic systems comparing a patient's cataract with standard photographs have been developed. These include: (1) LOCS I, II and III (Chylack et al., 1988; 1989; 1993), (2) the Wisconsin Clinical and Photographic Cataract Grading System (Klein et al., 1990), (3) the Wilmer Clinical and Photographic Grading System (Taylor and West, 1989), (4) the Oxford Clinical Cataract Grading System (Sparrow et al., 1986), (5) the AREDS (Age-Related Eye Disease Study) (Braccio et al., 1998; Kaffoff et al., 2001), (6) the NEI Clinical Cataract Grading System (Vivino et al., 1993), (7) the Japanese CCRG Cataract Grading System (Sasaki et al., 1990), (8) the WHO (World Health Organization) Cataract Grading System (Thyleflors et al., 2002), and (9) the systems for quantifying posterior capsule opacification in subjects who have had cataract surgery (Bender et al., 2004; Tetz et al., 1997).

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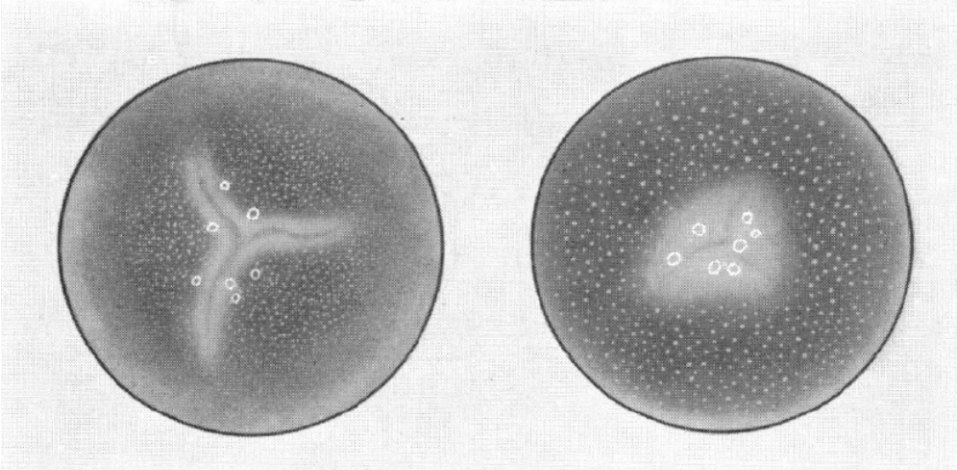

Fig. 4.4.a. Illustrations of the Merriam-Focht Cataract Scoring System (+1, +2, +3, and +4) are shown in Figures 4.4.a-d, in this figure two characteristic 1+ cataracts showing the early central postcapsular vacuoles and dots with widening of the suture lines and an increase in the light reflex (Merriam and Focht, 1962).

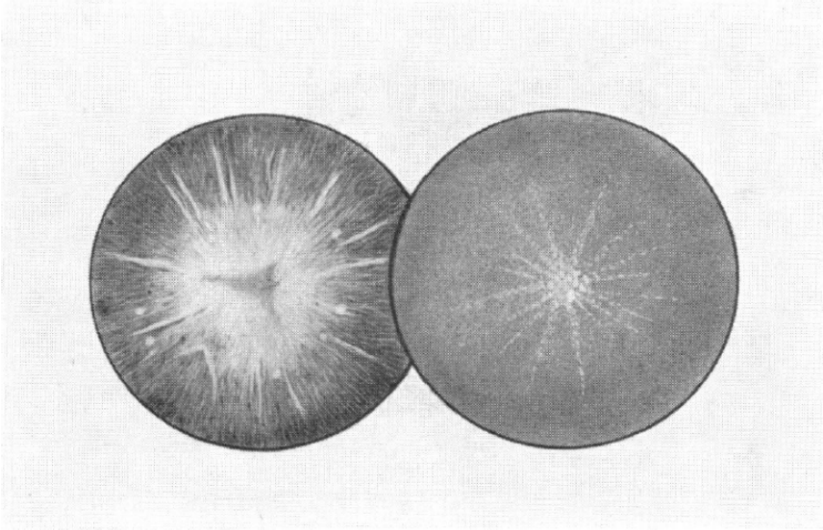

Fig. 4.4.b. A 2+ cataract showing the increase in the posterior cortical opacity, left, and the beginning of the central anterior subcapsular opacity, right (Merriam and Focht, 1962).

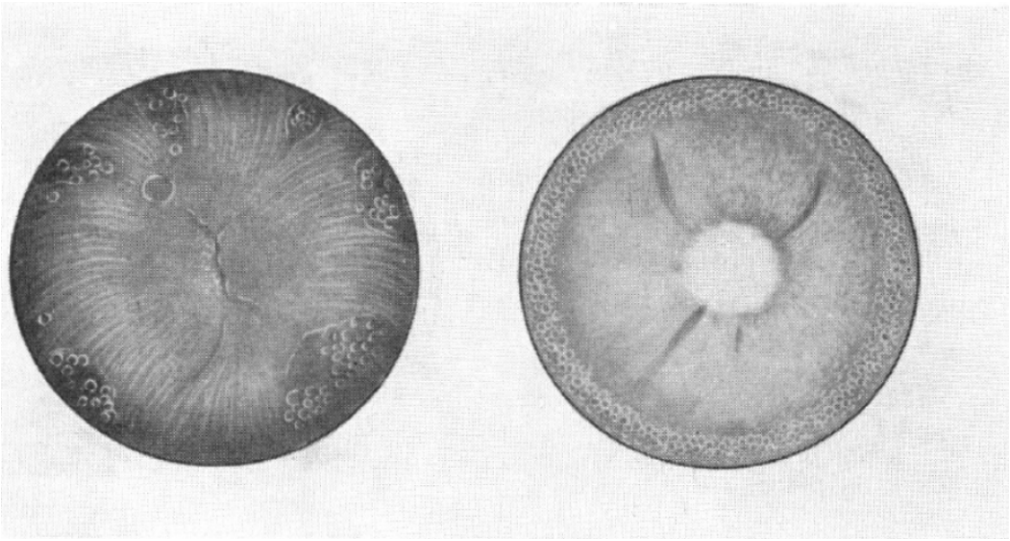

Fig. 4.4.c. This shows a stage 3+ opacity with extension of the changes in both the anterior and posterior cortex. The anterior cortical changes are on the left and the posterior cortical opacities are on the right (Merriam and Focht, 1962).

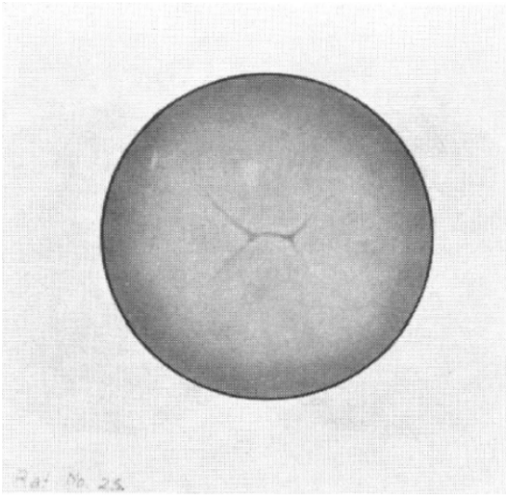

Fig. 4.4.d. A stage 4+ cataract in which the lens is completely opaque (Merriam and Focht, 1962).

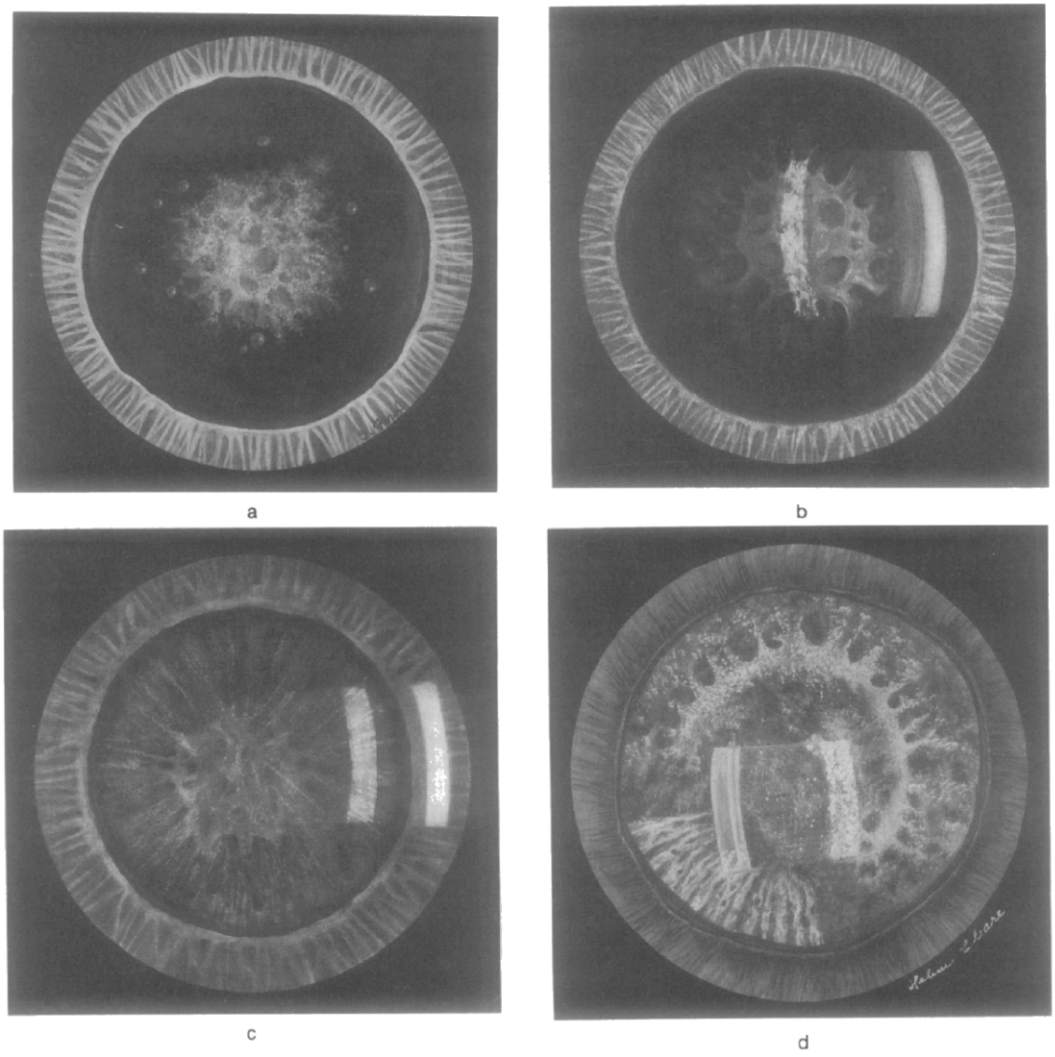

Fig. 4.5. Radiation-induced cataracts tend to develop in the posterior lens as shown in Panels a-d. Panel (a) shows early changes typically present in the central axis of the lens. Panel (b) shows that the central opacity may become denser, note the cross-sectional drawing in the center demonstrating on the left a dense posterior opacity. Panel (c) shows that the lenticular opacity may extend out to the periphery. Panel (d) shows that more advanced cataracts may also develop anterior changes. Note the wedge-shaped changes in the bottom left-hand corner representing opacification of the lenticular cortex. Also, note cross-sectional drawing demonstrating, from left to right, posterior, cortical, and anterior changes (Gordon et al., 1995).

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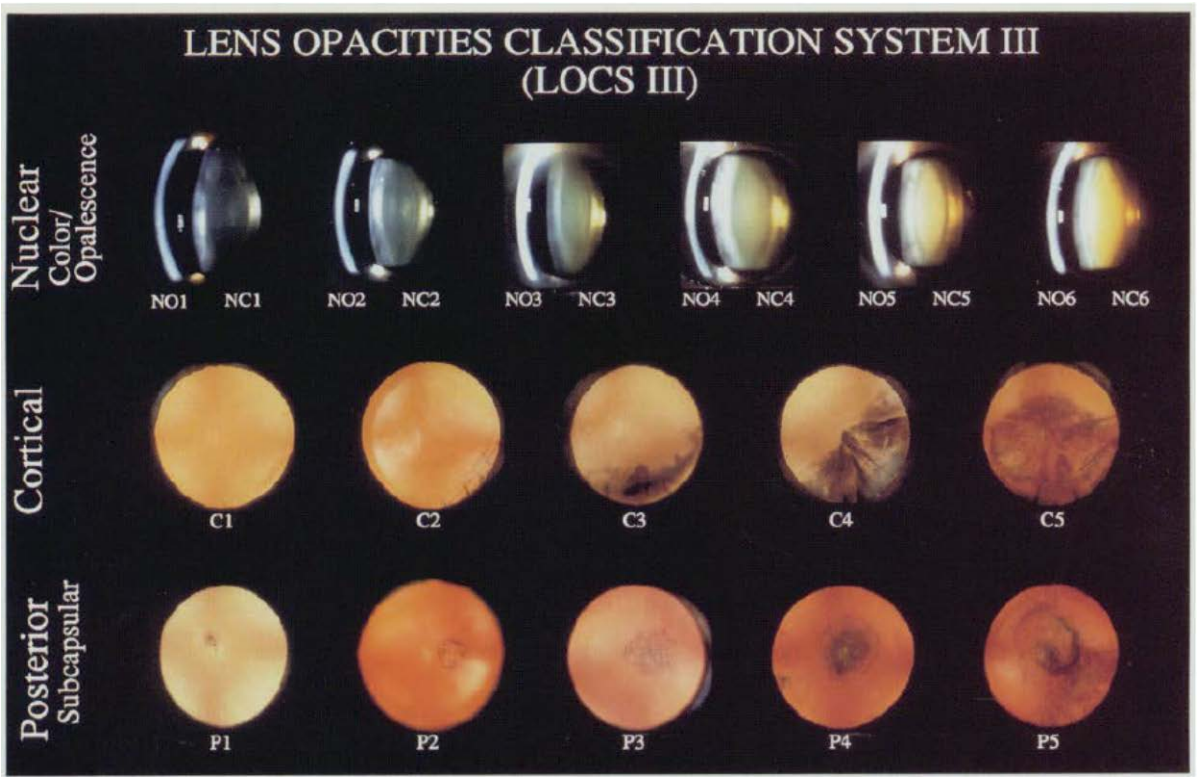

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1249 **Fig. 4.6.** A depiction of the LOCS III Cataract Scoring System (Chylack et al., 1993).

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Several new methods are under development to grade cataract, including quasi-elastic or dynamic light scattering (QELS/DLS) (Datiles et al., 2008), and magnetic resonance imaging (MRI) (Jones et al., 2005; Kasthuriragan et al., 2011; Koretz et al., 2004; Strenk et al., 2004).

There have been a number of experimental studies using the Scheimpflug scoring in animal model systems (Puk et al., 2013; Wegener et al., 2002; Worgul, 1988). An increasing number of reports have investigated reproducibility of cataract scoring systems or compared outcomes between systems with mixed results (Gupta et al., 2013; Kirkwood et al., 2009; Koretz et al., 2004; Sparrow, 1990; Tan et al., 2011). Software for cataract assessment to compare retro-illumination digital image analysis with that of the Nidek EAS-1000 software became available in 1999 (Gershenzon and Robman, 1999) (Figures 4.7.a-b). Overall, the methodology to score cataracts has become more objective over time, but some methods are better for scoring specific kinds of cataracts than others. For example, retro-illumination imaging is not ideal for scoring nuclear cataracts.

4.3 Radiation Effects on the Eye

In this section, an overview of how radiosensitivity varies among the different tissues of the eye is presented, with emphasis on the effects of radiation on the lens at the cellular and molecular level as well as the mechanisms and known or potential determinants of radiation cataractogenesis.

4.3.1 Normal Tissue Complications of the Eye

It has long been known that the various structures of the eye each respond differently to ionizing radiation (Rohrschneider, 1929). In general, there is a gradient of decreasing radiosensitivity from the anterior structures to the posterior structures, with the lens being one of the most radiosensitive structures, and the optic nerve and sclera amongst the most radioresistant.

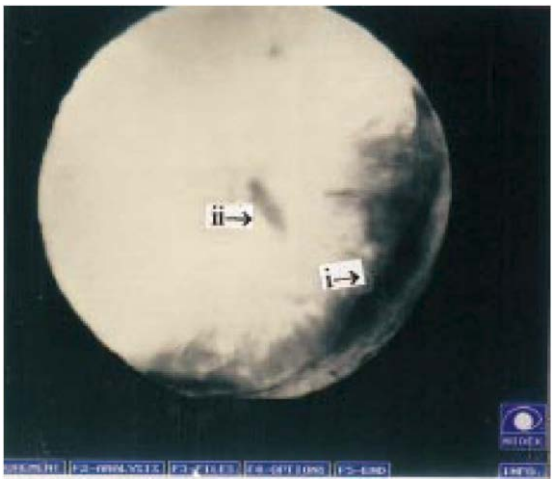

Fig. 4.7.a. The eye with i) cortical cataract and ii) PSC and uneven retroillumination due to polarizing effect of the camera, the original digital photo. Picture from the Nidek EAS-1000 (Nidek, Japan) (Gershenzon and Robman, 1999).

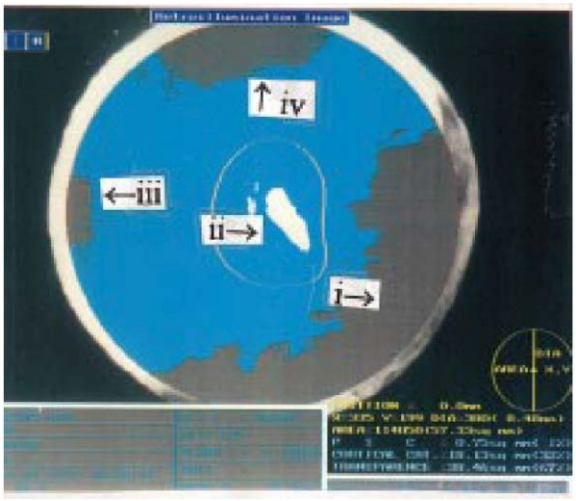

Fig. 4.7.b. The software analysis result is shown in this image with the threshold cutting off both the dark areas of cataract and the poorly illuminated pupil periphery (areas iii and iv) thus producing a 24 % error in measurement of cortical cataract (i) (Gershenzon and Robman, 1999).

The conjunctiva, cornea, uvea, and retina are somewhat intermediate in radiosensitivity. Many clinical investigators have confirmed these observations in numerous subsequent studies that are nicely summarized in several books and clinical reviews (Cox and Ang, 2010; Fajardo et al., 2001; Finger, 2009; Swetha et al., 2011).

Acute or late complications of the eye (e.g., those occurring within 3 months, or several months to years after exposure or completion of treatment, in regard to their first appearance, respectively) are dictated by several intrinsic and extrinsic factors, including the composition of the tissue of the irradiated eye structure, the capacity of the tissue to withstand the injury, the vascular integrity of irradiated volume, patient age, dose, dose rate, co-morbidities and dietary supplements or medications that the individual may have ingested before, during or after irradiation (Brady and Yaeger, 2001; Finger, 2009). In general, acute effects refer to damage sustained by rapidly proliferating cells, and many can be resolved by timely and appropriate medical management. Late effects usually result from vascular damage and subsequent ischemia, and are chronic in nature. Acute effects resulting in residual lesions may result in the appearance of 'consequential' late effects.

Several studies note possible effects with doses in the tens of Gy or greater to the sclera (Cox and Ang, 2010; Finger, 2009), cornea (Cox and Ang, 2010; Finger, 2009; Jeganathan et al., 2011), conjunctiva (Barabino et al., 2005), retina (Dhir et al., 1982; Jiang et al., 1994; Krema et al., 2011; Mewis et al., 1982; Parsons et al., 1994a; Viebahn et al., 1991), optic nerve (Jiang et al., 1994; Nakissa et al., 1983; Parsons et al., 1994b), lacrimal system and Meibomian glands (Brady, 1996; Durkin et al., 2007; Horwath-Winter et al., 2013; Jeganathan et al., 2011; Karp et al., 1979; Kennerdell et al., 1992; Parsons et al., 1994b), and the uvea (Sagerman and Alberti, 2003).

4.3.2 Radiation Cataractogenesis

It is well established that exposure to ionizing radiation leads to development of lens opacities. The latency and the severity of lesions are known to be dependent on a number of

factors, including age and gender, as well as exposure characteristics including dose, dose rate and fractionation. Evidence that these factors are inter-related further complicates efforts to elucidate dose-response relationships. The available data are discussed, with respect to a number of different confounding factors, in this section.

4.3.2.1 Absorbed Dose. Until recently, it was accepted that the induction of cataracts was considered to be a deterministic effect of radiation and that the threshold was ~ 2 Gy for opacities to develop (for acute exposures) for low-LET radiations such as gamma or x rays (Abdelkawi, 2012; Bendel et al., 1978; Merriam and Focht, 1962; Wolf et al., 2008).

A deterministic model is supported by the vast majority of the epidemiological evidence (Section 5). However, there is some evidence that lens opacities may follow an approximately linear non-threshold (LNT) theory with increasing dose for either low- or high-LET radiation exposures and across a range of doses. For instance, Hall et al. (2015) recently demonstrated a quadratic relationship between dose and the 5 y development of cataracts for patients receiving total body irradiation (TBI; Figure 4.8). Di Paola et al. (1978) showed an LNT relationship for numbers of lenticular opacities and doses of 0 to 3 Gy of x rays and 0 to 0.38 Gy of 14 MeV fast neutrons. Furthermore, the mechanistic evidence presented in Sections 4.3.3.5 and 4.3.3.6, particularly the genetic and DNA damage work, could be interpreted to suggest a stochastic mechanism of radiation cataractogenesis (Hamada and Fujimichi, 2015).

4.3.2.2 Dose Rate. The lack of concrete epidemiological evidence regarding dose rate dependence led ICRP to conclude that there is no dose rate effect for lens effects (ICRP, 2012; Section 5) and most recent studies confirm this observation [(e.g., the Hall et al. (2015) recent meta-analysis of patients undergoing radiotherapy following hematopoietic stem cell transplantation].

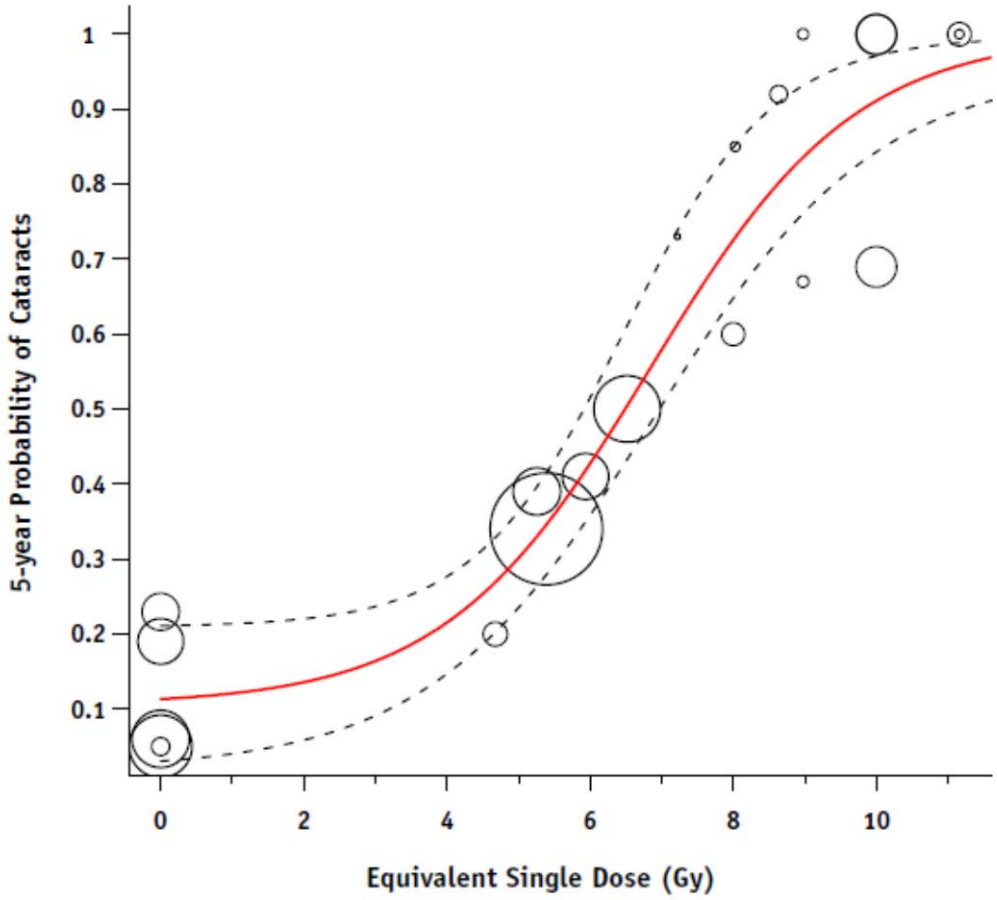

Fig. 4.8. The 5 y cataract incidence after hematopoietic stem cell transplantation as a function of dose. Solid curve indicates the model predicted probability standardized for an adult population and regular ophthalmologic surveillance. Dashed curves indicate the 95 % confidence interval (CI). Patient series included in the meta-regression were plotted as discrete points with area scaled according to the number of patients (Hall et al., 2015).

4.3.2.3 Fractionation. The role and contribution of dose fractionation to radiation cataract development has been examined in great detail in the animal eye (ICRP, 2012). Some studies have reported dose-rate effects at relatively high doses, for instance, in a study of radiotherapy patients carried out by Deng et al. (1984), 80 % of patients receiving single-dose 10 Gy ^{60}Co gamma-ray irradiation developed cataracts, compared to only 18 % of patients receiving fractionated TBI. Although the evidence for fractionated and protracted exposures in humans has been strengthened by a number of recent high quality studies considering medical workers and patients, overall, the data are still fairly sparse and somewhat conflicting (Hall et al., 2015). Furthermore, although studies in this category are sometimes lacking in statistical power, they do tend to have high quality dosimetry at low doses, which means that they are very important for assessing whether the prevailing risk model also applies to the low dose region. In summary, there is evidence of a modifying effect of dose fractionation.

4.3.2.4 Radiation Quality and RBE. The vast majority of epidemiological studies looking at radiation-induced cataract have focused on acute or chronic exposure to low-LET radiation (Minamoto et al., 2004; Nakashima et al., 2006). Those studies that do consider alternative exposure have generally not considered the influence of RBE; however, it is notable that the highest relative risks (RR) have been observed for astronauts who are exposed to a wider range of radiation types including a mixture of high-energy protons and heavy ions as well as secondary particles (Cucinotta et al., 2001) and pilots who have increased ionizing radiation exposure from solar particle events and galactic cosmic radiation (Jones et al., 2007; Rafnsson et al., 2005). There has been concern that individuals working in preparation of radiopharmaceuticals for nuclear medicine procedures may have relatively high lens exposures, but measurements suggest this is not the case (Kopec et al., 2011).

The RBE effect is well documented in animal studies, which have often focused on the need to elucidate the mechanistic response to high-LET (Di Paola et al., 1980) with the aim of investigating the implications for astronauts (Hall et al., 2005). A relationship between RBE and size of opacity has also been proposed for space radiations (Chylack et al., 2009). Inadequate

dose response data exist for photons or high-LET radiation sources to precisely calculate the RBE for cataracts induced in human populations. However, RBE data have been reported from animal studies investigating high-LET-induced radiation cataract. Based on these data, the estimated cataract grade-dependent RBE values for the $ATM^{+/-}$ haploinsufficient mouse were somewhat higher than those for the wild type mice, ranging from 5 to 24 (Hall et al., 2006). For the wild-type animals, the estimated RBE values of the iron-ions are in the range of 5 to 15. These RBE values, for 0.325 Gy of 148 keV/μm iron ions, are consistent with earlier measurements for heavy-ion induced cataractogenesis in wild-type animals, by doses including 0.025 and 0.5 Gy of 88 keV/μm argon ions, and 190 keV/μm iron ions (Brenner et al., 1993). In these earlier studies, only confidence bands for the RBE could be estimated, and the upper and lower 90 % confidence limits of the RBEs for the wild-type animals, 35 weeks after exposure, ranged from 8 to 30 at 0.25 Gy, and from 4 to 12 at 0.5 Gy. The RBE estimates for the wild-type animals are consistent with earlier results in other animal models. Riley et al. (1991) reported irradiation of Sprague-Dawley rats with 0.6 GeV/amu iron ion doses from 0.1 to 2 Gy, with estimated RBEs of about 7.4 for doses from 0.1 to 0.5 Gy. Similarly, Lett et al. (1985) reported an RBE of 4 to 6 for stationary cataract induction in rabbits with 0.5 to 5 Gy of 0.46 GeV/amu iron ions.

While this Commentary will not go into detail about high-LET exposures, studies have shown that neutrons are extremely effective at inducing cataracts at low doses, such as showing a 50 fold increase in cataract induction at low doses compared to low-LET x rays (Di Paola et al., 1978). Other studies are being done with astronauts exposed in space to high-LET high-Z particles (HZE) radiation (Cucinotta et al., 2001).

4.3.2.5 Age. The age dependence of radiation cataractogenesis has long been understood (Choshi et al., 1983; Dynlacht, 2013; Klein et al., 1998; 2000; Wang et al., 2014). In humans, several studies have shown that the young developing lens is especially sensitive to ionizing radiation exposure (Day et al., 1995; Hall et al., 1999; Wilde and Sjostrand, 1997). Radiation-induced cataracts usually originate in the PSC region (Dynlacht, 2013; Worgul et al., 1976). However, there is also evidence from human and animal studies that exposure to ionizing

radiation leads to early manifestation of cataracts that would otherwise be seen in old age (Dynlacht, 2013; Kleiman et al., 2007; Rafnsson et al., 2005; Smilenov et al., 2008; Worgul et al., 2002). This issue is discussed further below (Section 4.3.3).

The importance of age at exposure is evident in much of the epidemiological literature examining radiation cataract risk. It is clear from human studies of astronauts (Cucinotta et al., 2001) that ocular cataracts are appearing at younger ages as a consequence of exposure to a whole range of damaging agents, including ionizing radiation. It is equally clear that high-LET particles are much more effective than low-LET x rays, and that this may account for the reported cataracts in astronauts. Relevant examples of age at risk, from the atomic-bomb survivors' cohorts, suggest that relative risks for exposure to radiation decreased to a statistically significant extent with increasing age at examination (Minamoto et al., 2004; Nakashima et al., 2006; Neriishi et al., 2012). A great deal of published evidence suggests (Section 4.3.2.6) that the steroid sex hormones account for age- and gender-based differences in the progression and prevalence of cataract that normally occur spontaneously in humans and in animal models (Dynlacht, 2013). Medical workers developed radiation cataracts at earlier ages than expected (Milacic, 2009) and lens injuries were observed as a result of cumulative doses after several years of work (Jacob et al., 2013; Vano et al., 2013). Commercial airline pilots have been shown to develop cataracts at a younger age than non-pilots (Raffnsson et al., 2005), and age was found to be a highly statistically significant factor for development of radiation induced cataracts for NASA astronauts (Cucinotta et al., 2001). Both the airline pilot and astronaut cataract studies described the age at which the cataract was scored. The observed acceleration is known to be dose dependent (Dynlacht, 2013; UNSCEAR, 2013b). Furthermore, the epidemiological observations are supported by evidence in rodent models (Cogan and Donaldson, 1951; Dynlacht et al., 2012; 2013; Hudson et al., 2011; Merriam and Szechter, 1975).

4.3.2.6 Gender. Relatively few studies have specifically investigated the influence of gender in development of radiation-induced cataracts. It is known that females have a slightly higher incidence of spontaneously occurring (age-related) cataracts (Klein et al., 1998; Varvas et al., 2002). However, although the baseline difference means that most epidemiological studies adjust

for gender, few have considered the influence of gender on dose dependent risk, with the evidence to date being far from conclusive (Kawamoto et al., 1962; Minamoto et al., 2004; Neriishi et al., 2007; Worgul et al., 2002). In contrast, animal studies have generally indicated a relatively strong association between gender and radiation-induced cataract incidence with males being more sensitive than females, but not due to estrogen levels (Henderson et al., 2009), and rate of progression (Henderson et al., 2010). There is also evidence that both the age and gender effects may be dependent on species and radiation type, as discussed below (Section 4.3.3).

The issue of gender differences in cataractogenesis is complicated. Despite numerous confounding issues, the majority of experimental, clinical and epidemiological studies indicate that age and gender appear to be determinants for radiation cataractogenesis induced by high- and low-LET irradiation (Dynlacht, 2013). However, the type of radiation is an important factor in determining the age response of the lens. The latent period, rate of progression, and cataract severity after exposure to low-LET radiation depend on the age at irradiation. While species-related differences preclude the idea that the same patterns of cataractogenesis would be observed universally in both irradiated animals and humans, the published evidence demonstrates that male rats have a higher incidence compared to females exposed to low-LET radiation, and that older rats develop opacities that appear earlier, and progress faster than those in younger animals exposed to high-LET radiation. On the female side, the prevalence of spontaneously occurring cataracts increases with age, and is slightly higher for women compared to men (Vavvas et al., 2002). Administration of estrogen to postmenopausal women, however, results in a decrease in cataract formation, compared to age-matched postmenopausal women not receiving hormone replacement therapy (Benitez del Castillo et al., 1997; Cumming et al., 1997). Thus the data indicate that estrogen may promote or protect against cataractogenesis induced by ionizing radiation, depending on when it is administered relative to the time of the irradiation (Dynlacht, 2013).

4.3.2.7 Steroid Sex Hormones. A large amount of data suggest that steroid sex hormones (SSH) are involved in gender as well as age differences in radiation cataract incidence and progression (Benitez del Castillo et al., 1997; Cumming and Mitchell, 1997; Freeman et al., 2001; 2004;

Henderson et al., 2010; Klein et al., 1994). Dynlacht et al. (2013) comprehensively reviewed the data in this field and found that estrogen may promote or protect against cataractogenesis induced by ionizing radiation, depending on when it is administered relative to the time of irradiation (Bigsby et al., 2009; Dynlacht et al., 2006; 2008).

4.3.2.8 Latency. Latency is the time elapsed between radiation exposure and the detection of opacities. It varies roughly inversely with dose (Kleiman et al., 2008; 2012; Merriam and Focht, 1962; Smilenov et al., 2008). Figure 4.9 illustrates this relationship. Latency is also codependent on a number of influential factors, including the dose, the ionization density of the radiation, and the charged particle radiation species (Dynlacht, 2013).

The role and contribution of dose fractionation to radiation cataract development has been examined in great detail in the animal eye (ICRP, 2012). The data are also somewhat conflicting; however, when exposure to low-LET ionizing radiation is fractionated or administered over a protracted period, the latent period is usually increased and progression is slower (Dynlacht, 2013).

Very few valid, comprehensive studies have been performed to allow the determination of the relationship between age, gender, dose fractionation, and latency period for radiation-induced cataracts. Work done by Merriam and Focht (1962) is illustrated in Figures 4.10.a-d. Six-month old female rats (White Sherman strain) were used. One eye of each animal was irradiated and the contralateral eye was used as a control. The animals were anesthetized and immobilized. A small cone was used to limit the x-ray beam to one eye only with a lead shield covering the rest of the body. The dose to the eye was measured under experimental conditions with a phantom rat, using a small Baldwin-Farmer condenser ionization chamber. In all of the experiments the following factors were used: 200 kVp x rays, tube window half-value layer equivalent of 1.0 mm Cu, and tissue-to-source distance of 20 cm. Single doses of 500 R (~ 5 Gy), 1,000 R (~ 10 Gy), 1,500 R (~ 15 Gy), and 2,000 R (~ 20 Gy) were given to each group which consisted of approximately 20 to 30 rats. The dose rate was 180 R (~ 1.8 Gy) per minute.

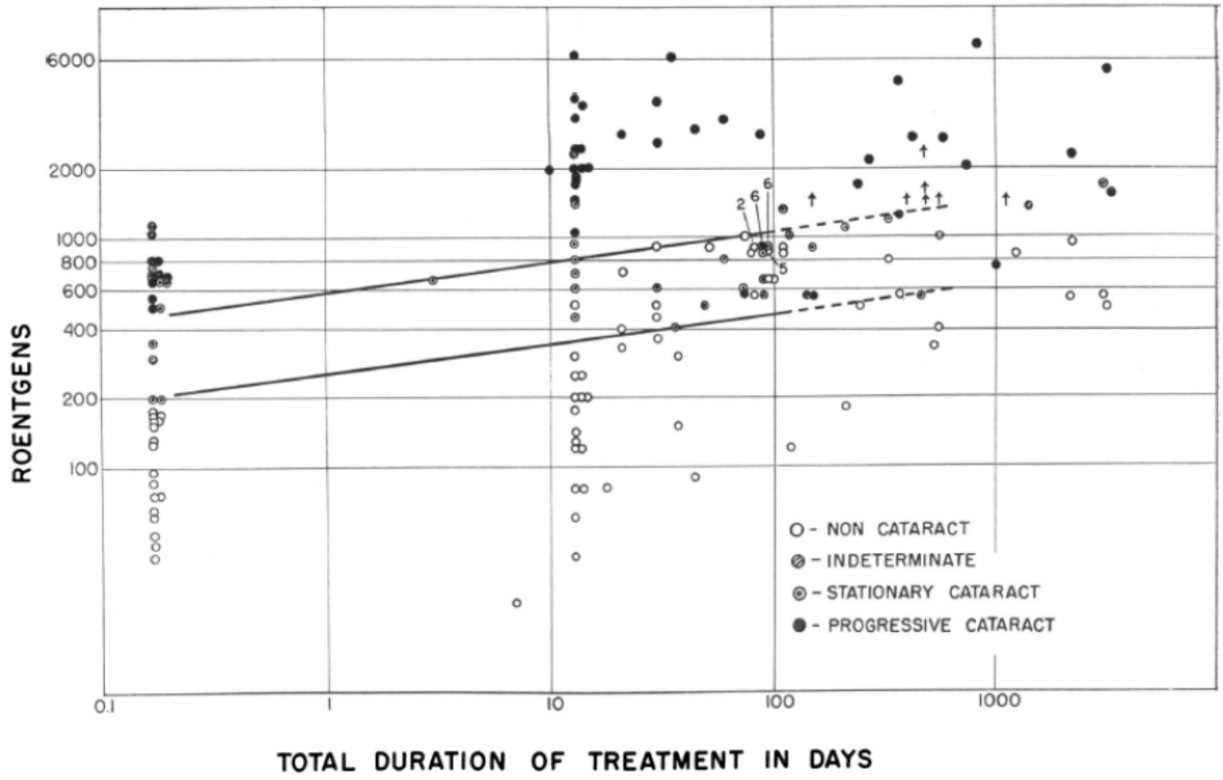

Fig. 4.9. Plot of doses to the lens of cancer radiotherapy patients in single acute exposures (see left side of the plot), for a treatment time of three weeks to three months, or a treatment time extended for more than three months (plotted on the right side). The different symbols indicate that there was no cataract at that dose, a stationary or progressive cataract, or it was not determined if there was a cataract. These data are the origin of the 200 R (~ 2 Gy) dose threshold for a single acute exposure to result in a cataract (Merriam and Focht, 1962).

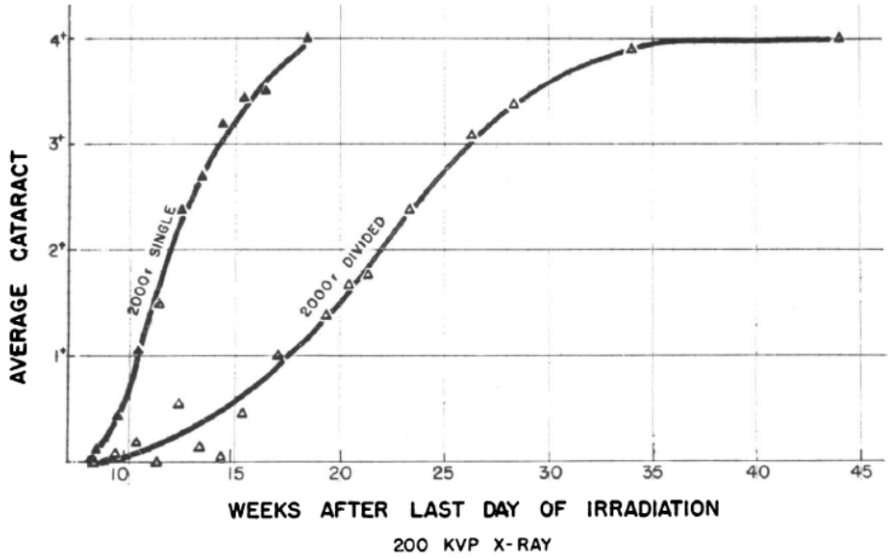

Fig. 4.10.a. Plots of average cataract for given radiation exposures against time elapsed after treatment as figure (a) curves for 2,000 R (~ 20 Gy) single and divided groups (Merriam and Focht, 1962).

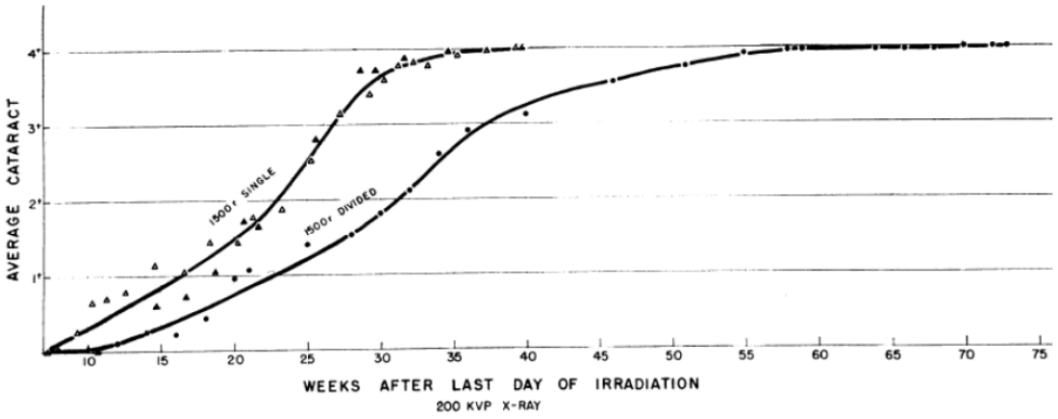

Fig. 4.10.b. Figure (b) curves for 1,500 R (~ 15 Gy) single and divided groups with the curve for the single treatment as the average of two experiments shown by the solid and open triangles (Merriam and Focht, 1962).

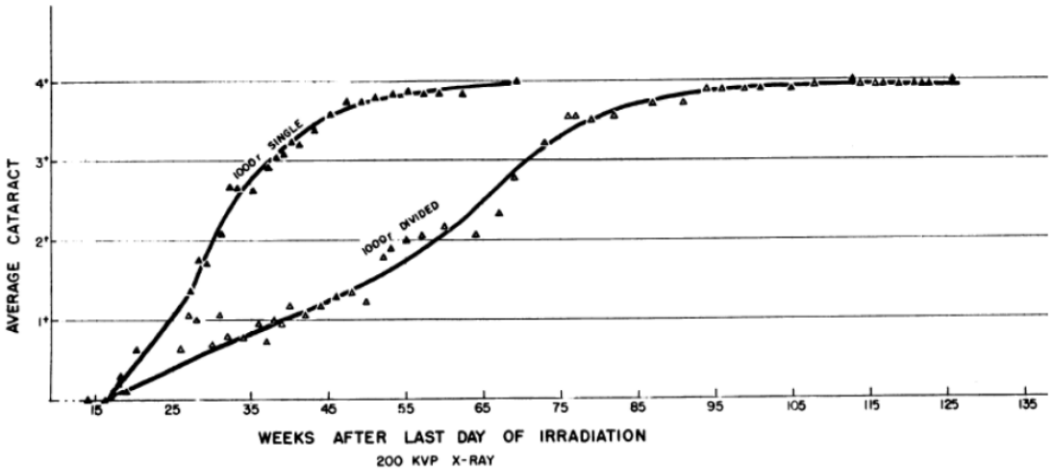

Fig. 4.10.c. Figure (c) curves for 1,000 R (~ 10 Gy) single and divided groups (Merriam and Focht, 1962).

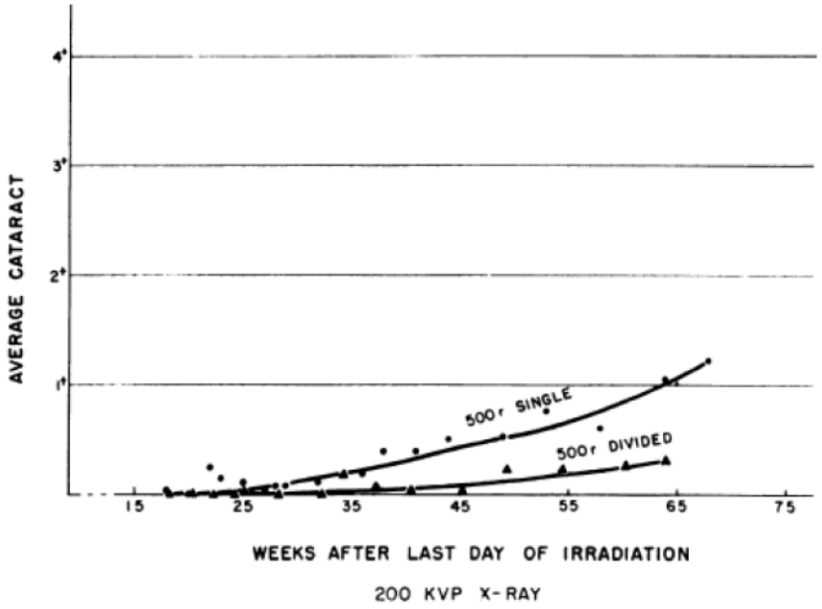

Fig. 4.10.d. Figure (d) curves for 500 R (~ 5 Gy) single and divided groups in which neither group had been followed sufficiently long to determine the final shape of each curve; however, a difference between them is apparent (Merriam and Focht, 1962).

Each animal was numbered individually by a coded ear punch, and the treated eye could be either the right or the left. Similar divided doses were delivered to one eye of each animal, in comparable groups, in a total of six days, given on the first, third and sixth days. This time interval was chosen since, as a fraction of their life span, it approximates the duration of treatment most commonly employed clinically for human radiotherapy with a treatment time of three weeks to three months. Each of the approximately 250 animals was examined with the slit-lamp (corneal microscope) before treatment, and weekly, or every few weeks, thereafter. The examiner had no knowledge as to which eye had been treated, or, in most cases, which dosage group was being examined. At random times a whole group was re-examined on the same day without the knowledge of the examiner. The two results so obtained showed no significant difference. The method chosen to score the cataracts was to estimate the average lens opacity at a given time of observation after exposure. The cataracts were graded 1+ to 4+ at each examination. In classifying the cataracts as 1+, 2+, 3+, or 4+ the Merriam-Focht criteria were used as depicted in Figures 4.4.a-d. Overall, the outcome of the study indicated dose sparing effects with fewer cataracts appearing with divided doses, and longer latencies with decreasing total doses.

4.3.3 Mechanisms of Radiation Cataractogenesis

Radiation-induced damage may deregulate normal lens cell functions leading to the formation of opacities in the lens. Several potential targets and pathways are discussed below.

4.3.3.1 Cellular Biology. During the course of normal lens fiber differentiation, the lens fiber cell nucleus disintegrates along with other cytoplasmic organelles in a rapid and highly coordinated manner and DNA is cleaved (Bassnett, 2002; Bassnett and Mataic, 1997). While on the surface the degradation of organelles and DNA that occurs in lens cells bears a striking resemblance to apoptosis, this process, which is critical for establishing lens clarity, is a completely separate process involving, at least in part, several different mechanisms (Nishimoto

et al., 2003). Pendergrass et al. (2010) have proposed that the failure to degrade nuclei and DNA may contribute to cataract development in young adult mice.

Differentiated lens epithelial cells do not contain nuclei or mitochondria, and are dependent on the overlying epithelial cell layer for nutrient transport and energy production. Thus damage leading to the formation of cataracts is generally assumed to occur in the germinative zones, where proliferation of lens cell fibers begins. Damage to the genome, resulting in mutation or misrepair is likely to be the dominant mechanism at low doses (rather than cell killing).

4.3.3.2 Protein Accumulation. It has been shown that lens fibers have a very high protein content to enable transparency and refractivity (Beebe et al., 2011). Lens protein accumulation and crystalline interactions are discussed in detail in Moreau and King (2012). Lens protein accumulation is thought to play a major role in radiation-induced cataract development, with abnormal accumulation of alpha-, beta- and gamma-crystallines (possibly due to post-translational modifications related to structure) leading to light scattering rather than light transmission, which results in the observable opacities (Hamada et al., 2014). Protein changes in gamma irradiation induced cataracts were reported to be similar to changes observed in age-related cataracts (Muranov et al., 2010). Misregulation of lens crystallines may be related to aging as well as radiation-induced opacity following, for example, fractionated low doses (Abdelkawi, 2012).

4.3.3.3 Molecular Biology. Abnormal cell proliferation, which is usually kept in check by p53 dependent pathways, may have a role in radiation cataractogenesis and also has mechanistic similarities to tumorigenesis (Wiley et al., 2011). Tumor related factors potentially associated with cataractogenesis have recently been reviewed, and human studies have demonstrated involvement of mutations in oncogenes, tumor suppressor genes and other tumor related genes (Hamada and Fujimichi, 2015). Abnormal functioning of cell cytokines, differentiation and cell adhesion molecules in irradiated cultured human lens cells is also implicated in cataractogenesis (Chang et al., 2000; 2005; 2007; McNamara et al., 2001).

It is postulated that aberrantly dividing and/or differentiating cells in the pre-equatorial region of the lens epithelium migrate predominately to the lens posterior pole, where they become lens fibers which lead to clinical cataracts (ICRP, 2012). Recent evidence has demonstrated that ionizing radiation can indeed induce unexpected proliferation in human epithelial lens cells (Fujimichi and Hamada, 2015) and that low dose irradiation may be particularly effective in this, although this requires much further investigation (Markiewicz et al., 2014).

4.3.3.4 Oxidative Stress. Oxidative stress is thought to be a contributor to radiation-induced damage leading to cataracts. The important role of antioxidants in the lens is reviewed in a recent paper by Hamada et al. (2014). As an example, in humans, antioxidant activity has been shown to decrease in patients > 70 y, leading to more severe nuclear and cortical cataracts (Hasanova et al., 2009). In animal studies with mice exposed to 11 Gy of x rays to the head, cataracts matured within a very short time scale (i.e., on the order of 30 days), but after a relatively long latent period (5 to 11 months). Descendants of the damaged and superficially repaired lens epithelial cells were found to differentiate and migrate abnormally. It was postulated that this resulted in critical uptake of environmental oxygen to the lens that overwhelmed the resident antioxidant protection machinery, resulting in coagulation of lens proteins and thus cataract formation (Wolf, 2008). Cataract formation in 11 Gy irradiated (head only) mice showed accelerated loss of epithelial cells and other damage (such as lens fibers with nuclei, nuclear fragments, reactive oxygen species, and oxidized DNA bases) that is also observed in age-related cataractogenesis (Pendergrass et al., 2010). Mechanistically, these data support the supposition that radiation leads to acceleration of cataract formation. Indeed, aging has been linked to the breakdown of antioxidant mechanisms leading to accumulation of oxidized components. Oxidation has thus been described as the hallmark of age-related nuclear cataract.

The key factor in preventing oxidation has been postulated to be the presence of the antioxidant glutathione (Truscott, 2005); however, intraperitoneally injected antioxidants (such

as melatonin) have been shown to augment antioxidant capacity in the lens and reduce oxidative stress (Taysi et al., 2005).

4.3.3.5 DNA Damage. While there are still a number of unanswered questions regarding the role of radiation-induced DNA damage in the induction or progression of cataracts, it has been proposed that the accumulation of, or failure to repair DNA lesions in lens epithelial cells may be a precursor to radiation cataractogenesis (Jose, 1978; Kleiman and Spector, 1993; Worgul et al., 1991). The consequences of DNA damage may not be known until the affected lens epithelial cells differentiate and migrate to the posterior cortex. A role for oxidative damage in the opacification process has been proposed (Avunduk et al., 2000). The free radicals produced in response to ionizing radiation can interact with DNA to form single strand breaks (SSBs), double strand breaks (DSBs), and base damage, such as the adduct 8-hydroxyguanosine (8-OHG). While radiation-induced SSBs are rapidly repaired (Aufderheide et al., 1987), mouse lenses may retain 8-OHG well after SSB repair is complete.

It is well known that unrepaired DSBs can lead to chromosomal aberrations; the presence or persistence of asymmetrical exchange-type aberrations correlates well with cell killing (Hall et al., 2005). Repair of DSBs in most cell lines irradiated with x rays is biphasic (Baumstark-Khan et al., 1999), but the slow component is much longer in lens epithelial cells. This could imply that unrestored DSBs remain long after irradiation (Aufderheide et al., 1987). The lens tolerates higher doses when the radiation dose is fractionated (i.e., the onset of opacification is delayed and incidence of cataracts is reduced), implying that DSB repair occurs between doses (Merriam and Focht, 1957; 1962). However, low dose rate studies suggest that the lens is slow at repairing DSBs (Brenner et al., 1996).

4.3.3.6 Genetic Susceptibility. Many of the more recent mechanistic studies have focused on the genetic basis of cataract development (Hamada and Fujimichi, 2015). The ATM, Rad9 and Brca1 genes are known to be critical to pathways controlling DNA damage response signaling, repair or apoptosis.

Opacities in ATM-deficient mice were observed earliest in ATM homozygotes, but cataracts also developed earlier in heterozygotes compared to wild-type mice for all doses (Worgul et al., 2002). The severity and latent period were directly related to the number of genomically damaged cells attempting differentiation. Because ATM is involved in cell cycle control and pathways to apoptosis, this would indicate that cataracts may be due to defective control of these pathways in response to DNA damage.

PSC opacities were found to develop earlier in x-ray irradiated double heterozygotes ($ATM^{+/-}/Rad9^{+/-}$) than in either of the single heterozygotes, which again developed earlier than in wild-type mice (Kleiman et al., 2007). Smilenov et al. (2001) investigated individual genetic susceptibility of cataracts in mice heterozygous for the ATM, Brca1 and Rad9 genes. Exposure to 0.5 Gy of 250 kVp x rays led to elevated cataract development in double-heterozygote combinations, and cataracts appeared earlier in double heterozygotes. Heterozygosity of the ATM and Brca1 genes resulted in increased resistance to apoptosis and heterozygosity of the ATM and Rad9 genes led to increased resistance to apoptosis and sensitivity to radiation. Worgul et al. (2002) showed that ATM heterozygous mice are also more sensitive to heavy-ion exposure. ATM gene polymorphism has also been indicated as a risk factor for cataract surgery among atomic-bomb survivors (Neriishi et al., 2009).

4.3.4 Research Gaps

More data are required in most of the areas discussed in this section, but in particular to elucidate the molecular responses to radiation in the lens, to provide a clearer link between the initial damage response and formation of lens opacities.

In terms of cataracts, it is important to first fully define the target cells for radiation cataractogenesis, in particular for PSC opacities. There is a lot of evidence to suggest that it is the germinative zone at the edges of the lens epithelium which are relevant for PSC development (Eshagian and Streetan et al., 1980; Von Sallman et al., 1955; Worgul et al., 1975), however it is not impossible that effects, for instance those linked to antioxidant action, may occur as a result

of exposure to the general lens microenvironment. The next question is how radiation incident on the target (cells or otherwise) triggers lens opacification. Many questions remain regarding the role of oxidation and DNA damage; the mechanisms of radiation response and the effect of radiation on genetic and molecular biological control of lens fiber formation; and finally, lens fiber migration and accumulation, as outlined above. In particular, it would be useful to answer specific mechanistic questions regarding: what are the oxidation effects that occur in the lens response to ionizing radiation, including the exact antioxidant response that follows; how the lens responds in terms of the role of accumulation of damage in proteins versus the role of post-translational modifications (Hamada et al., 2014); and, how/which genes play a part in the development of radiation-induced PSC.

Furthermore, intracellular communication in the lens has been the subject of a number of recent studies. For instance, structural changes in the murine lens, which are linked to pre-cataractous changes, have been identified as being due to a lack of the connexin43 gap junction protein (Gao and Spray, 1998). It recently has been suggested that a change in charge of amino acid 23 in connexin50 is linked to cataract formation (Thomas et al., 2008). Further, a single point mutation in the gamma D-crystalline gene has been shown to lead to reduced protein solubility and to the formation of intra-nuclear aggregates (Wang et al., 2007). The magnitude and relevance of these effects for radiation cataractogenesis require further elucidation.

Numerous in vitro and in vivo studies indicate that, in addition to targeted effects of damage induced directly in cells by radiation, a variety of non-targeted effects may contribute to determining the overall outcome after radiation exposure. Effects including genomic instability and bystander effect have been observed both in vitro and in vivo across many mammalian systems and cell types, including human tissues (Morgan, 2003a; 2003b).

There is active research in preventing and potentially reversing lens opacities in animal models of cataract. Clearly, more work needs to be done to determine whether these treatments will be adapted for use in humans (Makley et al., 2015; Zhao et al., 2015).

It is generally understood that apoptosis in the lens is a rare event. It is possible that accumulation of small scale lens epithelial cells (LECs) losses due to apoptosis may induce alterations leading to reduced transparency (Charakidas et al., 2005). Indeed exposure to UVB has been demonstrated to lead to apoptosis in LECs in a time- and dose-dependent manner (Ji et al., 2015). However, the implications for ionizing radiation exposure remain unclear.

Telomere damage is an area of current interest, and such damage can result from genotoxic and oxidative stress (Hewitt et al., 2012). Recently, shorter telomere lengths were observed in Chernobyl accident recovery workers diagnosed with cataract 23 y after recorded doses up to 300 mSv, however there was no significant association between telomere length and dose (Reste et al., 2014). Recent reviews of the association between oxidative stress and cataract have also indicated a potential role of premature senescence. Indeed, it has been suggested that such biomarkers of oxidative stress can be considered as general biomarkers for life expectancy in veterinary circles and cataract treatments focusing on prevention of loss of functional telomere length are already in development (Babizhayev and Yegorov, 2015).

For radiation protection purposes, it is also important to consider the role of RBE, dose protraction and fractionation, and to address what lies behind the inverse relationship between latency period and dose. In conclusion, studies involving more than one type of radiation and more than one type of exposure scenario would be highly useful in addressing the remaining research questions, including those discussed above.

5. Epidemiological Evidence Related to Ionizing Radiation and Cataracts

5.1 Introduction

Epidemiology is the study of the distribution of disease and its determinants or risk indicators in particular populations. Thus study of a given disease relies upon specification of the target population as well as an accurate description of the disease or phenotype. While a primary task of epidemiology is to find consistencies across populations and results so that one can make scientific generalizations when possible, for radiation-induced cataract there are also two important questions we face with regard to differences among cohorts: (1) What are the characteristics of the populations of interest: is it the general US population or special exposure cohorts, and, if the latter, what are the specifics of each cohort that may differ from other exposed cohorts and do they alter the estimates of risk related to exposure to ionizing radiation; and, (2) How is the phenotype defined; is it accurate and uniform across studies?

The response to the first question as outlined in this section is that there are very limited data concerning exposure to ionizing radiation in the general U.S. population. Estimates of such exposure from medical records often rely on self-report of diagnostic or therapeutic medical exposure and even then actual dose or doses are often inaccurate and the specific source of exposure may be inaccurate. Thus, the exposure data we consider in this Commentary are only those related to special cohorts where exposure is likely to be higher than that of the general U.S. population. Note that several of these studies have been performed in other populations that may or may not be directly relevant to general U.S. populations. There is additional limited reference to information from animal models. This is, in part, because the biology of lens opacities in animals may differ in important ways from those in humans, and laboratory breeding and housing may further the disparity between laboratory animals and humans. The intriguing observations regarding genetic effects on sensitivity to lens opacities in laboratory models (and limited data in humans) needs to be further evaluated in humans to understand the possibility of inherent susceptibility to (or protection from) the lens effects of ionizing radiation (Kleiman et al., 2007), reviewed in detail in Section 4.

Question two is perhaps a more important issue as the diagnostic criteria for labeling a cataract has not only varied from publication to publication but has also changed over time. As detailed in Section 4, there are a number of different types of cataract: those related to radiation and those related to other factors, including age, as well as the many different ways in which cataracts can be classified (e.g., those which are visually impairing or not). This is important because the different types of opacity may have a different profile of risk factors or risk indicators. Unfortunately, detailed data regarding all the possible modifying factors and confounders are rarely available and this must be kept in mind when evaluating the evidence of radiation-induced or related cataract. While estimates of dosages and sources of exposure have been made (NCRP, 1989a), we do not yet understand what types of lens damage from ionizing radiation must occur for opacifications to form, or whether a deterministic or stochastic model is appropriate.

This section contains detailed reviews of the available literature and further analysis based on categorization of the studies according to how well the risk factors have been characterized.

5.1.1 Recent Reviews of Radiation Cataractogenesis Epidemiological Studies

In spite of the well-documented history of radiation-induced cataracts, there is still considerable uncertainty surrounding the relationship between dose and radiation cataract development, which is of concern to the risk assessment community (ICRP, 2012). In recent years, a number of new studies have suggested an elevated risk of cataract development in populations exposed to low doses of ionizing radiation. Consequently, several reviews of these radiation cataractogenesis epidemiology studies have recently been published in the literature (Ainsbury et al., 2009; Blakely, 2012; Blakely et al., 2010; Bouffler et al., 2012; Cooper, 2009; Hamada and Fujimichi, 2014; Hamada et al., 2014; Hammer et al., 2013; ICRP, 2012; Little, 2013; Martin, 2011; Shore et al., 2010; Thorne, 2012). In general, these reviews have concluded that there is a strong likelihood of an association between exposure to ionizing radiation and

initiation or development of various cataracts and that, while there is uncertainty, a lower threshold or nonthreshold (i.e., a stochastic response) may be an appropriate model for radiation cataractogenesis risk (EPRI, 2014).

An earlier review of the epidemiologic literature indicated that some findings are consistent with the absence of a dose threshold (Shore and Worgul, 1999). More recent reviews, such as Cooper (2009) highlighted the possibility that cataracts may develop at absorbed doses below the threshold of ~ 1.5 Gy previously given by ICRP. Ainsbury et al. (2009) noted that "…much of the science is contradictory, and it is therefore very difficult to reach a firm conclusion between a threshold and a no-threshold dose response for cataract formation, which is likely to be a multifactorial process…" and judged that a threshold in the region of 0.5 Gy of low-LET radiation, or even the possibility of a non-threshold response with a doubling dose that may be of the order of ~ 2 Gy could exist. Blakely et al. (2010) summarized thirteen presentations on updated reviews of epidemiological and biological research on radiation cataractogenesis and emphasized that the most important recent epidemiological finding was that there was stronger evidence that low-LET radiation causes opacities at exposures lower than previously expected (i.e., a dose-effect threshold as high as 5 Gy for vision-impairing cataracts). Shore et al. (2010) not only suggested that radiation-associated opacities occur at much lower doses, but that the findings from various studies indicated that radiation risk estimates are probably not due to confounding by other cataract risk factors, and that risk is observed after both childhood and adult exposures. Thome (2012) suggested that the accumulating radiobiological and epidemiological evidence makes it more appropriate to treat cataract induction as a stochastic rather than a deterministic effect. Hammer et al. (2013) noted that substantial uncertainty about the level and the existence of a threshold subsists and that current studies are heterogeneous and inconclusive regarding the dose-response relationship. Little (2013) noted that radiation doses of 1 Gy or more are associated with increased risk of PSC and accumulating evidence suggests that cortical cataracts may also be associated with ionizing radiation. He further suggests that the dose-response appears to be linear, although a modest threshold of no more than ~ 0.6 Gy cannot be ruled out.

5.1.2 Previous Epidemiological Studies

In general, the very early radiation cataract studies were limited in that they failed to take into account increasing latency periods as doses decrease, did not have sufficient sensitivity to detect early lens changes, and only had a relatively few subjects with doses below a few Gy. Recently, EPRI completed a detailed review and evaluation of radiation cataractogenesis epidemiology studies (EPRI, 2014) in which they identified and selected 59 publications in the formal literature that report results on about 44 study populations. This is a larger number of studies than has been evaluated in previous reviews. See Appendix A, Tables A.1 through A.7 for a detailed summary of the specific study information including: reference, area of study, type of study, study period, study population (characteristics, study size), type of radiation exposure, reconstructed dose, exposure assessment, outcome assessment, results or risk estimates for cataract [at the 95 % confidence interval (CI)], and if adjustments were made to confounders in the main model. The identified studies report addressed various exposure conditions including acute exposures, mixed exposure situations, as well as protracted exposure to low doses of ionizing radiation and the development of a cataract or opacification. The types of studies are grouped and discussed below generally according to exposure conditions.

5.1.2.1 Atomic Bomb. Appendix A, Table A.1, summarizes information from cataract studies of atomic bomb survivors. These studies show increased risk of cataracts for acute exposures of ionizing radiation, perhaps 1 Gy or lower.

The earliest studies (Cogan et al., 1949; 1950) were initially performed within 5 y after the exposures and studied generally younger subjects (i.e., 2 to 16 y) and showed a prevalence of lens abnormalities using an ophthalmoscope in those individuals within 1 km of the atomic bomb's hypocenter. Larger studies (Nefzger et al., 1969; Otake and Schull, 1982; Otake et al., 1990; 1996) began to explore cataract dose responses, showing axial opacities with increases in the higher dose (i.e., > 2 Gy) group of exposed individuals. A major study in 1978 to 1980 compared the prevalence of lens opacities in participants of the Adult Health Study (AHS, a biennial clinical examination collective of both Hiroshima and Nagasaki survivors) to a 'non-

exposed' group (Choshi et al., 1983). Doses in the exposed group ranged from 0 to 6 Sv (based on the earlier T65DR dose estimates) and an increasing prevalence of PSC with increasing dose and with decreasing age at examination was observed, but no trends were estimated. However, no standardized lens opacity system was utilized. Yamada et al. (2004) who later updated non-cancer outcomes in the AHS cohort followed up for the longer period 1958 to 1998 and using the DS86 dosimetry noted an increased relative risk for opacities at 1 Sv, as well as a suggested linear dose-response effect for cataracts. However, again no standardized lens opacity system was utilized.

Minamoto et al. (2004) re-examined AHS and atomic bomb survivors who had previously participated in ophthalmological examinations. This study utilized the standardized LOCS II quantitative grading system (Section 4) and showed significant radiation effects for PSC and cortical cataracts, but not nuclear cataracts. Nakashima et al. (2006) updated the results by applying the new DS02 dosimetry finding similar results. Nakashima et al. (2006) also specifically addressed the question of dose threshold, finding 0.6 Sv for cortical cataract and 0.7 Sv for PSC, with 90 % CI including 0 Sv, suggesting that the thresholds were not significantly greater than 0 Sv. However, questions have been raised of the data quality used in the atomic bomb survivor studies and the data are currently being reviewed (RERF, 2013a; 2013b; 2014a; 2014b) (Section 5.3).

One important study evaluated cataract surgeries in AHS and related cohorts (Nakashima et al., 2013; Neriishi et al., 2007; 2012). The results agree with the earlier opacity evaluations and have shown an increased risk at about 1 Sv and possible thresholds below about 0.8 Sv. While there is a potential uncertainty introduced when using cataract extraction as an end point rather than lens opacification (i.e., quantifiable cataract scoring), since lensectomy is performed when visual impairment is strong, it is a subjective, individual decision (Hammer et al., 2013). It should be emphasized that in a cohort study, such surgery is likely an appropriate surrogate for VICs, the endpoint of greatest concern in terms of lens of the eye radiation protection.

5.1.2.2 Chernobyl. Appendix A, Table A.2, summarizes information on the cataract studies including Chernobyl liquidators and cleanup workers. In general, the two reported studies show increased risk of cataracts for acute (and possibly chronic) exposures to ionizing radiation, perhaps 1 Gy or lower.

A small cohort study was performed over the period of 1986 to 2000 in the Ukraine (Nadejina et al., 2002) that included people with acute radiation syndrome (ARS, N = 11) as well as Chernobyl recovery workers (N = 30). It was estimated that the ARS group had a mean dose of 3.2 Gy and the recovery workers had a mean dose of 0.2 Gy. Almost half of ARS cases had 'radiation cataracts' and none of the recovery workers developed 'radiation cataracts.' In addition to the small size of the study, a major uncertainty is introduced because the grading system was not reported.

A much more comprehensive study of 8,607 Chernobyl cleanup workers exposed between April 26, 1986 and December 31, 1987 was performed by examinations using the Merriam-Focht Cataract Scoring System about 12 to 14 y after exposure (Worgul et al., 2007) and attempted to address several important confounders. Lens doses for this cohort ranged from 0 to > 1 Gy with a median of 123 mGy. Significant increased risk was noted for PSC, cortical and mixed cataracts. In addition, the investigators selected a maximum likelihood central estimate of the dose threshold for stage 1 cataract and stage 1 PSC of less than 0.5 Sv. Some uncertainty is introduced by the dosimetric assessment methods for different groups of exposed persons.

5.1.2.3 Medical Patients. Appendix A, Table A.3, summarizes information from cataract studies of medical patient exposures. These exposures should be considered acute, clinical case exposures. Eleven case reports and/or cohort studies of clinical exposures of medical patients from radium, x rays, helium ions, or internal alpha emitters were evaluated. There are large uncertainties in many of the medical patient study results due to the varying outcome assessment methodologies employed, lens dosimetry estimation techniques, and unclear confounder adjustments. In general, studies of patients who received estimated lens doses > 2 Gy (and

especially higher doses) showed increased risk of cataracts. However, most of the medical patient studies had very few patients with < 2 Gy and had limited follow-up times. A few studies appear to suggest increased risk of cataract at doses < 2 Gy. Both the studies by Wilde and Sjostrand (1997) and Hall et al. (1999) appear to show that opacity grade increases with lens dose.

5.1.2.4 Health Care Personnel. Appendix A, Table A.4, summarizes information from cataract studies of health care personnel exposures. There were nine studies on chronic (i.e., protracted) exposures among health care personnel, mostly x-ray technologists and/or interventional radiology and cardiology personnel. While these studies suffer from various individual study quality limitations (e.g., dosimetry uncertainties, inconsistent cataract scoring, lack of confounder adjustments, and possible selection/reporting bias), in general they suggest the prevalence for cataracts in the chronically exposed groups and especially for those who did not employ protective eyewear or shielding. Most of the reported opacities were in the PSC region.

5.1.2.5 Flight Personnel and Astronauts. Appendix A, Table A.5, summarizes information from cataract studies of flight personnel and astronaut exposures. Several studies by NASA and others have investigated the exposure of flight personnel and astronauts to cosmic radiation and subsequent development of cataracts (Chylack et al., 2009; 2012; Cucinotta et al., 2001; Jones et al., 2007; Rafnsson et al., 2005; Rastegar et al., 2002). Although there are individual study limitations (based on small population sizes, potential for bias, questionable control groups, or handling of confounder effects) most of the results suggest that exposures to high-LET ionizing radiation could have different effects on the lens than does low-LET ionizing radiation (Blakely, 2012).

5.1.2.6 Other Occupationally Exposed Persons. Appendix A, Table A.6, summarizes information from cataract studies of other occupationally exposed persons. Persons with other occupational exposures were included in eight, mostly smaller-sized population, studies. Generally, protracted exposures below occupational limits did not appear to increase risk of cataracts, while higher

doses and especially high doses received acutely, may increase risk of cataract. However, these studies suffer from large uncertainties and limitations, making generalizations suspect.

5.1.2.6.1 External Exposure. The earliest of the studies evaluated 847 nuclear power workers at the National Reactor Testing Station with doses ranging from 1 to 253 mSv (based on dosimetry badge results) noting no lens changes related to occupational radiation exposure (Voelz, 1967). Okladnikova et al. (2007) assessed chronic external gamma radiation for nuclear workers at Mayak over 50 y and noted that such doses did not cause radiation-induced effects when they do not exceed the limit of the yearly dose for personnel (basically, ICRP limits at the time) and that cataracts could be considered a radiation effect at doses > 4 Gy when received acutely. In a separate study of occupational nuclear power workers with acute radiation syndrome (ARS, N = 37) or chronic radiation syndrome (ChRS, N = 1,828) Okladnikova et al. (1994) had earlier noted radiation cataract only for > 3 Gy in one case of ARS personnel and no cases of radiation cataract in ChRS personnel. Both studies were limited by unspecified cataract scoring methodology. Shang and Fu (2007) reported on a study of radiation workers and noted an increase in more advanced opacities with longer radiation working time. However, this study was limited by a lack of dosimetry and unspecified cataract scoring methodology.

5.1.2.6.2 Internal Exposure. Persons with occupational internal exposures were included in two small population studies. In each study, lens doses were not estimated and no standard cataract scoring methodology was utilized. In a cohort study based on medical records of radium dial painters, increased rates of cataract incidence were observed in persons having ingested 50 μCi or more of ^{226}Ra and ^{228}Ra compared to others, with increasing rates with time since exposure (Adams et al., 1983). In a report on 97 retired actinide-exposed radiation workers with a range of lifetime effective doses of about 0 to 600 mSv, a significant PSC incidence was observed (Jacobson, 2005).

5.1.2.6.3 Single Person Results. Two studies reported on a single case outcome. Hayes and Fisher (1976) noted some posterior light scattering upon examination of extracted lenses of a worker exposed periodically from about 1935 to 1950 to external gamma radiation from radium.

Griffith et al. (1985) noted premature (47 y old) PSC opacities in a worker who had experienced both internal and external exposures.

5.1.2.7 Population Studies and Residentially Exposed Persons. Appendix A, Table A.7, summarizes information from cataract studies of populations or residentially exposed persons.

Three large population cohort (i.e., cross sectional) studies evaluated cataracts, including the Beaver Dam Eye Study in the United States (Klein et al., 1993; 2000) and the Blue Mountains Eye Study in Australia (Hourihan et al., 1999). These studies investigated possible associations between medical imaging by computed tomography (CT) scans to the head and cataract development. The studies are limited by self-reporting of cataract endpoints and radiation exposures from CT and other medical imaging. The Beaver Dam Eye Study reported an OR for PSC of persons with a history of CT scans of 1.45 (95 % CI, 1.08 to 1.95), while in the Blue Mountains Eye Study it was 1.0 (95 % CI, 0.4 to 2.7).

Studies assessing cataracts in residents exposed to radioactive contamination have been performed in the Ukraine (Day et al., 1995) and Taiwan (Chen et al., 2001; Hseih et al., 2010). The Ukrainian study evaluated school children living in two towns with ^{137}Cs deposits leading to a cumulative effective dose of about 30 mSv compared to children living in a non-exposed city. There was a small excess of subclinical PSC in exposed versus non-exposed children. However, significant limitations of this study are that ophthalmologists were aware of the children's exposure status and that not all controls were randomly selected (Hammer et al., 2013). In the Taiwan study, persons were exposed for up to 15 y from ^{60}Co contaminated steel used in the construction of their houses with cumulative whole-body doses ranging from 1 to 1.204 mSv. A radiation effect based on minor subclinical lenticular changes was observed in the subgroup of persons below age 20 at the time of examination, but not in others (Chen et al., 2001; Hsieh et al., 2010). The dosimetry estimates for the study were based on the reliance on self-reported information regarding the time spent in each room of the contaminated buildings.

5.2 Uncertainties

As discussed in the literature reviews and elsewhere, the epidemiological studies informing radiation cataract risk differ in terms of many factors, including but not limited to: source of radiation, radiation quality, study design, study population, study size, time since exposure, range of lens doses, method of lens dosimetry/dose reconstruction, scoring of magnitude/severity of lens opacities, and the assessment of further risk factors and potential confounders.

5.2.1 Risk and Confounding Factors

There are a large number of known or suspected confounding factors for development of radiation cataracts and the epidemiological studies investigating these phenomena vary widely in the potential confounders considered. Most studies consider location, age at exposure (and/or age at examination) and gender. For example, in the right eyes 0.9 % of women 43 to 54 y of age in the Beaver Dam Eye Study had cataract while 57.5 % of women 75 years of age or older had cataract at the baseline visit (Klein et al., 1992). For men, the prevalence was about 5 % less than in women but the age trend was similar. The age effect was true for NSC, PSC and CC. Aside from age and gender (Graw et al., 2011), other factors related to cataract were smoking (Harding and Van Heyningen, 1989; Klein et al., 1993b; Leske et al., 1991; West et al., 1989), steroid use (Spencer and Andelman, 1965), diabetes (Klein et al., 1995), ultra-violet light exposure (Cruickshanks et al., 1992; Taylor et al., 1988), heavy drinking (Ritter et al., 1993), hypertension (Hiller et al., 1986; Klein and Klein, 1982; Klein et al., 1995b), and statin or other prescription medications (Leuschen et al., 2013; Robman and Taylor, 2005). The strength of the association of these factors differs by type of cataract.

The impact of potential confounders has been included in many of the epidemiologic studies of radiation effects on the lens of the eye. Appendix A provides a list of specific confounder adjustments in each study (Tables A.1 to A.7). Findings from various studies indicate

that radiation risk estimates are probably not due to confounding by other cataract risk factors and that risk is seen after both childhood and adult exposures (Shore et al., 2010). Also of interest is the potential increased sensitivity of the lens at young ages (ICRP, 2012; Nakashima et al., 2006; UNSCEAR, 2013b).

5.3 Evaluating the Epidemiological Evidence

5.3.1 Variety of Studies

Only a few of the epidemiological studies have investigated the association of low doses of ionizing radiation and the development of cataract (EPRI, 2014; Hammer et al., 2013). Overall, the studies differ in several important aspects, including the source of radiation, type of exposure scenario, study design, study size, range of lens doses, the method (if any) of dose estimation, the choice of lens detriment endpoint studied, the method (and possible scoring) of endpoints, and the adjustment (or assessment) of other risk factors and/or potential confounders. In addition, several of the studies suffer from significant methodological weaknesses.

5.3.2 Epidemiological Quality of Studies

Recently EPRI (EPRI, 2014) systematically assessed the available epidemiological literature to evaluate and conduct a meta-analysis of the results. All potentially relevant studies underwent a formal evaluation and were assigned a quality score according to their methodological strengths and weaknesses. The general approach involved awarding each study a zero for generally expected good study design (0), a point (+ 1) for each methodological strength, and penalizing with a negative score (- 1) for each evident shortcoming. Such a methodology is typically used when evaluating available epidemiologic evidence for outcomes due to exposures (e.g., U.S. EPA evaluations such as Wartenberg et al., 2000).

The evaluation quality scoring developed by EPRI was conducted according to the following criteria.

1. Study Design: proportionate incidence ratio studies or prevalence only studies = -1; cohort or case-control studies = 0.
2. Dosimetry: no dosimetric assessment = -1; dose reconstruction = 0; individually measured and/or verified doses = +1.
3. Age Adjustment: no = -1; yes = 0.
4. Confounding by Other Cataract Causes: likely but not addressed = -1; possible but not clearly evident = 0; unlikely or addressed = +1 (e.g., studies that accounted for other known cataract risk factors).
5. Numerical Risk Assessment: not included = -1; yes (e.g., HR, RR, OR) = 0.
6. Exposure-response Analysis: no = 0; yes = +1.
7. Account for Latency: if < 5 y since exposure = -1; ≥ 5 y since exposure = 0.
8. Reporting Bias: likely = -1; possible but not clearly evident = 0; unlikely/adjusted = +1 (e.g., case-control studies using recorded occupational histories).
9. Selection Bias: likely = -1 (e.g., due to a reliance on referral of cases to a clinic); possible but not clearly evident = 0 (e.g., in clinical-based case-control studies); unlikely/addressed = +1 (e.g., in cohort studies or population-based case-control studies).
10. Pathology Method: not specified = -1 (e.g., 'ophthalmological exam,' or surrogate measure such as 'cataract surgery'); slit-lamp evaluation by physician = 0; physician examination and slit-lamp evaluation documented with photos = +1.
11. Blinded Pathology or Scoring: not blinded = -1; blinded = 0.
12. Cataract Scoring: not specified or only by presence of opacities or 'increased luminescence' = -1; LOCS I or II or III or Merriam-Focht or other definitions = 0.

EPRI used the scoring as a formal approach to classify studies into three tiers. Tier III included studies that had an overall negative score (i.e., < 0) and were considered unreliable for the meta-analysis. Those studies that had scores of zero or above were divided into two groups. Studies with the higher (> 1) total score were included in Tier I and considered most informative. Tier II included the remaining studies that received a total score of 0 to 1 but were considered less useful due to methodological shortcomings.

EPRI quality scoring results are listed in Appendix A, Table A.8 (EPRI, 2014). Of 58 studies specifically reporting various cataract type results, 9 of the studies were categorized as Tier 1 (quality score > 1) and were considered the most informative. Fifteen of the studies were categorized as Tier 2 (quality score 0 to 1) and were considered important, but less useful due to methodological shortcomings. Thirty-four of the studies were categorized as Tier 3 (quality score < 1) and were considered unreliable from an epidemiologic study view, but were mentioned for completeness of the literature review process.

5.3.3 Odds Ratio Meta-analysis

Among the cataract epidemiology studies, there are several that provided either odds ratios or risk ratios for exposed versus unexposed persons for a given dose, usually at 1 Gy. These studies have been extracted from information in all the studies that are listed in Appendix B, Table B.1 (EPRI, 2014). The individual studies estimated the risk ratios at 1 Gy by using a linear no threshold dose-response function. The Tier 1 and 2 studies consisted of the Chernobyl clean-up workers by Worgul et al. (2007), several papers of the atomic-bomb survivors cohort, a clinical study of exposed infants by Hall et al. (1999), and a study of radiation technologists by Chodick et al. (2008). These studies are a combination of acute and chronic exposures as well as child versus adult exposures. It is of interest to see what a simple meta-analysis of this information would show.

It is important to note that there are some limitations associated with each of these studies. For example, the atomic-bomb survivor studies on cataracts did not utilize a standard photographic method, several of the photographs were not in sharp focus (making them difficult to judge), and a retro-illumination camera was not used for examination of cortical and PSC cataracts (RERF, 2013b). The study of radiological technicians is a low dose (i.e., < 60 mGy) questionnaire study with a relatively high estimated relative risk (RR) at 1 Gy, which was not statistically significant (Chodick et al., 2008). The Hall et al. (1999) study, which considered the effects of medical exposures to infants and combined the estimated effects with studies of

individuals exposed as adolescents and adults may present difficulties of interpretation. This may be illustrated by the study of atomic-bomb survivors by Nakashima et al. (2006), which included mostly adolescents as well as some adults, and which found PSC to have a strong age at time of exposure effect. Finally, in the Chernobyl study, the individual dose uncertainties were substantial.

Recognizing these study limitations, a meta-analysis estimate using the Tier 1 and 2 data given in Table B.1 was carried out. The updated Nakashima et al. (2006) data, with the newer dosimetry, was used in place of the earlier Minamoto et al. (2004) data. Appendix B, Table B.2, summarizes the results. The meta-analysis estimate for PSC gives a significant odds ratio of 1.45 Gy^{-1} when the Nakashima study was included. The meta-analysis estimate for cortical cataracts gives an odds ratio of 1.36 Gy^{-1} while excluding the Nakashima study raised the odds ratio slightly (1.50 Gy^{-1}). The meta-analysis estimate for mixed cataracts gives a value of an odds ratio of 1.75 Gy^{-1} while the meta-analysis estimate for nuclear cataracts gave a non-significant odds ratio of 1.07 Gy^{-1}.

The results of this evaluation show that data available from the four Tier 1 and 2 studies suggest that there is a likelihood of an association between exposure to ionizing radiation at 1 Gy and initiation or development of PSC, mixed, and/or cortical cataracts in humans for various exposure situations, but not for nuclear cataracts or opacities. It should be remembered that the degree of risk estimated at 1 Gy in a particular study does not mean that there is actually an increased risk at 1 Gy in that study, although in the ideal situation the model chosen would show a good fit to the observed data. It is simply that a dose-response function (typically a linear nonthreshold function) is fit to the observed data and an estimate of effect at a convenient exposure level (such as 1 Gy) is made. This then allows for a comparison of the magnitude of risk reported among the studies of interest.

5.3.4 Threshold Evaluations

Fewer studies attempted to estimate a specific threshold, namely the atomic-bomb survivor studies (Nakashima et al., 2006) and the Chernobyl study (Worgul et al., 2007). These values of the estimated cataract thresholds are given in Appendix B (Table B.3). There is considerable uncertainty in these estimates, which depend heavily upon the dose response function used and the uncertainties in the dose estimates.

While it is not yet possible to quantitatively estimate a specific threshold value for either acute or chronic lens exposures at this time, the data from Worgul et al. (2007) appear to suggest that if a chronic lens dose threshold for cataracts exists, it may be perhaps around 1 or 2 Gy. However, the data from Nakashima et al. (2006) indicate that there is statistically no difference in the choice of a threshold estimate for PSC between 0 and 2.5 Gy. Based on these two studies, it is concluded that there is currently not enough available information to make any new specific conclusions with regard to chronic or acute exposure thresholds for cataracts.

5.4 Conclusions from Eye Epidemiological Studies

5.4.1 Results of Eye Epidemiological Evaluation

With the very limited data (much of which is either uncertain or under question), it is not yet possible to quantitatively estimate a specific threshold value for either acute or chronic lens exposures. It is therefore also not possible to determine whether the effect is stochastic or deterministic. However, the systematic review of the current eye epidemiology data has shown that the probable risks for cataracts (i.e., specifically PSC, mixed, and/or cortical cataracts) are likely increased at an exposure level that is somewhat less than the earlier estimates of the ICRP or NCRP. Both ICRP and NCRP had earlier assumed threshold values for vision-impairing cataracts of 2 to 10 Sv for single brief exposures and > 8 Sv for protracted exposures (NCRP, 1989a; ICRP, 2007). ICRP has noted that ophthalmologically-detectable opacities might result from lower dose ranges of 0.5 to 2 Sv (50 to 200 rem) for acute exposures (ICRP, 1991; 2012).

Therefore, there is the possibility that effects (e.g., lens opacities and/or cataracts) could occur at lower doses than previously considered when developing occupational lens dose limits based on the potential for worker lens doses over time.

5.4.2 Future Work

It is suggested in ICRP Publication 118 (2012) that continued follow-up of study populations including atomic-bomb survivors (RERF, 2014a; 2014b), Chernobyl victims, and various occupationally exposed individuals may lead to a more precise estimate of any threshold. Hammer et al. (2013) recommended evaluation of German interventional cardiologists since they would have protracted exposures. Internationally, continued follow-up of uranium miners, individuals exposed at Chernobyl, as well as the Techa River and Mayak plant workers may also be of further interest. Ainsbury et al. (2014) recommended implementation of a systematic screening program for people exposed occupationally to ionizing radiation. Studies of aircrew and pilots have been identified as useful. Cohorts exposed to protracted doses and studies focused on childhood exposure are also particularly interesting, due to the lack of current data in these areas and the evidence that the developing lens may be more radiosensitive (Dynlacht, 2013; Hall et al., 1999; Nakashima et al., 2006; UNSCEAR, 2013b).

In terms of study design, accurate, individual cumulative/retrospective lens dosimetry and information regarding the exposure scenario (e.g., whole or partial body/gradient exposure, dose rate, and fractionation) are needed. Longitudinal studies should consider which endpoints are most suitable (i.e., ideally looking at progression in addition to prevalence). This is perhaps particularly relevant to dose protraction. Prospective as well as retrospective studies should also be undertaken. In addition, future work may be able to elucidate the role of radiation quality (e.g., RBE, LET, etc.) on lens effects. Objective, comprehensive, measurement of cataracts and quantification of lens changes are also very important to provide properly quantified information concerning incidence and progressive severity of opacities. Studies should also determine the degree of visual deficit associated with opacities and/or cataracts. Furthermore, sufficiently long follow-up periods have been identified as crucial factors for accurate assessment of the

relationship between dose and radiation-induced cataracts. Consideration of the large number of potential confounders is also necessary. Finally, large populations are key to ensure statistical power, particularly at the lowest doses.

6. Exposed Populations and Implications

A number of persons likely would be affected by ICRP's recommendations (2012). This section gives a brief summary of these groups of individuals and discusses the potential implications of the recommendations. The implications would apply chiefly to radiation workers.

6.1 General - Members of the Public and Occupational Exposures

Firstly, in terms of exposures to the general public, ICRP Publication 118 (2012) states: "No new limit has been recommended for public exposures to the lens of the eye, as the Commission judged that the existing limit was adequately protective, and therefore reduction of the limit could impose unnecessary restrictions. It seems highly improbable that any member of the public would receive a dose to the lens of the eye over a lifetime in excess of the nominal threshold of 0.5 Gy in a planned exposure situation considering: application of the effective dose limit of 1 mSv/year; the low likelihood of the lens of the eye being preferentially exposed for any significant period; and optimization of protection below the equivalent dose limit for the lens of the eye" (ICRP, 2012).

For practical radiation protection purposes, the European Union Basic Safety Standards (EU BSS) provides an example legal framework. The revised EU BSS was published in January 2014 after an extensive period of consultation regarding the ICRP's recommendations (it must be implemented by European Union member countries by February 6, 2018). The standard states that the current effective dose limits for public exposure should be maintained. However, it also states that there should be no further need for averaging over five years for public exposure (except in special circumstances specified in national legislation). In the EU BSS, the public exposure limit is therefore set to an effective dose of 1 mSv per year, with a limit on the equivalent dose for the lens of the eye at 15 mSv per year (BSS, 2014).

For occupational exposures, the EU BSS is in accordance with the ICRP recommendations, with the effective dose limit set at 20 mSv y^{-1} and the following statement

regarding lens doses: "…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." Apprentices and students have an additional equivalent lens dose limit of 15 mSv in a year, and workers are required to be classified as 'Category A' (i.e., subject to individual monitoring and medical surveillance) if equivalent lens doses greater than 15 mSv in a year might be expected (BSS, 2014).

IAEA TECDOC No. 1731 (2013) discusses specific implications for relevant occupational exposure scenarios. Medical, nuclear and industrial radiography settings have all been identified as important; these are discussed individually in the following sections. Notably in the EU BSS, medical exposures are exempt provided they are adequately justified, the patient is made fully aware of the risks and doses are monitored and recorded. For air and space crews, the EU BSS states the following: "The exposure of air crew to cosmic radiation should be managed as a planned exposure situation. The operation of spacecraft should come under the scope of this Directive and, if dose limits are exceeded, be managed as a specially authorised exposure…" (BSS, 2014).

It is worth noting that the EU BSS is applicable to human activities which involve the presence of natural radiation sources that lead to a significant increase in the exposure of workers or members of the public, with air and space crew and processing of materials with naturally-occurring radionuclides given as examples. It is not applicable to natural levels of radiation including cosmic radiation above ground exposure to radionuclides present in the undisturbed earth's crust which cannot easily be controlled (BSS, 2014).

6.2 Medical – Occupational and Patients

6.2.1 Patients

The early reports by Merriam (1956) and Merriam and Focht (1962) on the time-dose relationship for cataract production in animal models and radiotherapy patients served as the

basis for the frequently-cited threshold doses for cataracts, of ~ 2 Sv and ~ 5.5 Sv for single and fractionated exposures, respectively. While there is still some debate as to the minimum cataractogenic dose for fractionated/protracted exposures, epidemiological data for astronauts or individuals inadvertently exposed for long durations support much lower thresholds than originally proposed. Data from radiotherapy patients, though somewhat scant, may shed light on this issue.

Head and neck cancer patients that received fractionated doses to the lens of the eye of 4.5 to 30 Gy of ^{60}Co gamma rays or 5 MeV x rays delivered in 10 to 20 fractions began to develop opacities between 3 to 9 y post-irradiation and severity was dose-dependent (Henk et al., 1993). Doses and dose rates to the lens of the eye from eye plaque ^{125}I brachytherapy can vary widely (such as 0.4 to 1 Gy/h prescribed to the tumor over 3 to 7 days; dose to lens equal to 12 to 36 Gy). However, the median time to observe cataract was 2.5 y (range 0.5 to 5 y) after treatment, and at least half of the eyes developed cataracts within 5 y post-treatment, with latent periods significantly shorter for lenses exposed to ≥ 24 Gy (ABS, 2014; COMSG, 2014). Data from patients receiving total body irradiation (TBI) usually suffer from bias, since most will receive some form of chemotherapy (Belkacémi et al., 1996). There was a significant sparing effect with use of a fractionated protocol (Deeg et al., 1984). Cataracts due to fractionated doses to the human lens coincidental to radiotherapy for uveal melanoma have revealed that the fraction of the germinal epithelium irradiated correlates with the risk of cataract (Meecham et al., 1994).

Radiology imaging patients may also receive radiation doses to the lens of the eye. While optimization to reduce lens of the eye doses (e.g., use of gantry tilt in certain CT examinations) may be possible in some cases, completely avoiding lens exposure may be difficult even with state-of-the-art equipment.

Eye lens doses for CTs may range from 0.11 mGy for sinonasal digital tomosynthesis to 380 mGy for some interventional neuroradiology procedures (e.g., embolization) (IAEA, 2014c). It has also been reported that cumulative lens doses can be > 100 mGy in children exposed to

repeated CT scans (Michel et al., 2012). Lens doses to patients during perfusion CT of the brain have been reported by Ringelstein et al. (2014). Values were from 10.7 to 80.9 mGy. Sandborg et al. (2010) measured lens doses to patients during interventional neuroradiology procedures and obtained average and maximum doses to the left eye of 51 and 515 mSv (coiling) and 71 and 289 mSv (embolization). The dose to the adult lens from a dental cone beam CT has been measured to be about 0.14 mGy (Prims et al., 2011).

6.2.2 Workers

Medical practitioners performing fluoroscopically-guided interventional (FGI) procedures can receive relatively high ocular doses, especially when protection tools are not used (Dauer et al., 2010; Kim et al., 2008; 2012; NCRP, 2010b; Vano et al., 2006; 2008). Interventional radiologists and cardiologists are frequently positioned in close proximity to patients during procedures in which exposure to scattered radiation to the lens can be very high (e.g., during fluoroscopic examinations or image-guided interventional procedures). Kim et al. (2012) found that the mean dose per case measured over personal protective devices to operators performing FGI procedures ranged from 19 to 800 (median 113) μSv at eye level. Kim et al. (2008) found that the mean dose per case measured over personal protective devices to operators performing cardiac catheterization protocols ranged from 0.4 to 1,100 μSv at eye level. In a single high-volume imaging cancer center, the hospital average measured lens dose equivalent (LDE) was 2.1 mSv for all monitored medical staff, with inpatient nurses receiving the lowest average LDE at 0.4 mSv y^{-1} and FGI physicians receiving the maximum doses to the unprotected lens, with an average of 11.1 mSv y^{-1} and a 75^{th} percentile of 19.3 mSv y^{-1} (Dauer, 2014). The European ORAMED project has recently also provided detailed results on eye exposure for many procedures in interventional cardiology and radiology (Domienk et al., 2011; Farah et al., 2013). Large variations in operator lens of the eye doses suggest that optimizing procedure protocols and proper use of protective devices and shields could reduce occupational radiation dose to the lens substantially (Kim et al., 2012; NCRP, 2010b).

In an international study, the mean annual effective dose for interventional cardiologists was 0.7 mSv [ranging from 0.5 to 10 mSv h^{-1}, with procedures lasting anywhere from < 0.5 min to 90 min (such as during the treatment for an aortic aneurysm)]. However, there is some concern that these represent underestimated values (Le Heron et al., 2010); often the dose to the lens will be underestimated unless a dosimeter is worn at the collar. In another report, Picano et al. (2012) has reported that for interventional cardiologists effective doses per procedure range from 0.02 to 38 µSv for diagnostic catheterization, 0.2 to 31.2 µSv for percutaneous coronary intervention, 0.2 to 9.6 µSv for ablation, 0.3 to 17.4 µSv for pacemaker or intracardiac defibrillation implantations, and 50 to 200 µSv for procedures involving occlusions and valve/aneurysm repairs. Measurements received over personal protective devices in the examination room range from 0.4 µSv to 1.1 mSv at the eye level for each of perhaps hundreds or thousands of procedures each year. A cardiologist's head would receive approximately 100 µSv per single ablation procedure with perhaps more than 20 to 30 mSv y^{-1} if a ceiling-suspended screen is not used, resulting in an estimated eye dose of approximately 0.5 mGy/procedure, without eye protection (IAEA, 2014a). For a single coronary angiography session, an operator's eyes would receive a dose of 165 µSv or 37 µSv, without or with protection, respectively (Picano et al., 2012). Through the use of protective eyewear and proper placement of the viewing monitor, this population of workers can reduce the dose to the eyes by 90 % (Le Heron et al., 2010).

Since many fluoroscopic procedures are conducted outside radiology departments, one may assume that there are a multitude of doctors and nurses who may not have received sufficient training in radiation dosimetry and protection to achieve that level of protection in their examination rooms. A recent study by Sanchez et al. (2014) obtained individual measurements of lens of the eye doses during 33 clinical procedures carried out in catheterization cardiac laboratories with OSL and electronic dosimeters located on the cardiologists' goggles (left side). In most procedures, although not always, the ceiling suspended screen was used. The authors noted that the average value decreased to 40 µSv per procedure if the two highest values are removed from the sample. Radiologists performing neuroembolization procedures may receive a lens dose of 1.4 to 5.6 mSv per procedure, depending on distance from the patient and whether a movable shield or leaded glasses are utilized (Vano et al., 2008). Not surprisingly, in a study of

116 interventional cardiologists, Vano et al. (2010) found that 38 % had cataracts, compared to 12 % in matched controls. In a later follow-up study, Vano et al. (2013a) found that 50 % of interventional cardiologists and 41 % of nurses and technicians showed evidence of PSC opacifications after receiving eye doses ranging from 0.1 to 18.9 Sv over several years.

Lens of the eye doses in interventional fluoroscopy may be very different depending on the use of protection tools (e.g., screens and/or goggles). Individual dose measurements of lens of the eye doses were performed during cardiac clinical procedures with dosimeters located on cardiologists' goggles (left side). The average $H_p(0.07)$ per procedure measured with thermoluminescent dosimeters (TLD) or optically stimulated luminescent (OSL) dosimeters was 80 μSv, with a maximum value of 697 μSv in a single procedure (Sanchez et al., 2014). Scatter doses at the C-arm during cardiac catheterization procedures have been measured in about 2,000 procedures to range from 0.5 to 2.5 mSv/procedure, depending on the complexity of the procedures. The ratio between the scatter dose at the C-arm and the kerma area product resulted in about 10 μSv/ Gy·cm^2 of patient dose. These values may be a conservative estimation of the range of doses to the lens of the eye for the operators if radiation protection tools are not used (Vano et al., 2013b).

During PET/CT guided interventions, the median effective dose was 0.02 (range 0 to 0.13) mSv for the primary operator, 0.01 (range 0 to 0.05) mSv for the nurse anesthetist, and 0.02 (range 0 to 0.05) mSv for the radiological technologist. The median extremity dose equivalent for the operator was 0.05 (range 0 to 0.62) mSv. The median operator effective dose for the procedure was 0.015 mSv when conventional biopsy mode CT was used, compared to 0.06 mSv for in-room image guidance, although this did not achieve statistical significance due to the small sample size ($p = 0.06$). The operator dose from PET/CT-guided procedures is not significantly different than typical doses from fluoroscopically guided procedures. The major determinant of radiation exposure to the operator from PET/CT-guided interventional procedures is time spent in close proximity to the patient (Quinn et al., 2012; Ryan et al., 2013).

It has been suggested that anesthesiologists involved in lengthy neurointerventional radiology procedures may receive ocular radiation exposures similar to or exceeding those of radiologists. Anastasian et al. (2011) reported that the average radiation exposure to an anesthesiologist's face was 6.5 µSv per interventional procedure. Some anesthesia personnel involved with cardiac catheterization accumulate the equivalent of 1.3 to 1.8 mSv per month (Henderson et al., 1994).

In a recent survey of occupational doses worldwide, it was found that "…80 % of general and CT radiographers did not receive measurable doses…" (Le Heron et al., 2010). Kesavachandran et al. (2012) reported an annual radiation dose for the eyes of orthopedic specialists as varying between 0.06 to 23 mSv. Burns et al. (2013) reported that leaded eyeglasses reduce radiation exposure of orthopedic surgeons' eyes tenfold (i.e., a 90 % reduction in dose) during acquisition of typical fluoroscopic views of the hip and pelvis.

6.3 Nuclear Facilities

The majority of the occupational dose to the lens of the eye in nuclear facilities is the result of time spent in uniformly distributed radiation fields. The NRC in NUREG 0713 Volume 33 (NRC, 2011b) provides industry lens of the eye doses for 2011 that indicates that a very small fraction of workers exceeded 25 % of the current regulatory limit of 150 mSv y^{-1} (NRC, 2008). Of the over 65,000 monitored individuals, 18 individuals (inclusive of all uranium fuel cycle industries) had reported doses greater than 30.75 mSv with the maximum individual lens of eye dose equivalent (LDE) of 49 mSv. These data are inclusive of workers who are exposed under uniform and non-uniform radiation field conditions that also include fields with lower penetrating sources, such as low-energy gamma and higher-energy beta ionizing radiation.

6.3.1 Monitoring

Monitoring of eye dose as well as assessing field conditions with existing instrumentation will be impacted by any reduction in the lens of the eye dose limit. Currently, monitoring is

required when lens doses are likely to exceed 10 % of the regulatory limit (NRC, 2008). Procedure guidance for making lens of the eye monitoring decisions, in particular for workers exposed to non-uniform radiation fields in the course of their work, relies on adequate assessment of area dose rates and personnel monitors' energy responses. Existing federal limits for whole-body exposures allow for adequate and conservative dosimetry utilizing algorithms or stay-time assessments that are normally based on tissue depths and associated correction factors for the skin and deep tissue, not specifically for the 3 mm eye lens tissue depth. Most nuclear facilities do not currently estimate lens dose prior to entry to perform work since present limits for skin and whole-body exposures will assure doses well below existing limits. A lower limit would increase the importance of ensuring that lens dose assessments are not only accurate, but also not overly conservative.

Dosimetry algorithm reviews will be necessary and changes likely based on radiation exposure situations and radiation quality. At a minimum, new energy specific studies would be necessary to provide revised dosimetry correction factors. It is noteworthy that there are presently no peer reviewed standard dosimetry quantities or conversion factors for lens dose equivalent, although ICRP recently addressed considerations for assessing absorbed dose in the lens of the eye in ICRP Publication 116, Appendix F (ICRP, 2010).

Additional review with regard to the monitoring of external dose equivalent from external sources (EDEX) approaches may be required. The term EDEX describes the calculation of effective dose equivalent (EDE) as described in ICRP Publication 26 (1977), with respect to external radiation exposure. The nuclear power industry accomplishes this via U.S. NRC Regulatory Guide 8.40 (NRC, 2010). For doses that are primarily from above the head where the head is more highly exposed than the trunk, there are implications for the use of this weighting method in light of a reduced LDE limit. In certain situations, particularly those with a dose gradient above the head, the lens dose could be limiting where under present limits this is not a concern. The EDEX technique provides the practitioner the benefit of a more accurate dose record for doses to the body and can allow for longer effective stay times, which can be valuable in minimizing the need to switch out workers during certain activities. Overall task efficiency is

typically improved under such scenarios thereby reducing collective worker exposures. It is possible that a lowering of the eye dose limit would reduce or negate the ability to apply EDEX for effective dose assessment as facilities may subsequently require monitoring of the head as an indicator of eye dose and just assign this dose as the effective dose. While a special case, such aspects emphasize the possible implications of eye dose limits that are close to or below whole-body dose limits. Such a reduction would certainly drive reassessment of dose gradients as discussed above, which would raise awareness on the part of radiation protection professionals for those cases where head exposures may cause the lens of eye dose to become limiting.

6.3.2 Protection of the Eye Lens

Protection for the lens of the eye needs reassessment. Lower limits and a resulting need for more accurate assessments will likely drive a case for use of protection factors under certain exposure situations. It will be useful to have information available on reasonable protection factors that can be applied considering beta radiation thresholds for various type/thicknesses of protective materials. In this area, as with monitoring, dosimetry quantities and measurements will need additional technical information provided for implementation. Protection factor data for commonly used materials (e.g., respirator face shields, bubble suit masks, and goggles) with companion energy information may be necessary.

6.4 Industrial Radiography

Another group of workers for whom change in the limits on exposure of the lens of the eye might be significant is industrial radiographers. In 2009, IAEA established the Information System on Occupational Exposure in Medicine, Industry and Research (ISEMIR). ISEMIR was a project aiming to improve occupational radiation protection in those areas of radiation use in medicine, industry and research where non-trivial occupational exposures occur. As part of ISEMIR, a Working Group on Industrial Radiography (WGIR) was established to analyze information on individual and collective occupational radiation dose as well as on existing dose reduction techniques, both in normal operations and in accident situations in industrial areas.

Three questionnaires were developed by WGIR to gain insight into occupational radiation protection in industrial radiography around the world. These questionnaires were distributed to individual industrial radiographers (i.e., the operators), non-destructive testing companies, and national or state radiation protection regulatory bodies. Reported individual monitoring data for 2009 from the radiographer questionnaire (234 radiographers) and the regulatory body questionnaire (18,000 radiographers) gave average annual effective dose estimates for industrial radiographers of 3.4 and 2.9 mSv, respectively. Approximately 2 % of industrial radiographers received an annual effective dose in 2009 that exceeded 20 mSv (IAEA, 2014e). WGIR did not collect information on dose to the lens of the eye because industrial radiographers do not typically conduct separate monitoring of the dose to the lens of the eye since they work in a relatively homogeneous radiation field.

WGIR reviewed the Strahlenschutzkommission (German Commission on Radiological Protection) report entitled “Monitoring the eye lens dose” (Strahlenschutzkommission, 2010) and believed that for exposures in normal operations, the effective dose is a good estimate for dose to the lens of the eye for photons of energy > 200 keV, and that additional monitoring for the lens of the eye is not necessary since the exposures during industrial radiography are uniform. The consensus of WGIR is that there is no need for additional protective measures and the lens of the eye dose would benefit from dose constraints (i.e., action levels) put on effective dose. These conclusions would not apply to situations of accidental exposures, which occur frequently in industrial radiography. For accidental exposures, effective dose would not be a good estimate of the dose to the lens of the eye because the radiation field at the radiographer’s position might not be uniform as the distances between source and body are shorter (Van Sonsbeek et al., 2012).

6.5 Astronauts

Astronauts are exposed to a mixed field of electromagnetic and particulate radiation species derived predominately from galactic cosmic radiation (GCR) and solar particle events (SPE). The annual dose range measured within the habitable volume of the International Space Station (ISS) is 44 to 105 mGy (NASA, 2014). It has been estimated that for a 12-month

roundtrip to Mars with current propulsion systems, the dose equivalent for crew members from the GCR component alone would be 0.66 Sv (a potentially significant upward adjustment to the dose equivalent would be necessary if one were to include time spent on the surface of Mars) (Zeitlin et al., 2013). Astronauts are exposed to a number of stressors in addition to SPE and GCR that may impact health risks including high gravitational forces at launch and microgravity during the mission. The risk of radiation-induced cataract has been one of the first health detriments from space flight reported for the astronaut corps, but it is not a primary concern for NASA during space missions, even though lens opacities could compromise crew performance during missions and could impact the quality of life upon return to Earth.

7. Conclusions and Recommendations

Cataracts of the lens of the eye induced by ionizing radiation are a visible change long recognized as a detriment to clear vision. However, the apparent simplicity of the association between 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. These issues have challenged the preparation of guidance on radiation dose limits for the lens of the eye.

This Section summarizes the conclusions drawn by the Committee on the four key questions, and discusses several pertinent recommendations.

7.1 Detailed Conclusions and Recommendations

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

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. The review of mechanistic studies by several authors summarized in this Commentary indicates that radiation-induced opacities may be stochastic in nature and not deterministic as long thought. However, the link between the induction of any, even minor, opacities in animal models and the occurrence of clinically-relevant, visually-impairing cataracts in humans is still far from clear. Because of 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 determined that this model should continue to be used for radiation protection purposes at this time.

The value of the threshold for detectable opacity or vision-impairing cataracts is less clear, with the epidemiological evidence currently pointing to a threshold for vision-impairing cataracts in the region of 1 to 2 Gy. However, NCRP has concluded that it is not possible to make specific quantitative estimates of lens effects thresholds at this time.

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

The epidemiological evidence presented in Section 5 of this Commentary demonstrates that, although different studies have looked at many of these factors independently, there is still very little evidence upon which to base an answer to this question. The mechanistic evidence is clearer in some instances (e.g., in terms of a differential effect of increased radiation ionization qualities enhancing the induction and progression of opacities) but, as noted above, the relationship between the results from animal models and risks of vision-impairing cataracts in humans is still not clear. The 'normal' lens loses clarity with attained age due to a number of physiological aging processes. As such, the Committee has determined that further, 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. Improvements in methods to determine lens doses in the clinic and the workplace, and in technical approaches to score the different types of lens opacifications arising in different anatomical regions of the lens will strengthen the quality of the new dose-dependent cataract data obtained. Advancement of more basic research on the exact biological target for species-specific differences in radiation-induced cataract formation could lead to the development of biochemical countermeasures that may be applied to attenuate or prevent cataract formation.

7.1.3 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). ICRP Publication 118 (2012) noted that acute doses up to about 0.1 Gy produce no functional impairment of tissues, that

detectable lens changes can be identified as low as between 0.2 and 0.5 Gy, and concluded that a nominal threshold of 0.5 Gy for acute or protracted exposure for lens tissue effects is an appropriate method for evaluating lens detriment. 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.

7.1.4 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 that there is an association between exposure to ionizing radiation and initiation or development of PSC, mixed and/or cortical visually-impairing cataracts in humans for various exposure situations. The systematic review of the current eye epidemiology data has shown that the probable risks for cataracts (i.e., specifically PSC, mixed, and/or cortical cataracts) are likely increased at an exposure level that is somewhat less than the earlier estimates of ICRP or NCRP. Both ICRP and NCRP had earlier assumed threshold values for visually-impairing cataracts of 2 to 10 Sv for single brief exposures and > 8 Sv for protracted exposures (ICRP, 2007; NCRP, 1989a). ICRP has also noted that ophthalmologically-detectable opacities might result from lower dose ranges of 0.5 to 2 Sv (50 to 200 rem) for acute exposures (ICRP, 1991; 2012).

NCRP acknowledges that most of the available data on lens effects have large associated uncertainties and limitations that do not yet support a quantitative estimate of a specific threshold value for effects from either acute or chronic lens exposures. However, the preponderance of evidence appears to suggest the possibility that effects (e.g., lens opacities and/or cataracts) could occur at lower doses than previously considered when developing occupational lens dose limits based on the potential for worker lens doses over time. Therefore, NCRP has determined that it is

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 effective dose limit of 50 mSv (NCRP, 1993b). 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.

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). If it is necessary 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 in gray.

7.2 Additional Recommendations for Evaluation and Research

While the currently available information for the effects of ionizing radiation on the lens has provided input on appropriate guidance with regard to radiation protection, much more work is needed to develop a complete understanding of such detriments. NCRP recommends ongoing evaluation and additional research in the following areas: comprehensive evaluation of the overall effects of radiation on the eye, dosimetry methodology and dose-sparing optimization, additional high quality epidemiology studies, and a basic understanding of the mechanisms of cataract development.

7.2.1 Comprehensive Evaluation of Overall Effects of Radiation on the Eye

NCRP should consider developing a comprehensive evaluation of the overall effects of radiation on the eye [e.g., similar to NCRP Report No. 159 (2008) on risk to the thyroid from

ionizing radiation]. A comprehensive evaluation of the eye doses accumulated by the eye over time by susceptible populations and radiation workers is warranted.

7.2.2 Dosimetry Methodology and Dose-sparing Optimization

ICRP Publication 116 (2010) in Appendix F provided revised dose conversion coefficients for the lens from a significantly refined eye stylized phantom set. Dose conversion coefficients are now available for several external irradiation conditions and geometries. These can be utilized for assessing absorbed dose in the lens of the eye. NCRP emphasizes that there is a continued need for more accurate lens of the eye dosimetry and monitoring, as well as an on-going opportunity for dose-sparing optimization and the need for more education for all workers. Additional lens of the eye dose-sparing optimization and more accurate dose assessment for patient populations with the potential for significant eye exposures are also necessary.

7.2.3 Additional High Quality Epidemiologic Studies

Several gaps in knowledge cloud our understanding about the existence of dose thresholds and the determinants of radiation cataractogenesis. Significant fundamental questions still remain unanswered. What doses of ionizing radiation are required to trigger lenticular opacifications that do not result in impairment of vision, and what doses will result in opacities that impair vision? Some of these gaps in knowledge may be addressed by reanalysis of existing data sets or through new prospective studies, from which reliable data can be obtained over prolonged periods.

An evaluation of lens of the eye doses received during routine procedures performed by interventionalists and the dose received by patients during selected radiotherapy regimens, as well as high-dose diagnostic or interventional procedures could prove important. The same populations can be followed to determine the time-dose relationship for progression of radiation-induced lens opacities from non-vision impairing to vision impairing, and to determine the

mechanisms underlying the dependence of dose rate, age or gender as determinants in radiation cataractogenesis.

Longitudinal studies should be carried out on radiotherapy patients and radiation workers, where baseline lens clarity and the dose to the lens of the eye are well documented, to determine whether low doses of ionizing radiation induce cataracts that will continue to progress and become vision-impairing, or remain static. Ideally, these studies would involve the use of biomarker technologies that would allow non-invasive measurement of changes at the cellular and molecular level that precede actual opacification of the lens.

As highlighted by UNSCEAR (2013b), children exposed to ionizing radiation may be twice as sensitive to cataract development compared to adults, although the evidence currently cited may be characterized as 'weak.' Data obtained from adults and children exposed to ionizing radiation as a result of radiotherapy may help determine whether the difference in radiosensitivity between adults and children is substantial, but care must be taken to analyze data from individuals without confounding factors.

Having information on age at exposure, as well as all the other relevant factors for a population exposed to a range of relatively low-dose exposures (e.g., radiation workers) and then following that population for a significant time after exposure would greatly contribute to reducing the uncertainty of whether a dose threshold exists. Concurrently, there is also a need to develop lens-specific dosimetry or methods to accurately assess doses to the lens of the eye.

7.2.4 Understanding the Mechanisms of Cataract Development

In terms of mechanisms of cataract development, there is a need to provide a clearer link between the initial damage response and the formation of lens opacities. There is strong evidence that the modifying factors discussed in Section 4 (e.g., age, gender, dose rate, and dose fractionation) all affect cataract risk, and this should be taken into account in future studies. There is a need to fully define the target cells for radiation cataractogenesis as well as the genetic

makeup and molecular-biological mechanisms of action that lead to protein accumulation (including the role of protein damage accumulation and post-translational modifications). A science-informed model for abnormal lens fiber migration and accumulation with the potential progression to visually impairing cataracts is still required. The role of radiation on the latency period is not yet well understood.

Systematic studies are required to identify the specific dose-dependent targeted and non-targeted molecular mechanisms contributing to radiation-induced cataracts in relevant experimental model systems. In addition, investigations aimed at determining the best ways to administer agents that will result in high levels of antioxidants like glutathione in the lens of the eye could provide future nonsurgical methods for cataract prevention.

For radiation protection purposes, it is also important to consider the role of radiation quality, LET, RBE, dose protraction and fractionation, and to address what lies behind the inverse relationship between latency period and dose. Studies involving more than one type of radiation and more than one type of exposure scenario would be highly useful in identifying the complex issues triggering progressive lens opacification after exposure to ionizing radiation, and identifying what would be required to maintain normal lens transparency.

Appendix A

Previous Epidemiological Studies Tables

Tables A.1 to A.7 support the discussion in Section 5.1.2 of this Commentary and have the following legend:

- AHS = adult health study
- DS = dosimetry system
- LOCS = lens opacification classification system
- N = number in study
- 95 % CI = 95 % confidence interval
- OR = odds ratio
- PSC = posterior subcapsular cataract
- TLD = thermoluminescent dosimeter
- T65DR = tentative 1965 dose estimates revised (Kerr and Solomon, 1976)

Table A.8 supports the discussion in Section 5.2.3 where the scoring criteria used may be found.

Table A.1—Exposure to doses of ionizing radiation: Acute exposures in atomic bomb survivors and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder adjustments
Choshi et al. (1983)	Japan	Cohort Study	1978-1980 (33-35 y)	Atomic bomb survivors; Ages from prenatal to >50 y; 62% female; N = 7,227 persons from Atomic Health Study (AHS)	External: Gamma, Neutron	Lens dose range: 0-600 rad	T65DR	Own grading system	300+ rem PSC- RR = 5.28 for < 50 y; 3.99 for 50-59 y and 2.34 for 60+ y. No dose-related differences were seen for cortical or nuclear.	City, Age, Sex
Cogan et al. (1949); Cogan et al. (1950)	Japan	Cohort Study	1949 (4 y)	Atomic bomb survivors; Age mostly 2-16y; N = 1,000 persons within 2,000 m of hypocenter	External: Gamma, Neutron	-	-	Ophthalmoscope; Some slit-lamp	81 lens abnormalities noted in 231 individuals within 1,000 m	Other ocular findings noted
Minamoto et al. (2004); Nakashima et al. (2006)	Japan	Cohort Study	2000-2002 (55-57 y)	Atomic bomb survivors; All ages (mean 8.8 y) N = 873 (M) N = 701 (N) both from AHS	External: Gamma, Neutron	Eye dose range: <0.005-2 Sv (M) Eye dose range: 0-4.90 Sv (N)	DS86 (M) DS02 (N)	LOCS II	(M) OR at 1 Sv for PSC = 1.41 (1.21-1.64); Cortical = 1.29 (1.12-1.49); Nuclear = 1.12 (0.94-1.30). (N) OR at 1 Sv for PSC = 1.44 (1.19-1.73); Cortical = 1.30 (1.10-1.53).	City, Age, Sex, Smoking
Nakashima et al. (2013)	Japan	Cohort Study	1986-2005 (41-60 y)	Atomic bomb survivors; N = 685 cases out of 3,055 participants	External: Gamma, Neutron	Lens dose range: 0-5.14 Gy	DS02	Reported cataract surgery confirmed by ophthalmoscopic exam	OR at 1 Gy = 1.33 (1.28-1.38).	Not discussed
Nefzger et al. (1969); Otake and Schull (1982); Otake et al. (1990); Otake et al. (1996)	Japan	Cohort Study	1963-1983 (18y+)	Atomic bomb survivors; All ages plus in utero; N = up to 2,468: 1,627 in Hiroshima, 841 in Nagasaki	External: Gamma, Neutron	High >200 rad Low <200 rad	Estimates. Later publications DS86	Ophthalmoscope; Some slit-lamp	76 axial opacities with increases in high-dose group	Age
Neriishi et al. (2007)	Japan	Cohort Study	2000-2002 (55-57 y)	Atomic bomb survivors; N = 3,761 from AHS	External: Gamma, Neutron	Eye dose range: <0.005 – 4.90 Sv	DS02	Lens extraction documented by eye examination	OR at 1 Sv = 1.39 (1.24-1.55) Threshold dose best estimate of 0.1 Gy (<0-0.8).	City, Age, Sex, Diabetes
Neriishi et al. (2012)	Japan	Cohort Study	1986-2005 (41-60 y)	Atomic bomb survivors; N = 6,066	External: Gamma, Neutron	Lens dose mean: 0.54 Gy range: 0-5.14 Gy	DS02	Reported cataract surgery confirmed by opthalmoscopic exam	1,028/6,066 underwent cataract surgery. Dose response nearly linear.	Age, Sex, and several medical and social
Yamada et al. (2004)	Japan	Cohort Study	1958-1998 (14-54 y)	Atomic bomb survivors; N = 10,339 from AHS	External: Gamma, Neutron	Mean weighted shielded Kerma 0.92 +/- 1.06 Sv	DS86	No grading of opacities	RR at 1 Sv = 1.11 (1.03-1.19)	City, Age, Smoking, Alcohol

Table A.2—Exposure to doses of ionizing radiation: Exposures in Chernobyl liquidators and cleanup workers and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder adjustments
Nadejina et al. (2002)	Ukraine	Cohort Study	1986-2000 (14 y)	*N* = 11 people with ARS; *N* = 30 Chernobyl recovery workers	External: Gamma, Beta	ARS minimum 2.6 Gy, mean 3.2 Gy. Recovery Mean 0.2 Gy	Not reported	Ophthalmologic examinations; cataracts grading system not reported	5 of 11 ARS cases had 'radiation cataracts'. No 'radiation cataracts' but 3 'senile cataracts' in the recovery workers	Not reported
Worgul et al. (2007); Chumak et al. (2007)	Ukraine	Cohort Study	1986-1987 (12-14 y)	Chernobyl liquidators and cleanup workers; *N* = 8,607	External: Gamma, Beta	Lens dose range: 0-1+ Gy, median: 123 mGy, 44% between 100-199 mGy, 4% received >0.5 Gy	TLD; analytical dose estimated; group dosimetry where possible; doses assessed using teeth where available	Merriam-Focht method	OR at 1 Gy for PSC = 1.42 (1.01-2), Superficial cortical stage 1 = 1.51 (1.1-2.1), Non-nuclear stages 1-5 = 1.65 (1.2-2.3), Nuclear stages 1-5 = 1.07 (0.5-2.0), Threshold estimate for stage 1 PSC = 0.34 Gy (0.18-0.51); stage 1 PSC opacity = 0.35 (0.19-0.66)	Age, sex, smoking, diabetes, steroids, occupations with exposure to chemicals, radiation, UV radiation, infrared, examiner scoring variations, and others

Table A.3—Exposure to doses of ionizing radiation: Acute exposures in medical patients and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Albert et al. (1968)	USA	Cohort Study	1940-1959 (10 y)	Medical treatment with x-ray epilation for Tinea capitis; screening of subsample; N = 234 exposed; N = 232 unexposed	X-ray	Eye dose ~0.5 Gy	Eye dose estimated by calculation model	Slit-lamp examination; abnormal luminescence and early PSC opacities	No difference in unexposed versus exposed for abnormal luminescence or non-PSC opacities. PSC opacities: 13 irradiated and 2 controls OR = 5.9 (1.4-24)	Age, sex, race
Chmelevsky et al. (1988)	Germany	Cohort Study	1945-1952 (30+ y)	Medical treatment with injected radium-224; N = 831 in Spiess Group, N = 58 with cataract	Internal: Alpha; Gamma	Not reported	Injected activity used as dose surrogate	Not reported	Strong correlation between frequency of cataracts and the injected activity with a linear dependence beyond a threshold of 0.5 MBq kg^{-1}.	Age
Cogan and Dreisler (1953)	USA	Case reports	Not reported (1.3-14 y)	Medical patients with reported x-rays near eyes; N = 40	100-200 kV x-ray; one case 1200kV	23-2,400 rad	Phantom Measurement	Ophthalmoscope or slit-lamp; lens changes 'characteristic of irradiation'	5 'radiation' cataracts noted, none of which were among the 33 persons with <500 rad	Not Reported
Cogan et al. (1952)	Japan, USA	Case reports	Not reported (not reported)	Mixed population of medical, cyclotron, and Atomic bomb; N = 20	Varied per individual	Not reported	Not reported	Ophthalmoscope or slit-lamp; lens changes 'characteristic of irradiation'	'Radiation' cataracts noted, mostly located at the posterior pole of the lens	Not reported
Hall et al. (1999)	Sweden	Cohort Study	1920-1959 (~36-54 y)	Medical therapy from radium-226 or contact x-ray (<=60 kVp) as child; N = 448 exposed; N = 89 non-exposed	External: Gamma or x-ray	Mean 0.4 Gy (0-8.4 Gy)	Based on mean dose rate to lenses of 0.13 Gy/h (0.05-3.0)	LOCS system; score>=1 considered positive; cortical and PSC opacities	Cortical + PSC prevalence by dose in mGy; 0 = 9/178 (5%) 1-499 = 89/747 (12%) 500-999 = 20/115 (18%) >=1,000 = 20/89 (22%); Cortical RR = 1.50 (1.15-1.95) PSC RR = 1.49 (1.07-2.08)	Diabetes, Steroids, Family history, Other eye disorder, Other radiotherapy
Meecham et al. (1994)	USA	Cohort Study	<May 1991 (3-159 months)	Medical therapy with helium ion irradiation of the eyes for uveal melanomas; N = 336 chart reviews; N = 292 in study	Helium ions	Tumor doses range 48-80 Gy	Radiation therapy treatment planning algorithm; RBE of 1.3	Radiation induced cataract defined as an asymmetric unilateral grade 3+ or 4+ cortical or PSC lesion	129 patients with radiation induced cataract. Risk of cataract peaked at 3 y. Percentage of lens included in the treatment port was predictive correlate with time to development. RR 2.97 for a 25% increase in lens percent in the treatment. If more than ½ lens was in the beam, the risk exceeded 90% within 7 y. 10 Gy RR 1.20 (0.98-1.47).	Age, Preexisting opacities, Tumor height, Ciliary body and tumor dose

Table A.3—(continued).

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Kal et al. (2009)	Various	Review Meta-analysis	<2009 (not reported)	Medical therapy with total body irradiation (TBI); N = 302 identified patients in 17 articles	External: High energy x-ray	Estimated lens biologically equivalent dose	Dose estimation model	Not reported	Severe cataracts seen above a threshold of BED~40 Gy. High-dose rate TBI was more effective in cataract induction than low-dose rate TBI.	Fractions, Dose rate, Steroids, Heparin
Merriam and Focht (1957); Merriam et al. (1972)	USA	Case reports	Not reported (mean 4.8 y if cataract; mean 9.3 y if no cataract)	Medical radiation therapy patients; N = 173	100-140 kV; or 200-250 kV; or radium plaque/ seed	25-6,900 rad	Phantom Measurement	Ophthalmoscope or slit-lamp; any clinically recognizable opacity having characteristic of a 'radiation' cataract	73 had head irradiation with no cataracts. 200 rad for any opacity, ~500 rad for 'progressive' cataracts. 750-950 rad delivered to the lens in 3-13 weeks had 60 % probability that cataract will develop and 50 % chance that it will be progressive, with corresponding vision loss.	Age, Informally other factors such as hemorrhage, glaucoma, or uveitis
Qvist and Zachau-Christiansen (1959)	Denmark	Cohort Sample	1913-1933 (~20-40 y)	Medical fractionated radium therapy in childhood; N = 855 in cohort with treatments to the head. N = 112 who received lens dose > 100 rad selected; N = 56 examined	Radium applicator External: Gamma	>100 rad selected	Lens dose estimated by calculation model	Ophthalmological examination; methods unspecified	4 cases of cataract with doses ≥690 rad	Not reported
Whelan et al. (2010)	USA	Cohort Recall Study	1970-1986 (5-25 y)	Medical radiation therapy in childhood or adolescence; N = 8,507 treated; N = 3,901 sibling controls	External: High energy x-ray	Eye dose range 0-4,000 cGy	Calculated from water phantom measurement (corrected for eye blocking if utilized)	Recall questionnaire about cataracts; self-reported outcomes, including cataracts	Increased risk of cataracts 5+ years following diagnosis RR = 10.8 (6.2-18.9); If > 200 cGy to the eye RR = 3.2 (2-5.2); median time to onset of cataracts 4.7, range 0-24.1 y	Age, Sex, Steroids
Wilde and Sjostrand (1997)	Sweden	Cohort Study	1930-1964 (30-46 y)	Medical therapy with radium-226 for hemangioma of the eyelid in early childhood (2-13 months); N = 20	External: Gamma	Eye dose range 1-11 Gy to treated side; 0.02-0.12 Gy to untreated side	Treatment planning models	Slit-lamp biomicroscopy and retroillumination photography; 'radiation cataract'	All treated eyes had opacities. Opacity grade increased with lens dose. 13 of 20 contralateral lenses had very minor opacities. Punctate opacities at 100 mGy.	Not reported

Table A.4—Exposure to doses of ionizing radiation: Chronic exposures in health care personnel and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Chodick et al. (2008)	USA	Cohort Study	1983-2004 (median 19.2 y)	Occupational – Radiological Technologists; N = 35,705	External: Primarily Scattered X-ray	Median lens dose: 21.8 mGy	Film badge readings; occupational history	Self-reported	Hazard of cataract for workers in highest dose group (mean 60 mGy) versus lowest dose group (mean 5 mGy): HR = 1.18 (0.99-1.40). ERR/Gy = 1.98 (-0.69-4.65)	Age, Sex, BMI, Smoking, Diabetes, Diagnostic X-ray and several other
Junk et al. (2004) Haskal and Worgul (2004)	USA	Cohort Sample Screen	2004 (5-36 y)	Occupational – Interventional Radiology; N = 59	External: Scattered X-ray	Not reported	Not reported	Scheimpflug examination after pupil dilation; Precataract changes and PSC cataracts	22 showed 'small paracentral dot-like opacities' in PSC region, and PSC cataracts found in 9 eyes of 5 persons. Concluded that the frequency and severity of PSC opacities increased with age and number of years in the field	Not reported
Kleiman et al. (2009)	Various	Cohort Sample Screen	2008 (1-40 y)	Occupational – Interventional Cardiologists (IC) and other staff; N = 78 volunteers	External: Scattered X-ray	Not reported	Years of service noted	Slit-lamp examination after pupil dilation	18/42 IC doctors had PSC changes consistent with radiation exposure. 3/34 IC nurses or technicians had mild PSC changes.	Not reported
Milacic (2009)	Serbia	Case-Control	1992-2002 (1-10 y)	Occupational – Medical Workers; N = 1,560 exposed N = 1,680 unexposed	External: X-ray	TLD (mean): 1.59 ± 1.30 mSv/y for cataract cases within ionizing zone; 1.63 ± 1.45 mSv/y for those without cataracts	TLD measurement	Visual acuity examination performed, but no grading reported	Prevalence of cataract 7.3% of workers in ionizing zone, compared to 1.5% outside. Radiological technicians had highest prevalence of cataracts (63.5%).	Age, Years worked, Sex, Blood sugar, Blood pressure, Heart disease, Alcohol, Smoking, others
Vano et al. (1998)	Spain	Case Study	1997 (~1-8 y)	Occupational - Interventional Radiology; N = 2 radiologists with lens injuries; N = 2 nurses with lens injuries	External: Scattered X-ray	As high as 450-900 mSv/y. About 1-2 mSv per procedure	Measurement on the equipment	Ophthalmological examination; dot-like paranuclear and discrete PSC	Cataracts seen for doses likely above 150 mSv/y; Left eye of interventional radiologist had higher number of opacities	Not reported

Table A.4—(continued).

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Ciraj-Bjelac et al. (2010)	Inter-national	Cohort Sample Screen	Conference April 17-19 2009 (~9 y IC, ~6 y others)	Occupational – Interventional Cardiologists N = 58 exposed; N = 22 control	External: Scattered X-rays	Estimated cumulative ocular dose range 0.02-43 Gy; median 1.1 Gy for IC, 0.64 Gy for nurses	Estimated from workload information as self reported, technical equipment and dosimetry reports	Merriam-Focht method; Grade 0.5 or higher in posterior subcapsular region	PSC in 51% of exposed group compared to 9% in controls; PSC in exposed group OR = 10.3 (2.2-48) RR = 5.6 (1.4-21)	Left/right, Sex
Jacob et al. (2010) Jacob et al. (2013)	France	Cohort Sample Screen	2009-2011 (10+ y)	Occupational – Interventional Cardiologists; N = 106 exposed; N = 99 unexposed	External: Scattered X-rays	Not reported	Not reported	LOCS III; No opacity through stage 5 (severe); opacities localized as cortical, nuclear, posterior subcapsular	No significant difference for either nuclear or cortical lens opacities; PSC lens opacities significantly more frequent among IC (17% vs. 5%, p=0.006) for an OR = 3.9 (1.3-11.4). Risk appeared lower for regular users of protective lead glasses OR = 2.2 (0.4-12.8)	Age, Sex, BMI, Smoking, Diabetes, Myopia, Eyeglasses, Steroids
Mrena et al. (2011)	Finland	Cohort Sample Screen	Not reported (> 15 y)	Occupational – Radiologists; N = 59	External: Scattered X-rays	Whole body; 10-30 mSv group; 30-204 mSv group	Whole body radiation dose measured by film dosimeters worn above lead apron	LOCS II and Scheimpflug imaging (Nidek EAS-1000); opacities	Excess odds ratio for any lens opacity per 10 mSv: 0.13 (-0.02-0.28). Mean dose for those with PSC was 10 mSv.	Age, Sex, Smoking
Vano et al. (2010)	Columbia, Uruguay	Cohort Sample Screen	09/2008 and 04/2009 (1-40 y)	Occupational – Interventional Cardiologists; N = 58; Associated personnel; N = 52; N = 93 unexposed	External: Scattered X-rays	Lens doses of 0.5 mSv per procedure; median 6.0 mSv IC, 1.5 mSv others	Estimated from workload and typical doses per procedure	Modified Merriam-Focht method; eye opacities and early lens changes	IC compared to unexposed RR = 3.2 (1.7-6.1) ($p<0.005$) for PSC	Not reported

Table A.5—Exposure to doses of ionizing radiation: Exposures in flight personnel or astronauts and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Chylack et al. (2009); Chylack et al. (2012)	USA	Cohort Sample Study	2004-2006 (5+ y)	Occupational – Astronauts; N = 171 who flew at least 1 mission in space; Comparison group of N = 53 astronauts who had not flown in space; N = 95 military aircrew personnel; N = 99 non-aircrew ground-based	Cosmic radiation; high-energy protons and heavy ions and secondary particles	Lens dose Overall median 12.9 mSv	TLD measurement	LOCS III	PSC opacity risk for astronauts exposed to higher space radiation dose; OR = 2.33 (1.16-4.26); Per year of age OR = 1.04 (1.01-1.08); Space radiation may be associated with increased PSC area and size. No association with nuclear cataracts.	Age, Sun exposure, occupation, nutritional intake, others
Cucinotta et al. (2001)	USA	Cohort	1977-1988, and more since 1989 (various)	Occupational – astronauts; N = 295 as part of Longitudinal Study of Astronaut Health	Cosmic radiation; high-energy protons and heavy ions and secondary particles	TLD range 0.1-43.2 mGy; Lens dose Range 0.2-91.0 mSv	TLD measurement and reconstructed lens dose from diagnostic x-ray exams	Slit-lamp biomicroscopy under pupil dilation; subjective lens opacification grading system	48 cases of lens opacifications. For lens dose from space radiation only, HR = 2.35 (1.01-5.51) at age 60 y and HR = 2.44 (1.20-4.98) at age 65 y	Diabetes, Renal failure, Steroids, Eye disorders
Jones et al. (2007)	USA	Cohort	1953-2000 (various)	Occupational – Flight personnel (USAF and USN pilots and NASA astronauts); person-years = 13,560,303	Cosmic radiation	Not reported	Employment record	Subjective lens opacification grading system	Hazard ratio (USAF/NASA) HR = 2.6 (1.5-4.8); Hazard ratio USN/NASA) HR = 4.1 (2.1-8.0)	Age
Rafnsson et al. (2005)	Iceland	Case-Control	1996-2001 (Not reported)	Occupational – Airline pilots; N = 274 pilots; N = 374 population-based controls	Cosmic radiation	Range 1-48 mSv	Estimated by employment records, flight profiles, aircraft type	Slit-lamp microscopy and WHO simplified grading system; Nuclear, cortical, central optical zone involvement, or PSC	Nuclear cataract risk if ever been a pilot.	Age, Smoking, Sunbathing habits
Rastegar et al. (2002)	Inter-national	Cohort Sample Study Pilot	Conference November 13-17, 2000	Occupational – former astronauts and cosmonauts; N = 21 exposed; N = 395 comparison (307 retired German Air Force pilots with few flights and ground personnel, 88 eye patients)	Cosmic radiation; high-energy protons and heavy ions and secondary particles	Not reported	Self reported time spent in space	Calibration units of a Schiempflug camera system	Descriptive analysis. Most opacity values for lens posterior capsule and posterior cortex region are above the average values in comparison group.	Not reported

Table A.6—Exposure to doses of ionizing radiation: Exposures in other occupationally exposed persons and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Adams et al. (1983)	USA	Cohort	First exposure prior to 1930 (not reported)	Occupational – Female radium dial workers; N = 813	Internal: Ra Alpha	Two dose groups: 0-50 and ≥50-5,467 µCi (more than ¾ in low dose group)	Extrapolated estimate of radium-226 and radium-228 in blood	Medical records, grading not reported; Cataracts	Prevalence in low-dose group: 14.1%, in high-dose group: 17.1%	Age, Duration of employment
Griffith et al. (1985)	UK	Case Study	1950-1974 (23-47 y)	Occupational – Radiation Worker; N = 1	Internal: Pu ingestion; External: Beta, Gamma, Neutron	External: 70-87 rem Internal: ~ 2 nCi Pu burden	Dosimeters for external dose; internal unknown	Not reported	Premature (47 y old) subcapsular opacities more marked in the region of the posterior pole	Not reported
Hayes and Fisher (1979)	UK	Case Study	1935-1950 (26 y)	Occupational – Radiation Worker; N = 1	External: Gamma from radium-226	Not reported	Employment history	Examination of extracted lenses with slit-lamp photography, thin-section light microscopy, and electron microscopy	Some posterior light scattering noted.	Not reported
Jacobson (2005)	USA	Cohort	Not reported (Not reported)	Occupational – retired DOE actinide exposed workers; N = 97 (with lifetime dosimetric records)	Internal: Actinides External: Gamma	Range 0-600 mSv	Routine monitoring, generally by external dosimeters; worker records	Medical records, grading not reported; Cataracts	Incidence (%) reported, OR = 0.0034+/-0.0016 per mSv (~1.40 at 100 mSv)	Age
Okladnikova et al. (1994)	USSR	Case Study	Not reported (35 y)	Occupational – Nuclear Power Workers; N = 37 with Acute Radiation Syndrome (ARS); N = 1828 Chronic Radiation Syndrome (ChRS)	External: Gamma, Neutron	1 ARS case with 3+ Gy; ChRS Range 0.5 – 8 Gy (2-3 Gy/y)	Not reported	Not reported	One case of occupationally associated radiation cataract (dose >3Gy) reported among 37 ARS cases; No case of radiation cataract in ChRS cases	Not reported
Voelz (1967)	USA	Cohort	1952-1966 (~13 y)	Occupational – Nuclear Power Workers; N = 847 (from long-term eye examination program at National Reactor Testing Station)	External: Gamma, Neutron	Range 0.1-25.3 rem;	Dosimetry badge results	Ophthalmoscope and/or slit-lamp; subjective lens opacification grading system	No lens changes related to occupational radiation exposure were identified.	Not reported

Table A.6—(continued).

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Okladnikova et al. (2007)	USSR	Cohort	1949-1990s (~1-50+ y)	Occupational – Nuclear Power Workers Mayak; N not reported	External: Gamma	Not reported	Not reported	Not reported	Chronic external gamma-radiation does not cause radiation-induced effects when it does not exceed the limit of the yearly dose for personnel. Consequences of acute radiation disease included radiation-induced cataracts at a dose > 4 Gy	Not reported
Shang and Fu (2007)	China	Case-Cohort	Not reported (~1-35 y)	Occupational – Radiation Workers; N = 584 exposed; N = 340 controls	Not reported	Not reported	Years of radiation work, range 4 mos-35 y, mean 11.6 y	Slit-lamp; Opacities and early changes method not reported	Found increase in more advanced (but still early) opacities with longer radiation working time	Not reported

Table A.7—Exposure to doses of ionizing radiation: Exposures in populations or residentially exposed persons and development of cataract.

Reference: First author (year)	Area of Study	Type of Study	Study Period (follow-up time)	Study population characteristics and study size	Type of ionizing radiation exposed	Estimated Dose	Exposure assessment	Outcome assessment	Results or Risk estimates for cataract (95% CI)	Confounder Adjustment
Chen et al. (2001)	Taiwan	Cohort	1983-1997 (<1->5 y)	Residents – contaminated buildings; N = 114	External: Gamma	Cumulative whole body dose range: 1.11 mSv – 1.49 Sv	Taiwan cumulative dose exposure assessment	LOCS III; FLD – minor focal lens defect scores	Increase in FLD in the exposed group found in the anterior cortex, but not the posterior cortex or nucleus	Steroid, Diabetes, Sun, Eye disorder
Day et al. (1995)	Ukraine	Cohort	1991 (5.7 y)	Residents – Chernobyl; N = 991 living in high deposition towns/areas; N = 791 living in no deposition areas	External: Gamma; Internal: Gamma	Estimates of cumulative whole body doses in exposed area range from 29 – 85.6 mSv depending on the assessment method	Self-reported	LOCS III; If ≥2 considered cataract	No differences in cortical opacities. Small excess (3.6 versus 1.1%, p=0.0005) of subclinical posterior subcapsular opacities in exposed versus not exposed children	Exposure level, Sex, Age, Diabetes, Radiotherapy and medications
Hourihan et al. (1999)	Australia	Cross-Section	1992-1994 (various)	Residents – urban population, Blue Mountains Eye Study; N = 3,654	External: X-rays	Not reported	Self-reported	Wisconsin Cataract Grading System	If history of >1 CT scan: OR = 1.0 (0.4-2.7) for PSC; OR = 1.7 (0.8-3.5) for nuclear cataract; OR = 0.9 (0.5-1.6) for cortical cataract	Age, Sex, Education, Diabetes, Others
Hsieh et al. (2010)	Taiwan	Cohort	1998-2002 (1-5 y)	Residents – contaminated buildings; N = 84 (< 20 y)	External: Gamma	0.19 +/- 0.36 Sv	Taiwan cumulative dose exposure assessment	LOCS III; FLD – minor focal lens defect scores	For exposed (>50 mSv) versus unexposed, RR = 1.39	Age, Relocation time
Klein et al. (1993)	USA	Cross-Section	09/1987-05/1988 (various)	Residents – Beaver Dam; Population cross-sectional study – Beaver Dam Eye Study (also assessed medical imaging with X-ray); N = 4,926	External: X-rays	Not reported	Self-reported	Wisconsin Cataract Grading System.	History of head CT scan: OR = 1.45 (1.08-1.95) for PSC opacity; OR = 1.28 (1.02-1.61) for nuclear sclerotic opacity; OR = 1.17 (0.88-1.55) for cortical opacity	Age, Sex
Klein et al. (2000)	USA	Cohort 5 y follow-up study	1993-1995 (various)	Residents - Beaver Dam – Beaver Dam Eye Study 5 year(also assessed medical imaging with X-ray); N = 3,684	External: X-rays	Not reported	Self-reported	Wisconsin Cataract Grading System	Incidence of PSC with history of head CT: 7.2 versus 4.6% without (p<0.005)	Age, Sex, Diabetes

Table A.8–Cataract epidemiology scoring evaluation summary (EPRI, 2014).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Albert et al., 1968	Opacities (Axial/PSC)	0	0	0	-1	0	1	0	1	-1	-1	0	-1	-2	3
Chen et al., 2001; Hsieh et al., 2010	Opacities	0	0	0	-1	-1	0	-1	1	-1	1	-1	0	-3	3
Chmelvsky et al., 1988	Mixed	-1	-1	0	-1	-1	1	0	1	-1	-1	-1	-1	-6	3
Chodick et al., 2008	Mixed (Clinical)	0	0	0	1	1	1	0	0	1	-1	-1	-1	1	2
Chodick et al., 2008	Mixed (Occupational)	0	0	0	1	1	1	0	0	1	-1	-1	-1	1	2
Choshi et al., 1983	Opacities (Axial, PSC)	-1	0	0	-1	-1	0	0	1	-1	1	0	-1	-3	3
Chylack et al., 2009; 2012	PSC	-1	1	0	1	0	1	-1	1	0	1	0	1	4	1
Ciraj-Bjelac et al., 2010	Mixed	-1	0	0	-1	0	1	0	1	-1	0	0	0	-1	3

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Cogan and Dreisler, 1953	Opacities (Axial)	-1	0	-1	-1	-1	1	0	1	-1	0	-1	-1	-5	3
Cogan et al., 1949; Cogan et al., 1950	Opacities (Axial/PSC)	0	-1	-1	0	-1	0	-1	1	1	0	-1	-1	-4	3
Cogan et al., 1952	Opacities	-1	-1	-1	-1	-1	0	-1	1	-1	0	-1	-1	-8	3
Cucinotta et al., 2001	Opacities	-1	0	-1	-1	-1	0	-1	1	-1	0	-1	-1	-7	3
Day et al., 1995	≥ LOCS 2 Cortical	0	-1	-1	1	1	0	0	1	-1	1	0	0	1	2
Day et al., 1995	≥ LOCS 2 PSC	0	-1	-1	1	1	0	0	1	-1	1	0	0	1	2
Griffith et al., 1985	Mixed	-1	1	-1	-1	-1	0	-1	1	-1	-1	-1	-1	-7	3
Hall et al., 1999	Cortical	-1	0	-1	1	0	1	0	1	-1	1	-1	0	0	2

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Hall et al., 1999	PSC	-1	0	-1	1	0	1	0	1	-1	1	-1	0	0	2
Hayes and Fisher, 1979	Mixed	-1	-1	-1	-1	-1	0	0	1	-1	0	-1	-1	-7	3
Hourihan et al., 1999	Cataract	0	-1	-1	1	-1	0	-1	-1	1	0	-1	0	-4	3
Jacob et al., 2010; 2013	Mixed Opacity	0	-1	0	1	0	0	0	1	-1	1	-1	0	0	2
Jacobson, 2005	PSC	-1	1	-1	0	0	1	0	1	0	-1	0	-1	1	2
Junk et al., 2004; Haskal and Worgul, 2004	Opacities (or PSC)	-1	-1	-1	-1	-1	0	-1	1	-1	0	-1	-1	-8	3
Kai et al., 2009	Mixed	-1	0	-1	1	-1	0	-1	0	-1	-1	-1	-1	-7	3
Kleiman et al., 2009	Opacities (or PSC)	-1	-1	-1	-1	-1	0	-1	1	-1	0	-1	0	-7	3

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Klein et al., 1993	Cortical or PSC	0	-1	0	-1	-1	0	-1	1	1	0	-1	0	-3	3
Meecham et al., 1994	Cortical or PSC	-1	1	0	1	-1	1	-1	1	-1	-1	-1	-1	-3	3
Merriam and Focht, 1957	Opacities	-1	1	0	0	-1	1	0	1	0	0	-1	-1	-1	3
Milacic et al., 2009	Mixed	-1	-1	0	1	-1	0	0	1	1	-1	-1	-1	-3	3
Minamoto et al., 2004	Cortical	-1	0	0	1	0	1	0	1	0	1	0	0	3	1
Minamoto et al., 2004	PSC	-1	0	0	1	0	1	0	1	0	1	0	0	3	1
Mrena et al., 2011	Non-nuclear (Cortical or PSC)	-1	1	0	1	0	0	0	1	-1	1	-1	0	1	2
Mrena et al., 2011	Opacities	-1	1	0	1	0	0	0	1	-1	1	-1	0	1	2

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Nadejina et al., 2002	Mixed	-1	0	-1	-1	-1	0	0	1	-1	-1	-1	-1	-7	3
Nakashima et al., 2006	Cortical	-1	0	0	1	0	1	0	1	-1	1	-1	0	1	2
Nakashima et al., 2006	Nuclear Color	-1	0	0	1	0	1	0	1	-1	1	-1	0	1	2
Nakashima et al., 2006	Nuclear Opacity	-1	0	0	1	0	1	0	1	-1	1	-1	0	1	2
Nakashima et al., 2006	PSC	-1	0	0	1	0	1	0	1	-1	1	-1	0	1	2
Nakashima et al., 2013	Mixed (Removal)	-1	0	-1	-1	0	1	0	1	-1	-1	-1	-1	-5	3
Nefzger et al., 1969; Otake and Schull, 1982; Otake et al., 1990; 1996	Opacities	-1	0	-1	-1	-1	1	0	1	0	0	-1	-1	-4	3

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk Assessment	Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Neriishi et al., 2007	Mixed	0	0	0	1	0	1	0	-1	0	-1	-1	-1	-2	3
Neriishi et al., 2012	Mixed (Removal)	-1	0	-1	1	0	1	0	1	-1	-1	-1	-1	-3	3
Neriishi et al., 2012	Mixed (Removal)	-1	0	-1	1	-1	1	0	1	-1	-1	-1	-1	-4	3
Okladnikova et al., 2007	Mixed	0	1	0	0	0	0	0	0	0	-1	0	-1	-1	3
Qvist and Zachaue-Christiansen, 1959	Mixed	-1	0	-1	-1	-1	0	0	1	-1	-1	-1	-1	-7	3
Rafnsson et al., 2005	Nuclear	-1	0	0	1	0	1	0	1	1	0	0	0	3	1
Rastegar et al., 2002	PSC	-1	-1	0	-1	-1	0	0	0	-1	1	-1	-1	-6	3
Shang and Fu, 2007	Opacities	0	-1	-1	-1	-1	0	-1	1	1	0	-1	-1	-5	3

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk Assessment	Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Vano et al., 1998	Opacities (PSC)	-1	0	-1	-1	-1	0	-1	1	-1	-1	-1	-1	-8	3
Vano et al., 2010	Mixed (Cardiologists)	-1	0	0	1	0	0	0	1	-1	0	0	0	0	2
Vano et al., 2010	Mixed (Nurses)	-1	0	0	1	0	0	0	1	-1	0	0	0	0	2
Voelz,1967	Opacities (Cortical/PSC)	-1	1	0	0	-1	0	-1	1	1	0	-1	-1	-2	3
Whalen et al., 2010	Mixed	-1	0	0	1	0	1	0	0	1	-1	-1	-1	-1	3
Wilde and Sjostrand, 1997	Mixed	-1	0	-1	-1	-1	1	0	1	-1	1	-1	-1	-4	3
Worgul et al., 2007; Chumak et al., 2007	Mixed	-1	0	0	1	1	1	0	1	0	0	-1	0	2	1
Worgul et al., 2007; Chumak et al., 2007	Non-nuclear	-1	0	0	1	1	1	0	1	0	0	-1	0	2	1

Table A.8–(continued).

Study References	Cataract Type	Study Design	Dosimetry	Age Adjustment	Confounding	Numerical Risk	Assessment Exposure-response Analysis	Latency	Reporting Bias	Selection Bias	Pathology Method	Blinded Pathology	Cataract Scoring Type	Total Score	Tier
Worgul et al., 2007; Chumak et al., 2007	Nuclear	-1	0	0	1	1	1	0	1	0	0	-1	0	2	1
Worgul et al., 2007; Chumak et al., 2007	PSC	-1	0	0	1	1	1	0	1	0	0	-1	0	2	1
Worgul et al., 2007; Chumak et al., 2007	Superficial Cortical	-1	0	0	1	1	1	0	1	0	0	-1	0	2	1
Yamada et al., 2004	Non-nuclear	-1	0	0	-1	0	1	0	1	0	0	-1	0	-1	3

Appendix B

Evaluating the Epidemiological Evidence Tables

Tables B.1 and B.2 support the discussion in Section 5.3.3 and Table B.3 supports the discussion in Section 5.3.4 of this Commentary.

Table B.1—Cataract epidemiological study: Odds/risk/hazard ratio evaluations.

Tier	Study Reference	Cataract Type	Study Size (N)	Ratio Type	Ratio Value	95% LCL[a]	95% UCL[b]
	Risk calculated at 1 Gy						
1	Worgul et al. (2007)	Cortical (superficial)	8,607 total in study	OR at 1 Gy	1.51	1.09	2.10
1	Minamoto et al. (2004)	Cortical	873 total cases	OR at 1 Gy	1.29	1.12	1.49
2	Hall et al. (1999)	Cortical	573 total, 484 exposed	OR at 1 Gy	1.50	1.15	1.95
2	Nakashima et al. (2006)	Cortical	873 total cases	OR at 1 Gy	1.30	1.10	1.53
1	Worgul et al. (2007)	PSC	8,607 total in study	OR at 1 Gy	1.42	1.01	2.00
1	Minamoto et al. (2004)	PSC	873 total cases	OR at 1 Gy	1.41	1.21	1.64
2	Hall et al. (1999)	PSC	573 total, 484 exposed	OR at 1 Gy	1.49	1.07	2.08
2	Nakashima et al. (2006)	PSC	873 total cases	OR at 1 Gy	1.44	1.19	1.73
1	Worgul et al. (2007)	Mixed	8,607 total in study	OR at 1 Gy	1.70	1.22	2.38
2	Chodick et al. (2008)	Mixed	35,705	RR at 1 Gy	2.98	0.31	5.65
3	Yamada et al. (2004)	Mixed	10,339	RR at 1 Gy	1.11	1.03	1.19
3	Neriishi et al. (2007)	Mixed	3,282 controls, 479 cases	OR at 1 Gy	1.39	1.24	1.55
3	Neriishi et al. (2012)	Mixed (removal)	6,066 total, 1,028 surgery	HR at 1 Gy	1.26	1.17	1.52
3	Nakashima et al. (2013)	Mixed (removal)	3,055 total, 685 cases	OR at 1 Gy	1.33	1.28	1.38
1	Worgul et al. (2007)	Non-nuclear	8,607 total in study	OR at 1 Gy	1.65	1.18	2.30
3	Yamada et al. (2004)	Non-nuclear	3,484 cases	OR at 1 Gy	1.06	1.01	1.11
1	Worgul et al. (2007)	Nuclear	8,607 total in study	OR at 1 Gy	1.07	0.5	2.0
2	Nakashima et al. (2006)	Nuclear opacity	873 total cases	OR at 1 Gy	1.07	0.89	1.30
2	Nakashima et al. (2006)	Nuclear color	873 total cases	OR at 1 Gy	1.01	0.83	1.24
	Not based on exposure level						
1	Day et al. (1995)	Cortical (>= LOCS 2)	991 cases, 791 controls	OR	1.20	0.50	2.60
1	Day et al. (1995)	PSC (>= LOCS 2)	991 cases, 791 controls	OR	2.80	1.30	6.10
1	Rafnsson et al. (2005)	Nuclear	445 total, 71 cases	OR	3.02	1.44	6.35
1	Chylack et al. (2009/2012)	PSC	171	OR	2.23	1.16	4.26
2	Vano et al. (2010)	Mixed	41	RR	3.20	1.70	6.10
2	Vano et al. (2010)	Mixed	28	RR	1.70	0.80	3.70
2	Jacob et al. (2010/2013)	Mixed opacity	106 cases, 99 controls	OR	3.90	1.30	11.40
2	Mrena et al. (2011)	Non-nuclear	59	OR	1.04	0.80	1.28
2	Mrena et al. (2011)	Opacities	59	OR	1.13	0.98	1.28
2	Jacobson (2005)	PSC	113 total, 97 exposed, 20 PSC	OR	4.05	-	-
3	Albert et al. (1968)	PSC opacities	234 cases, 232 controls	OR	5.90	1.40	24.00
3	Milacic et al. (2009)	Mixed	241	RR	4.60	-	-
3	Whalen et al. (2010)	Mixed	14,362	RR	3.20	2.00	5.20
3	Ciraj-Bjelac et al. (2010)	Mixed	67 total, 34 with lens changes	RR	5.60	1.40	21.00

[a]LCL = lower control limit

[b]UCL = upper control limit

Table B.2—Results of odds ratio meta-analysis at 1 Gy by cataract type.

Cataract Type	Odds Ratio (1 Gy)	95 % Confidence Interval	Relevant Studies with the Specific Cataract Type
Cortical	1.37	1.20 to 1.56	Hall, 1999; Nakashima, 2006; Worgul, 2007
	1.50[a]	1.21 to 1.87[a]	
Mixed	1.75	1.26 to 2.46	Chodick, 2008; Worgul, 2007
Nuclear	1.07	0.89 to 1.28	Nakashima, 2006 (nuclear opacity); Worgul, 2007
	1.07[a]	0.5 to 2.0[a]	
PSC	1.45	1.25 to 1.68	Hall, 1999; Nakashima, 2006; Worgul, 2007
	1.45[a]	1.15 to 1.85[a]	

[a]Nakishima 2006 excluded.

Table B.3—Cataract epidemiological study: Threshold evaluation.

Tier	Study Reference	Cataract Type	Study Size (N)	Time since exposure	Threshold (Gy)	95% LCL[a]	95% UCL[b]
	Thresholds with 95% CI reported						
1	Worgul et al. (2007)	Cortical (superficial)	8,607 total in study	12-14 y	0.34	0.18	0.51
2	Nakashima et al. (2006)	Cortical	873 total cases	56 y	0.6	0.0	1.4
1	Worgul et al. (2007)	PSC	8,607 total in study	12-14 y	0.35	0.19	0.66
2	Nakashima et al. (2006)	PSC	873 total cases	56 y	0.7	0.0	2.9
1	Worgul et al. (2007)	Mixed	8,607 total in study	12-14 y	0.50	0.17	0.65
3	Neriishi et al. (2012)	Mixed (removal)	6,066 total, 1,028 surgery	~60 y	0.50	0.10	0.95
3	Neriishi et al. (2012)	Mixed (removal)	6,066 total, 1,028 surgery	~60 y	0.45	0.10	1.05
3	Nakashima et al. (2013)	Mixed (removal)	Up to 685 cases, 3,055 participants	42-60 y	0.41	0.04	1.03
1	Worgul et al. (2007)	Non-nuclear	8.607 total in study	12-14 y	0.50	0.17	0.69
	Thresholds no 95% CI reported						
3	Qvist et al. (1959)	Mixed	56 of 855	~20-40+ y	6.9		
3	Nefzger et al. (1969) Otake and Schull (1982) Otake et al. (1990) Otake et al. (1996)	Mixed opacities	2,125	18-19 y	1.54-1.68		

[a]LCL = lower control limit

[b]UCL = upper control limit

Glossary

acute radiation exposure: Radiation exposure received during a short time period (e.g., hours).

angiography: The radiographic visualization of blood vessels following introduction of contrast material.

as low as reasonably achievable (ALARA): A principle of radiation protection philosophy that requires that exposures to ionizing radiation be kept as low as reasonably achievable, economic and societal factors being taken into account. The ALARA principle is satisfied when the expenditure of further resources would be unwarranted by the reduction in exposure that would be achieved.

ataxia telangiectasia mutated (ATM): Ataxia telangiectasia (AT) is a rare, hereditary, slowly progressive multisystem, neurodegenerative disorder that includes dilation of small blood vessels and recurrent infections. Individuals homozygous defective in the AT mutated (ATM) gene have cancer predisposition and significantly increased radiosensitivity.

bystander effect: In radiobiology, the term is used to describe an effect on cells in which the energy had not been directly deposited. In most instances, the cells so affected were neighbors of the cells directly impacted by the radiation.

cataract: A cataract is a clouding or opacification that occurs in the normally clear lens of the eye. Some cataracts are clinically unimportant and do not impair vision in any way. But, without intervention, cataracts remain the most common cause of blindness.

confidence interval (CI): A measure of the extent to which an estimate of risk, dose or other parameter is expected to lie within a specified interval (e.g., a 95 % confidence interval of a risk estimate means that, based on available information, the probability is 0.95 that the true but unknown risk lies within the specified interval).

cornea: The transparent epithelial structure forming the anterior part of the external covering of the eye.

deoxyribonucleic acid (DNA): Genetic material of cells; a complex molecule of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases which are arranged as two long chains that twist around each other to form a double helix joined by hydrogen bonds between the complementary components.

deterministic effects: Detrimental health effects for which the severity varies with the dose of radiation (or other toxic substance), and for which a threshold usually exists (i.e., causally determined by preceding events). ICRP Publication 103 has restated this as: "Injury in a population of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. Also termed tissue reactions. In some cases, deterministic effects are modifiable by post-irradiation procedures including biological response modifiers." It is common for deterministic effects to be termed tissue reactions.

detriment: Measure of stochastic effects from exposure to ionizing radiation that takes into account the probability of fatal cancers, probability of severe hereditary effects in future generations, probability of nonfatal cancers weighted by the lethality fraction, and relative years of life lost per fatal health effect.

dose: General term denoting the mean energy imparted from ionizing radiation to a tissue or organ from either an external source or from radionuclides in the body. When unspecified, dose refers to the quantity of absorbed dose, measured in gray (1 Gy = 1 $J \cdot kg^{-1}$) or rad (1 rad = 100 $ergs \cdot g^{-1}$). Depending upon the context in which it is used, the generic term dose may also refer to equivalent dose, effective dose or other dose-related quantities.

dose limit: A limit on radiation dose that is applied for exposure to individuals in order to prevent the occurrence of radiation-induced deterministic effects or to limit the probability of radiation-induced stochastic effects to an acceptable level.

dose rate: Dose per unit time; often expressed as an average over some time period (e.g., a year).

dosimetry: The science or technique of determining radiation dose.

electrons: Subatomic charged particle. Negatively charged particles are parts of atoms. Both negatively and positively charged electrons may be expelled from a radioactive atom when it disintegrates.

exposure: Most often used in a general sense meaning to be irradiated. When used as the specifically defined radiation quantity, exposure is a measure of the ionization produced in air by x or gamma radiation. The unit of exposure is coulomb per kilogram ($C\ kg^{-1}$). The special unit for exposure is roentgen I, where $1\ R = 2.58 \times 10^{-4}\ C\ kg^{-1}$.

fluoroscopically-guided interventional (FGI) procedures: An interventional diagnostic or therapeutic procedure performed via percutaneous or other access routes, usually with local anesthesia or intravenous sedation, which uses external ionizing radiation in the form of fluoroscopy to: localize or characterize a lesion, diagnostic site, or treatment site; monitor the procedure; and, control and document therapy.

fluoroscopy (fluoro): The process of producing a real-time image using x rays. The machine used for visualization, in which the dynamic image appears in real time on a display screen (usually video) is a fluoroscope.

fractionation: The delivery of a given total dose of radiation as several smaller doses, separated by intervals of time.

gamma radiation: Electromagnetic radiation emitted in de-excitation of atomic nuclei, and frequently occurring in decay of radionuclides. Also called gamma ray and sometimes shortened to gamma (e.g., gamma-emitting radionuclides) (see **photon** and **x ray**).

genetic effects: Changes in reproductive cells that may result in detriment to offspring.

gray (Gy): The SI special name for the unit of the quantities absorbed dose and air kerma. 1 Gy = 1 J kg^{-1}.

heavy ions: Synonymous with heavy charged particles, heavy nuclei, high-Z particles, or HZE particles [see **high atomic number, high-energy (HZE) particles**].

heritable effects: Changes in reproductive cells that may be passed on to offspring of persons or animals. Often called genetic effects (see **genetic effects**).

high atomic number, high-energy (HZE) particles: Heavy ions having an atomic number greater than that of helium (such as boron, carbon, nitrogen, neon, argon, or iron ions that are positively charged) and having high kinetic energy.

HZE: A heavy ion having an atomic number greater than that of helium and having high kinetic energy.

incidence: The rate of occurrence of a disease, usually expressed in number of cases per million.

interventionalist: In this Report, an individual who has been granted clinical privileges to perform or supervise FGI procedures in the facility, and who is personally responsible for the use of radiation during a specific FGI procedure in that facility.

ionization: The process by which a neutral atom or molecule acquires a positive or negative charge through the loss or gain of an orbital electron.

ionizing radiation: Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions. Examples include alpha radiation, beta radiation, gamma or x rays, and cosmic rays. Minimum energy of ionizing radiation is a few electron volts (eV); $1\ \text{eV} = 1.6 \times 10^{-19}$ J.

irradiation: Exposure to ionizing or nonionizing radiation (see also exposure).

justification: The part of the decision-making process in which the options that are expected to do more good than harm are identified.

lifetime risk: The probability during one's lifetime of expressing a given health outcome.

LET: Linear-energy transfer, the average amount of energy lost per unit of particle track length and expressed in keV μm^{-1}.

low-LET: Radiation having a low linear-energy transfer (e.g., electrons, x rays, and gamma rays).

high-LET: Radiation having a high linear-energy transfer (e.g., protons, alpha particles, heavy ions, and the interaction products of fast neutrons).

meta-analysis: In statistics evaluating epidemiological studies, this comprises the use of statistical methods for contrasting and combining results from different studies reported in the literature in the hope of identifying patterns among study results, sources of disagreement among those results, or other interesting relationships that may come to light in the context of multiple studies.

neutrons: Particles with a mass similar to that of a proton, but with no electrical charge. Because they are electrically neutral, they cannot be accelerated in an electrical field.

noncancer: Health effects other than cancer (e.g., cataracts, cardiovascular disease) that occur in the exposed individual.

occupational dose: The dose received by an individual in a restricted area, or in the course of employment in which the individual's duties necessarily involve exposure to radiation (medical doses involving diagnosis or treatment of the exposed individual that are not required as a condition of employment are excluded).

odds ratio (OR): The ratio of the number of people incurring an event to the number of people having non-events.

optimization: Although the term ALARA is used as equivalent to or in replacement of the term optimization used in ICRP Publication 121 (ICRP, 2013), ALARA is only a part of the concept of optimization. The entire concept implies, more precisely, keeping patient exposure to the minimum necessary to achieve the required medical objective (either diagnostic or therapeutic) when applied to the clinical use of ionizing radiation.

photon: Quantum of electromagnetic radiation, having no charge or mass, that exhibits both particle and wave behavior, such as a gamma or x ray.

posterior subcapsular (PSC) cataract: Posterior subcapsular cataracts begin in the back of the lens, adjacent to the capsule in which the lens is situated. PSC have been associated with steroids, diabetes and ionizing radiation exposure.

protons: The nucleus of the hydrogen atom. Protons are positively charged.

radionuclide: An unstable (i.e., radioactive) nuclide. A species of atom characterized by the constitution of its nucleus (i.e., the number of protons and neutrons) and the excess energy available in the unstable nucleus.

relative biological effectiveness (RBE): For a specific radiation (A), the ratio of absorbed dose of a reference radiation required to produce a specific level of response in a biological system to absorbed dose of radiation (A) required to produce an equal response. The reference radiation normally is x or gamma rays with an average linear energy transfer of 3.5 keV μm^{-1} or less. Relative biological effectiveness generally depends on dose, dose per fraction if the dose is fractionated, dose rate, and biological endpoint.

relative risk: The ratio of the risk of a given disease in those exposed to the risk of that disease in those not exposed.

risk: Probability of harm, combined with potential severity of that harm.

risk coefficient: The increase in the annual incidence or mortality rate per unit dose: (1) absolute risk coefficient is the observed minus the expected number of cases per person year at risk for a unit dose, and (2) the relative risk coefficient is the fractional increase in the baseline incidence or mortality rate for a unit dose.

Scheimpflug principle: Describes an optical imaging condition, which allows documentation of an obliquely tilted object with the maximally possible depth of focus and minimal image distortion under given conditions. It is a geometric rule that describes the orientation of the plane of focus of an optical system (such as a camera) when the lens plane is not parallel to the image plane. The principle can be applied to images of the eye with a camera at an angle to a slit-beam creating an optic section of the eye from the anterior corneal surface to the posterior lens surface..

sclera: The tough supporting tunic of the eyeball covering it except for the segment covered by the cornea.

severe hazard: A hazard that has the potential to cause death, severe injury, or occupational illness, significant risk to the public, extensive environmental harm, or significant property damage.

severity: In the context of this Report, the quality or power of afflicting, distressing, or paining an individual or organ system from exposure to an environmental insult, such as ionizing radiation, that in the extreme would cause pain or anguish and possible clinical sequelae in the individual.

sievert (Sv): Special name for the SI unit of dose equivalent, equivalent dose, and effective dose. $1\ \mathrm{Sv} = 1\ \mathrm{J\ kg^{-1}}$.

somatic effect: Biological effects (of radiation or otherwise) that occur in the exposed individual, as opposed to genetic (or heritable) effects which occur in the descendants of exposed individuals due to genetic mutations in the germline.

stochastic: Describes random events leading to effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) is a direct function of dose; these effects are commonly regarded as having no threshold; cancer and hereditary effects are regarded as being stochastic.

telangiectasia: Dilation of capillary vessels and very small arteries.

tissue reaction (deterministic effect): Injury in populations of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. In some cases, tissue reactions are modifiable by post-irradiation procedures including

biological response modifiers. Examples for irradiation of the embryo or fetus are radiation-induced malformations and mental retardation in the live-born child.

vitreous: The semifluid, transparent substance which lies between the retina and the lens of the eye.

Symbols, Abbreviations and Acronyms

ALARA	as low as reasonably achievable
AHS	Adult Health Study (RERF)
ALI	annual limit on intake
ANSI	American National Standards Institute
ARS	acute radiation syndrome
ATM	ataxia-telangiectasia mutated gene
EU BSS	European Basic Safety Standard
BWR	boiling water reactor
CED	committed effective dose
ChRS	chronic radiation syndrome
CNS	central nervous system
CT	computed tomography
DDREF	dose and dose-rate effectiveness factor
DSB	double-strand break
EAR	excess absolute risk
EDEX	external dose equivalent from external exposure
EPRI	Electric Power Research Institute
ERR	excess relative risk
FGI	fluoroscopically-guided interventional procedure
HZE	heavy ion ($Z > 2$) that is highly energetic
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IR	interventional radiology
LDE	lens of the eye dose equivalent
LET	linear energy transfer
LNT	linear nonthreshold assumption or hypothesis model
NCRP	National Council on Radiation Protection and Measurements

NIR	non-ionizing radiation
PSC	posterior subcapsular
RBE	relative biological effectiveness
REL	recommended exposure limit
RELID	retrospective evaluation of lens injuries and dose
RERF	Radiation Effects Research Foundation
SSB	single strand break
TBI	total body irradiation
TEDE	total effective dose equivalent
VIC	vision-impairing cataract

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4291 **Scientific Committee**

Eleanor A. Blakely, Co-Chair, is a Senior Staff Biophysicist at the Lawrence Berkeley National Laboratory with more than 38 y of professional experience in molecular, cellular and animal radiobiological research directed at studying the basic mechanisms of radiation responses, with an emphasis on charged particle radiation effects. She also holds a Faculty Affiliate Appointment in the Department of Radiological Health Sciences at Colorado State University, Fort Collins, and is a Clinical Professor of Radiation Medicine (nontenured) at Loma Linda University, School of Medicine, Loma Linda, California. Dr. Blakely earned a PhD in Physiology from the University of Illinois at Champaign-Urbana as a U.S. Atomic Energy Commission Special Fellow in Radiation Science and Protection. Her professional activities have included service on advisory panels for several hospitals, universities, and numerous federal agencies including the U.S. Department of Energy, the National Institutes of Health (NIH), and the National Aeronautics and Space Administration (NASA); on Editorial Boards for several journals: Space Power, Radiation Research, and Journal of Radiation Research; Appointed Member, Diagnostic Radiology Study Section-Division of Research Grants, NIH; Advisory Committee Member, International Atomic Energy Agency; Scientific Director, NASA Space Research Summer School; and Elected Officer of the Radiation Research Society: Biology Councilor and Secretary-Treasurer. In 2000 she was elected to NCRP, and has served on Scientific Committee (SC) 75 that produced NCRP Report No. 132, Radiation Protection Guidance for Activities in Low-Earth Orbit; and SC 1-7 that produced NCRP Report No. 153, Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit. She has received several awards including the Robert Emerson Graduate Teaching Award, School of Life Sciences, University of Illinois, the Lawrence Berkeley Laboratory Outstanding Performance Award, the DOE Office of Science Outstanding Mentor Award, the Lawrence Berkeley Laboratory Technology Transfer Award, and a RD100 award from Research and Development Magazine. In 2011, she was chosen to give the NCRP 35th Lauriston S. Taylor Lecture. She serves as consultant in support of clinical radiotherapy trials, and of issues pertinent to radiation protection.

Lawrence T. Dauer, Co-Chair, is Associate Attending Physicist, and Associate Clinical Member in the Departments of Medical Physics and Radiology at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City. He earned an MS in Health Physics and a PhD in Adult Education. He is certified in comprehensive health physics by the American Board of Health Physics and is past chair of the Radiation Safety Committee of the American Association of Physicists in Medicine (AAPM), past President of the Greater New York Chapter of the Health Physics Society (HPS), Executive Council Member of the Medical Physics Section of the HPS, a Member of the

joint Safety Committee of the Society for Interventional Radiology and the American College of Radiology, past council member of the Radiological and Medical Physics chapter of the AAPM, and a member of editorial and review boards of several scientific journals. He serves as the Chair of the MSKCC Emergency Management Committee, a member of the Radiation Injury Treatment Network. In 2005, he received the Elda E. Anderson Award from the Health Physics Society. He is currently a Council member of the NCRP. He also serves as a member of International Commission on Radiological Protection Committee 3 on protection in medicine, a member of the science council for the International Organization for Medical Physics, and was on the program committee for the International Atomic Energy Agency's International Conference on Radiation Protection in Medicine—Setting the Scene for the Next Decade. He has several publications in the topical areas of radiation protection and risks in the fields of detection, radiology, interventional radiology, x-ray imaging, nuclear medicine, and radiation oncology, as well as surgery and medicine.

Elizabeth Ainsbury is a Principal Radiation Protection Scientist at the Public Health England (PHE) Centre for Radiation, Chemical and Environmental Hazards, with 7 y of experience in the field of biomarkers of radiation exposure, in particular in mathematical and statistical analysis of data. In recent years, Dr. Ainsbury has taken a growing interest in radiation induced cataracts and has helped to initiate a growing scientific and public health policy research program at PHE, with the core aim of contributing both to scientific understanding of the mechanisms of cataract induction and providing the context for appropriate translation of the basic research to current and future radiation protection policy and practise. Recent work includes publishing a comprehensive review of the current status of knowledge in the field, completing a survey of occupational lens doses for U.K. medical sector workers, reviewing the implications of the International Commission on Radiological Protection's recent proposals for U.K. stakeholders. Dr. Ainsbury is also participating in a number of ongoing collaborative research projects focussed on low dose-induced early lens changes.

Joseph R. Dynlacht is an Associate Professor in the Department of Radiation Oncology at the Indiana University School of Medicine and a member of the Experimental Therapeutics Division of the Indiana University Simon Cancer Center. He received a BS degree in Biology from Florida State University and a PhD in Cellular and Molecular Radiobiology from Colorado State University before completing a post-doctoral fellowship at the University of California, San Francisco. Dr. Dynlacht teaches a course entitled "Radiation and Cancer Biology" to radiation oncology residents and radiation therapy students annually, and is Co-director of the School of Medicine's Clinical Problem Solving course for first year medical students. He received a Trustee Award for his teaching efforts and involvement in resident training in 2012. Dr. Dynlacht's research interests include the development of agents that reduce normal tissue damage after irradiation (specifically damage to the lens),

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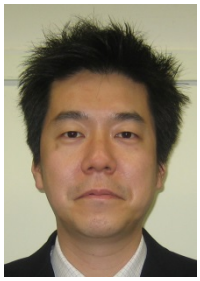
Lee Goldstein, Consultant,



Nobuyuki Hamada, Consultant, is a Research Scientist at the Radiation Safety Research Center in the Central Research Institute of Electric Power Industry (CRIEPI). For over 16 y, he has conducted a series of radiobiological studies. His past projects include nontargeted effects and heavy-ion effects. His ongoing projects aim to elucidate the radiation response of primary normal human lens epithelial cells and to establish a mouse model system allowing a life-long chase of damaged cells. He has also been involved in several health physics studies.

Currently, Dr. Hamada is Assistant Scientific Secretary of the International Commission on Radiological Protection (ICRP), a member of Expert Group on Radiation Protection Science for the Organization for Economic Co-operation and Development/Nuclear Energy Agency/Nuclear Energy Agency/Committee on Radiation Protection and Public Heath, Consultant for NCRP Scientific Committee 1-23 on Guidance on Radiation Dose Limits for the Lens of the Eye, and a member of Expert Committee on Radiation Protection of the Ocular Lens for Japan Health Physics Society. He serves as Associate Editor for the Annals of the ICRP and editorial board members for several scientific journals.

Dr. Hamada received a BSc in radiological sciences from Ibaraki Prefectural University of Health Sciences, and his MSc and PhD in pharmaceutical sciences from Nagasaki University. He was also a visiting PhD student at the Gray Cancer Institute. He was a postdoctoral fellow at the National Institute of Radiological Sciences and in Tohoku University Institute of Development, Aging and Cancer, and a COE Associate Professor in Gunma University Graduate School of Medicine. He joined CRIEPI in 2010. Since 2001, he has published 77 papers in peer-reviewed international journals, which have gained over 1,600 citations. Since 2006, he has received 16 awards, including the Michael Fry Research Award of the Radiation Research Society.

David G. Hoel is a Distinguished University Professor in the Department of Medicine at the Medical University of South Carolina in Charleston and Principal Scientist at Exponent, Inc. He received an AB in mathematics and statistics from University of California at Berkeley, a PhD in mathematical statistics from University of North Carolina in Chapel Hill, and was a post-doctoral fellow in preventive medicine at Stanford University. Prior to joining the Medical University of South Carolina Dr. Hoel was Division Director for Risk Assessment at the National Institute of Environmental Health Sciences in North Carolina. Dr. Hoel is a Fellow of the American Academy of Arts and Sciences, a member of the Institute of Medicine of the National Academies, and a National Associate of the National Academies. His awards include the Spiegleman Gold Medal in Public Health and the Ramazzini Award in Environmental and Occupational Health. He has served on numerous governmental and National Academy committees including the EHC and RAC of U.S. Environmental Protection Agency's Science Advisory Board and the BEIR V committee of the National Academy of Sciences. He was a member of International Agency for Research on Cancer's committee on ionizing radiation (report 100D) and contributed to the United Nations Scientific Committee on the Effects of Atomic Radiation 2006 report. Dr. Hoel's research has focused on risk assessment methods with particular interest in low-dose radiation exposures and cancer. This work has included stays in Hiroshima as a Director at Radiation Effects Research Foundation (RERF) and currently is a member of RERF's Scientific Advisory Committee. Until a year ago, he was a member of National Academies' Board on Nuclear and Radiation Studies. Finally he has testified several times in both the House and Senate on human health issues.

Barbara E.K. Klein graduated from Brooklyn College with BS in 1965 and from New York University School of Medicine in 1969. She then completed a medical internship and Master of Public Health before completing ophthalmologic training with a subspecialty in glaucoma. She has been involved in population based studies of age-related eye disease and of diabetes and complications since 1978. She is Professor of Ophthalmology and Visual Sciences at the University of Wisconsin-Madison having been on the faculty there since 1980.

Don Mayer serves at Indian Point Energy Center as Director of Indian Point Unit 1 and Special Projects. Mr. Mayer has more than 30 y of experience in the nuclear power industry. He joined the New York Power Authority (NYPA) in 1982 as a radiological engineer at Indian Point Unit 3 and worked in the radiation protection field for 20 y, including as Radiation Protection Manager. Mr. Mayer also spent approximately 2 y as General Manager of Unit 3 plant services under NYPA where he was responsible for site security, emergency planning, radiation protection licensing and corrective action programs. Since that time Mayer has lead various major projects for Entergy including site integration after Entergy's plant acquisition of Unit 2 and led the Unit 1 project culminating in the removal and dry storage of the spent fuel.

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Mr. Mayer holds a BS in Biology from Syracuse University, an MS in Radiological Science from the University of Lowell; a Master's in Business Administration from Mt. St. Mary's College and is a Certified Health Physicist.

Christina R. Prescott is an assistant professor at the Wilmer Eye Institute of Johns Hopkins School of Medicine. She specializes in medical and surgical management of complex cataracts and serious corneal diseases. She is active in teaching the Wilmer residents and fellows both clinically and surgically and has developed and implemented a new surgical curriculum utilizing surgical simulators, laboratory training, and checklists. Her own surgical practice focuses on cataract surgery, including laser-assisted cataract surgery and specialty lenses, and modern forms of corneal transplants such as Descemet's stripping endothelial keratoplasty and deep anterior lamellar keratoplasty.

Dr. Prescott received her BA in biophysics from Columbia University and earned her MD and PhD (neuroscience) from the University of Colorado Health Sciences Center. She completed an internship at the Hospital of St. Raphael in New Haven, Connecticut, and her ophthalmology residency at Yale University. Dr. Prescott then completed a fellowship in cornea, refractive surgery and external disease at the Massachusetts Eye and Ear Infirmary of Harvard University.

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Gayle E. Woloschak is a Professor of Radiation Oncology and Radiology at Northwestern University Feinberg School of Medicine in Chicago. She and her group have been involved in studies of molecular consequences of radiation exposure, late tissue effects associated with radiation, and the use of radiation-inducible nanomaterials for cancer imaging and therapy. Dr. Woloschak also teaches radiation biology to radiation oncology and radiology residents, cardiology trainees, and graduate students and manages the Advanced Grant Writing Workshop for the Radiological Society of North America (RSNA). She earned her PhD in medical sciences from the University of Toledo (Ohio) and did post-doctoral studies in molecular biology at the Mayo Clinic. She has served on review panels for various federal agencies including the National Institutes of Health, the National Aeronautics and Space Administration, the U.S. Department of Energy, RSNA, the U.S. Army Medical Research and Materiel Command, and others. She is currently an associated editor for Radiation Research, the International Journal of Radiation Biology, PLOS One, and Nanomedicine. She is a member of NCRP Program Area Committee 1, has served on organizational committees for several NCRP meetings, and has been involved in committees for several NCRP reports. She is currently Vice-President Elect for the Radiation Research Society.

Cindy Flannery is a Senior Health Physicist in the Office of Federal and State Materials and Environmental Management Programs at the U.S. Nuclear Regulatory Commission (NRC). In this position, she serves as office lead for safety culture activities and is also a member of the working group tasked with developing the regulatory basis for the revisions to the radiation protection regulations (10 CFR Part 20). She joined NRC in 2004 and served as the Team Leader of the Medical Radiation Safety Team for 5 y. Ms. Flannery has 20 y experience as a health physicist in the medical industry as well as in military and research organizations. Prior to NRC, she served as Branch Chief and Radiation Safety Officer for the Defense Threat Reduction Agency and as the Radiation Safety Officer/Health Physicist at the Food and Drug Administration. Before her employment by the federal government, she worked as a Health Physics Consultant and as a Nuclear Medicine Technologist. Ms. Flannery graduated from Georgetown University with an MS in Health Physics and from the University of Wisconsin with a BS in Nuclear Medicine Technology. She was certified by the American Board of Health Physics in 2001. She currently serves as Chair of the American Board of Health Physics Part I Examination Panel.

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Michael P. Grissom, Staff Consultant, is a Technical Staff Consultant for NCRP and is the President of MPG-HP, Inc., Riverside, California a private consulting firm. He is a recognized authority on operational health physics issues, particularly related to radiation protection in management, military, reactor, medical, and accelerator operations. During 20 y of service in the U.S. Navy, Mr. Grissom served as a Radiation Safety/Laser Safety Officer (hospital) and provided Radiation Health Officer support to the Naval Radiological Controls Program (propulsion, industrial and weapons). Mr. Grissom conducted research in biophysics and radiobiological effects at the Armed Forces Radiobiology Research Institute, Bethesda, Maryland as a junior then senior scientist and served as the Director of Medical Records Search for the Navy Nuclear Test Personnel Review, Office of the Chief of Naval Operations, Washington, DC. Mr. Grissom provided support to the Effluent and Dose Assessment Group, Three Mile Island Unit 2 Recovery Team in 1979 to 1980. He has delivered numerous presentations at scientific and professional society meetings. In 2012, Mr. Grissom became a Fellow of the Health Physics Society (HPS). He previously received the HPS Volunteer Award for services associated with the Medical Health Physics Section and is a Past President of the HPS Accelerator Section. He also served in a number of positions for Stanford University over a period of 16 y at the Stanford Linear Accelerator Center National Accelerator Laboratory, Menlo Park, California including Department Head, Operational Health Physics, and Assistant Associate Director for Environment, Safety and Health.