From:	Katherine Gaudreau <personal information redacted>
Sent:	July 16, 2019 11:47 AM
To:	Consultation (CNSC/CCSN)
Cc:	Douglas Boreham; Christopher Thome
Subject:	NOSM Comments on Proposed Changes to the Equivalent Dose Limits for the Lens of the Eye
Attachments:	NOSM Comment on Proposed Radiation Protection Changes 16JUL2019.pdf

Dear Mr. Brian Torrie,

Please find attached a letter and publication from the Northern Ontario School of Medicine in response to the proposed changes to the equivalent dose limits to the lens of the eye as detailed in the Canada Gazette, Part 1, Volume 153 dated June 15, 2019.

Sincerely,

Katherine Gaudreau, RN, BNSc, MSc
Epidemiologist, Northern Ontario School of Medicine
personal information redacted

Northern Ontario
School of Medicine
École de médecine
du Nord de l'Ontario
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July 16, 2019

Brian Torrie
Director General, Regulatory Policy Directorate
Canadian Nuclear Safety Commission
280 Slater Street
P.O. Box 1046, Station B
Ottawa, ON K1P 5S9

Dear Mr. Brian Torrie,

Please find enclosed our comments on the proposed revisions to *Regulations Amending Certain Regulations Made Under the Nuclear Safety and Control Act (Radiation Protection)*, specifically regarding the revision to the equivalent dose limits for the lens of the eye to 20 mSv per year (100 mSv over a defined 5-year period, with no single year exceeding 50 mSv) and a lower threshold dose estimate for deterministic effects of 0.5 Gy as published in *Canada Gazette*, Part 1, Volume 153, dated June 15, 2019. Overall, there is no conclusive scientific evidence to justify lowering the existing dose limits and thresholds.

Review of Past Human Epidemiological Studies on Radiogenic Cataract Formation

We have recently published a review of human epidemiological studies of radiogenic cataract formation (attached) (1). This publication evaluated data from a number of different exposure cohorts, including atomic bomb survivors, radiotherapy patients, medical workers and astronauts. The publications that were reviewed were the same studies that were cited by the ICRP in support of lowering the cataract threshold dose. It was determined that the calculated cataract risk in many of the data sets did not correlate to the cataract risk from occupational exposures due to differences in the type of exposure, the age at exposure, the radiation quality and the latency period. For example, atomic bomb survivors were exposed acutely while most occupational exposures are chronic or protracted. Additionally, many of the data sets focused on childhood exposures, as opposed to adult worker populations, and there are known differences in the lens radiosensitivity with age. Lastly, cataract risk from exposure to high linear energy transfer (LET) radiation in space is very different than the low LET occupational exposures on earth. Overall, in this review we concluded that with chronic low LET radiation exposures there is no epidemiological evidence to justify lowering the threshold dose for deterministic effects to the lens of the eye down to 0.5 Gy. There is no direct evidence that exposures to low doses (<100 mSv) of chronic low LET radiation (occupational exposures) increases cataract risk. Consequently, lowering annual dose limits is not supported by scientific epidemiological data.

Epidemiological Study of the Association between Head CT Scans and Cataracts

The International Atomic Energy Agency (IAEA) estimates that typical doses to the lens of the eye from routine head Computed Tomography (CT) scans varies between 25 mGy and 103 mGy (2). This estimate of a single acute low dose radiation exposure to the lens of the eye is similar in magnitude (but not in dose rate) to the proposed annual equivalent dose limit to the lens of the eye.

Over the past two years, we completed an epidemiological study to determine if there is a correlation between radiation exposure to the lens of the eye from head CT scans and the frequency and timing of getting cataract surgery. By accessing the data holdings of the Institute for Clinical Evaluative Sciences, we were able to identify and obtain information about all Ontarians who received head CT scans and had cataract surgery from 1994 to 2015. This research provides important information relevant to making an informed decision concerning revising regulatory limits for radiation-induced cataracts.

Using a dataset of 16 million Ontarians, we compared the time to getting cataract surgery for the 3 million individuals who had received at least one head CT scan to the 13 million individuals that had received no head CT scans. We looked at the number and timing of the head CT scans received prior to having cataract surgery. We found no evidence of a dose-response relationship between head CT scans and the incidence of first cataract surgery.

It is expected that there would be a significant lag time between radiation exposure at low doses and the development of radiogenic cataracts (1). We found that after a 5-year period following one to three head CT scans, there is a small (3-8%) increase in the risk of first cataract surgery. However, in some of the higher exposure groups (4, 6, 8, or 10 head CT scans) there was a significant decrease in cataract risk (4-17%) compared to unexposed individuals. Adding additional lag times of seven and ten years respectively showed no change in the risk. No dose-response relationship was seen between the number of head CT scans received and first cataract surgery with lag times of up to ten years.

This epidemiological study uses well-defined exposure and outcome data obtained from billing records for publicly funded health care services in Ontario over 22 years. As a result of using administrative data, we have completed the largest epidemiological study to date of the association between low-dose radiation exposure and cataract formation. The use of a population survey approach has allowed us to examine exposure groups with higher counts of head CTs than previous similar work.

If additional dose from more head CTs was associated with cataract surgery risk, we would expect to see an increase in risk with an increasing number of head CTs (i.e. a dose-response). Additionally, there can be significant lag time between radiation exposure and cataract formation (1), however with the addition of up to ten years of lag time there was a reduction in risk with increasing numbers of head CT scans. The lack of a dose response and the attenuation of the risk with increasing number of head CTs does not support a causative association between low-dose radiation exposure to the lens of the eye and cataract formation.

We are in the process of preparing our data for peer review and publication. We hope that you will consider the above results once published prior to making a decision on the proposed changes to the equivalent dose limits for the lens of the eye. Based on current science, the cost versus the benefits of such changes needs to be considered.

Sincerely,

Dr. Chris Thome
Assistant Professor, Medical Sciences Division (MSD),
Northern Ontario School of Medicine (NOSM)

Dr. Douglas Boreham
Division Head, MSD,
NOSM

Ms. Katherine Gaudreau
Epidemiologist, NOSM

References

1. Thome C, Chambers DB, Hooker AM, Thompson JW, Boreham DR. Deterministic Effects to the Lens of the Eye Following Ionizing Radiation Exposure: is There Evidence to Support a Reduction in Threshold Dose? Health Phys. 2018 Mar;114(3):328–43.

2. Radiation protection of patients with cataract [Internet]. International Atomic Energy Agency. 2019 [cited 2019 Jul 2]. Available from: https://www.iaea.org/resources/rpop/health-professionals/radiology/cataract/patients

Review Paper

DETERMINISTIC EFFECTS TO THE LENS OF THE EYE FOLLOWING IONIZING RADIATION EXPOSURE: IS THERE EVIDENCE TO SUPPORT A REDUCTION IN THRESHOLD DOSE?

Christopher Thome,*† Douglas B. Chambers,‡ Antony M. Hooker,§
Jeroen W. Thompson,** and Douglas R. Boreham*†**

***Abstract*—Ionizing radiation exposure to the lens of the eye is a known cause of cataractogenesis. Historically, it was believed that the acute threshold dose for cataract formation was 5 Sv, and annual dose limits to the lens were set at 150 mSv. Recently, however, the International Commission on Radiological Protection has reduced their threshold dose estimate for deterministic effects to 0.5 Gy and is now recommending an occupational limit of 20 mSv per year on average. A number of organizations have questioned whether this new threshold and dose limit are justified based on the limited reliable data concerning radiation-induced cataracts. This review summarizes all of the published human epidemiological data on ionizing radiation exposure to the lens of the eye in order to evaluate the proposed threshold. Data from a variety of exposure cohorts are reviewed, including atomic bomb survivors, Chernobyl liquidators, medical workers, and radiotherapy patients. Overall, there is not conclusive evidence that the threshold dose for cataract formation should be reduced to 0.5 Gy. Many of the studies reviewed here are challenging to incorporate into an overall risk model due to inconsistencies with dosimetry, sample size, and scoring metrics. Additionally, risk levels in the studied cohorts may not relate to occupational scenarios due to differences in dose rate, radiation quality, age at exposure and latency period. New studies should be designed specifically focused on occupational exposures, with reliable dosimetry and grading methods for lens opacities, to determine an appropriate level for dose threshold and exposure limit.**
Health Phys. 114(3):328–343; 2018

Key words: analysis, risk; epidemiology; exposure, occupational; regulations

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The authors declare no conflicts of interest.

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INTRODUCTION

THE INTERNATIONAL Commission on Radiological Protection (ICRP) provides recommendations for annual occupational dose limits from ionizing radiation exposure. Effective dose limits are 20 mSv per year, averaged over five consecutive years, with a maximum of 50 mSv in a single year. In addition to effective dose limits, equivalent dose limits have been applied to specific organs such as the skin and eye. These organs have been identified as radiosensitive or have lower tissue weighting factors and therefore may not be protected from deterministic effects by effective dose limits.

Dose limits to the lens of the eye were first evaluated in 1977 in ICRP Publication 26 (ICRP 1977). It was determined that an equivalent dose of 15 Sv, accumulated over an occupational lifetime, would not produce any vision impairing opacities, and dose limits were set at 300 mSv per year. Several years later, this dose limit was reduced following the 1980 ICRP meeting (ICRP 1980) and the release of ICRP Publication 41 (ICRP 1984). It was estimated that the threshold for vision-impairing cataracts was 5 Sv for a single acute exposure and greater than 8 Sv for fractionated or protracted exposures. Thresholds were slightly lower for detectable opacities (not vision impairing). It was recommended that annual occupational dose limits to the eye be set at 150 mSv. Radiation exposure to the eye was reevaluated in 1990 in ICRP Publication 60 (ICRP 1991) and in 2007 in ICRP Publication 103 (ICRP 2007). In both of these publications, the annual dose limit of 150 mSv remained unchanged. However, in ICRP 103 it was acknowledged that new data concerning cataract formation at lower doses was forthcoming, and a task force was established to assess whether this dose limit should change (ICRP 2007). The findings of the task force were published in 2012 in ICRP Publication 118 (ICRP 2012). The threshold for cataract formation was lowered 10-fold to an absorbed dose of 0.5 Gy[††] from low linear energy transfer (LET) radiation.

Interestingly, unlike earlier publications, no adjustment was made for dose rate, and the same threshold of 0.5 Gy was applied to both acute and protracted exposures. The recommended equivalent dose limit to the eye was subsequently lowered from 150 mSv per year and is now identical to effective dose limits; 20 mSv y^{-1}, averaged over 5 y, with a maximum exposure of 50 mSv in a single year.

The recent reduction in threshold and dose limit was met with some controversy. The International Atomic Energy Agency (IAEA) is in agreement with the ICRP and has adopted the same dose limit in their most recent International Basic Safety Standards, published in 2014 (IAEA 2014). The National Council on Radiation Protection and Measurements (NCRP) is suggesting reducing the annual lens dose limit to 50 mGy (NCRP 2016). However, other organizations, including the International Radiation Protection Association (IRPA) and the Society for Radiological Protection (SRP), questioned whether there was sufficient data to support a reduction in dose limit (Broughton et al. 2015; Englefield 2011; Martin 2011). The Energy Production Research Institute (EPRI) concluded that cataract risk may be higher than previously thought, but currently there is not adequate data to accurately calculate a threshold dose for chronic exposures (EPRI 2014).

This paper will review the published human data on deterministic effects to the eye to evaluate whether the suggested reduction in dose threshold is justified. The studies reviewed here cover a wide range of different exposure cohorts, including atomic bomb survivors, medical workers, and radiotherapy patients. Published studies will be evaluated with respect to total dose, dose rate, radiation quality, age at exposure, and latency to assess their relevance to occupational exposure scenarios and determine if their calculated risk should be considered when determining dose limits. Animal models, although a useful basis for mechanistic studies, are not a strong indicator of the absolute level of risk to humans. Therefore, this review will focus primarily on human epidemiological data. The results of these studies are summarized in Table 1.

Cataracts

Cataracts are a clouding of the lens of the eye leading to blurred vision and in more severe cases vision loss. They are classified into three general types depending on the location: nuclear (centre of lens), cortical (edge of lens) and posterior subcapsular (PSC; back of lens). Numerous factors will increase the risk of cataract formation, including genetics, age and diseases such as diabetes. All of these factors can be linked to an increase in oxidative stress (Spector 1995; Vinson 2006). The incidence of age-related cataracts in the general population is high. Cataract rates in the United States are approximately 25% at age 65 and over 70% at age 80, with levels slightly higher in females compared to males (Congdon et al. 2004).

Most cataracts are easily treated through surgical replacement of the lens. The damaged lens is removed, and an artificial intraocular lens is implanted. Cataract surgeries are generally performed as outpatient procedures relying only on local anaesthesia and can be completed in less than 30 min (Potvin 2016). In Ontario alone, over 140,000 cataract surgeries are performed annually, approximately one for every 100 people (Szigiato et al. 2016). Cataract surgery has a high success rate of greater than 90% based on improvements in visual acuity (Hahn et al. 2011; Lundstrom et al. 2001).

Radiation-induced cataracts

Exposure to ionizing radiation can result in cataract formation. Several different mechanisms have been proposed to explain how radiation induces lens opacifications (Ainsbury et al. 2009; Bouffler et al. 2012; Hamada and Fujimichi 2015; Lipman et al. 1988). It is believed that radiation damages actively dividing epithelial cells, which are mainly located at the anterior periphery of the lens, both directly and indirectly through reactive oxygen intermediates (Shore et al. 2010). These cells can then migrate toward the posterior of the lens, resulting in opacities. Cellular damage leading to cataract formation can occur from radiation interactions with both DNA and proteins (Bouffler et al. 2012). The lens is avascular; however, damaged cells can still be removed by phagocytosis (Michael et al. 1998) or autophagy (Brennan et al. 2012; Frost et al. 2014). The most common type of cataract induced by ionizing radiation is PSC, followed to a lesser extent by cortical (Hamada and Fujimichi 2015). A latency period exists between exposure and the onset of cataracts, which is inversely related to dose and can range from years to decades (Ainsbury et al. 2009).

Classification and risk assessment

Several classification systems have been designed for ranking the severity of cataracts. One of the most common methods is the Lens Opacities Classification System (LOCS). The most recent version is the LOCS III (Chylack et al. 1993), which replaced the older LOCS II (Chylack et al. 1989) and LOCS I (Chylack et al. 1988). Individual grades are chosen for all three classes of cataracts (nuclear, cortical and PSC) as well as nuclear color. Slit-lamp photographs of a subject's lens are compared to a set of standard images, from which grades are assigned on a decimal scale (higher numbers represent more damage) ranging from 0.1 to 5.9 for cortical and PSC cataracts, and from 0.1 to 6.9 for nuclear cataracts and nuclear color. The World Health Organization

[††]The ICRP has changed their convention for dose units. When referring to deterministic effects (tissue reactions), an equivalent dose measured in Sv is no longer used. For low LET radiation an absorbed dose measured in Gy is used. For high LET radiation a relative biological effectiveness-weighted dose measured in Gy is used. Annual dose limits are still stated in Sv.

Table 1. Summary of human epidemiological studies on lens opacities following ionizing radiation exposure.[a]

Radiation quality	Dose range	Exposure type	Age at exposure	Latency (y)	Sample size	Endpoint	Risk calculation	Results	Reference
Atomic bomb survivors									
Neutron and gamma	0 – 10+ Gy[b]	Acute	0 – 50+ Mean: HIR — 29.1 NAG — 23.9	18 – 19	2,468	Presence of opacities	% increase and threshold	• Increase in cortical and PSC opacities in high dose group (>2 Gy) • Threshold: 1.09 Gy (0.64 – 1.54)[c] to 1.47 Gy (0 – 2.57)[c]	Nefzger et al. 1969[d]; Otake and Schull 1982
Neutron and gamma	0 – 6+ Gy[b]	Acute	0 – 50+ Mean: HIR — 29.3 NAG — 23.4	37	1,983	Presence of opacities	Threshold	• Threshold: 1.46 Gy (0 – 3.34)[c]	Otake and Schull 1990[d]
Neutron and gamma	0 – 6+ Gy[b]	Acute	0 – 30+	33 – 35	2,301 (1,176 exposed)	Presence of opacities	RR	• Increase in cortical and PSC opacities in all age groups above 3 Gy • Increase in PSC opacities in youngest age group (<15 y at exposure) at 1 Gy, RR: 2.79	Choshi et al. 1983[d]
Neutron and gamma	0 – 3+ Sv[b] Mean: 0.92 Sv	Acute	0 – 40+ Mean: HIR —30.6 NAG — 24.5	53	10,339 (6,385 exposed)	Presence of cataracts	RR	• RR at 1 Sv: 1.06 (1.01 – 1.11)[c]	Yamada et al. 2004
Neutron and gamma	0 – 2+ Sv[b]	Acute	0 – 38 Mean: 8.8	55 – 57	873	LOCS II	OR and threshold	• OR at 1 Sv: - Cortical: 1.29 (1.12 – 1.49)[c] - PSC: 1.41 (1.21 – 1.64)[c] • Threshold: - Cortical: 0.6 Sv (<0 – 1.2)[c] - PSC: 0.7 Sv (<0 – 2.8)[d]	Minamoto et al. 2004; Nakashima et al. 2006
Neutron and gamma	0 – 3+ Gy[b]	Acute	0 – 20+	55 – 57	3,761	Cataract surgery	OR and threshold	• OR at 1 Gy: 1.39 (1.24 – 1.55)[c] • Threshold: 0.1 Gy (<0 – 0.8)[c]	Neriishi et al. 2007
Neutron and gamma	0 – 5.14 Gy[b] Mean: 0.5 Gy	Acute	0 – 54 Mean: 20.4	41 – 60	6,066	Cataract surgery	ERR, EAR and threshold	• ERR at 1 Gy: 0.32 (0.2 – 0.47)[c] • EAR per 10,000 person-years at 1 Gy: 19.0 (11.7 – 27.2)[c] • Threshold: - ERR model: 0.5 Gy (0.1 – 0.95)[c] - EAR model: 0.45 Gy (0.1 – 1.05)[c]	Neriishi et al. 2012[d]
Chernobyl									
Beta and gamma	0 – 1+ Gy[b] Median: 123 mGy	Protracted	<25 – 40+ Mean: 32.7	12 – 14	8,607	Modified Merriam-Focht	OR and threshold	• OR at 1 Gy: - Stage 1 non-nuclear: 1.52 (1.10 – 2.12)[c] - Stage 1–5 non-nuclear: 1.65 (1.18 – 2.30)[c] • Threshold: - Stage 1 non-nuclear: 0.50 Gy (0.17 – 0.69)[c] - Stage 1–5: 0.50 Gy (0.17 – 0.65)[c]	Worgul et al. 2007
Beta and gamma	29 – 86 mSv[f]	Protracted	0 – 17	0 – 9	1,787 (996 exposed)	FLD	% increase	• 3.6% increase in subclinical PSC lens changes (non-vision impairing) in exposed group	Day et al. 1995

Radiation therapy									
X ray, Ra, Au seeds	0.2 – 66 Gy[b]	Fractionated	0.08 – 84	1.3 – 28.5	173	Presence of opacities	Minimum cataract producing dose	• Single exposure: 1.92 Gy • Short fractionation (3 wk – 3 mo): 3.84 Gy • Long fractionation: (>3 mo): 5.28 Gy	Merriam 1956[d]
^{60}Co, 4 MV x ray or 12 MeV electrons	21 – 45 Gy[b] Median: 36 Gy	Fractionated	<1	0.5 – 21.6 Median: 10.6	33	Presence of cataracts (clinically significant)	% increase	• PSC cataracts in 85% of irradiated eyes between 1 – 4 y post treatment	Fontanesi et al. 1996[d]
2 – 23 MV x ray, ^{60}Co, or ^{222}Rn	0.3 – 22 Gy[b]	Fractionated	Mean: 1	16 – 86 Mean: 32	753	Cataract surgery	HR	• HR at >5 Gy: 6 (1.33 – 27.15)[c] • HR increased with number of treatments: - 1 treatment: 57.27 (5 – 656.5)[c] - 2 or 3 treatments: 332.7 (26.5 – 4181.5)[c]	Chodick et al. 2009[d]
External photon beam	0 – 40+ Gy[b]	Fractionated	0 – 20	>5	14,362	Presence of cataracts	RR	• Increase in cataracts at a dose of >2 Gy • RR at 2 – 5 Gy: 3.2 (2.0 – 5.2)[c]	Whelan et al. 2010[d]
External photon beam	0 – 66 Gy[b] Median: 2.8 Gy	Fractionated	0 – 21 Mean: 8.3	0 – >35 Mean: 21.4	13,902	Presence of cataracts	EOR and OR	• EOR at 1 Gy: 0.92 (0.65 – 1.20)[c] • OR at 0.5 – 1 Gy: 2.17 (1.29 – 3.67)[c]	Chodick et al. 2016[d]
External photon beam	Mean: 2.5 – 2.6 Gy[b]	Fractionated	0 – 17 Mean: 4	0 – 67 Mean: 32	1,833	Presence of cataracts and cataract surgery	HR and ERR	• Increased cataract risk of 4.4 fold (1.5 – 13)[c] • Median latency period: 18 years • HR for cataracts at 0 - 0.5 Gy: 2.1 (0.6 – 7.3)[c] • HR for surgery at 0 - 0.5 Gy: 1.4 (0.4 – 5.5)[c] • ERR at 1 Gy: 0.99 (0.06 – 1.91)[c]	Allodji et al. 2016[d]
Beta, gamma, x ray or ^{226}Ra	0 – 8.4 Gy[b] Mean: 0.4 Gy	Fractionated	0 – 1.33 Mean: 0.41	34 – 74	573 (484 exposed)	LOCS I	OR	• Age corrected OR at 1 Gy: - Cortical: 1.50 (1.15 – 1.95)[c] - PSC: 1.49 (1.07 – 2.08)[c]	Hall et al. 1999
^{226}Rn	1.1 – 8.4 Gy[b]	Protracted	0.2 – 1.1 Median: 0.5	31 – 46	20	8 grade system	% increase	• Mild to moderate PSC cataracts in treated eye at >2 Gy • Minor non-vision impairing opacities in untreated eye (0.06 – 0.12 Gy)	Wilde and Sjostrand 1997
^{224}Ra	0 – 5 MBq kg^{-1}	Fractionated	0 – 80	0 – 43	831	Presence of cataracts	Threshold	• Threshold: 0.5 MBq/kg	Chmelevsky et al. 1988
X ray	Mean: 0.47 Gy[b]	Acute	Mean: 7	Mean: 15	466 (234 exposed)	Presence of minor opacities	OR	• OR for PSC opacities at 0.5 Gy: 5.9 (1.4 – 24)[c]	Albert et al. 1968
Diagnostic imaging									
X ray	Not reported	Acute	Not reported	Not reported	4,926	Presence of opacities	OR	• Correlation between CT scans and PSC or nuclear opacities: - PSC OR: 1.45 (1.08 – 1.95)[c] - Nuclear OR: 1.28 (1.02 – 1.61)[c]	Klein et al. 1993

Continued next page

Table 1. *(Continued)*

Radiation quality	Dose range	Exposure type	Age at exposure	Latency (y)	Sample size	Endpoint	Risk calculation	Results	Reference
X ray	Not reported	Acute	Not reported	>5	3,684	Presence of opacities	% increase	• Correlation between CT scans and PSC opacities • No correlation when other cranial scans were included in the analysis	Klein et al. 2000[d]
X ray	Not reported	Acute	31 – 79	1 – 18	3,654 (651 exposed)	Presence of opacities	OR	• No significant correlation between CT scans and cataract prevalence	Hourihan et al. 1999
X ray	Not reported	Acute	10 – 50 Mean: 40	Mean: 10	30,537 (2,776 exposed)	First cataract appearance	HR	• HR in exposed group: 1.76 (1.18 – 2.63)[c] • Increased risk associated with multiple CT scans	Yuan et al. 2013[d]
Medical professionals									
X ray	0 – 80 mGy[b] Median: 28 mGy	Protracted	14 – 43	Mean: 19.2	35,705	Presence of cataracts	ERR and HR	• ERR at 1 Gy: 1.98 (−0.69 – 4.65)[c] • HR for high dose group (average: 60.1 mGy) compared to low dose group (average: 5.1 mGy): 1.18 (0.99 – 1.40)[c]	Chodick et al. 2008
X ray or gamma	0 – 236 mSv[b] Mean: 70 mSv	Protracted	18 – 56 Mean: 25	Mean: 11.4	3,279 (1,401 exposed)	LOCS III	HR	• Cortical HR: 2.58 (1.36 – 3.82)[c] • PSC HR: 3.57 (1.27 – 4.79)[c] • Combined HR: 3.64 (1.78 – 5.52)[c]	Lian et al. 2015[d]
X ray	10 – 300 mSv[b] Mean: 60 mSv	Protracted	Mean age at reporting: 58	>15	57	LOCS II	EOR	• No significant correlation between radiation and cortical or PSC opacities	Mrena et al. 2011[c]
X ray	Mean: 102 mSv[f]	Protracted	Mean age at reporting: 54	>15 Mean: 20	37 (21 exposed)	LOCS II	ERR	• No significant correlation between radiation and cortical or PSC opacities	Auvinen et al. 2015[d]
Mixed	Mean: 1.63 $mSv\ yr^{-1}$ [f]	Protracted	Mean age at reporting: 41 – 46	1 – 40	3,240 (1,560 exposed)	Presence of cataracts	RR	• RR in exposed group: 4.6	Milacic 2009[d]
X ray	0.1 – 27 Sv[b] Mean: 1.5 – 6 Sv	Protracted	Age at reporting: 20 – 69	1 – 40 Mean: 7 – 14	209 (116 exposed)	Modified Merriam-Focht	RR	• RR for PSC cataracts in interventional cardiologists (average: 6 Sv): 3.2 (1.7 – 6.1)[c] • No significant RR for nurses/ technicians (average: 1.5 Sv)	Vano et al. 2010
X ray	0.1 – 18.9 Gy[b] Mean: 1.8 - 8.3 Gy	Protracted	Age at reporting: 20 – 66	Mean: 8 – 16	215 (127 exposed)	Modified Merriam-Focht	% increase	• Increased frequency of PSC opacities in cardiologists (50%) and nurses (41%) compared to controls (10%)	Vano et al. 2013[d]
X ray	0.01 – 43 Gy[b] Mean: 3.4 Gy	Protracted	Age at reporting: 25 – 64	1 – 33 Mean: 6 – 9	89 (67 exposed)	Modified Merriam-Focht	RR	• RR for PSC cataracts in interventional cardiologists (average: 3.7 Gy): 5.7 (1.5 – 22)[c] • RR for PSC cataracts in nurses (average: 1.8 Gy): 5.0 (1.2 – 21)[c]	Ciraj-Bjelac et al. 2010
X ray	0.02 – 21 Sv[b] Mean: 1.1 – 1.8 Sv	Protracted	Age at reporting: 19 – 67	1 – 20 Mean: 5 – 8	86 (52 exposed)	Modified Merriam-Focht	RR	• RR for PSC cataracts in interventional cardiologists (average: 1.1 Sv): 2.6 (1.2 – 5.4)[c] • RR for PSC cataracts in support staff (average: 1.8 Sv): 2.2 (0.98 – 4.9)[c]	Ciraj-Bjelac et al. 2012[d]

X ray	Median: 7 – 21 mSv[f]	Protracted	Median age at reporting: 43 – 44	Median: 10	746 (466 exposed)	Presence of cataracts	OR	• OR for cataracts in exposed workers: 6.3 (1.5 – 27.6)[c] • OR for high exposure group: 9.0 (2 – 41)[c]	Andreassi et al. 2016[d]
X ray	Not reported	Protracted	Mean age at reporting: 50	Mean: 21.9	205 (106 exposed)	LOCS III	OR	• OR for PSC opacities: 3.56 (1.25 –10.13)[c]	Jacob et al. 2013[d]
X ray	>1 mSv[b] Mean: 4 – 17 mSv	Protracted	Mean age at reporting: 37 – 44	>4 Mean: 5 – 10	95 (81 exposed)	LOCS III	RR	• RR in exposed workers: 11.06 (1.67 – 73.37)[c]	Bitarafan Rajabi et al. 2015[d]
X ray	0 – 2.75 mSv[b] per mo Mean: 0.35 – 0.83 mSv	Protracted	Age at reporting: >40 Mean: 48.9	4 – 40 Mean: 15.3	66 (44 exposed)	LOCS III	% increase	• No significant increase in risk	Thrapsanioti et al. 2017[d]
Nuclear workers									
Neutron and gamma	<250 mSv[f]	Protracted	18 – 60	0 – 13	847	Presence of opacities	% increase	• No significant correlation between radiation and opacities	Voelz 1967
Neutron and gamma	Mean neutron (brain): 0.002 Gy Mean gamma: 0.46 – 0.54 Gy[f]	Protracted	<20 – 40+	26 – 60	21,060	Presence of cataracts	RR, ERR	• RR in low dose group (0.5 – 0.75 Sv): 1.13 (1.00 – 1.28)[c] • RR in highest dose group (>2 Sv): 1.61 (1.41 – 1.83)[c] • ERR at 1 Gy (gamma only): 0.28 (0.20 – 0.37)[c] • ERR at 1 Gy (gamma and neutron): 0.31 (0.22 – 0.40)[c]	Azizova et al. 2016[d]
Mixed	0 – 600 mSv[f]	Protracted	Median at reporting: 76	Not reported	97	Presence of cataracts	% increase	• Higher cataract frequency of 37.5% in the high dose group (200 – 600 mSv) compared to 15.1% in low dose group (<200 mSv)	Jacobson 2005
^{226}Ra, ^{228}Ra	$0 – 2 \times 10^8$ Bq	Protracted	Mean: 19	>50	813	Presence of cataracts	% increase	• Higher cataract frequency of 17.1% in high dose group ($>1.85 \times 10^6$ Bq) compared to 14.1% low dose group ($<1.85 \times 10^6$ Bq)	Adams et al. 1983[d]
Astronauts									
Cosmic	Not reported	Protracted	Age at reporting: 40 – 69	3 – 29 Mean: 15.3	416 (21 exposed)	Presence of opacities	% increase	• Higher degree of opacification (not significant) in astronauts compared to age matched reference population	Rastegar et al. 2002
Cosmic	0.2 – 91 mSv[b]	Protracted	39 – 45 Mean: 41.8	0 – 30	295 (222 exposed)	Presence of opacities	HR	• HR for high dose group (>8 mSv) compared to low dose group (<8 mSv): - Age 60: 2.35 (1.01 – 5.51)[c] - Age 65: 2.44 (1.20 – 4.98)[c]	Cucinotta et al. 2001
Cosmic	0 – 130 mSv[b] Median: 12.9 mSv	Protracted	Median at reporting: 41–53	0 – 41	418 (171 exposed)	LOCS III	OR	• OR for PSC opacities at high exposures (>10 mSv): 2.23 (1.16 – 4.26)[c]	Chylack et al. 2009

Continued next page

Table 1. *(Continued)*

Radiation quality	Dose range	Exposure type	Age at exposure	Latency (y)	Sample size	Endpoint	Risk calculation	Results	Reference
Cosmic	0 – 270 mSv[b]	Protracted	>5	0 – 42	227	LOCS III	Progression rate	• Non-significant ($p = 0.062$) progression rate for cortical cataracts: 0.25 ± 0.13 % yr^{-1} Sv^{-1} (−0.012 – 0.507)[c]	Chylack et al. 2012[d]
Airline pilots									
Cosmic	1 – 48 mSv[f]	Protracted	Age at reporting: >50	0 – 38	79	WHO	OR	• OR for nuclear cataracts at 1 mSv: 1.02 (1.00 – 1.03)[c] • No significant correlations between radiation and cortical or PSC cataracts	Rafnsson et al. 2005[d]
Cosmic	Not reported	Protracted	21 – 65	0 – 44	13,565,389 person-years	Presence of cataracts	% increase	• Higher cataract frequency in astronauts compared military pilots • Earlier incidence of cataracts in military pilots compared to astronauts	Jones et al. 2007
Contaminated buildings									
^{60}Co	1.11 – 1,493 mSv[f]	Protracted	0 – 64	1 – 15	114 (all exposed)	LOCS III and FLD	% increase	• No dose-response in LOCS III score • Significant dose-response in FLD score in younger individuals (<20 y) • No dose-response in FLD score in older individuals (>20 y)	Chen et al. 2001
^{60}Co	0.1 – 2,206 mSv[f]	Protracted	0 – 18 Mean: 0.9	2 – 20	173 (73 exposed)	LOCS III and FLD	% increase	• No dose-response in LOCS III score • Increase in FLD scores with time post exposure	Hsieh et al. 2010

[a]HIR: Hiroshima, NAG: Nagasaki, PSC: Posterior subcapsular, RR: Relative risk, LOCS: Lens Opacities Classification System, OR: Odds ratio, ERR: Excess relative risk, EAR: Excess absolute risk, FLD: Focal Lens Defect System, HR: Hazard ratio, EOR: Excess odds ratio, CT: Computed tomography, WHO: World Health Organization.

[b]Lens absorbed or equivalent dose.

[c]95% confidence interval.

[d]Reference not included in ICRP Publication 118.

[e]90% confidence interval.

[f]Effective dose.

(WHO) developed a similar alternative grading system for scoring the three classes of cataracts (Thylefors et al. 2002). Merriam and Focht (1962) presented a simpler method than the LOCS system, which was specifically designed for radiation-induced cataracts, where opacities to the lens are ranked using a single integer value on a scale from one to four. Minor subclinical opacities (non-vision impairing) have been quantified using the Focal Lens Defect (FLD) system (Day et al. 1995). Many studies have also classified subjects based only on the presence or absence of cataracts without any scale ranking for severity. The variety of different grading systems combined with person-to-person variability in assigning scores adds some uncertainty to the interpretation and comparison of human studies.

In addition to the various classification systems used, a further complication in interpreting human studies in the range of different metrics that have been used to calculate risk. Some studies look at the first appearance of cataracts while others focus on operable cataracts. Since cataracts are generally viewed as a deterministic effect, attempts have been made to calculate a threshold dose for cataracts or pre-cataract lens opacities. The ICRP defines the threshold as a dose where an observable effect is detected in 1% of the exposed population (ICRP 2012). Cataractogenesis has also been correlated to radiation dose using odds ratios or excess odds ratio (OR or EOR), relative risk or excess relative risk (RR or ERR), excess absolute risk (EAR) and hazard ratio (HR).

EPIDEMIOLOGICAL DATA

Atomic bomb survivors

One of the largest cohorts documenting radiation exposure to the lens is atomic bomb survivors. A number of preliminary studies were conducted within the first 17 y post-exposure (reviewed in Miller et al. 1967); however, many of these were criticized for their sampling methods and dosimetry. Overall, a general increase in PSC opacities was observed in individuals who were close to the epicenter, receiving a high dose and high dose rate exposure. Following these preliminary studies, Nefzger et al. (1969) found an increase in cortical and PSC opacities at 20 y post-exposure but almost exclusively at lens doses greater than 2 Gy. Threshold calculations ranged from 1.09 Gy (0.64–1.54)[‡‡] to 1.47 Gy (0–2.57), depending on which dose-response model and dosimetry system was used (Otake and Schull 1982). These same subjects were re-evaluated in 1982, nearly 40 y post exposure, using the updated DS86 dose estimates (Roesch 1987), and a similar threshold of 1.46 Gy (0–3.34) was found (Otake and Schull 1990). Choshi et al. (1983) examined a different cohort 30 y post exposure and also found an increase in cortical and PSC opacities following a lens dose of 3 Gy or more. Younger individuals (<15 y at exposure) were more sensitive and showed an increase in opacities down to 1 Gy with a RR of 2.79. Overall, these initial studies that followed individuals up to 40 y post exposure identified an increase in cortical and PSC opacities but only at lens doses in excess of 1–3 Gy.

More recent studies have examined long-term effects in atomic bomb survivors and generally found lower thresholds for cataract formation compared to earlier data. Many of the subjects in these studies, however, were children at the time of exposure. Yamada et al. (2004) examined 10,339 survivors up to 53 y and found a RR at 1 Sv of 1.06 (1.01–1.11). Minamoto et al. (2004) found an increase in cortical and PSC opacities and calculated an OR at 1 Sv of 1.29 (1.12–1.49) and 1.41 (1.21–1.64), respectively. Interestingly, a difference was seen between dose-matched individuals in Hiroshima and Nagasaki, which the authors suggest is the result of intercity differences in UV radiation (Minamoto et al. 2011). These differences could also be linked to radiation quality, since the dose contribution from neutron radiation was much higher in Hiroshima compared to Nagasaki (Young and Kerr 2006). The Minamoto et al. (2004) results were reanalyzed, and a threshold of 0.6 Sv (<0–1.2) was calculated for cortical opacities and 0.7 Sv (<0–2.8) for nuclear opacities (Nakashima et al. 2006). Based on confidence intervals, the authors concluded that this threshold was not significantly different from zero, a suggestion that has since been challenged (Doss et al. 2014).

The incidence of more severe cataracts requiring surgery was examined by Neriishi et al. (2007), who found an OR at 1 Gy of 1.39 (1.24–1.55) and a threshold dose of 0.1 Gy (<0–0.8). Since a threshold of less than 1 Gy was found, the authors proceeded to re-evaluate the data looking only at individuals exposed to a lens dose of less than 1 Gy. In this refined cohort, no statistically significant threshold was found. The authors published later findings on a larger cohort of 6,066 subjects with over 1,000 receiving cataract surgery up to 60 y post exposure (Neriishi et al. 2012). A higher threshold of 0.5 Gy (0.1–0.95) was identified based on the ERR model and 0.45 Gy (0.1–1.05) based on the EAR model.

Chernobyl

Cataracts have been examined in individuals exposed to ionizing radiation as a result of the Chernobyl Nuclear Power Plant disaster in 1986. The largest exposures were to clean-up workers, known as liquidators. Protracted dose estimated to the lens were modeled for 8,607 liquidators and ranged from 0 to > 1 Gy with a median of 123 mGy (Chumak et al. 2007). Using a modified version of the Merriam-Focht scale, Worgul et al. (2007) found an OR at 1 Gy of 1.52 (1.10–2.12) for stage one non-nuclear opacities

[‡‡]Values in parentheses represent 90% or 95% confidence intervals.

and a threshold of 0.50 Gy (0.17–0.69). When the combined risk for all cataract classes (stage 1–5) was calculated, the OR at 1 Gy increased to 1.65 (1.18–2.30) with a similar threshold dose of 0.5 Gy (0.17–0.65). Day et al. (1995) studied the incidence of minor lens opacities using the FLD system in 1,787 children (5–17 y) residing near Chernobyl. Whole body effective dose estimates were between 29 and 86 mSv; however, there are large uncertainties in the reliability of the dosimetry. A small 3.6% increase was found in subclinical (non-vision impairing) PSC lens changes in the exposed group, but no dose threshold was calculated. These two studies on Chernobyl exposures have followed individuals up to a maximum of 14 y post exposure, and most of the study participants were still relatively young, so there is the potential for cataract incidence to rise compared to the general population as follow-up times increase.

Radiation therapy

Exposure to the lens can occur during whole-body radiation therapy or targeted therapy for cranial cancers. The benefit of these studies, compared to atomic bomb survivors, is the general reliability of the dosimetry resulting from accurate treatment planning. One of the earliest studies was conducted by Merriam (1956). Following a single treatment, opacities were found at doses greater than 1.9 Gy, whereas following fractionation (>3 mo), the minimum cataractogenic dose increased to 5 Gy. The latency period for the onset of opacities ranged from 4 mo to 24 y and was inversely related to dose. Children under the age of 1 y were found to be more sensitive compared to adults. A pair of studies have examined cataract rates following childhood treatment for retinoblastoma. Fontanesi et al. (1996) found an increase in clinically significant PSC cataracts between 12 and 49 mo post treatment; however, lens doses were between 21 and 45 Gy. A larger study was completed by Chodick et al. (2009), who found a sixfold (1.3–27.2) increase in cataract extraction rates following a lens dose of 5 Gy or more, but no excess risk was identified at doses below 2.5 Gy. The average latency period until cataract extraction was between 30–50 y depending on the number of treatments.

A more general study was conducted by Whelan et al. (2010) as part of the Childhood Cancer Survivor Study. Cataract incidence was measured at least 5 y post radiotherapy treatment for a variety of different cancers. A significant increase in opacities was found following irradiation but only at lens doses in excess of 2 Gy. This same cohort was recently re-evaluated with a mean follow up time of 21.4 y post diagnosis, and a significant increase in cataract frequency was detected as low as 0.5 Gy with an EOR at 1 Gy of 0.92 [0.65–1.20 (Chodick et al. 2016)]. A similar study was conducted by Allodji et al. (2016) in children treated for a variety of non-retinoblastoma cancers with a mean follow-up time of 32 y. A 4.4-fold (1.5–13) increase in cataract risk was found following radiotherapy with a median latency period of 18 y. Following a dose of less than 0.5 Gy, compared to patients not receiving radiation therapy, the HR for cataracts was 2.1 (0.6–7.3) and the HR for cataract removal surgery was 1.4 (0.4–5.5).

Several studies have looked at cataract formation following total body irradiation prior to stem cell transplantation (Belkacemi et al. 1996; Benyunes et al. 1995; Deeg et al. 1984; van Kempen-Harteveld et al. 2000, 2002). The majority of these studies observed an increase in cataract frequency with radiation, as high as 89% (van Kempen-Harteveld et al. 2000). However, the whole-body doses in these studies ranged from 8–16 Gy; therefore, these results do not provide insight into the risk associated with lower doses.

Ionizing radiation has historically been used to treat benign diseases. Hall et al. (1999) examined long-term cataract formation in children treated for facial hemangiomas, many using ^{226}Ra, with a mean lens dose of 0.4 Gy. The age-corrected OR at 1 Gy was 1.50 (1.15–1.95) for cortical and 1.49 (1.07–2.08) for PSC opacities. Wilde and Sjostrand (1997) observed cataracts graded as mild to moderate at doses of 2 Gy and above when measured up to 46 y post ^{226}Ra treatment. Mild non-vision impairing opacities were also observed in the non-targeted eye, receiving 1–3% of the targeted eye dose. Lens opacities were detected in patients receiving ^{224}Ra doses greater than 0.5 MBq kg^{-1} for treatment of tuberculosis and ankylosing spondylitis; however, the intake concentration was not directly correlated to a lens dose (Chmelevsky et al. 1988). A pair of studies have examined cataracts following the treatment of tinea capitis, a fungal infection to the scalp, with x rays. Approximately 15 y post treatment, a minor increase in early PSC lens changes was found (Albert et al. 1968); however, in a follow up study 10 y later, no lens differences were seen between control and irradiated populations (Shore et al. 1976).

Diagnostic imaging

A small number of studies have looked at cataract formation following diagnostic imaging procedures; however, many of these relied on self-reporting from subjects and did not directly calculate a radiation doses. Klein et al. (1993) found a relationship between computed tomography (CT) scans and PSC opacities with an OR of 1.45 (1.08–1.95) in the Beaver Dam Eye Study Cohort. An increase was also found in nuclear opacities. The same group was re-evaluated with at least a 5-y latency post scan (Klein et al. 2000). A similar correlation was found between CT scans and PSC opacities; however, when all other head x-ray scans were included in the analysis, no significant relationship was found. A second cohort was analyzed by Hourihan et al. (1999) in the Blue Mountain Eye Study, but no significant correlation was found. Yuan et al. (2013)

examined medical records from individuals receiving at least one CT scan and found an HR of 1.76 (1.18–2.63) compared to an unexposed population. A correlation was also found between the number of CT scans received and cataract risk.

Medical professionals

Lens opacities have been examined in physicians, nurses, and technologists receiving occupational exposures. A large cohort of 35,705 radiation technologists was followed for 20 y with an estimated median lens dose of 28.1 mGy (Chodick et al. 2008). A non-significant ERR per Gy was calculated as 1.98 (−0.69–4.65), although cataracts in this study were self-reported with no clinical confirmation. Similarly, Lian et al. (2015) compared 1,401 exposed Chinese radiographers to 1,878 unexposed workers and found a combined HR for cortical and PSC cataracts of 3.64 (1.78–5.52). Several studies have found minimal cataract risk from occupational exposures. Mrena et al. (2011) studied a group of Finnish physicians consisting mainly of radiologists with an average effective dose of 60 mSv. Opacities were detected but were mostly nuclear, and it was concluded that they were not radiation based. A follow-up study confirmed these results finding no increase in PSC or cortical cataracts in 47 exposed physicians with a mean whole body effective dose of 102 mSv (Auvinen et al. 2015). Milacic (2009) found a higher frequency of cataracts in radiation-exposed Serbian health care workers with a RR of 4.6. However, the authors also compared cataract frequency to radiation-induced DNA damage and found no correlation, so they concluded that radiation was not the cause of cataracts.

Some of the largest medical occupational exposures are to interventional cardiologists and radiologists. Vano et al. (2010) found a significant increase in PSC opacities in South American cardiologists who received an average lens dose of 6 Sv compared to a control population, equating to a RR of 3.2 (1.7–6.1). However, no significant increase was detected in nurses and technicians who received an average lens dose of 1.5 Sv. A follow-up study on a second South American cohort did find a higher frequency of PSC opacities in nurses compared to a control population, but no risk calculation was included (Vano et al. 2013). Ciraj-Bjelac et al. (2010) examined a group of cardiologists and nurses in Malaysia whose average lens doses were 3.7 Gy and 1.8 Gy, respectively. The RR for early PSC opacities (not vision impairing), compared to a control population, was 5.7 (1.5–2.2) for cardiologists and 5.0 (1.2–2.1) for nurses. However, a follow-up study 2 y later calculated a lower RR by approximately half (Ciraj-Bjelac et al. 2012). An increase in cataract frequency was found in Italian and French cardiology unit workers, with an OR of 6.3 (1.5–27.6) and 3.56 (1.25–10.13), respectively, but data were self-reported and no specific lens doses were calculated (Andreassi et al. 2016; Jacob et al. 2013). Bitarafan Rajabi et al. (2015) examined Iranian cardiologists whose average lens dose was between 5 and 17 mSv and found a significant increase in PSC lens changes with a RR of 11.06 (1.67–73.37). Conversely, Thrapsanioti et al. (2017) found no increase in lens opacities in exposed Greek interventional cardiologists.

Nuclear workers

Very few studies have examined occupational cataracts in non-medical fields, and most do not directly calculate an absorbed or equivalent lens dose. Voelz (1967) followed 847 nuclear reactor workers with low dose exposures and found no correlation between radiation and lens opacities. Azizova et al. (2016) studied 21,060 Russian workers in the Mayak Production Association. Cataract incidence was compared to whole body gamma exposures or brain-specific neutron exposures. A significant increase in RR was found in worker receiving a gamma dose of greater than 0.5 Gy. The ERR per Gy was calculated as 0.28 (0.20–0.37) for gamma exposure alone and 0.31 (0.22–0.40) when neutron doses were included. Jacobson (2005) compiled medical histories from 97 retired nuclear workers on the United States Transuranium and Uranium Registries (USTUR). PSC cataracts were detected in 20.6% of subjects who had an average effective dose of 168 mSv, compared to the expected age-related incidence of 2-11%. When the workers were separated into two groups based on dose (200–600 mSv or < 200 mSv), individuals in the high dose group had a significantly greater cataract frequency of 37.5% compared to 15.1% in the low dose group. This study, however, is based on a small sample size of only 20 detected PSC cataracts in USTUR workers. Medical records were also examined for 813 radium dial painters (Adams et al. 1983). A slight increase in cataracts was found following high intake concentrations, but no risk calculation was included.

Astronauts

Astronauts represent a unique cohort for studying the impacts of high LET exposure to the eye. There are issues, though, regarding the small sample size of people who have traveled to space and the relevance of high LET space radiation to exposure scenarios on Earth. A small study was conducted by Rastegar et al. (2002) examining 21 astronauts and cosmonauts. An increase in PSC opacities (not statistically tested) was found compared to a reference population; however, no direct correlation was made to radiation dose. The first large-scale epidemiological study was conducted by Cucinotta et al. (2001), who examined 295 NASA astronauts up to 30 y post spaceflight. Individuals were divided into one of two exposure categories: high dose (>8 mSv, average of 45 mSv) and low dose (<8 mSv, average of 3.6 mSv). In the high dose group, compared to low dose, astronauts aged 60 and 65 had a significantly elevated

HR for cataract formation of 2.35 (1.01–5.51) and 2.44 (1.20–4.98), respectively. A latency period was found in the high dose group of 5–10 y.

More recently, a study group was created called the NASA Study of Cataracts in Astronauts [NASCA (Chylack et al. 2009)]. Compared to Cucinotta et al. (2001), these studies included a control population of astronauts who did not travel into space, and cataracts were scored using the LOCS III method. The first preliminary report was published in in 2009 (Chylack et al. 2009). Average lens doses ranged from 15 to 130 mSv, depending on the mission. A significant correlation was found between radiation and PSC opacities with an OR at high exposures (>10 mSv) of 2.23 (1.16–4.26). These findings were updated in 2012, examining the longitudinal progression of cataracts (Chylack et al. 2012). A non-significant correlation ($p = 0.062$) was identified between radiation exposure and progression rate, where opacities became more severe with age depending on dose at a rate of 0.25 ± 0.13 % y^{-1} Sv^{-1} (−0.012–0.507). No relationship was found between dose and progression rate for PSC or nuclear opacities.

Airline pilots

Airline pilots experience a larger annual radiation dose due to increased cosmic ray exposure from traveling at high altitudes. Rafnsson et al. (2005) completed a small population-based case-control study on 79 Icelandic pilots. Effective dose was estimated based on employment history, but no lens dose was reported. An OR for nuclear cataracts at 1 mSv was calculated as 1.02 (1.00–1.03). The highest exposure group (22–48 mSv) had a nuclear cataract OR of 4.19 (1.04–16.86). Surprisingly, no significant increase in risk was found for cortical or PSC cataracts. UV radiation from sunbathing habits was considered in the risk calculations, but no correction was applied for UV exposure during flight, which the authors cite as minimal. Jones et al. (2007) compared cataracts in U.S. Air Force, Navy and NASA astronauts. Cataract incidence was higher in astronauts, but cataracts appeared significantly earlier in military aviation pilots. The authors did not provide any risk estimates with respect to an unexposed control population.

Contaminated buildings

Accidental radiation exposure occurred in Taiwan when buildings were constructed in 1983 and 1984 using steel that was contaminated with ^{60}Co. It took nearly a decade to identify the contaminated material, resulting in several years of low-dose exposure to occupants. Effective dose was indirectly determined through dose reconstruction based on self-reporting by subjects regarding where they resided. Chen et al. (2001) found no significant dose-response when cataracts were scored using the LOCS III system, but a correlation was identified between dose and non-vision impairing FLD scores in younger individuals (<20 y). No radiation effects were found in older age groups where some individuals had cumulative effective doses up to 1.5 Sv. A follow-up study was then conducted 5 y later looking only at individuals under the age of 20 (Hsieh et al. 2010). FLD scores were higher compared to the earlier data suggesting a progression of opacities with time. Again, however, no dose-response relationship was found when the LOCS III scoring method was used.

DISCUSSION

This review highlights the published human epidemiological data on lens opacities and cataract formation resulting from ionizing radiation exposure. Included are all of the publications that were considered by the ICRP in determining the new threshold dose for radiation-induced cataracts of 0.5 Gy, as well as several additional citations. The three most reliable cohorts, encompassing a large portion of the published data, are the atomic bomb survivors, radiotherapy patients, and medical workers. Early studies on atomic bomb survivors suggested a threshold dose of greater than 1 Gy; however, lower thresholds in the range of 0.5 Gy were identified when latency times were extended to 50 y or more. Data from radiotherapy patients followed a similar trend to that of atomic bomb survivors, although no studies formally calculated a threshold dose. Studies on radiologists and interventional cardiologists demonstrated a large discrepancy in dose calculations and a correspondingly large range in risk estimates. Apart from these three cohorts, there is a collection of data from other occupational and non-occupational exposure scenarios, including Chernobyl liquidators, diagnostic imaging patients, nuclear workers, astronauts, airline pilots, and residents of contaminated buildings.

Several studies that demonstrated minimal cataract risk from low dose exposures were absent from ICRP 118 or have been published since its release. Mrena et al. (2011) and Milacic (2009) found no correlation between radiation exposure and cataract formation in European health care workers. The study by Klein et al. (1993) was cited in ICRP 118 demonstrating an increase in PSC opacities with CT scans; however, the follow-up study 7 y later, which found no increase in risk after cranial scans, was not included (Klein et al. 2000). More importantly, there are confounding factors across many of the studies that were cited by the ICRP in support of a lower threshold, such as subject age, latency, dosimetry and scoring metric, which make it difficult to compare the results between data sets and to relate the calculated risk to an occupational setting.

The age of subjects at the time of exposure is an important consideration when evaluating cataract risk. Many of the data sets focused on childhood exposures (Albert et al. 1968; Day et al. 1995; Hall et al. 1999; Minamoto et al. 2004; Wilde and Sjostrand 1997); however, there are known differences in the lens radiosensitivity between children and adults (Merriam 1956; Merriam and Worgul 1983). This was evident in contaminated building exposures where lens changes were observed only in subjects under the age of 20, with no significant impact at older ages (Chen et al. 2001). Occupational dose limits are intended for a much older population compared to what was examined in these studies, and the threshold dose and risk estimates based on childhood exposures may not accurately describe the risk to an adult population.

There is a long latency period between radiation exposure and cataract formation that is thought to be dose dependent. This latency period needs to be considered when evaluating cataract data and is one of the main reasons for the change in occupational dose limits; as large cohorts such as the atomic bomb survivors aged, cataract rates generally increased. On the other hand, Chylack et al. (2012) found no dose-dependent longitudinal increase in the severity of opacities in astronauts. When applying risk to occupational exposures, lengthy latency periods may overestimate risk. Some of the studies that include childhood exposures followed subjects for over 60 y (Allodji et al. 2016; Neriishi et al. 2012), which is beyond the life expectancy for most middle-aged workers. Studies examining long latency periods also run into issues with the natural high frequency of cataracts in older populations.

As is often the case with epidemiological data, there are uncertainties concerning many of the dosimetric calculations. Very few study populations included direct measurements from personal dosimeters. Most of the atomic bomb and medical exposures were calculated by dose reconstruction using subject location and work history. Questionable dosimetry has been an issue with much of the preliminary atomic bomb, Chernobyl and cardiologist data. To illustrate, there was a large range in the occupational doses reported in the case studies on interventional cardiologists. Vano et al. (2010) examined cardiologists working for an average of 14 y and calculated a lens dose of 6 Sv, whereas Bitarafan Rajabi et al. (2015) calculated an average dose of only 9 mSv, almost 1,000 times less, in a similar cohort. One reason for this discrepancy is compliance issues with personal dosimetry, where workers neglect to wear dosimeters, thereby underestimating cumulative doses (Vano et al. 2006). A large number of studies simply relied on patients self-reporting their exposures with no direct measurement of radiation dose (Hourihan et al. 1999; Klein et al. 2000) and therefore cannot be included in absolute risk calculations.

The dose rate of exposure could have a large impact on risk assessment calculations. The new ICRP recommendations ignore dose rate and assume the same threshold for acute and protracted exposures. However, dose rate effects have been shown in both human and animal studies following low-LET exposure where fractionation can increase the dose threshold (Merriam 1956) and delay the onset and progression rate of cataracts (Merriam and Focht 1962) compared to single acute exposures. Most occupational exposures can be classified as chronic or protracted. Conversely, many of the studies cited by the ICRP in support of a reduced threshold, particularly atomic bomb survivors, were acute exposures and may be overestimating occupational risks. In addition to dose rate, radiation quality will also impact risk calculations. An increase in cataract rates was detected in most astronaut cohorts; however, the high LET radiation qualities in space are much different from the low LET occupation exposures on earth and are likely more damaging to the lens. In order to assign finite dose thresholds and occupational limits, further considerations of dose rate and radiation quality are essential.

A variety of different methods of classification have been used for evaluating the type and severity of cataracts. Several of the studies, particularly the more recent publications, used the LOCS or Merriam-Focht scales. The advantage of these metrics is that they provide an accurate quantification of cataract severity and location, which can be compared easily between data sets and limits variability between different individuals assigning the grades. Many of the studies, however, simply report whether or not subjects had cataracts and fail to provide information regarding grading or location. Furthermore, a large number of these relied on self-reporting. The location of cataracts can provide important information to distinguish radiation-induced cataracts from age-related cataracts. It is generally accepted that radiation exposure results in PSC cataracts and to a lesser extent cortical cataracts, but rarely nuclear cataracts. Conversely, the most common type of age-related cataracts is nuclear. This fact draws into question several studies that identified an increase in nuclear cataracts associated with radiation exposure (Cucinotta et al. 2001; Klein et al. 1993; Rafnsson et al. 2005).

A threshold dose for cataracts or early lens opacities was only calculated in a small number of studies, all of which used a similar method. Data were fitted using one of several dose response models (linear, linear-quadratic, logistic, or log-linear), including a threshold variable. The optimal threshold value was then calculated using the method of maximum likelihood. Many of the threshold calculations had large confidence intervals, ranging from 0 to greater than 2 Gy (Nakashima et al. 2006; Otake and Schull 1990). All of these thresholds were calculated in either atomic bomb survivors or Chernobyl liquidators, who were subjected to acute or short-term protracted exposures. No thresholds were calculated following chronic occupational exposures. Based on their review, EPRI concluded that there is currently not enough data to support the accurate calculation of a threshold value for chronic exposure (EPRI 2014). The ICRP defines the threshold as a dose where an observable effect (not necessarily vision impairing) is observed in 1% of the population. An incidence rate of 1% for minor opacities is highly conservative considering that more severe vision-impairing cataracts can be easily treated with a high success rate using non-invasive surgery.

Adopting a lower dose limit could result in substantial economic burden to the nuclear industry and medical fields. Broughton et al. (2013) surveyed the Associate Societies of the IRPA regarding potential consequences of the new ICRP limit. Medical workers, specifically interventional cardiologists and radiologists, were identified as the most at-risk field to be impacted by the proposed changes. Reducing annual dose limits could necessitate the implementation of eye-specific dosimeters (Behrens and Dietze 2010) and increased shielding such as leaded glasses and scatter-shielding drapes (Thornton et al. 2010). Additionally, employers may need to increase radiation safety training for workers, hire additional staff and implement mandatory eye examinations. Although no formal cost-benefit analysis has been conducted, it is likely that lowering the dose threshold to 20 mSv would have economic consequences for several fields.

CONCLUSION

As a result of recently published data, the ICRP has recommended that the threshold dose for deterministic effects to the lens of the eye should be reduced to 0.5 Gy and that occupational dose limits should be lowered almost 10-fold to 20 mSv per year. Based on the data reviewed here, it is not conclusive that radiation exposure down to 0.5 Gy increases the risk of cataract formation. Very few of the publications that were cited in support of a reduced dose limit have formally calculated a threshold dose, and only a limited number of studies directly relate to occupational exposure scenarios. The cataract risk from occupational exposures may not coincide with the calculated risk in many of the data sets reviewed here due to differences in the type of exposure, age at exposure, radiation quality and latency. In addition, several publications that were omitted from ICRP 118 or were published since its release suggest minimal cataract risk following low dose exposures. Lowering the dose limit to 20 mSv per year could result in an economic cost to the nuclear industry or medical fields. Before this lower limit is accepted, additional studies are required to quantify the level of risk to the lens from ionizing radiation exposure scenarios specific to occupational settings. Taking into account the limitations in many of the previous data sets, new studies should be designed to achieve adequate sample sizes of the proper age cohort, provide accurate dosimetry for all individuals, and base their results on reliable identification of lens opacities by qualified individuals using previously validated scoring systems.

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