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Cataractogenesis following high-LET radiation exposure

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ABSTRACT

Biological effectiveness of ionizing radiation differs with its linear energy transfer (LET) such that high-LET radiation is more effective for various biological endpoints than low-LET radiation. Human exposure to high-LET radiation occurs in cancer patients, nuclear workers, aviators, astronauts and other space travellers. From the radiation protection viewpoint, the ocular lens is among the most radiosensitive tissues in the body, and cataract (a clouding of the normally transparent lens) is classified as tissue reactions (formerly called nonstochastic or deterministic effects) with a threshold below which no effect would occur. To prevent radiation cataracts, the International Commission on Radiological Protection (ICRP) has recommended an equivalent dose limit for the lens according to the threshold for vision-impairing cataracts. ICRP recommended the threshold of >8 Gy in 1984 and an occupational dose limit of 150 mSv/year in 1980. These remained unchanged until 2011, when ICRP recommended lowering the threshold to 0.5 Gy and the dose limit to 20 mSv/year (averaged over 5 years with no single year exceeding 50 mSv). Although such reduction of the threshold was based on findings from low-LET radiation, the dose limit was recommended in Sv. Historically, the lens is the exceptional tissue for which ICRP had assigned a special factor in addition to a general radiation weighting factor, predicated on a belief that the lens is more vulnerable to high-LET radiation than other tissues. Considering such radiosensitive nature of the lens, a deeper understanding of a cataractogenic potential of high-LET radiation is indispensable. This review is thus designed to provide an update on the current knowledge as to high-LET radiation cataractogenesis. To this end, changes in ICRP recommendations on lenticular radiation protection, epidemiological and biological findings on high-LET cataractogenesis are reviewed, and future research needs are then discussed.

1. Introduction

The discovery of X-rays in 1895 was immediately followed not merely by its use in medicine and industry but also by observations of its cancer and non-cancer effects. Take cataract (a clouding of the normally transparent crystalline lens of the eye) for example – the first case of radiogenic cataracts in experimental animals and humans was reported in 1897 and 1903, respectively [1,2]. In 1928,

Abbreviations: A-bomb, atomic bomb; amu, atomic mass unit; ATM, ataxia telangiectasia mutated; BNCT, boron neutron capture therapy; BPA, boronophenylalanine; BSH, sodium borocaptate; CDK1, cyclin dependent kinase 1; CDKN1A, cyclin dependent kinase inhibitor 1A; CHK2, checkpoint kinase 2; CI, confidence interval; DSB, DNA double strand break; DS86, dosimetry system 1986; DS02, dosimetry system 2002; Gy-Eq, gray-equivalents; ICRP, International Commission on Radiological Protection; ICRP-X, ICRP Publication X; ISS, International Space Station; IXRPC, International X-ray and Radium Protection Committee; JAXA, Japan Aerospace Exploration Agency; LEC, lens epithelial cell; LET, linear energy transfer; LQ, linear-quadratic; LFC, lens fiber cell; LSAH, Longitudinal Study of Astronaut Health; MMP, matrix metalloproteinase; MN, micronucleation; MPD, maximum permissible dose; MR, meridional row; NASA, National Aeronautics and Space Administration; NASCA, NASA Study of Cataract in Astronauts: NZW New Zealand white; PSC, posterior subcapsular cataract; Q, quality factor; $\overline{Q}$, effective quality factor; QF, quality factor; $Q(L)$, quality factor as a function of LET; RBE, relative biological effectiveness; RBE_m, relative biological effectiveness maximum for nonstochastic/deterministic effects or tissue reactions; RBE_M, relative biological effectiveness maximum for stochastic effects; RBEs, relative biological effectiveness values; SD, Sprague-Dawley; SSB, DNA single strand break; TIMP1, tissue inhibitor of matrix metalloproteinase 1; TG, Task Group; T65DR, tentative 1965 dose estimates revised; VIC, vision-impairing cataract; w_R, radiation weighting factor.

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the International X-ray and Radium Protection Committee (IXRPC) issued the first recommendations to avoid the dangers of overexposure [3]. Its initial concern was protection against X-rays and radium, but rapid developments in nuclear physics and its applications in the 1930s and 1940s raised an issue of exposure to neutrons and heavy ions. The terms "relative biological effectiveness" (RBE) and "linear energy transfer" (LET) were coined in 1931 and 1952, respectively [4,5]. It was proposed in 1948 that the mouse lens is especially sensitive to neutrons [6]. Two Science papers published in 1949 attracted attention to radiation protection of the lens: one paper was on atomic bomb (A-bomb) cataracts [7], and the other was on cyclotron cataracts [8], both of which involved neutron exposures. In 1950, IXRPC was renamed the International Commission on Radiological Protection (ICRP), which issued its first recommendations including those on the lens and various types of radiation in addition to photons [9].

RBE varies with LET, dose, dose rates, tissues/organs and endpoints, but it has widely been accepted that high-LET radiation (e.g., neutrons and heavy ions) is more effective than low-LET radiation (e.g., photons and protons) [10,11]. Hereinafter, helium and heavier ions are referred to as heavy ions, and radiation with LET of >10 keV/μm to as high-LET radiation. For radiation protection purposes, a radiation weighting factor (w_R) that is used to reflect RBE of high-LET radiation is largely predicated on RBE for low dose clastogenic effects (i.e., stochastic effects with no threshold). Cataract has been classified as a tissue reaction (formerly called a nonstochastic or deterministic effect) with a dose threshold below which no effect would occur [12]. ICRP has recommended an equivalent dose limit for the lens for prevention of cataract. To calculate equivalent dose to the lens in Sv, absorbed dose in Gy is multiplied by w_R, based on the judgment that RBE for tissue reactions is generally smaller than that for stochastic effects in corresponding tissues [13]. However, cataracts have not been included in such analyses to judge this, and application of w_R to cataracts has yet to be justified. It is noteworthy that the lens is historically the sole tissue for which ICRP recommended a special factor in addition to a general radiation weighting factor in 1964–1977 [14,15]. This was due to the belief that the lens is more sensitive to high-LET radiation (especially neutrons) than other tissues. Taken together, ICRP Publication 92 (ICRP-92) issued in 2003 was unable to recommend w_R or RBE for cataracts owing to lack of human data and concern regarding how to apply the experimental data [13]. Moreover, ICRP has recommended the occupational dose limit for the lens of 150 mSv/year since 1980, but in 2011, recommended reducing it to 20 mSv/year (averaged over 5 years with no single year exceeding 50 mSv) [12,16,17]. Such lowering was based on findings from low-LET radiation [17], although the dose limit was recommended in Sv. Altogether, further analyses are warranted as human exposure to high-LET radiation takes place, such as in cancer patients, nuclear workers, cyclotron workers, aircraft crew and passengers, astronauts and other space travellers [18,19].

This paper reviews changes in ICRP recommendations on lenticular radiation protection, epidemiological and biological findings on high-LET cataractogenesis. The companion articles in this issue review epidemiological and experimental findings on low-LET cataractogenesis [20,21].

2. Changes in ICRP recommendations for radiation protection of the lens

Tables 1 and 2 summarize changes in dose limits for the lens and radiation weighting factors for protons, neutrons and heavy ions recommended by ICRP.

2.1. Changes in 1950s and 1960s

In 1950, ICRP firstly listed cataracts in "the effects to be considered" [9]. The lens was assigned as one of the "critical organs" because the lens was empirically shown to be particularly vulnerable and thus considered critical from the viewpoint of radiation protection. Various types of radiation were considered besides X- and γ-rays, and the "relative biological efficiency" was defined. In 1954, "maximum permissible dose" (MPD) was set for workers and public assuming no threshold, and "rem" (1 rem = 10 mSv) was defined as the absorbed dose in "rad" (1 rad = 10 mGy) multiplied by RBE. RBE values (RBEs) for protons, fast neutrons and heavy recoil nuclei were given considering cataract [22]. In 1958, ICRP-1 [23] recommended ophthalmological examinations with particular reference to lenticular changes following exposure to neutrons and heavy particles. In 1959, the use of eye shields or other suitable shielding was advised to keep lens dose within MPD [24].

In 1964, ICRP-6 [14] abandoned RBE due to misgivings over its use in both radiobiology and radiation protection. The dose equivalent in rem was thus defined as the absorbed dose in rad multiplied by the "quality factor" (QF) and other modifying factors. On one hand, because "the lens seems not to assume a greater importance than other tissues when X-, γ-, and β-radiations only are concerned", the lens was no longer designated as a critical organ. On the other hand, because "the lens may be specifically radiosensitive only to particulate radiation of high-LET", a special QF of 30 was recommended for cataractogenic effects of high-LET

Table 1
Changes in the dose limit for the lens recommended by the International Commission on Radiological Protection (ICRP).

Name	Years (Publication)	Recommended values	
		Workers	Public
Maximum permissible dose	1954[a]	3 mSv/week	0.3 mSv/week
	1956[a]	3 mSv/week or 30 mSv/13 weeks	0.3 mSv/week or 3 mSv/13 weeks
	1958 (ICRP−1)[a]	50 mSv/year or 600 mSv up to age 30 (age <18) 30 mSv/13 weeks or 50(age−18) mSv (age ≥18)	5 mSv/year[b] or 15 mSv/year[c]
	1964 (ICRP−6)[a]	40 mSv/13 weeks or 150 mSv/year	5 mSv/year[d] or 15 mSv/year[c]
	1966 (ICRP−9)[a]	150 mSv/year	N.A.
Dose limit	1966 (ICRP−9)[a]	N.A.	15 mSv/year
	1977 (ICRP−26)	300 mSv/year	50 mSv/year
	1980 (Brighton Statement)	150 mSv/year	Ditto
	1990 (ICRP−60)	Ditto	15 mSv/year
	2011 (Seoul Statement)	100 mSv/5 years, ≤50 mSv/year	Ditto

Abbreviations: ICRP−X, ICRP Publication X; N.A., not accounted.
[a] Dose originally recommended in rem was converted to dose in mSv.
[b] For public who reside in the neighborhood of controlled areas.
[c] For adults who do non-radiation work in the vicinity of controlled areas or enter controlled areas occasionally.
[d] For the population at large.