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Radiation-Induced Cataracts

Recommendation of the German Commission on Radiological Protection
with Scientific Reasoning

Adopted at the 234th session of the Commission on Radiological Protection on 14 May, 2009

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In the event of any doubts about the meaning, the German original as published shall prevail.

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The lens of the eye is highly sensitive to radiation.

Radiogenic lens opacities (cataracts) occur after a latency period which is inversely related to dose and can last for several decades. Localisation is not limited to posterior subcapsular cataracts; cortical defects, up to and including total opacification, can also occur. Not all opacities become clinically relevant, but progression will ultimately cause blindness unless the affected lens is replaced through surgery.

ICRP [ICRP 07] estimates the threshold dose for acute exposure to be in the 0.5 - 2 Gy range, and 5 - 6 Gy for prolonged exposure. ICRP's estimate is based, firstly, on data gathered in animal experiments and, secondly, on epidemiological studies on humans. The informative value of many clinical/epidemiological studies is limited, however, by the considerable variation in the ophthalmological diagnostics used and by the fact that the time periods for follow-up observations are too short.

The national and international radiological protection bodies have recognised the lens's particular radiation sensitivity and introduced specific limit values for the lens. For example, paragraph 55 of the German Radiation Protection Ordinance sets a limit value for the lens of the eye (organ dose) of 150 mSv/year for occupational exposure and 15 mSv/year for people under 18 years of age.

Recent epidemiological studies have focussed particularly on Hiroshima and Nagasaki atomic bomb survivors [Nak 06, Ner 07], Chernobyl clean-up workers [Wor 07] and radiologic technologists in the U.S. [Cho 08]. Here, the lowest measured/reconstructed radiation doses lie in the 5 - 100 mGy range. According to these studies, there is a high probability that the threshold dose is <0.8 Gy. As the 95% confidence interval for possible threshold doses included zero in many cases, however, the existence of a threshold dose below which damage to the lens of the eye from ionising radiation can definitely be ruled out can no longer be assumed with certainty.

In various studies, an increase in the cataract rate was observed after radiation exposure of around 0.5 Gy and relative hazard ratios of around 1.5 were observed after exposure to 1 Gy. As comparable effects were observed after short-term exposure and after more prolonged exposure, these dose and hazard ratio values should not be viewed in relation to a limit value for an annual lens dose but in relation to lifetime dose. The current annual limit value for lens dose established by the German Radiation Protection Ordinance of 150 mSv would amount to a cumulative dose of 3 Gy over a 20-year exposure period. This dose is higher, by a factor of almost 6, than the dose at which additional cataracts were observed, and according to current knowledge, would more than double the spontaneous cataract risk.

In light of the current data situation, the Commission on Radiological Protection recommends:

- that the provisions of the German Radiation Protection Ordinance (StrlSchV) and the German X-ray Ordinance (RöV) on the protection of the lens be brought into line with the latest scientific findings;
- that during activities which are known to be associated with possible significant lens exposure (e.g. in cardiological or radiological interventions), targeted recording of the lens dose must take place. Other activities which may possibly be associated with the

risk of significant lens exposure should be identified in relevant research projects and actual lens dose should be measured or estimated in an appropriate manner. Appropriate protection measures (especially protective eyewear, lead glass shields, etc.) must be used.

- Examination of the lens should be included as appropriate in the medical monitoring of people occupationally exposed to radiation, if there is potentially high lens exposure.
- Recent experimental results point to a paradigm shift in the assessment of the risk of radiation-induced cataracts. For that reason, research strategies must also be adopted in Germany to develop a basic understanding of the mechanisms underlying radiation-induced cataracts. In this context, systematic analysis of genetic predisposition to higher sensitivity to radiation-induced cataract must be promoted, along with clinical/epidemiological research which studies the dose-effect relationship between radiation exposure and cataract formation quantitatively on the basis of independent observation.

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Radiation-Induced Cataracts

Scientific Reasoning
for the Recommendation of the
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Adopted at the 234th session of the Commission on Radiological Protection on 14 May, 2009

1 Introduction and definitions

The healthy **lens** (crystalline lens, or *lens crystallina*) is a transparent, elastic body which focusses light rays, which enter the eye through the pupil, onto the retina at the back of the eye so that a sharp image is created (Figure 1).

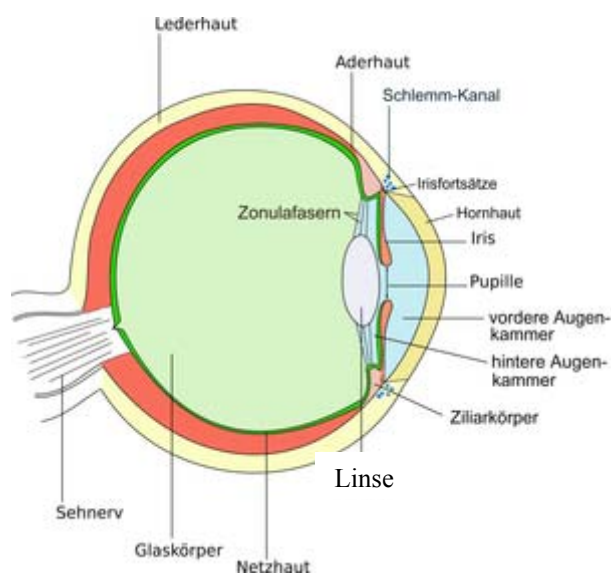


Figure 1: Anatomy of the human eye (based on: www.bsvw.de/auge_quer_g.html)

Key:

Sehnerv = optic nerve

Iris = iris

Hornhaut = cornea

Glaskörper = vitreous humour

Netzhaut = retina

Linse = lens

Ziliarkörper = ciliary body

Vordere Augenkammer = anterior chamber

Hintere Augenkammer = posterior chamber

Pupille = pupil

Aderhaut = choroid

Lederhaut = sclera

Schlemm-Kanal = Schlemm's canal

Zonulafasern = zonular fibres

Irisfortsätze = ciliary muscles

The lens consists of the capsule, the lens cortex and the lens nucleus (Figure 2). Although the epithelial cells in the lens are very metabolically active, the lens has no blood vessels; the nutrient supply to the cells takes place solely via diffusion from the aqueous humour. The lens also has no nerves.

During the development of the embryo, the lens is formed through the invagination of the ectodermal lens placode. The optic cup formed in this way separates completely; primary fibre cells in the posterior half of the lens vesicle elongate to fill the cavity of the lens vesicle. All fibre cells are retained within the lens throughout an individual's lifetime; the cells in the lens nucleus stem from the time when the individual concerned was still an embryo.

On the anterior side, the lens epithelium arises as a single layer of cells which contains a ring-shaped germinative zone (*zona germinativa*) (Figure 2); cell division takes place here on an ongoing basis throughout the individual's lifetime ("stem cell niche"). The daughter cells migrate to the lens equator (meridional zone, Figure 2), where they differentiate into elongated secondary fibre cells. New lens fibres are formed in layers like an onion around the primary fibres, with the newest lens fibres always found in the outermost layer. As the differentiation process continues, the cell nuclei and cell organelles are broken down.

The individual fibre cells are connected to each other and to the anterior epithelium by numerous gap junctions in the cell membranes, allowing the exchange of substances between the cells to take place freely. Water content in the lens is relatively low (around 65%); the correspondingly high protein content results from specific folding properties of specialised proteins (crystallins).

The lens is encased by the lens capsule, which contains collagen. The lens is therefore isolated and lacks a blood supply. In terms of the concentrations of Na^+ and K^+ , the ion milieu within the lens is inversely related to blood; the corresponding concentration gradients in the aqueous humour are maintained by ion pumps in the epithelial cell membranes.

The only metabolically active cells in the lens are the epithelial cells; they supply the fibre cells with important metabolites. Due to a high concentration of RNase inhibitors, the lifespan of many transcripts is surprisingly long.

Various factors contribute to the transparency of the lens. They include the absence of organelles and cell nuclei in the lens fibres, the regular and dense formation of the fibres, which are hexagonal in cross-section, protein synthesis which allows a densely packed cellular arrangement (crystallins), low water content, and the virtually identically refractive index of the cell membranes and cytoplasm.

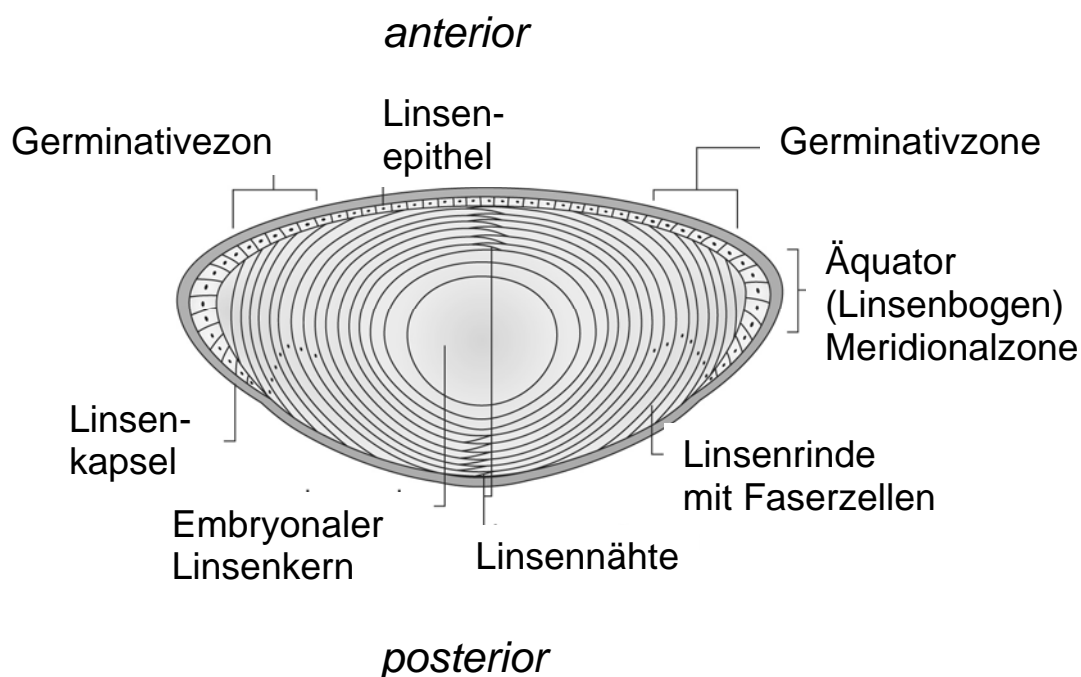


Figure 2: Structure of the mature lens (based on [Gra 03])

Key:

Germinativzone = Germinative zone

Linsenkapsel = Lens capsule

Embryonaler Linsenkern = Lens embryonic nucleus

Linsen-epithel = Lens epithelium

Äquator (Linsenbogen) = Equator (lens bow)

Meridionalzone = Meridional zone

Linsenrinde mit Faserzellen = Lens cortex with fibre cells

Linsennähte = Lens sutures

Anterior

Posterior

A **cataract** is a clouding that develops in the lens of the eye. Cataracts can be classified by age of onset (congenital vs. age-related cataracts); in developed countries, age-related cataracts account for more than 90% of all cases. The clouding can affect the entire lens or only parts of it. In ophthalmological literature, various morphological descriptions are therefore used, including:

- nuclear cataract (*cataracta centralis*)
- cortical cataract (anterior, posterior)

- subcapsular cataract (anterior, posterior)
- total cataract (*cataracta totalis*).

The main symptom of a cataract is slow and progressive vision loss, i.e. a loss of the acuity of vision, varying in degree from clinically insignificant opacities to total opacification of the lens. People with cataracts are also increasingly prone to glare sensitivity as the clouded areas scatter light into the eye. Cataracts can sometimes cause double vision, and cataract patients may also see halos and starbursts around lights. Light/dark adaptation slows down, and spatial vision is reduced. The “red-eye” effect sometimes caused by flash photography does not occur in people with cataracts.

2 Basic principles

2.1 Diagnostic and therapeutic options

The usual *diagnostic method* used in ophthalmological routine to detect changes in the lens is examination of the eye using a **slit lamp**. This device can be focussed to shine a thin stripe of light into the eye to allow simultaneous examination with a reflected-light microscope. In this way, lens opacities can be detected and in most cases localised. However, classification using this method is subjective and is extremely imprecise. In particular, examinations performed without adequate dilation of the pupil (diameter > 6 mm) provide little reliable information [Wor 96]. In many clinical studies, as well as in experimental studies on animals, classification is imprecise or, indeed, is not defined due to the stated diagnostic limitations, and in most cases, little meaningful comparison can be made between the studies. Thus the increasing grades of cataract noted in some studies can only be interpreted as qualitatively progressive changes.

A **Scheimpflug camera** is a computer-based instrument for quantitative and accurate examination of the anterior segment of the eye. As a tool for anterior eye segment biometry, it provides detailed information about lens opacities. This and other techniques (e.g. retroillumination) allow objective detection and quantification of lens changes to take place.

Various systems have been developed specifically for the diagnosis of age-related cataract and to monitor the various stages of cataract development; the *Lens Opacities Classification System* (LOCS-III [Chy 93]) should be mentioned in particular. This classification system takes account of the fact that lens opacity, and therefore vision loss, is progressive.

The gold standard of *cataract treatment* is surgical removal of the clouded lens and implantation of an artificial lens in the eye. In theory, this is a routine procedure, but post-operative complications arise in many cases because remaining lens cells can grow back and cause secondary opacities (“post-surgical cataract”) [Auf 05, Gre 08, Pow 94]. A further problem is the increased incidence of glaucoma and age-related macular degeneration (AMD) after early cataract surgery, possibly due to the absence of the UV protection normally provided by the natural lens [Boc 08].

2.2 Incidence, age and gender dependency, ethnic predisposition

In Germany, around 50% of the 50-64 age group has cataract with no impairment of vision. Almost all 65-75-year olds have some lens opacification, with clinical manifestation in the form of vision impairment occurring in around 50% of cases. Age is thus the key factor influencing cataract formation (Figure 3). Some studies have also noted an earlier onset and increased prevalence in women compared with men [e.g. Kle 93, Wor 07, Cho 08].

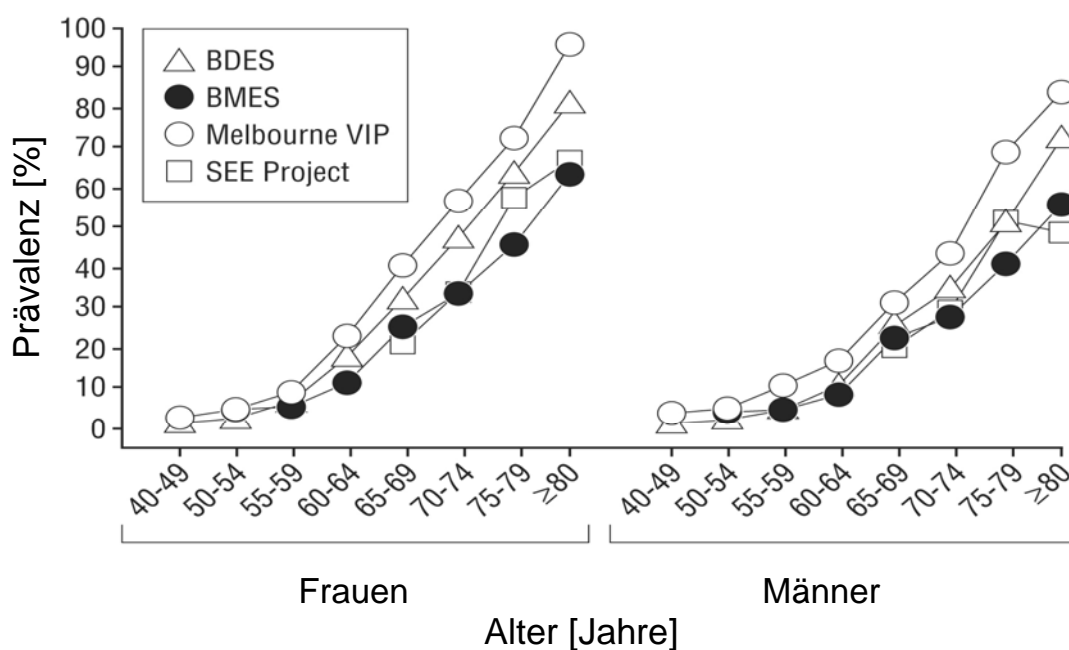


Figure 3: Prevalence of cataract by age (based on [Con 04]).
Prevalence of cataract in women (left-hand chart) and men (right-hand chart), by age, at 10-year intervals. The figure summarises the results of various studies (BDES: Beaver Dam Eye Study, USA; BMES: Blue Mountains Eye Study, Sydney, AUS; Melbourne VIP: Melbourne Visual Impairment Project, AUS; SEE Project: Salisbury Eye Evaluation Project, USA).

Key:

Frauen = Women

Männer = Men

Alter [Jahre] = Age, y

Prävalenz = Prevalence

It should be noted that age-related lens opacities are not evenly distributed across all parts of the lens. They mainly occur in the anterior of the lens. No significant age-related increase in opacities in the posterior has been described. In various epidemiological studies (with incidence showing sometimes substantial scatter ranges), various forms of age-related cataract

are described (e.g. nuclear cataracts ~ 20%, cortical cataracts ~ 8%, posterior subcapsular cataracts ~ 5% [Con 03]).

A comparison of populations of Asian and European descent, known as the Leicester Study [Das 90, 94], found that Asians had a significantly higher prevalence of age-related cataract, and the onset of cataract seemed to be earlier in Asians. A strict vegetarian diet was found to be a significant risk factor for age-related cataract. It should be noted that the population group of Asian descent mainly originated in the Indian sub-continent and that unlike the studies undertaken among Hiroshima and Nagasaki atomic bomb survivors, virtually no people of Japanese descent were included in the study.

Ethnic predisposition was also demonstrated in a comparison of cataract risk among African Americans and Caucasians in the United States. The odds of having cataracts were 4.0 times greater among African Americans than among Caucasians [Wes 98].

2.3 Causes and risk factors

Congenital cataracts in developed industrialised countries almost always have genetic causes (mutations in genes for the crystallins, membrane molecules, enzymes for galactose metabolism and iron metabolism). Co-natal cataracts (following exposure to the measles, mumps or rubella virus before or during birth) are very rare [Gra 03].

Acquired cataracts (age-related cataracts) generally occur without any obvious aetiology being identifiable. It is probable that poorer supply of the lens cells due to “ageing” of the cell junctions, as well as prolonged increased concentration of reactive oxygen species (ROS) which can be observed in smokers, for example, but which is also associated with various medical conditions, play a role. The spectrum of risk factors for these cataracts is broad, and not all factors have been identified yet. Known risk factors include [Abr 06, Con 03]:

- gender (women face a higher risk than men)
- genetic predisposition (family history of cataract)
- medical conditions (diabetes mellitus, hypertension, hypercholesterolaemia)
- smoking (nicotine)
- medication (steroid hormones and analogs)
- mechanical effects (“tennis ball” trauma)
- injuries to the lens capsule (foreign bodies, surgery)
- chronic choroiditis
- infrared, UV radiation (occupational exposure, leisure activities)
- ionising radiation.

3 Pathogenesis, progression and clinical picture of cataract following exposure of the lens to ionising radiation

3.1 Animal experimental data

An overview of the available animal experimental studies is provided in Table 1 in the Annex. Animal experimental studies have by preference been carried out on mice and rats. As a rule, doses of ≥ 1 Gy were applied; only one study used 0.3 Gy [Upt 56]. These studies allow sound conclusions to be drawn about the mechanisms which result in cataract formation after treatment with ionising radiation, as the morphological, physiological and biochemical parameters of the lenses of laboratory rodents and primates do not differ fundamentally [Mal 06].

Radiation-induced DNA damage is quickly repaired. In recent animal experiments [Wol 08], after irradiation with 11 Gray (Gy), DNA strand breaks in lens epithelial cells were demonstrated by comet assay for up to 30 minutes, but not after 4 hours. However, other DNA changes remained as shown 72 h post-irradiation, along with chromosomal aberrations [Wol 08]. Within a few hours of radiation exposure, a decrease in division activity in the equatorial lens epithelium can be observed; the duration of this phase increases with increasing dose. After the resumption of mitotic activity, there follows a wave of increased and abnormal cell division beyond the normal level [Wor 89]. In parallel, a few days after irradiation, there was an increase in the volume of the lens epithelial cells, and subsequently of the surface lens fibres which becomes permanent at higher doses (12 vs. 4 Gy) [Zin 86].

Within a matter of days, the organised structure of the zone, in which the epithelial cells begin with differentiation and in which fibre formation is initiated (meridional zone, Figure 2), starts to dissolve, based on atypical differentiation processes [Wor 89]. The result is an accumulation of untypical lens fibres, some containing nuclear fragments, which ultimately manifest clinically as cataract [Wor 86, Wol 08].

Lens opacities occur after long latency periods in which no clinical changes can be observed, but then show relatively rapid progression. Wolf et al. [Wol 08], in studies on mice (C57Bl/6), describe the development of complete opacity of a mature cataract over a 30 day period after minimal latency periods of 4 months.

However, the development of cataract is heavily dependent on the age of the irradiated animals and the radiation dose. These aspects were first studied in detail by Merriam and Szechter [Mer 73, 75] using rats. A complex relationship was observed which is shown in Figure 4.

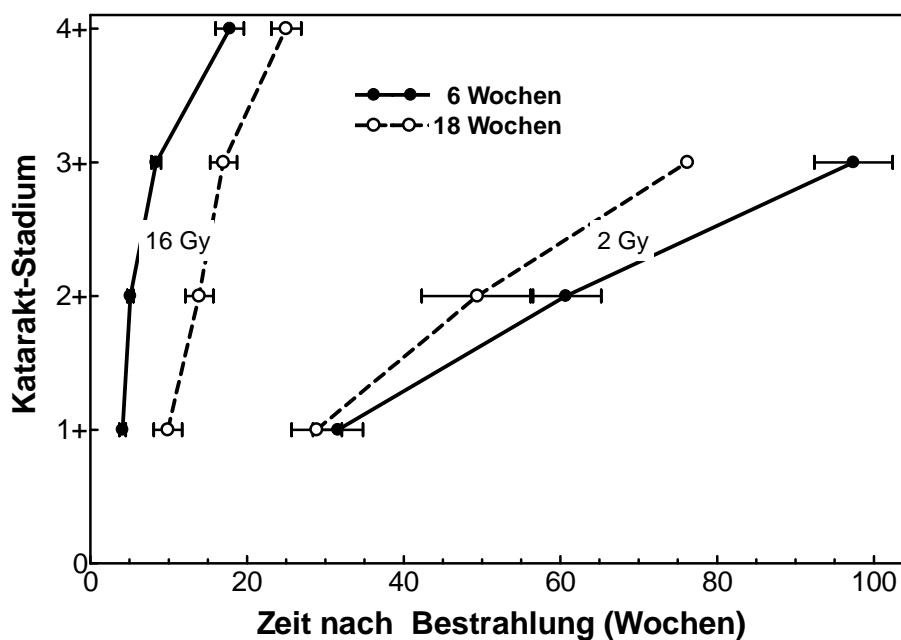


Figure 4: The effect of age on cataract formation.

At low doses (2 Gy), the lens changes occurred sooner and progressed faster in older animals (18 weeks at the time of irradiation) than in young animals (6 weeks at irradiation). At higher doses (16 Gy), the changes occurred sooner in young animals, but progression was somewhat slower. The stages of cataract were graded as follows in this study: 1+ early posterior subcapsular vacuoles; 2+ additional changes posteriorly plus early, anterior subcapsular opacities; 3+ an extension of both the anterior and posterior changes plus some generalised cortical and nuclear sclerosis; and 4+ a complete opacity. Based on Merriam & Szechter [Mer 75].

Key:

Katarakt-Stadium = Stage of cataract

6 Wochen = 6 weeks old

18 Wochen = 18 weeks old

Zeit nach Bestrahlung (Wochen) = Period after irradiation (weeks)

Similar studies on age dependency were also carried out on mice, albeit with only one dose (300 rad = 3 Gy). Here too, particular sensitivity to radiation was noted for the first three days after birth. In the subsequent 1-3 weeks, the lens appears to be more resistant to radiation, reaching a plateau at a relatively low level at 3-10 weeks, with resistance to radiation then increasing again [Gaj 77]. Similar studies on humans are not known.

Depending on the radiation dose, the opacities may remain stationary in the early stages or develop slowly to an intermediate stage and remain stationary for years, or progress to a fully mature cataract [Mer 83].

In animal experiments, characteristically, the opacities which occur after exposure to radiation at low doses initially appear in the posterior subcapsular region of the lens and consist of small granules and vacuoles that tend to form a roughly circular opacity. With further progression, opacities can also occur in the sub-epithelial region or in the entire lens. After high doses of radiation, anterior changes may precede the posterior opacities [Mer 84].

In mice with defects in their DNA repair, radiation-induced cataracts occur sooner than in wild-type mice [Klei 07]. These studies particularly underline the important role of DNA repair mechanisms in the development of radiation cataracts.

3.2 Human studies

In qualitative terms, the findings of studies on the progression of cataract development in humans are in line with those resulting from animal experimentation. An overview of the available studies is provided in Table 2 (see Annex).

In early studies [e.g. Nef 69, Wor 89, 96], posterior subcapsular changes in the lens were described as a consistent finding after exposure to radiation. However, it should be borne in mind that steroids and possibly other risk factors can cause posterior subcapsular cataracts [Jam 07]. Subsequently, cataracts in other localisations (cortical cataracts) have been linked to radiation exposure as well [Fer 06, Nak 06].

The data situation for the induction of nuclear cataracts is unclear. In their re-analysis of atomic-bomb cataract data, Nakashima et al. [Nak 06] – like earlier studies – found no dose dependency in induction. The same applies to studies on astronauts [Ras 02, Jon 07]. By contrast, Rafnsson et al. [Raf 05] have described an increased hazard ratio for nuclear cataracts in commercial airline pilots. A possible link with increased UVA exposure must be considered here [Fra 08].

Many epidemiological studies have shown that increased UVB exposure is a significant risk factor for cataracts (especially cortical and posterior subcapsular cataracts) [McC 02]). Ocular UVB exposure is thought to explain 10% of cases of cortical cataract [McC 00]; however, the dose is difficult to estimate. It must also be borne in mind that due to its morphological characteristics (recessed position in the eye socket, shielded well by the brow ridge), the human eye is relatively well-protected from radiation from above, whereas radiation from below (reflected by snow, water etc.) reaches the lens unhindered.

4 Dose dependency and threshold dose

In the following, the threshold dose is defined as the minimum dose that will produce any given effect. In experimental studies or epidemiological analyses, tests are generally conducted to determine whether an effect significantly different from zero is produced; in other words, the aim is to define the dose at which a statistically significant effect can be demonstrated. Tests can also be run to determine whether a model with a threshold dose explains the data better than a model with no threshold dose. In principle, when using this methodology, no conclusions can be drawn about the absence of a (albeit very low) threshold.

4.1 Animal experimental data

Although the results of animal experimental studies cannot be transferred quantitatively to humans, the data obtained from animal experiments are nonetheless of relevance here. In particular, the findings of animal experiments are of qualitative relevance when exploring the issue of a threshold dose. A detailed overview is provided in Table 1 in the Annex.

A number of experimental observations point to the clear influence of the mouse species used on the incidence and time progression of cataract formation even without radiation exposure, e.g. [Upt 56]. It should be noted that none of the species of mouse/rat used has ever been systematically studied to identify possible (genetic) variations in their sensitivity to radiation.

A further genetic influence is apparent when mice with hetero- or homozygous mutation of the ataxia-telangiectasia mutated gene (ATM) are irradiated. Relevant studies [Kle 07, Wor 02, 05] clearly show that at all the doses used, heterozygous ATM mutants developed a low grade of cataract much earlier than wild-type controls; this difference increased with decreasing dose (inverse correlation). It is possible that at lower doses, compensatory mechanisms (the nature of which has yet to be identified) come into play in the resistant species, and that these mechanisms are saturated at higher doses. The description of genetic differences in cataract risk is particularly important as it thus demonstrates a genetic predisposition to radiation-induced cataracts experimentally for the first time. This aspect has not yet been studied systematically in humans (but see comments on the influence of genetic background in Section 2.2).

Upton et al. [Upt 56] showed that the mild forms of cataract occur much earlier after irradiation from a dose as low as 0.3 Gy compared with non-irradiated controls (~ 8 months vs. ~ 13 months). All the studies based on animal experimentation that permit such analysis show an inverse relationship between the latency period until manifestation of a specific grade of cataract and increasing dose. However, this relationship is not linear but is particularly evident at lower doses (< 6 Gy) (e.g. [Mer 73, Ril 56, Dar 70, Sche 75, Gaj 77]).

4.2 Human studies

The overwhelming majority of clinical studies investigated the *prevalence* of cataract in a given population at a specific point in time after exposure. However, to determine *incidence*, follow-up observation of the population over a given period is required.

Prevalent cases consist of the incident cases in the period under review and the prevalent cases at the start of this period. Prevalence studies can only approximate the incidence risk very inaccurately. In addition, age effects and the dose-dependent latency period also influence the estimation of the dose-effect relationship on the basis of prevalence data.

The data on cataracts in humans following exposure to ionising radiation are based primarily on the following populations; atomic bomb survivors, people with occupational exposure, including pilots and astronauts, Chernobyl clean-up workers, patients who have undergone diagnostic and/or therapeutic irradiation, and groups with a high level of exposure to naturally occurring radiation from the environment.

The effects of early childhood exposure to radiation merit particular attention; here, the situation among humans appears to be as complex as it is with the animal models (cf. Figure

4). Studies among atomic bomb survivors in the 1980s showed that people who were less than 15 years old at the time of the bombing in Hiroshima developed axial and posterior subcapsular cataracts more frequently than children from Nagasaki [Chos 83]. A similar study 20 years later [Min 04] showed an increase in the hazard ratio of cortical and posterior subcapsular cataracts by a factor of 3 with age at the time of the atomic bombing (per 10 years; OR = 3.7 for cortical cataract and 2.1 for posterior subcapsular cataract); Nakashima et al. [Nak 06] arrive at qualitatively similar results. Of particular interest in this context are studies carried out among very young children who underwent radiation therapy to treat other medical conditions. Children exposed to a lenticular dose of 1 Gy had a 50% increased risk of developing a posterior subcapsular opacity, and the risk of developing cortical cataract was increased by around 35% with a follow-up observation period of at least 40 years [Hal 99]. In 1997, Wilde and Sjöstrand reported a higher radiation sensitivity than expected in the lens in an infant cohort who had received treatment at a median age of 6 months. During treatment with one or two radium-226 needles located at or within the orbital rim of one eye, the untreated contralateral lens received irradiation varying from 0.06 - 0.12 Gy; after 30-45 years, the increased presence of subcapsular punctate opacities and vacuoles in the lenses on the untreated side could be observed [Wil 97].

An overview of the results of the various studies is presented in Table 2 in the Annex.

4.2.1 *Study of the Hiroshima and Nagasaki atomic bomb survivors*

Otake and Schull [Ota 90] produced a re-analysis of earlier published data collected among atomic bomb survivors in Hiroshima and Nagasaki using the recently revised DS86 dosimetry system [Ota 82]. They compared various models with and without thresholds. It was found that the model with a 0.7 Gy threshold for gamma rays gives the same “safety” zone as the 0.07 Gy threshold for neutrons, although these models were only marginally superior to any other. This study was based on only 795 people and 15 recorded cases of cataracts in the dose range < 1 Gy. Furthermore, a very large number of investigators were involved in carrying out the (subjective) slit lamp examinations, and some of the examinations took place without pupil dilation [Chos 83]. A subsequent analysis [Ota 92] draws attention to the lack of a threshold dose, but in essence, does not produce any viable results as all the grades of lens opacity, from minimal to clinically manifest changes, were analysed together.

More recent analyses have been carried out using the new DS02 dosimetry system and other parameters (e.g. cataract surgery in particularly severe cases). Nakashima et al. [Nak 06] estimate threshold dose points of 0.6 Sv (90% CI, <0.0 - 1.2 Sv) and 0.7 Sv (90% CI, <0.0 - 2.8 Sv) for cortical cataract and posterior subcapsular opacity respectively, which therefore do not demonstrate a threshold dose reliably. With a no threshold model, cortical cataract showed a significant dose effect ($p = 0.002$), with an odds ratio (OR)/Sv of 1.30 (95% CI, 1.10 - 1.53); posterior subcapsular opacity showed a significant dose effect ($p < 0.001$), with an OR/Sv of 1.44 at age of exposure of 10 years (95% CI, 1.19 - 1.73). The dose effect decreased significantly with increasing age at exposure and could no longer be demonstrated at an exposure age of 30 years. Neriishi et al. [Ner 07] arrived at similar results among 3761 A-bomb survivors, including 479 postoperative cataract cases. The analyses indicated a statistically significant dose-response increase in the prevalence of postoperative cataracts (odds ratio (OR), 1.39; 95% confidence interval (CI), 1.24 - 1.55) at 1 Gy. A nonsignificant dose threshold of 0.1 Gy (95% CI, <0 - 0.8) was found.

4.2.2 *People with occupational exposure to ionising radiation*

Studies of the risk associated with occupational exposure to ionising radiation have been carried out among various occupational groups. They include radiologic technologists, people with actinide exposure, commercial airline pilots and astronauts. A major prospective cohort study among more than 37,000 U.S. radiologic technologists [Cho 08] showed that the lowest cumulative ionising radiation dose to the lens of the eye that can produce a progressive cataract is lower than 2 Gy, i.e. less than previously thought. Workers in the highest category were exposed to a mean dose of around 60 mGy; their risk of developing cataract is around 20% higher than workers in the lowest category of occupational dose. The additional relative risk of cataract development, according to this study, was 2.0% per Gy (95% confidence interval, -0.7 - 4.7) and therefore not significantly different from zero. The analysis showed a clear dependency on age at the start of exposure, with a relative hazard ratio (compared with people < 30 years of age) of 7.6 (95% CI: 6.4 - 9.0) for 40- to 44-year-olds. This study is based on questionnaires and therefore only covers the clinically relevant cases. As experience has shown, self reporting shows a positive predictive value of 76% for cataracts and 95% for cataract surgery [Bow 03].

A cohort study carried out among retired workers (mean age: 76 years) with previous occupational exposure to actinides who were included in the U.S. Transuranium and Uranium Registries [Jac 05] looked at the number of cataract cases. In 97 cases with lifetime exposure records, 65 cataract cases were described, with 31% reported to have posterior subcapsular type. Of 24 individuals with recorded lifetime doses above 200 mSv, 18 (75%) had cataracts, compared with 47 out of 73 workers (64%) with doses of less than 200 mSv. In each case, the share of posterior subcapsular cataracts was higher than in population-based studies with subjects with no radiation exposure [Jac 05]. However, the influence of age and gender was not taken into account.

A case-control study of 445 airline pilots [Raf 05] looked at 71 people with nuclear cataracts, 102 with cortical lens opacification, 69 with central optical zone involvement, and 32 with posterior subcapsular lens opacification. This study has aroused controversy [Fac 06]. Here too, the “quantification” of lens opacification was undertaken using a slit lamp; Scheimpflug and retroillumination data – although collected – were not used in the analysis. Due to a lack of data, only 79 people were included in the analysis. The association between the radiation exposure of pilots and the risk of cataracts was adjusted for age, smoking status, and sunbathing habits. A cataract was defined as any reaction of grade 1 or above according to the World Health Organization (WHO) cataract grading system [Thy 02], irrespective of clinical relevance. The relative ratio for *nuclear* cataract risk was 3.0 (95% confidence interval, 1.4 - 6.4) for pilots compared with the control group. UVA exposure, which might explain the localisation of the cataracts (see above), was not discussed.

A study of 222 astronauts who had undertaken at least one space flight found 48 cataract cases [Cuc 01]. The number of space flights, the astronauts’ age and the inclination of the flight (due to the increased presence of heavy-ion radiation in orbits over the Earth’s polar regions, and thus the greater biological effectiveness of radiation (see 5.2.)) were identified as risk factors. Two groups of astronauts were compared (space radiation dose above or below 8 mSv) and the interval between the onset of cataract and the time of the first space mission was determined; flights to the Skylab and Mir space stations resulted in the highest “lens doses” from space radiation (87 and 91 mSv respectively). Cataracts occurred in 10% of cases in the high-dose group just 8 years after the first space flight, but only after more than 15

years in the low-dose group. The relative hazard ratio for the high-dose group was 2.35 (95% CI: 1.01 - 5.51) and 2.44 (95% CI: 1.20 - 4.98) for 60- and 65-year-olds respectively for all types of cataract. As for the specific types of cataract, in both age groups, only the hazard ratio for the mixed types (nuclear/posterior subcapsular cataract) was significantly increased; in the age group to 65, the hazard ratio was increased only for the nuclear type. A comparison with a non-exposed control group was not carried out, although data were also available for 73 astronauts who had not undertaken any space flights. Possible effects of UV radiation were discussed but due to a lack of data about exposure, were not included in the detailed analysis.

Initial results of a study of astronauts/cosmonauts (n = 21) using the Scheimpflug system indicated that opacity values in most of the astronauts and cosmonauts were slightly to strongly increased in the posterior cortex and posterior capsule [Ras 02, Jon 07]. By contrast, among conventional U.S. Navy/Airforce flight personnel – unlike the above-mentioned study of commercial airline pilots [Raf 05] – cataracts were primarily detected in the posterior subcapsular region.

Numerous other studies, albeit with very small case numbers and/or short follow-up observation periods in most cases, indicate that the threshold dose for cataract development lies well below 1 Gy. These studies will not be discussed further.

4.2.3 *Chernobyl clean-up workers*

Following the Chernobyl nuclear power plant disaster [Wor 07], the eyes of a prospective cohort of 8607 Chernobyl clean-up workers (liquidators) were assessed for cataract at 12 and 14 years after exposure (slit lamp with pupil dilation). In this study, the grades of cataract are specified in detail. The average age of the cohort at the time of exposure was 33 (± 7 ; SD); average age at the time of first examination was 45 and at the time of second examination was 47. The prevalence of strictly age-related (nuclear) cataracts was low (< 4%), as expected. However, posterior subcapsular or cortical cataracts characteristic of radiation exposure were present in 25% of the subjects. Significantly increased risks were identified for higher-grade non-nuclear cataracts from doses of 0.4 Gy, and for various other end points (e.g. grade 1 - 5 cataract, grade 1 - 5 non-nuclear cataract) from doses of 0.6 Gy. The authors derive threshold doses of 0.5 Gy for all grades of cataract, including a threshold dose of 350 mGy for grade 1 (i.e. clinically non-relevant types of cataract). It is likely, however, that as more time elapses following exposure, that the number and severity of the lens opacities will increase. An increase in cataract risk with age at exposure was identified, with a cumulative incidence of 8.5% for < 25 years and up to 53.4% \geq 40 years.

In individuals who developed symptoms of acute radiation sickness after high radiation exposure, cataracts developed from a dose of 2.6 Gy. The number of people in the cohort decreased from the original figure of 83 during the period 1986-1990 to 69 in 2005 [Nad 03; Gal 07].

4.2.4 *Patients after diagnostic and/or therapeutic radiation exposure*

Early studies on radiation-induced cataract generally have little informative value due to methodological shortcomings in the diagnostics. Merriam and Focht [Mer 57] studied 233 radiation therapy patients of whom 128 developed cataract within around 9 years. The lowest dose at which cataract was observed was 2 Gy with an exposure duration of 3 weeks, 4 Gy with an exposure duration of 3 months, and 5.5 Gy over longer treatment periods. It should be noted, in this context, that only a small number of patients (34/233) had received low doses

and that the follow-up observation period may have been too short to observe cataract development at these low doses.

Hall et al. [Hal 99] studied more than 400 children with skin hemangiomas (mainly on the face) who were treated with radiotherapy before the age of 18 months (lenticular doses of less than 0.5 to more than 1.0 Gy); around 100 children who were not exposed to radiation were used as a control group. The study found an increased risk of around 50% per Gy for cortical and posterior subcapsular cataracts; findings were adjusted to take account of age at the time of study, dose rate and steroid treatment.

Benyunes et al. [Ben 95] studied cataracts in adults who underwent total body irradiation (TBI) as part of their treatment for leukaemia. TBI was administered in a single dose of 10 Gy or in fractionated doses totalling 12 - 15.75 Gy over several days. Dose fractionation was found to have a clear effect (see 5.1), with an incidence of cataract of 30 - 35% after a mean of 5 years, compared with around 80% after single exposure. Patients who received an additional cortisone treatment showed a significantly increased incidence of cataract (45% vs. 38%, $p < 0.0001$). Van Kempen-Harteveld et al. [vKem 00] produced similar results.

In patients who had undergone CT scans [Kle 93], researchers described an increased prevalence of posterior subcapsular cataracts and conclude that doses of just 0.1 - 0.3 Gy may be cataractogenic.

In the study of radiation technologists [Cho 08] who had ≥ 3 x-rays to the face/neck, performed for non-occupational reasons, a significantly increased incidence of cataract and a hazard ratio of cataract of 1.25 was demonstrated (95% confidence interval: 1.06 - 1.47) compared with people having fewer or no x-rays to the face/neck.

4.2.5 *People with increased exposure to environmental radiation in their daily lives*

Chen et al. [Che 01] studied a total of 114 individuals who were exposed to chronic low-dose-rate γ radiation due to spending time in buildings contaminated with ^{60}Co in Taiwan. The lenticular opacities were evaluated by slit-lamp biomicroscopy after full pupil dilatation. These individuals were further divided into those less than 20 years old, those between 20 and 40 years old, and those more than 40 years old to evaluate the effects of age. The cumulative doses were assessed for each individual using the Taiwan Cumulative Dose (TCD) estimation system. A significant dose-dependent increase in the numbers of focal lens defects in those less than 20 years old was demonstrated.

5 Factors influencing the radiation effect

5.1 Fractionation/dose rate effect and time factor

In considering the influence of total exposure time, a clear distinction must be made between two quite distinct processes: (i) recovery from so-called sub-lethal radiation damage and (ii) proliferation of target cells during protracted exposure or between individual exposures. Both processes result in increased radiation tolerance.

The effectiveness of a defined radiation dose decreases if it is fractionated or if irradiation is administered over the course of several hours/days (*fractionation/dose rate effect*).

In total body irradiation (TBI) for bone-marrow or stem cell transplantation with various dose rates, all studies show a clear reduction in the incidence of cataract if the dose rate is reduced. For example, Van Kempen-Hartefeld et al. [vKem 02] observe a reduction in cataract frequency after 14 years from 100% following irradiation with 10 Gy at a dose rate of 0.25 Gy/min to around 10% at 8 Gy with 0.02 Gy/min. Similarly, Belkacémi et al. [Bel 1998] report a significant reduction in cataract frequency in fractionated irradiation as compared with single irradiation and with a low dose rate (< 0.05 Gy/min) compared with a moderate or high dose rate. Analysis of data by Van Kempen-Hartefeld et al. [vKem 02] and Thames et al. [Tha 84] reveals a very clear fractionation/dose rate effect value. These findings clearly accord with studies on the repair of DNA damage in lenticular cells after radiation exposure (see above).

A further factor influencing a tissue's tolerance to radiation is the time factor, i.e. an increase in radiation tolerance with long intervals between exposure or with protracted exposure over weeks/months. This is based on repopulation of target cells and therefore results in an increase in the dose required to achieve a specific effect.

In a comparison of cataract incidence among populations with protracted occupational exposure over a long period [Cho 08, Raf 05] or high environmental doses [Che 01], no systematic differences are identified compared with groups of people with single or short-term exposure.

Thus a reduction in the cataract risk can only be anticipated if the duration of exposure – with identical dose – is extended from a single exposure and administered over hours or days and the fractionation/dose rate effect comes into play. With the extension of exposure over months or years up to lifetime exposure, no significant reduction in the cataract hazard risk can be assumed.

5.2 Influence of radiation quality

There are several (experimental) studies on the influence of radiation quality (relative biological effectiveness – RBE) on cataract production. These primarily focus on exposure to neutrons, as well as heavy ions. Worgul et al. [Wor 96] conclude from their own studies on rats and a review of the relevant literature that for low neutron doses (< 10 mGy), an RBE well above 20 must be assumed. A similar conclusion is drawn by Merriam et al. [Mer 84] and Brenner et al. [Bre 91] for argon ions. Such high RBE values result from the low effectiveness of the reference radiation (x-radiation) in the dose range studied. The RBE decreases with increasing dose.

5.3 Summary and evaluation

The lens of the eye is highly sensitive to radiation; after a latency period which may last for several decades, exposure to ionising radiation results in progressive opacification of the lens (cataract) and therefore often causes blindness unless the clouded lens is replaced through surgery. The national and international radiological protection bodies have recognised this fact and introduced specific limit values for the lens (German Radiation Protection Ordinance (StrlSchV) para. 55 (2), German X-ray Ordinance (RöV) para. 31a (3): 150 mSv/year; people under 18 years of age 15 mSv/year).

Recent epidemiological studies, especially among Hiroshima and Nagasaki atomic bomb survivors [Nak 06, Ner 07], Chernobyl clean-up workers [Wor 07] and radiologic technologists in the U.S. [Cho 08], have not demonstrated any threshold value below which damage to the lens of the eye from ionising radiation can be ruled out with certainty; however, there is a strong probability that the threshold dose is <0.8 Gy. The lowest measured/reconstructed radiation doses lie in the 5 - 100 mGy range. The 95% confidence intervals for possible threshold doses include zero value in many cases, so that the existence of a threshold dose can no longer be assumed with certainty.

There is a significant genetic predisposition for spontaneous cataracts; studies here are possible using genetically modified laboratory animals. It must be assumed that genetic risk factors come into play in humans too; this is indicated by the different incidences of cataract among populations of different ethnic origin living in similar conditions.

In various studies, an increase in the cataract rate was observed after radiation exposure of around 0.5 Gy and relative hazard ratios of around 1.5 after exposure to 1 Gy radiation. As comparable effects were observed after short-term exposure and after exposure over longer periods, these dose and risk values should not be viewed in relation to a limit value for an annual lens dose but in relation to lifetime dose. The current limit value for lens dose established by the German Radiation Protection Ordinance, i.e. 0.15 Gy, would amount to a cumulative dose of 3 Gy over a 20-year exposure period. This dose is higher, by a factor of almost 6, than the dose at which additional cataracts have been observed, and according to current knowledge, would more than double the risk of spontaneous cataract.

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Table 1: Studies of cataract formation after radiation exposure in mice (x- and γ -radiation)

Initial damage (dose; period after irradiation)	Doses applied	Threshold dose	Observation period (in total)	End point	Energy	Dose rate	Age	Species of mouse	Reference
33 rep; 8 mo [1 rep = 9.3 mGy]	33-333 rep	0.15-0.30 rep	36 months	Grade 1-4	250 kV	70-80 rep/min	8-14 wks	RF LAF1 RF	Upt 56
100 r; 1 y (1 rep = 9.3 mGy)	100-1000 rep	Not calculated [CD ₅₀ : 775 rep]	1 year	Grade 1-3	200/250 kV	33 rep/min	10-14 wks	Swiss albino	Ril 56
50 rad, 117 days	50-456 rad	Not calculated	500 days	2%, 10% opacity	300 kV	60-90 R/min	8 wks	RF only females used	Dar 70
900 R; 6 mo	700-2200 R	Not calculated; [CD ₅₀ : 835 R]	6 months	Grade 1-3; results only for grade 3	270 kV	130 R/min	14-16 wks	Ha/ICR	Sche 75
Complex age dependency 0.5 Gy; 10 wks	300 R	Not calculated	Lifetime (>700 days)	Grade 1-5	170 kV	42 R/min	1-7 days 1-52 wks	A	Gaj 77
0.5 Gy; 10 wks	0.5-4.0 Gy	Not calculated	Lifetime	Grade 1-4	250 kV	0.5 Gy/min	4 wks	Atm ^{+/+} ; Atm ^{-/-} 129SvEv, Black Swiss	Wor 02
0.5 Gy; 10 wks	0.5 Gy	Not calculated	Lifetime	Grade 1-4	250 kV	0.5 Gy/min	4 wks	Atm ^{+/+} ; Mrad9 ^{+/+} 129SvEv, Black Swiss	Klei 07

All doses are original, i.e. as stated in the relevant publications.
 Threshold dose: minimum dose that will produce any given effect.
 For an interpretation of the grades of cataract, see 2.1.

rep: röntgen equivalent physical

Table 2: Studies of cataract formation after radiation exposure in humans (x- and γ -radiation)

Initial changes	Threshold dose	OR	Observation period (in total)	End point	Energy/result	Dosimetry	Age	Reference
No data	Not calculated	1.45 CI: 1.08-1.95	Lifetime	Cataract (nuclear, posterior subcapsular)	Questionnaire about med. irradiation (0.47 R-37.75 R)	None	43-84 y	Kle 93
20% cataract after 2 years	Not calculated	Not calculated	2-18 years	Cataract (nuclear, posterior subcapsular)	Radiation therapy (1x10 - 7x2.25 Gy)	Treatment schedule	\geq 16 y	Ben 95
0.06-0.12 Gy to untreated eye	Not calculated	Not calculated	30-45 years	Grade 1-8	Radiation therapy 1-11 Gy	Calculated	2-13 mo	Wil 97
0.5 Gy	Not calculated	1.35-1.50 (per Gy) CI: 1.07 – 2.08	34-54 years	LOCS \geq Grade 1 (nuclear, cortical, posterior subcapsular)	Radiation therapy (<0.5 - >1.0 Gy)	Calculated, phantom; measured with dosimeter	<18 mo	Hal 99
30 mo	Not calculated	Not calculated	up to 10 years	Grades 1-4	Radiation therapy (1x8 -> 2x6 Gy)	Treatment schedule	14-56 y	vKem 00
No figures	Not calculated	Not calculated	14 years	LOCS III (Grades 1-2)	>5 mSv / y environmental dose	Estimation	\leq 20; 20-40; >40 y	Che 01
< 8mSv	Not calculated	Comparison only <8 mSv vs. >8mSv	30 years+	Cataract (nuclear, posterior subcapsular etc.)	Astronauts; no controls	Dosimeter	~39-45 y	Cuc 01
0.2 Sv	Not calculated	1.29-1.41 CI: 1.12-1.64	55-57 years	LOCS II	A-bomb	DS86	0-13 y >13 y	Min 04

Initial changes	Threshold dose	OR	Observation period (in total)	End point	Energy/result	Dosimetry	Age	Reference
0-50 mSv	Not calculated	Not calculated	Occupational lifetime	Ophthalmologists surveyed	Actinium workers	Dosimeter	~76 years (mean)	Jac 05
22-48 mSv.	Not calculated	4.19 CI: 1.04-16.86	up to 43 years	>Grade 1 (WHO)	Pilots	Calculation (CARI-6)	<40 y	Raf 05
0.005-0.5 Sv	0.6 Sv CI (90%): <0.0 - 2.8	1.44 (per Sv, for age = 10 y) CI: 1.19-1.73	55-57 years	Cataract: cortical, posterior subcapsular	A-bomb	DS02	0-≥15 y	Nak 06
No data	No data	No data	Lifetime	Cataract	Commercial airline pilots, astronauts	Rough estimation	52-85 y	Jon 07
0.005-0.5 Sv	0.1 Gy CI: <0 - 0.8 Gy)	1.39 (per Sv) CI: 1.24-1.55	55-57 years	Cataract surgery	A-bomb	DS02	all	Ner 07
100-249 mGy	0.34 Gy (95% CI: 0.19-0.68 Gy)	1.28-2.56 (per Gy) CI: 1.1-5.4 (various groups)	12-14 years	Grades 1-5	Chernobyl	Individual or group dosimetry, EPR (teeth), calculation	33±7 y	Wor 07
3.2 Gy; 70 mo	Not calculated	Not calculated	21	Cataract in 11 patients	Chernobyl	Patients with acute radiation syndrome	No data	Gal 07
60 mGy	Not calculated	1.18 (per Gy) CI: 0.99-1.40	20 years	Cataract	US radiologic technologists	Questionnaire	22-44 y	Cho 08

All doses are original.

Threshold dose: minimum dose that will produce any given effect. CI: confidence interval: 95% unless otherwise stated. For interpretation of the various grades of cataract, see II.1. For [Wor 07], grades are defined in the reference article. Many publications make no reference to "confounders"; this must be taken into account when interpreting the data.