Classification of harmful radiation-induced effects on human health for radiological protection purposes

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On behalf of TG123

ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

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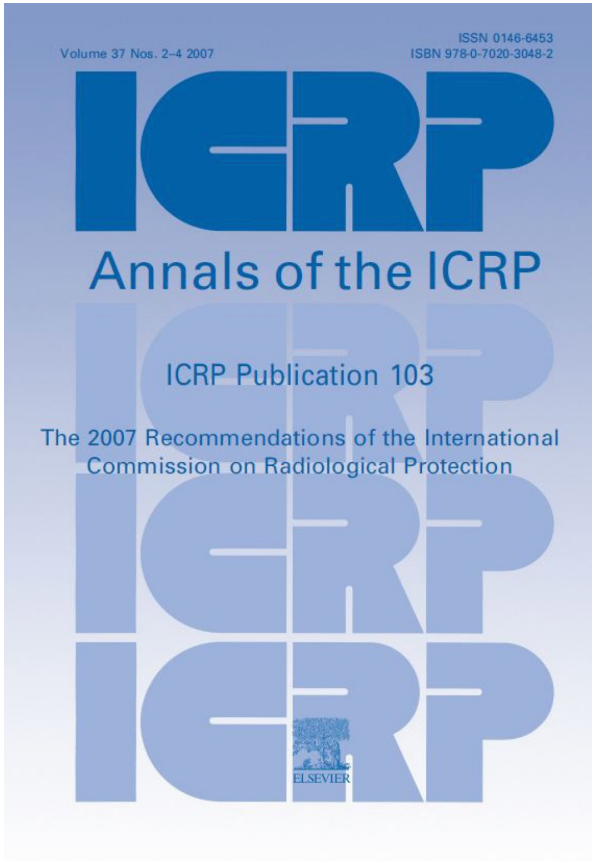
Objective of the system of radiological protection

The primary aim of ICRP recommendations is to contribute to an appropriate level of protection for people against the detrimental effects of radiation exposure, without unduly limiting the desirable human actions that may be associated with such exposure.

Radiological protection deals with two types of harmful effect […] harmful tissue reactions which only appear if the dose exceeds a threshold value and […] stochastic effects (cancer or heritable effects), which may be observed as a statistically detectable increase in the incidences of these effects occurring long after exposure.

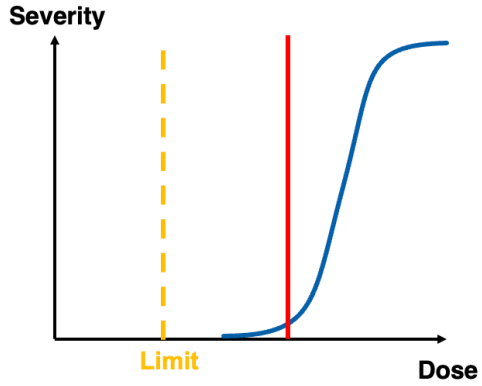


Objective of the system of radiological protection

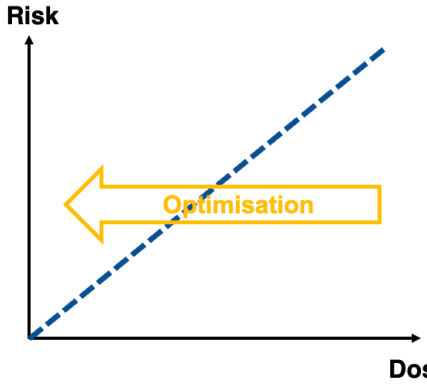
Tissue reaction (also termed deterministic effects): injury in populations of cells characterised by a threshold dose and an increase in the severity of the reaction as the dose is increased further.

Stochastic effect (of radiation): effects resulting from damage in a single cell (cancer and heritable effects). The frequency of the event, but not its severity, increases with an increase in the dose. For protection purposes, it is assumed that there is no threshold dose.

ICRP system of radiological protection health objectives are relatively straightforward: to manage and control exposures to ionising radiation so that harmful tissue reactions are prevented, and the risks of stochastic effects are reduced to the extent reasonably achievable.



Harmful tissue reactions are prevented



The risks of stochastic effects are reduced to the extent reasonably achievable

Disease of circulatory system in Publication 103 (2007)

3.1. The induction of deterministic effects (harmful tissue reactions)

(58) The induction of tissue reactions is generally characterised by a threshold dose. The reason for the presence of this threshold dose is that radiation damage (serious malfunction or death) of a critical population of cells in a given tissue needs to be sustained before injury is expressed in a clinically relevant form. Above the threshold dose the severity of the injury, including impairment of the capacity for tissue recovery, increases with dose.

(59) Early (days to weeks) tissue reactions to radiation in cases where the threshold dose has been exceeded may be of the inflammatory type resulting from the release of cellular factors, or they may be reactions resulting from cell loss (*Publication 59*, ICRP, 1991a). Late tissue reactions (months to years) can be of the generic type if they arise as a direct result of damage to that tissue. By contrast other late reactions may be of the consequential type if they arise as a result of early cellular damage (Dörr and Hendry, 2001). Examples of these radiation-induced tissue reactions are given in Annex A.

(60) Reviews of biological and clinical data have led to further development of the Commission's judgements on the cellular and tissue mechanisms that underlie tissue reactions and the dose thresholds that apply to major organs and tissues. However, in the absorbed dose range up to around 100 mGy (low LET or high LET) no tissues are judged to express clinically relevant functional impairment. This judgement applies to both single acute doses and to situations where these low doses are experienced in a protracted form as repeated annual exposures.

(61) Annex A provides updated information on dose thresholds (corresponding to doses that result in about 1% incidence) for various organs and tissues. On the basis of current data the Commission judges that the occupational and public dose limits, including the limits on equivalent dose for the skin, hands/feet and eyes, given in *Publication 60* (ICRP, 1991b) remain applicable for preventing the occurrence of deterministic effects (tissue reactions); see Section 5.10 and Table 6. However, new data on the radiosensitivity of the eye are expected and the Commission will consider these data when they become available. In addition, in Annex A, reference is made to the clinical criteria that apply to dose limits on equivalent doses to the skin.

3.3. The induction of diseases other than cancer

(91) Since 1990 evidence has accumulated that the frequency of non-cancer diseases is increased in some irradiated populations. The strongest statistical evidence for the induction of these non-cancer effects at effective doses of the order of 1 Sv derives from the most recent mortality analysis of the Japanese atomic bomb survivors followed after 1968 (Preston et al., 2003). That study has strengthened the statistical evidence for an association with dose – particularly for heart disease, stroke, digestive disorders, and respiratory disease. However, the Commission notes current uncertainties on the shape of the dose-response at low doses and that the LSS data are consistent both with there being no dose threshold for risks of disease mortality and with there being a dose threshold of around 0.5 Sv. Additional evidence of the non-cancer effects of radiation, albeit at high doses, comes from studies of cancer patients receiving radiotherapy but these data do not clarify the issue of a possible dose threshold (Annex A). It is also unclear what forms of cellular and tissue mechanisms might underlie such a diverse set of non-cancer disorders.

(92) Whilst recognising the potential importance of the observations on non-cancer diseases, the Commission judges that the data available do not allow for their inclusion in the estimation of detriment following low radiation doses, less than about 100 mSv. This agrees with the conclusion of UNSCEAR (2008), which found little evidence of any excess risk below 1 Gy.

'The Commission judges that the data available do not allow for their inclusion in the estimation of detriment following low radiation doses, less than about 100 mSv'.

Disease of circulatory system in Publication 118 (2012)

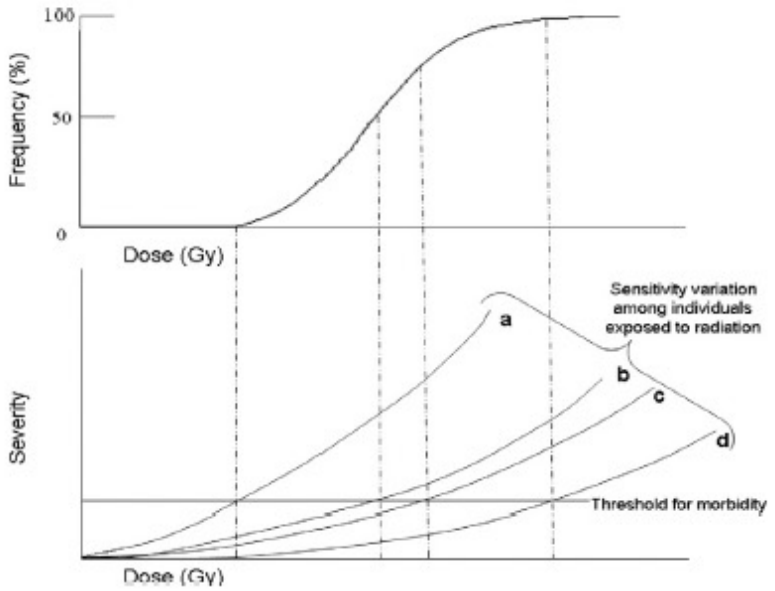


Fig. 1.1. Relationships between dose and the frequency or severity of tissue reactions. Upper panel: the incidence (frequency) of morbidity as a function of dose in a population of individuals of varying sensitivities. Lower panel: the dose vs reaction severity relationship for four subpopulations with different radiosensitivities ('a' being most radiosensitive, 'd' being least radiosensitive) comprising the total population. Adapted from *Publication 60* (ICRP, 1991; Hendry et al., 2006).

'A threshold dose for a given effect can be defined as a dose below which the effect does not occur. This dose is often difficult to determine. One way in which epidemiological evidence for a threshold can be assessed is by examination of the lowest dose at which a significant positive dose-response relationship can be detected […] In this report, the 'threshold dose' is defined as ED1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation' (§13)

Disease of circulatory system in Publication 118 (2012)

‘Whilst the estimates of the ERR/Gy, based on a linear dose-response analysis, vary between studies and between specific types of circulatory disease, an ERR/Gy of around 0.1 would seem to be a reasonable summary value, particularly in the case of the atomic bomb study. A recent report (Table 8 in AGIR, 2010), calculating aggregate risks from many studies, estimated an ERR/Gy of 0.10 (95% CI 0.07-0.13) for morbidity and 0.08 (95% CI 0.04–0.12) for mortality from circulatory disease taken as a whole’.

‘If an ERR/Gy of this magnitude were to apply at doses in the range of 0.5 Gy, and the baseline incidence is 30-50%, this would imply that a dose of 0.5 Gy might increase mortality from circulatory disease by approximately 0.08 x 0.5 x (30-50)% = 1.2-2%’.

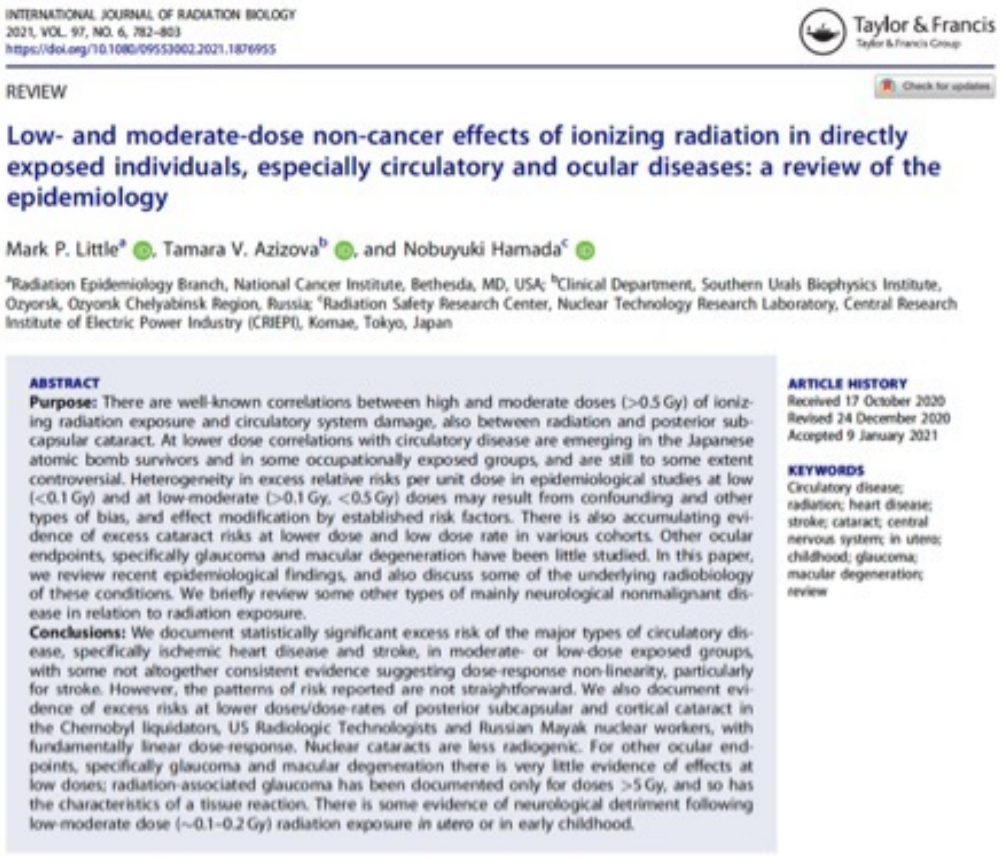
‘Given that not all cases of circulatory disease are fatal, the corresponding percentage for morbidity would be expected to be greater. Overall, and subject to the assumptions outlined here, a dose of around 0.5 Gy might lead to approximately 1% of exposed individuals developing circulatory disease’.

Disease of circulatory system nowadays

4. Conclusion

So, where does that leave us? At the outset of this article, it was noted that whether low-level exposure to radiation increases the risk of DCS is one of the most important questions currently facing those responsible for reviewing the ICRP system of radiological protection [37, 38]. Certainly, there are reports from some epidemiological studies of associations between the cumulative dose of gamma radiation and a proportional increase in the risk of DCS [3]. However, there are substantial challenges to overcome before a confident interpretation of these epidemiological associations can be made. DCS incidence data from the Russian studies require close examination, including why there is a striking difference between ERR/Gy estimates for CeVD incidence and mortality in the Mayak workforce. Then, there are the perplexing temporal patterns of DCS mortality rates with respect to cumulative external dose in the Mayak and Sellafield workforces. The puzzling issue of why DCS mortality ERR/Gy estimates for external doses received by Sellafield (and possibly other) workers are governed by the status of monitoring for potential exposure to internal emitters needs to be explored, as does the difference in the internal exposure monitoring findings for UK workers between INWORKS and the original NRRW analysis (especially for CeVD). Further, recent studies of DCS mortality rates in US workforces provide little evidence of an increase in radiation-associated risk, although an expanded database is anticipated. Finally, this article has focussed on the problems of interpretation of epidemiological evidence, but these difficulties are exacerbated by the lack of knowledge of candidate mechanisms that might underlie a putative link between DCS risk and low-level radiation exposure (see, for example, the recent review of Tapio *et al* [6] and the mechanistic model for atherosclerosis proposed by Simonetto *et al* [39]). There is much to be done before a proper understanding of these epidemiological associations is reached.

Risk of diseases of the circulatory system after low-level radiation exposure - an assessment of evidence from occupational exposures
Richard Wakeford 2022 J. Radiol. Prot. 42 020201



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REVIEW

Low- and moderate-dose non-cancer effects of ionizing radiation in directly exposed individuals, especially circulatory and ocular diseases: a review of the epidemiology

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ABSTRACT

Purpose: There are well-known correlations between high and moderate doses (>0.5 Gy) of ionizing radiation exposure and circulatory system damage, also between radiation and posterior subcapsular cataract. At lower dose correlations with circulatory disease are emerging in the Japanese atomic bomb survivors and in some occupationally exposed groups, and are still to some extent controversial. Heterogeneity in excess relative risks per unit dose in epidemiological studies at low (<0.1 Gy) and at low-moderate (>0.1 Gy, <0.5 Gy) doses may result from confounding and other types of bias, and effect modification by established risk factors. There is also accumulating evidence of excess cataract risks at lower dose and low dose rate in various cohorts. Other ocular endpoints, specifically glaucoma and macular degeneration have been little studied. In this paper, we review recent epidemiological findings, and also discuss some of the underlying radiobiology of these conditions. We briefly review some other types of mainly neurological nonmalignant disease in relation to radiation exposure.

Conclusions: We document statistically significant excess risk of the major types of circulatory disease, specifically ischemic heart disease and stroke, in moderate- or low-dose exposed groups, with some not altogether consistent evidence suggesting dose-response non-linearity, particularly for stroke. However, the patterns of risk reported are not straightforward. We also document evidence of excess risks at lower doses/dose-rates of posterior subcapsular and cortical cataract in the Chernobyl liquidators, US Radiologic Technologists and Russian Mayak nuclear workers, with fundamentally linear dose-response. Nuclear cataracts are less radiogenic. For other ocular endpoints, specifically glaucoma and macular degeneration there is very little evidence of effects at low doses; radiation-associated glaucoma has been documented only for doses >5 Gy, and so has the characteristics of a tissue reaction. There is some evidence of neurological detriment following low-moderate dose (~0.1–0.2 Gy) radiation exposure *in utero* or in early childhood.

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KEYWORDS
Circulatory disease; radiation; heart disease; stroke; cataract; central nervous system; in utero; childhood; glaucoma; macular degeneration; review

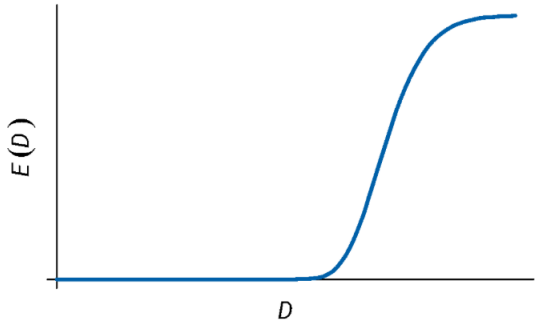
Disease of circulatory system nowadays

While diseases of the circulatory system cannot be considered as a stochastic effect (e.g. it is probably not resulting from damage in a single cell), should it be, nevertheless, considered as a health outcome at low doses?

Should ionising radiation be considered as a risk factor contributing, together with other risk factors, to damages resulting to disease of circulatory system?

While biological plausibility at low dose is not well established and despite sometimes opposite views among the scientific community, the question has not been clearly answered so far.

Radiation alone



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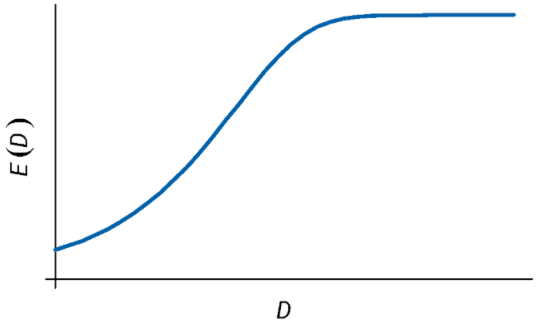

Keeping the ICRP recommendations fit for purpose

'The classification of harmful radiation-induced health effects into 'stochastic effects' and 'harmful tissue reactions' for protection purposes should be revisited to ensure that it remains fit for purpose. […] Some health effects may not fit well into either category (e.g. cataract, diseases of the circulatory system). Whatever classification is adopted, it will be necessary to assess the impact on the management of radiological risks in terms of the tolerability of risks and putting them into perspective with other risks. Any reclassification will not affect the fundamental requirements to prevent severe tissue reactions and optimise protection against effects at low doses and low dose rates, principally cancer'.

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Memorandum

Keeping the ICRP recommendations fit for purpose

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ICRP TG123 - Classification of harmful radiation-induced effects on human health for radiological protection purposes

ICRP TG123 is a joint Committee 1 and Committee 4 Task Group aiming at:

Clarify the rationale behind the current classification (based on a review of relevant ICRP Publications),

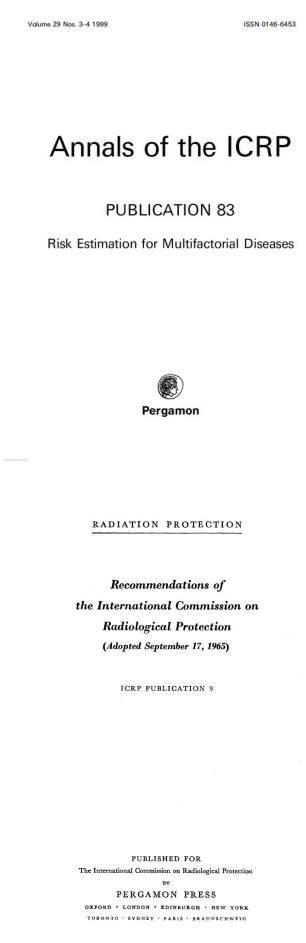
Assess the reasons calling for an evolution based both on a review of scientific literature and relevance for the radiological protection objectives and,

If any evolution is deemed desirable from a scientific point of view, assess the impact on practical management of radiological risk with regards to the radiological protection system objective, for both the prevention of harmful tissue reactions and the limitation of stochastic effects.

On-going work

Review the development of the current classification over relevant ICRP Publications to identify the rationale of the classification, both scientific aspects and expert judgement, and its evolution.

Consider current challenges based on a review of scientific evidence (cancer, heritable effects, in utero exposure related effects, disease of circulatory system, cataract, etc.).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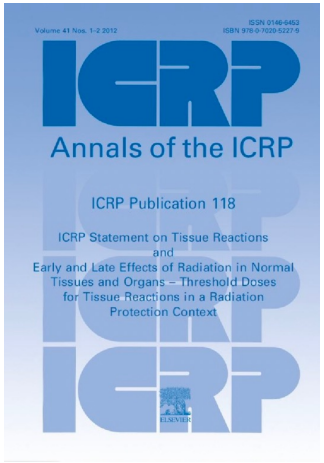
Risk Estimation for Multifactorial Diseases

Pergamon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ICRP

Annals of the ICRP

ICRP Publication 118

ICRP Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context

ELSEVIER

RADIATION PROTECTION

Recommendations of the International Commission on Radiological Protection

(Adopted September 17, 1965)

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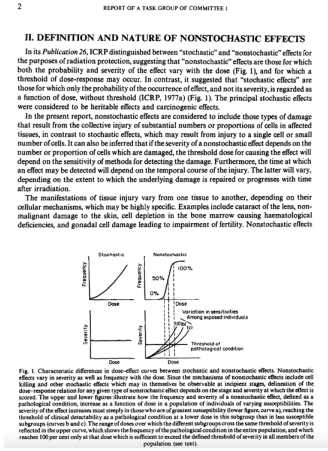

2 REPORT OF A TASK GROUP OF COMMITTEE 1

II. DEFINITION AND NATURE OF NONSTOCHASTIC EFFECTS

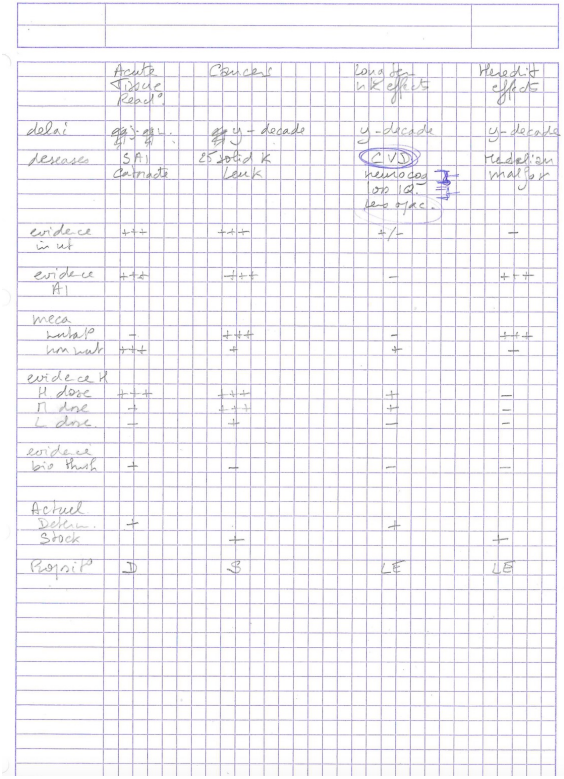
In its *Publication 26*, ICRP distinguished between "stochastic" and "nonstochastic" effects for the purposes of radiation protection, suggesting that "nonstochastic" effects are those for which both the probability and severity of the effect vary with the dose (Fig. 1), and for which a threshold of dose-response may occur. In contrast, it suggested that "stochastic effects" are those for which only the probability of the occurrence of effect, and not its severity, is regarded as a function of dose, without threshold (ICRP, 1977a) (Fig. 1). The principal stochastic effects were considered to be heritable effects and carcinogenic effects.

In the present report, nonstochastic effects are considered to include those types of damage that result from the collective injury of substantial numbers or proportions of cells in affected tissues, in contrast to stochastic effects, which may result from injury to a single cell or small number of cells. It can also be inferred that if the severity of a nonstochastic effect depends on the number or proportion of cells which are damaged, the threshold dose for causing the effect will depend on the sensitivity of methods for detecting the damage. Furthermore, the time at which an effect may be detected will depend on the temporal course of the injury. The latter will vary, depending on the extent to which the underlying damage is repaired or progresses with time after irradiation.

The manifestations of tissue injury vary from one tissue to another, depending on their cellular mechanisms, which may be highly specific. Examples include cataract of the lens, non-malignant damage to the skin, cell depletion in the bone marrow causing haematological deficiencies, and gonadal cell damage leading to impairment of fertility. Nonstochastic effects

Fig. 1. Characteristic differences in dose-effect curves between stochastic and nonstochastic effects. Nonstochastic effects vary in severity as well as frequency with the dose. Since the mechanisms of nonstochastic effects include cell killing and other stochastic effects which may in themselves be observable at incipient stages, delineation of the dose–response relation for any given type of nonstochastic effect depends on the stage and severity at which the effect is scored. The upper and lower figures illustrate how the frequency and severity of a nonstochastic effect, defined as a pathological condition, increase as a function of dose in a population of individuals of varying susceptibilities. The severity of the effect increases most simply in those who are of greatest susceptibility (lower figure, curve a), reaching the threshold of clinical detectability as a pathological condition at a lower dose in this subgroup than in less susceptible subgroups (curves b and c). The range of doses over which the different subgroups cross the same threshold of severity is reflected in the upper curve, which shows the frequency of the pathological condition in the entire population, and which reaches 100 per cent only at that dose which is sufficient to exceed the defined threshold of severity in all members of the population (see text).

Future work - review potentially relevant classification criteria



	Cancer	DCS	Heritable
Current stochastic	+		+
Current tissue reaction		+	
Epi - low dose	++	-	-
Epi - med dose	+++	+	-
Epi - high dose	+++	++	-
Animal studies	+++	?	+++
Radiation-induced (mutation)	++	-	++
Radiation-enhanced	++	?	-
Threshold	-	?	-

Conclusion (so far)

Review of the classification is an on-going work, to be performed in close relationship with other ICRP Task Groups (TG119, etc), international organizations and the RP community

Review of the classification is not only a scientific task, radiological protection values (prudence) and expert judgement must be considered (‘*absence of evidence is not evidence of absence*’)

Any evolution should be justified and potential impacts on practices must be carefully considered

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