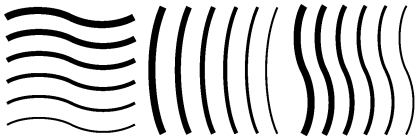
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Human Exposure to Ionising Radiation for Clinical and Research Purposes: Radiation Dose & Risk Estimates

NEDERLANDSE COMMISSIE VOOR STRALINGSDOSIMETRIE

Publication of the Netherlands Commission on Radiation Dosimetry

May 2016



Netherlands Commission on Radiation Dosimetry
Subcommittee Radiation Doses & Risk Estimation for Medical Diagnostics and Research
May 2016

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This report should be revised before May 2021

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Preface

The Nederlandse Commissie voor Stralingsdosimetrie (NCS, Netherlands Commission on Radiation Dosimetry, http://www.radiationdosimetry.org) was officially established on 3 September 1982 with the aim of promoting the appropriate use of dosimetry of ionising radiation both for scientific research and practical applications. The NCS is chaired by a board of scientists, installed upon the nomination of the supporting societies, including the Nederlandse Vereniging voor Radiotherapie en Oncologie (Netherlands Society for Radiotherapy and Oncology), the Nederlandse Vereniging voor Nucleaire Geneeskunde (Dutch Society of Nuclear Medicine), the Nederlandse Vereniging voor Klinische Fysica (Dutch Society for Medical Physics), the Nederlandse Vereniging voor Radiobiologie (Netherlands Radiobiological Society), the Nederlandse Vereniging voor Stralingshygiëne (Netherlands Society for Radiological Protection), the Nederlandse Vereniging voor Medische Beeldvorming en Radiotherapie (Dutch Society for Medical Imaging and Radiotherapy), the Nederlandse Vereniging van Klinisch Fysisch Medewerkers (Dutch Society for Medical Physics Engineers), the Nederlandse Vereniging voor Radiologie (Radiological Society of the Netherlands) and the Belgische Vereniging voor Ziekenhuisfysici/Société Belge des Physiciens des Hôpitaux (Belgian Hospital Physicists Association). To pursue its aims, the NCS accomplishes the following tasks: participation in dosimetry standardisation and promotion of dosimetry intercomparisons, drafting of dosimetry protocols, collection and evaluation of physical data related to dosimetry. Furthermore, the commission shall maintain or establish links with national and international organisations concerned with ionising radiation and promulgate information on new developments in the field of radiation dosimetry.

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Human Exposure to Ionising Radiation for Clinical and Research Purposes: Radiation Dose & Risk Estimates

May 2016

This report was prepared by a subcommittee of the Netherlands Commission on Radiation Dosimetry (NCS) with input from the “Werkgroep Stralingsnormen Medisch Onderzoek” of the Dutch Society of Nuclear Medicine (NVNG), and was initiated at the request of the Dutch Ministry of Volksgezondheid, Welzijn en Sport (VWS) and the Centrale Commissie Mensgebonden Onderzoek (CCMO).

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Summary

In August 2014, the NCS installed a new subcommittee to collect and concisely summarise the existing literature on radiation risks for patients and volunteers participating in clinical research. The aim of the report is threefold:

1. To summarise threshold radiation doses regarding the risk of tissue and organ reactions and to approximate stochastic effects in humans exposed to ionising radiation.
2. To provide guidelines for weighing risks associated with ionising radiation used in diagnostic and interventional procedures in patients or volunteers participating in scientific medical research against potential societal benefits.
3. To serve as input for additional educational demands on ionising radiation for medical doctors, depending on radiation doses administered as part of their clinical work.

Obviously, being a summary of the existing literature on the effects of ionising radiation, the report may also be used for educational purposes.

Chapter 2 and 3 summarise the existing literature on the radiation response of tissues and organs and stochastic effects of ionising radiation, respectively. Chapter 4 provides a scheme for balancing the risks stated in Chapters 2 and 3 against benefits for the general public or patient groups with a certain disease.

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1. Introduction

The required knowledge, skills and competence (KSC) of physicians making use of X-rays for diagnostic or interventional procedures have been laid down in 2013 [1]. In addition to these KSC, the Dutch Ministry of Health (VWS) has requested an overview of current literature data on the biological effects of radiation exposure of the human body as well as of specific tissues and organs within the context of radiation protection. Both tissue reactions – i.e. tissue and organ damage for which the severity varies with the dose and for which a threshold exists – and stochastic effects – i.e. carcinogenic risk for which the probability rather than severity is a function of the radiation dose and for which it is assumed that there is no threshold [2] – should be considered. Together, these data may serve as input for the design of a practical radiation risk assessment strategy for patients undergoing radiological procedures and subjects participating in biomedical research in which ionising radiation is used.

The purpose of the present report is to define: 1) threshold radiation doses regarding the risk on tissue reactions, 2) stochastic effects following exposure to ionising radiation, 3) a framework for assessing the magnitude of risks and benefits associated with radiation exposure as a function of gender and age, and 4) guidelines for acceptable radiation doses within the context of medical research.

The focus of the risk assessment framework presented in this report is on medical diagnostic, interventional and research procedures on humans; radiation therapy dose levels are not considered. This framework is based on risk categorisation and offers the flexibility to define additional educational requirements – KSC level – for physicians employing ionising radiation. In addition, it can be used as an element in patient risk management approaches like, e.g. the Healthcare Failure Mode and Effect Analysis (HFMEA). In the end the use of ionising radiation in daily medical practice should be considered within the context of the balance between benefits and risks.

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2. Tissue and organ reactions: threshold doses

The International Commission on Radiological Protection (ICRP) in its report 118 [3] provides a review on the effects of ionising radiation on tissues and organs. The particular focus of this report is on implications for dose limits in radiation protection and for assessing health risks after accidental or therapeutic exposure. ICRP 118 provides a critical evaluation of the radiation response of various tissues for radiation protection purposes with special reference to those tissues and organs that are considered most important, based on analysis of relevant human data, supported by information from in vitro and in vivo experimental data. Therefore, the content and conclusions presented here are largely based on ICRP 118 [3].

2.1 Tissue radiation response

Tissue reactions following high doses of radiation may occur early (days to few weeks) and/or late (months to years) after exposure. The time-point of manifestation of reactions is tissue specific, depending on cell type and proliferation rate, intrinsic radiation sensitivity and DNA repair capacity. The severity of the effect is directly related to the amount of cell killing, but in addition, non-lethal effects of radiation, such as disturbances in molecular cell signalling, play a role in the tissue response to radiation. Late tissue reactions are generally caused by damage to the vasculature or extracellular matrix. The threshold dose is dependent both on the type of injury and the way this injury is assessed. For details on the response of normal tissues and organs to irradiation, see e.g. [2-5].

Threshold irradiation doses are largely dependent on the irradiated volume for most, but not all, normal tissues. The typical tissue / organ architecture plays a major role in the response to irradiation. Tissues are thought to be organised as functional subunits (FSUs). FSUs are either anatomically delineated structures whose relationship to tissue function is clear, like nephrons in the kidney, liver lobules, etc., or do not have a clear anatomical demarcation, like the mucosa or spinal cord [e.g. 2]. In organs with a serial arrangement of FSUs, such as in the spinal cord, the irradiated volume is subordinate to the radiation dose: radiation injury to a small volume would result in function loss of a large part or the whole organ. Organs with parallel arrangement of FSUs show large reserve capacity by sparing of non-exposed critical parts of the organ; hence, the tolerance dose is less dependent on the irradiation volume.

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2.2 Tissue threshold dose

A *threshold dose* can be defined as the dose below which a tissue specific reaction does not occur. This particular dose is difficult to determine [3]. Here, the 'threshold dose' is defined as the estimated dose that is required to cause a specific, observable effect in 1% of the exposed individuals. Although the ED1 is not a 'true' threshold, it is a practical value to be used as guideline in radiation protection; the ED1 does not imply that no biological effects occur at lower doses [3]. It should be noted that ED1 refers to effects just starting to rise above baseline levels in non-irradiated, age-matched individuals. For example, for skin burns, the ED1 refers to a dose that would result in an absolute *increase* in the relatively high natural incidence or mortality of 1%.

Table 1 lists threshold doses for tissue reactions to a single radiation exposure for a number of healthy tissues and organs. The values were derived from literature reports covering many decades. Latency period estimations ('time to develop effect') are given.

Table 1. Estimates of threshold doses for an approximate 1% incidence of morbidity for various adult human tissues and organs following acute exposure to radiation, modified after Table 4.4 from [3].

Organ/tissue	Threshold dose (mGy)	Biological effect	Latency period
Testis	~100	Temporary sterility	3-9 weeks
Testis	~6 x 10^3	Permanent sterility	3 weeks
Ovaries	~3 x 10^3	Permanent sterility	< 1 week
Bone marrow	~500	Depression of Haematopoiesis	3-7 days
Skin (large areas)	< 3-6 x10^3	Main phase of skin reddening	1-4 weeks
Skin (large areas)	5-10 x10^3	Skin burns	2-3 weeks
Skin	~4 x10^3	Temporary hair loss	2-3 weeks
Skin (large areas)	10 x10^3	Late atrophy	>1 year
Skin (large areas)	10 x10^3	Telangiectasia at 5 years	>1 year
Eye	~100 per 5 years**	Cataract (visual impairment)	>20 years
Brain	100-200	Cognitive defects infants <18 months	Several years
Carotid artery	~500	Cardiovascular disease	>10 years
Heart	~500	Cardiovascular disease	>10-15 years

Notes: ** For workers, ICRP 2011 [6] recommends an equivalent dose limit for the lens of the eye of 20 mGy per year, averaged over defined periods of 5 years, with no single year exceeding 50 mGy.

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Threshold doses for acute exposure are applicable to diagnostic and interventional radiation exposures as well as most medical research exposures.

2.3 Hereditary effects and exposures to the unborn child

Regarding the hereditary effects of radiation, there is no direct evidence of hereditary risks in humans. From Danish and American studies focusing on the offspring of parents who were treated with radiation therapy during their childhood, only a minor (0.3-0.5% per 1000 mGy) increase in occurrence of these effects was found [7,8]. In other reports [9,10], the total risk of genetic effects per 1000 mGy gonadal dose, including multi-factorial and congenital defects, has been calculated to be between 0.4 and 0.6% of the naturally occurring incidence.

Several international reports specifically address the effects of radiation exposure to the unborn child. Both radiation Protection 100 by the European Commission [11] and ICRP 84 [12] provide excellent background information and guidelines. During pregnancy several stages are recognised based on the relative sensitivity to radiation induced morbidity. For foetal doses below 100 mGy, no tissue effects are to be expected and consequently there is no reason for abortion based on radiation alone [12]. For doses between 100 and 500 mGy, an informed decision should be based on individual circumstances. For foetal doses higher than 500 mGy, however, there can be significant foetal injury. The magnitude and type of this injury is a function of dose and stage of pregnancy.

2.4 Conclusions regarding tissue reactions and hereditary effects

Based on existing evidence it can be concluded that acute doses of up to 100 mGy produce no functional impairment of tissues and are unlikely to affect the unborn child.

It should be noted that the basic principle in limiting radiation exposure is ALARA (As Low As Reasonably Achievable) [13], which in general can be achieved by using optimal techniques, equipment and procedures (“best practices”). Nevertheless, in some medical diagnostic and interventional procedures as well as research applications of ionising radiation, organ doses in excess of 100 mGy may occur. Possible examples are repeat CT scans, (thoracic) endovascular aneurysm repair (EVAR) sessions and other extended interventional procedures. In these cases, justification should be based on individual circumstances, balancing risks and benefits for both patient and society (see chapter 3 for guidelines).

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3. Stochastic effects: cancer induction risks based on effective dose

For most applications in occupational or medical (research) situations, stochastic risks of cancer induction are the principal ones to consider.

The effective dose (E) concept was developed by the ICRP and provides a single measure of the dose to a reference person (of average age, gender and nationality) that is roughly proportional to the total 'radiation detriment' from stochastic effects associated with the exposure. Effective dose can be useful for comparing (1) relative doses from different diagnostic procedures, (2) similar technologies and procedures in different hospitals and countries, and (3) different technologies for the same medical examination [14]. Furthermore, the concept of effective dose makes it possible to express radiation exposure to a subject in a single number by summing the contributions of radiation doses from different organs using tissue weighting factors.

Although ICRP has not made specific recommendations on how to derive radiation risks from medical examinations, except for medical research (see section 4), it has become common practice to convert estimates of E for particular examinations to radiation risks using nominal probability coefficients for fatal cancer or aggregated detriment. In recent years, a number of international bodies (BEIR VII, UNSCEAR, ICRP) have developed radiation risk models, which allow for calculation of the Lifetime Attributable Risk (LAR) of radiation induced cancer and mortality as a function of effective dose, age and gender of the exposed reference person [7,14,16]. These bodies all based their analyses on the Japanese atomic bomb survivors' lifespan study, but used different risk projection and transfer models. BEIR VII published a LAR for incidence of all cancers of 0.012% per mSv and a LAR for mortality from all cancers of 0.006% per mSv (averaged over both genders and all ages in the USA population) [16]. The ICRP found the LAR for incidence of all cancers to be 0.017% per mSv and the LAR for mortality for all cancers 0.004% per mSv (averaged over both genders and all ages in 7 populations) [14]. Differences are mainly due to assumptions underlying the extrapolation of cancer incidence levels in Japanese atom bomb survivors to those expected in the general population, exposed to low levels of radiation [9,15]. As the ICRP is the recognised international authority on radiation protection, the remainder of this report is based on ICRP guidelines and risk models.

Differences in risk incidence data reflect the fact that LAR is difficult to estimate. By definition, LAR represents the cancer risk in addition to a matched population cancer risk. Cancer induction following exposure to ionising radiation depends on many factors, such as:

- Exposed volume
- Total dose, dose rate and dose per fraction

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- Organ / tissue specific sensitivity for cancer induction
- Host susceptibility (genetic predisposition, immunodeficiency)
- Biological factors (e.g. hormonal status, tissue repopulation rate)
- Organ specific shape of the dose-cancer risk incidence curve
- Age at exposure
- Gender
- Environmental factors
- Various other biological, chemical and physical factors

It should be noted that the effective dose concept was never intended to provide a measure for the risk to an individual, but rather for a standard person. In addition, the LAR assumes a linear relationship (without threshold dose) between effective dose and probability of cancer induction, known as the 'linear-non-threshold' or LNT model. Although this lack of a threshold dose has been questioned, the LNT model is adopted by the ICRP, providing a worst-case scenario for estimating radiation risks. Therefore, despite large uncertainties in estimates of dose related cancer risk and effective dose as such, this report is based on risk assessment strategies of effective dose and probability coefficients as proposed in ICRP reports 62 and 103 [14,17]. LAR estimates for cancer incidence following exposure to 10 mSv are presented in Table 2.

Table 2. Lifetime attributable risk of cancer incidence. The percent increase in cancer cases (all types incl. leukaemia) following human male or female exposure to 10 mSv as function of age at exposure, modified after table 2 from Wall et al. [9]. The values given should not be taken to imply undue precision, but are presented to 3 significant figures to facilitate the traceability of the calculations made.

	0 - 9	**10 - 19**	**20 - 29**	**30 - 39**	**40 - 49**	**50 - 59**	**60 - 69**	**70 - 79**	**80 - 89**	**90 - 99**
Males	0.0998	0.0800	0.0622	0.0512	0.0422	0.0327	0.0223	0.0132	0.0055	0.0004
Females	0.1440	0.1100	0.0854	0.0678	0.0576	0.0441	0.0310	0.0183	0.0070	0.0002

Data listed in table 2 show that the risk of radiation induced cancer for young patients/subjects is about 2-3 times higher than that for adults, while for elderly it is about a factor 5-10 lower. To put these numbers into perspective, it should be noted that the life time risk for developing any type of cancer prior to the age of 75 years is 31 and 27% for males and females, respectively (Dutch cancer registration data, period 2005-2009, www.cijfersoverkanker.nl). Hence, the contribution of radiation exposure to the general risk of developing cancer is relatively small. For example, for a boy of five, the life time cancer risk is estimated to be 30.92% (www.cijfersoverkanker.nl), which would increase to 31.02% when exposed to 10 mSv.

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4. Risk assessment framework for human exposure to ionising radiation

As outlined above, quantifying radiation induced cancer risks with radiological examinations is not an easy task [18]. Here, effective dose has been particularly useful, especially for radionuclide applications.

Within the context of biomedical research, ICRP 62 [17] focused on this topic and reviewed the risks and benefits of research involving exposure of humans to radiation, aiming to assist medical ethics committees in their evaluation of research proposals. Following the WHO, the ICRP proposed three different risk categories depending on effective dose to the subjects, and added a corresponding classification in terms of benefits.

ICRP103 [14] incorporates exposure of volunteers in biomedical research under the category of medical exposure. Therefore, the present report follows ICRP 62 and ICRP 103 in using three risk categories providing a basis for a risk assessment framework for human exposure to ionising radiation, both for clinical and research purposes. For additional guidance, categories II and III have been subdivided further in two subcategories.

This report proposes the following framework:

(1) Adopt ICRP defined risk categories (Table 3) to assess the balance between radiation risks and benefits of the protocol, except that for each risk category the range of risk levels is given rather than a single number indicating the order of magnitude.
(2) Weigh risks equally for patients and healthy volunteers.
(3) In case tissue or organ reactions are to be expected, follow-up of subjects should be provided.
(4) Involve a clinical physicist (medical physics expert), who is responsible for optimising and estimating radiation dose to each subject with respect to a) tissue and organ effects, and b) effective dose, providing a signed copy to the Medical Ethics Review Committee.
(5) For categories IIIa and IIIb these calculations should be reviewed by the radiation protection expert of the Medical Ethics Review Committee. Nevertheless, the clinical physicist (medical physics expert) remains responsible for the radiation dose estimation.

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Table 3. Effective dose with corresponding risk category and associated level of benefit for an adult male aged 30-39 years.

Effective dose (mSv)[1)]	Risk Category[2,3)]	Level of Benefit
<0.1	I ($< 5 \cdot 10^{-6}$)	Acquisition of knowledge
0.1 – 1	IIa ($5 \cdot 10^{-6} – 5 \cdot 10^{-5}$)	Acquisition of knowledge, resulting in health benefit
1- 10	IIb ($5 \cdot 10^{-5} – 5 \cdot 10^{-4}$)	Acquisition of knowledge, directly aimed at prevention or cure of disease
10 - 20	IIIa ($5 \cdot 10^{-4} – 10^{-3}$)	Acquisition of knowledge, directly aimed at prevention or cure of serious disease
>20	IIIb ($> 10^{-3}$)	Acquisition of knowledge, directly aimed at saving lives or mitigation of serious diseases

Notes:

1) For females and other age groups (section 4.1), and for patients with a short life expectancy (section 4.2), these numbers need to be adjusted.
2) The values between brackets represent the sum of the total probability of fatal cancers and the total weighted probability of non-fatal cancers [9].
3) Note that the associated risk levels are given in ranges rather than a single value as in the original ICRP publication (Table 2 in [17]).

In Table 3 only a classification according to the (cumulative) effective dose of radiation exposure(s) over 12 months is given. To put these numbers into perspective, they can be related to the effective dose limits stated in article 77 of the Dutch legislation on radiation protection [13], where an effective dose of 20 mSv per year is in the same category as a lens equivalent dose of 150 mSv per year, a skin dose of 500 mSv per year (averaged per exposed cm^2) and effective doses to hand, feet and ankles of 500 mSv per year. This should be taken into account when using the values given in Table 3.

The inclusion of pregnant females in biomedical research is not prohibited according to Dutch law. Nevertheless, following ICRP guidelines, this report discourages their participation unless pregnancy itself is part of the clinical or research question [14].

4.1 Age and gender adjusted risk categories

The classification in Table 3 relates to adults in the age range from 30 to 39 years. It is common practice to adjust the dose levels for both younger and older subjects. As an indication, Table 4 lists age and gender adjusted effective dose values per risk category.

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Table 4. Indicative effective dose values (mSv) per year for males and females in different age groups and corresponding risk categories. Again, values given should not be taken to imply undue precision, but are presented to facilitate the traceability of the calculations made

		Risk Category			
Gender	Age	I	IIa	IIb	IIIa
Male	0 - 9	0.1	0.5	5.0	10.0
	10 - 19	0.1	0.6	6.3	12.5
	20 - 29	0.1	0.8	8.0	16.1
	30 - 39	0.1	1.0	9.8	19.5
	40 - 49	0.1	1.2	11.8	23.7
	50 - 59	0.2	1.5	15.3	30.6
	60 - 69	0.2	2.2	22.4	44.8
	70 - 79	0.4	3.8	37.9	75.8
	80 - 89	0.9	9.1	90.9	181.8
	90 - 99	12.5	125.0	1250.0	2500.0
Female	0 - 9	0.0	0.3	3.5	6.9
	10 - 19	0.0	0.5	4.5	9.1
	20 - 29	0.1	0.6	5.9	11.7
	30 - 39	0.1	0.7	7.4	14.7
	40 - 49	0.1	0.9	8.7	17.4
	50 - 59	0.1	1.1	11.3	22.7
	60 - 69	0.2	1.6	16.1	32.3
	70 - 79	0.3	2.7	27.3	54.6
	80 - 89	0.7	7.1	71.4	142.9
	90 - 99	25.0	250.0	2500.0	5000.0

Finally, it should be noted that in patients who receive radiotherapy whole body exposure will be in the range of 50–70 mSv (i.e. 0.1% of the therapeutic dose), whilst the dose near the target volume (~10cm) can even be a factor 10 higher. For those patients, the additional risk from exposure to radiation as part of a research procedure will usually be negligible.

4.2 Interpreting risk categories

Communication of the risks associated with the radiation dose received by a patient or healthy volunteer is a task of the (clinical) investigator. To put these risks into perspective, it is useful to consider the annual background radiation level in the Netherlands (~2.5 mSv), and to be aware that those levels in other European countries and elsewhere can be in the order of 10 mSv or even higher (http://www.world-nuclear.org). It should be noted that the risk categories listed in Table 3 apply to normal healthy adults. In case of children or elderly volunteers, correction factors as indicated in section 4.1 should be applied before using Table 3. On the basis of the data presented

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in Tables 2 and 3, age and gender adjusted risk categories and corresponding dose constraints are given in Table 4. In addition, case specific correction factors for patients with a short life expectancy may be required. For the latter it should be noted that the anticipated time-to-event for cancer induction is more than ten years. Both life expectancy and time-to-event should be taken into account before communicating radiation risks to patients.

Category I

This is the lowest risk category with a statistical probability of less than five in a million to develop radiation induced cancer, to be compared with the natural incidence of cancer, which is about 30%. The dose in this category is less than 0.1 mSv. Each member of the public in the Netherlands will receive this dose within a few weeks, just from natural background radiation. In addition, this dose is equivalent to that received during a transatlantic return flight.

Only a minor level of benefit is sufficient for approval of research in this category, including investigations that aim to increase knowledge.

Category IIa

This category represents an intermediate level of risk. The range of 0.1 to 1 mSv corresponds with a maximum risk of five in hundred thousand and is less than the annual background dose.

To justify these risks a research proposal should at least lead to potential health benefit for future patients. Examples are repeated mammography procedures or X-ray examinations of the thorax to gather data for prospective cohort studies.

Category IIb

This category represents a moderate level of risk. The range of 1 to 10 mSv corresponds to a maximum risk of five in ten thousand, and is of the same order of magnitude as the annual natural background radiation in various parts of the world.

To justify these risks a moderate benefit is required, which will be more directly aimed at the diagnosis, cure or prevention of diseases in the future. Examples are the following studies in both patients and healthy controls that use investigational or routine CT/PET/SPECT scans: drug development studies (i.e. imaging studies before and after administration of a therapeutic drug), studies needed for better understanding of pathophysiological mechanisms underlying disease (e.g. the study of cognition from healthy controls to patients with dementia, blood pressure in relation to hypertension, body weight in relation to obesitas, etc), and studies primarily intended for the development of novel imaging procedures, including the evaluation of new radiopharmaceuticals. Preclinical data should support the value of such studies.

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Category IIIa

Category IIIa represents a substantial level of risk. The range of 10-20 mSv corresponds with a maximum risk of one in a thousand. To place this level into context, the maximum allowed dose for radiological workers is 20 mSv per year.

To justify research in this category, its benefit has to be related directly to prevention or cure of serious diseases in the future. Examples are repeat CT/PET/SPECT scans and scans using tracers labelled with long lived radionuclides, such as ^{89}Zr labelled monoclonal antibodies.

Category IIIb

Category IIIb exceeds the maximum allowed dose level that radiological workers may receive annually. To justify research in this category, the benefit will have to be directly related to saving lives or mitigating serious diseases in the future. For this category benefits also have to be weighed against possible tissue reactions that may be induced (Table 1). These effects should be communicated explicitly to the subject, along with the stochastic effects. Examples are studies in cancer patients who receive radiotherapy, such as repetitive PET/CT scans during radiation treatment, and extensive PET/CT response monitoring scans (with or without ^{89}Zr labelled monoclonal antibodies) during experimental chemotherapy in terminal cancer patients who themselves may or may not benefit from the treatment.

The risk categories mentioned above assume that the subject has not undergone research studies involving exposure to radiation within a year preceding inclusion in a research protocol associated with one of the categories. In particular for healthy volunteers, it is their own responsibility to report any exposure to radiation within the preceding 12 months. Nevertheless, it is the responsibility of the investigator to explicitly ask subjects for such exposure. In case of healthy volunteers, it is advised to incorporate a statement concerning previous exposure in the Informed Consent Form. The dose associated with that exposure should be taken into account in the risk evaluation. As a general principle, each investigator should emphasise that it is undesirable for the same healthy volunteer to repeatedly take part in studies involving exposure to radiation.

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5. Concluding remarks

The guidelines provided in this report are based on the risk categories as proposed in the internationally accepted ICRP reports 62 and 103. The present report first provides an overview of risks associated with exposure to radiation. Next, guidelines are provided based on the balance between risks and benefits of medical procedures. Therefore, this report can be used in three different ways:

1. As a reference document for (clinical) investigators and medical ethics review committees to weigh risks associated with ionising radiation against benefits derived from a proposed research protocol and/or risks associated with other procedures such as surgery, drug treatment or radiotherapy.
2. As a guideline for determining the level of (additional) education in radiation risks needed for medical professionals who use ionising radiation in clinical practice.
3. As a means to put risks associated with exposure to radiation in the broader context of unwanted clinical outcomes in patient risk management and risk prioritisation approaches, such as the Healthcare Failure Mode and Effect Analysis (HFMEA).

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