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Risk assessment for skin cancer due to ionising radiation

Statement by the German Commission on Radiological Protection

Adopted at the 329th meeting of the German Commission on Radiological Protection on 7/8 December 2023

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Risikoabschätzung für Hautkrebs durch ionisierende Strahlung
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Preface

The consideration of skin cancer due to ionising radiation plays a special role in radiation protection. In the basic recommendations given in ICRP Publication 103 (ICRP 2007), skin cancer is described as the cancer with the greatest difference between the incidence risk and the mortality risk. In terms of incidence, its contribution to the total cancer risk is greater than that of all other cancers together, while mortality contributes less than 1% to the total risk.

Furthermore, the choice of parameters that are included in estimating the detriment, along with the models for transferring risk estimates to other populations, differs considerably for skin cancer compared with other types of cancer. These models, along with the underlying risk estimates, are based on data that date as far back as the 1990s.

This prompted the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) to ask the German Commission on Radiological Protection (SSK) to update the current scientific data basis and to review whether the data, parameters and models underlying the current level of radiation protection for skin cancer still reflect the current state of knowledge.

This statement is the product of the advisory mandate and was drawn up by an SSK working group comprised of the following members:

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- Prof. Dr Hans Drexler,
- Prof. Dr Michael Hauptmann,
- Prof. Dr Guido Hildebrandt,
- Dr Heinz Otten,
- Dr Beate Volkmer.

The working group was supported by substantial input from Luca Caramenti M.Sc., who was assigned to the group as a guest.

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1 Introduction

The skin, the largest organ of the human body with a variety of possible types of exposure, plays a special role in radiation protection. The high global incidence of skin cancer is attributable mainly to exposure to solar and artificial UV radiation. However, special consideration is also given to the skin when assessing the risk of exposure to ionising radiation. Currently, the general assumption is that ionising radiation can mainly cause basal cell carcinoma (BCC), a subtype of skin cancer.[1] There is a weak association with the occurrence of squamous cell carcinoma (SCC), while malignant melanoma (MM) is considered not inducible by ionising radiation. Throughout this statement the term radiation, unless otherwise indicated, refers to ionising radiation.

In determining the effective dose, as for other organs, the contribution of radiation-induced skin cancer risk to the total stochastic risk is expressed in the tissue weighting factor w_T. The tissue weighting factor is based on the incidence risk coefficients for the respective organ and the subsequent calculation of the detriment (amount of damage). For almost all organs, the risk coefficient differs from the detriment, which mainly includes lethality, by no more than a factor of 2. In contrast, skin cancer not only has by far the highest incidence risk coefficients of all organs (higher than all others together) but also, due to the very low lethality of the prevalent BCC, a very low detriment. This leads to a difference between the detriment and the risk coefficient by the remarkably high factor of 250, i.e. more than 100 times the difference for the other organs (ICRP Publication 103 (ICRP 2007), Annex A, Table A.4.1)). Although the contribution of the skin risk coefficient to the total risk coefficient is around 60%, the skin detriment makes up only about 0.7% of the total detriment under the assumptions made in ICRP Publication 103. This situation mainly has far-reaching significance when comparing the radiation-induced risk for skin cancer to the skin cancer risk due to other agents. The detriment for skin cancer due to ionising radiation is a factor 250 lower than the incidence risk coefficient (cf. Table A.4.1, ICRP 2007). In any risk assessment of ionising radiation, reference is generally made to the detriment. However, for other risk factors, such as UV radiation, the increase in the incidence relative to exposure is used instead. Consequently, when comparing the risks, this means that ionising radiation is given a significance that is 250 lower than that, for example, given to UV radiation, which is not assigned any damage weighting and which relates only to the increase in incidence.

The data on which these relationships are based partly date back to investigations conducted in the 1990s. In view of the particular significance of skin cancer among all radiation-induced cancers, as outlined above and emphasised by the ICRP, there is a need to update the existing scientific data and, based on these updated data, to review whether the currently accepted qualitative and quantitative statements concerning the risk of skin cancer continue to apply. The present statement contains the results of the advisory mandate of the BMUV of 26 June 2020 in which the SSK was asked to

- review the current scientific data on radiation-induced skin cancer,
- determine whether the current international recommendations for protection against ionising radiation take adequate account of these data, particularly with regard to the assessment of the risk and detriment of skin cancer,
- assess the possible impact of these insights on the tissue weighting factors of the skin and the dose limit for the skin equivalent dose.

[1] In the present document, the term skin cancer includes all malignancies of the skin.

2 Data resources for the determination of the risk coefficient for skin cancer from ICRP Publication 103

The tissue weighting factor $w_T = 0.01$ for the skin indicated in ICRP Publication 103 (ICRP 2007) is derived from the corresponding risk coefficient for the skin and the subsequent estimation of the detriment. With 0.1 Sv^{-1}, the incidence risk coefficient[2] ("nominal risk coefficient") is by far the highest risk coefficient of all tissues and organs. The additional cancer risk per dose unit expressed by this risk coefficient relates to the incidence of BCC, for which there is a clear association with radiation exposure. According to ICRP Publication 103 the association with SCC is weaker, while MM is considered not to be inducible by radiation.

When determining the risk coefficients of the individual tissues and organs, ICRP Publication 103 relies mainly on the incidence studies of the Life Span Study (LSS) conducted by Preston et al. (2007). This work, as well as that of Ron et al. (1998), provides detailed particulars on MM and on the non-melanoma skin cancers BCC and SCC. Regarding their suitability for deriving risk coefficients, however, ICRP Publication 103 attributes little significance to these data: "While the LSS studies do provide some information on skin cancer risks (Ron et al. 1998), it was judged that they may not be adequate for a general population because of differences in risk related to skin pigmentation" (see Annex A 113).

Rather than drawing on the then quite new LSS incidence data, ICRP Publication 103 uses the unchanged risk coefficients from ICRP Publication 60 (ICRP 1991a), which are based, in turn, on ICRP Publication 59 "The biological basis for dose limitation in the skin" (ICRP 1991b). ICRP Publication 103 states the following: "Therefore, the Commission used the nominal skin cancer risk estimate of 0.1 per Gy from Publication 59 (ICRP, 1991a). This estimate was also used in Publication 60 (ICRP, 1991b)" and: "… the nominal risk estimates for bone and skin are those used in Publication 60 (ICRP 1991b). These estimates are largely based on studies of groups with medical exposures" (see Annex A 118).

Furthermore, ICRP decides against the use of a mixed model that takes account of the multiplicative (excess relative risk [ERR] model) and the additive (excess absolute risk [EAR] model) contribution to the background risk. For most organs, ICRP Publication 103 applies a weighting of 50% ERR and 50% EAR. In contrast, for skin cancer, ERR alone is used: "Weights of 0.5 were used for all tissues except … skin for which only an ERR model was used" (see Annex A 140). This choice and ultimately the decision not to use the LSS data (Preston et al. 2007) are both due to the large uncertainties when transferring the risk estimates to other populations. In Japan, the incidence rate of basal cell carcinoma is very low (e.g. Hiroshima prefecture, NMSC: 4.2/100 000, IARC 2021), while the incidence rates particularly in Europe (e.g. Germany, NMSC: 137/100 000, GEKID 2021) are exceedingly high, the highest of all types of cancer. In a mixed model, the ratio of EAR and ERR strongly influences the resulting risk coefficients. If, instead of the ERR favoured in ICRP Publication 103 (100% ERR to 0% EAR), the EAR model (0% ERR to 100% EAR) were used and transferred to populations with significantly higher background rates of skin cancer, the value of the risk coefficient for the skin would be several orders of magnitude lower. This difficulty in transferring risk between populations with very different and also difficult-to-determine background rates for non-melanoma skin cancers led the ICRP to leave the risk estimates in Publication 103 unchanged from ICRP Publication 60 (ICRP 1991a).

[2] According to ICRP Publication 103, the risk coefficient expresses the risk relative to an entire lifetime and is used synonymously with the term "lifetime excess absolute risk" (LEAR).

ICRP Publication 103 states that while skin cancer[3] exhibits an exceptionally high nominal risk coefficient, it is also characterised by very low lethality. The lethality fraction (for skin cancer: 0.002) is the most important variable when estimating the detriment. However, ICRP Publication 103 contains barely any details of the data sources or procedures used in determining the lethality fraction. A possibly similar approach that comes to comparable results is described in Breckow et al. (2018).

According to ICRP Publication 103, due to the very low lethality of BCC and despite the very high risk coefficient, there is an only very small detriment of $4 \cdot 10^{-4}$ Sv^{-1}, which ultimately amounts to only a small contribution of the skin of 0.7% to the total detriment and the low tissue weighting factor for the skin. By being assigned the "minimal reduction in quality of life" $q_{min} = 0$ in the detriment, only a very minor reduction in quality of life is attributed to skin cancer, dominated by the subtype BCC. In ICRP Publication 103 skin cancer is the only tissue with $q_{min} = 0$. If, in addition to BCC, the subtypes SCC or even MM, which is associated with a higher lethality, should become more significant for radiation-induced skin cancer and thus be included in the assessments of the risk for skin cancer, there would be considerable changes not only for the reduction in quality of life but also for the lethality. This could result in a change in the estimate for the detriment and, as a result, in the tissue weighting factor for the skin.

3 Material and methods (description of the semi-systematic literature search)

An alternative semi-systematic method known as "pearl growing", "citation mining" or "snowballing" (Badampudi et al. 2015) was used in lieu of a systematic review with an elaborate search strategy in various databases. Initially, 19 reviews and reports relating to skin cancer and radiation published between 1978 and 2019 that were known to the authors of this statement were identified (see Annex A-1). A search in the publication databases PubMed and Web of Science (date of access: May 2021) identified 1,508 publications that were either cited in or that cited these 19 articles. The titles and abstracts of these 1,508 publications were then evaluated to further identify publications that met the following inclusion criteria:

- Endpoint: BCC, SCC, MM or non-epithelial skin cancer (sarcoma), incidence or mortality, separately or combined,
- Exposure: any type of ionising radiation,
- Radiation-related risk level: dose-response relationship including dose surrogate,
- Original article with human data,
- Not a case report,
- English or German language,
- Published as of 1990.

During the further course of the review, six additional publications were added to 100 publications which potentially met the inclusion criteria. These six publications were known to the authors of this statement and were thought to be of possible relevance but were not among the 1,508 publications identified. Three of these publications concerned radon-exposed individuals, the other three were related to the LSS. The full-text versions of all 106 publications were then

[3] In general, ICRP Publication 103 (ICRP 2007) almost exclusively uses the term "skin cancer". From certain passages, however, it becomes clear that the text refers to BCC (e.g. A 145: "… because radiogenic skin cancer is almost exclusively of the basal cell type …").

screened to verify that the inclusion criteria were met. If several publications presented results on the same endpoint using the same data, only the most recent or largest study was considered. Where available, relevant publications were replaced by newer follow-on publications. Using this approach, 30 of the 106 publications were finally identified for further evaluation. The 76 excluded publications are listed in Annex A-2.

Among the 30 publications are three pooled studies (Pukkala et al. 2002, Cardis et al. 1995, Cardis et al. 2007) which, in turn, contain individual cohorts of the 30 selected publications. Two of the 30 identified studies (Cardis et al. 1995, Haldorsen et al. 2000) were excluded as they were either fully or mostly included in one of the three pooled studies.

Specifically, the study by Haldorsen et al. (2000) was excluded, as it is contained in the pooled study by Pukkala et al. (2002). Haldorsen et al. (2000) analyse the same Norwegian cohort that is contained in Pukkala et al. (2002) with the same follow-up, but only present the results for MM, while Pukkala et al. (2002) additionally report results for BCC and SCC. The cohort of 551 Icelandic pilots analysed in Gudmundsdottir et al. (2017) is partly contained in Pukkala et al. (2002). However, the cohort studied by Gudmundsdottir et al. (2017) is more than twice the size of the Icelandic cohort contained in Pukkala et al. (2002) and has a longer follow-up (until 2015 versus 1997). A decision was therefore made to include this study in the review.

Furthermore, the three-country study by Cardis et al. (1995) was excluded. The study contains 95,673 individuals including 6,638 Rocky Flats workers. The 15-country study by Cardis et al. (2007) includes these 95,673 individuals, but not the 6,638 Rocky Flats workers[4]. The study by Cardis et al. (2007) also contains Canadian and French cohorts which are analysed in full or in part by Sont et al. (2001), Metz-Flamant et al. (2013) and Samson et al. (2011). Of the 191,133 Canadian workers in whom Sont et al. (2001) analysed the incidence of skin cancer up to 1988, Cardis et al. (2007) only contains a subgroup of 54,492 workers, for whom there is a longer follow-up until 1994, but only with regard to skin cancer mortality. Cardis et al. (2007) contains the full French cohort studied by Metz-Flamant et al. (2013), who however analyse NMSC as a further endpoint with a longer follow-up than Cardis et al. (2007). Samson et al. (2011) analyse a cohort of 29,204 CEA Cogema workers exposed to internal and external radiation. The workers exposed to internal and neutron radiation were excluded in Cardis et al. (2007) and Metz-Flamant et al. (2013). It was therefore decided to keep Metz-Flamant et al. (2013), Sont et al. (2001) and Samson et al. (2011) in the list. After this adjustment, 28 publications remained.

[4] Since the exposure situation involved intended exposure to ionising radiation, many of the individuals studied are purely male cohorts. In some studies, women were excluded from the analysis because their case numbers within the studied group were too low. In many cases, a more general gender-neutral wording would therefore be objectively incorrect. It therefore appears appropriate to generally use the male form in the relevant sections of this statement.

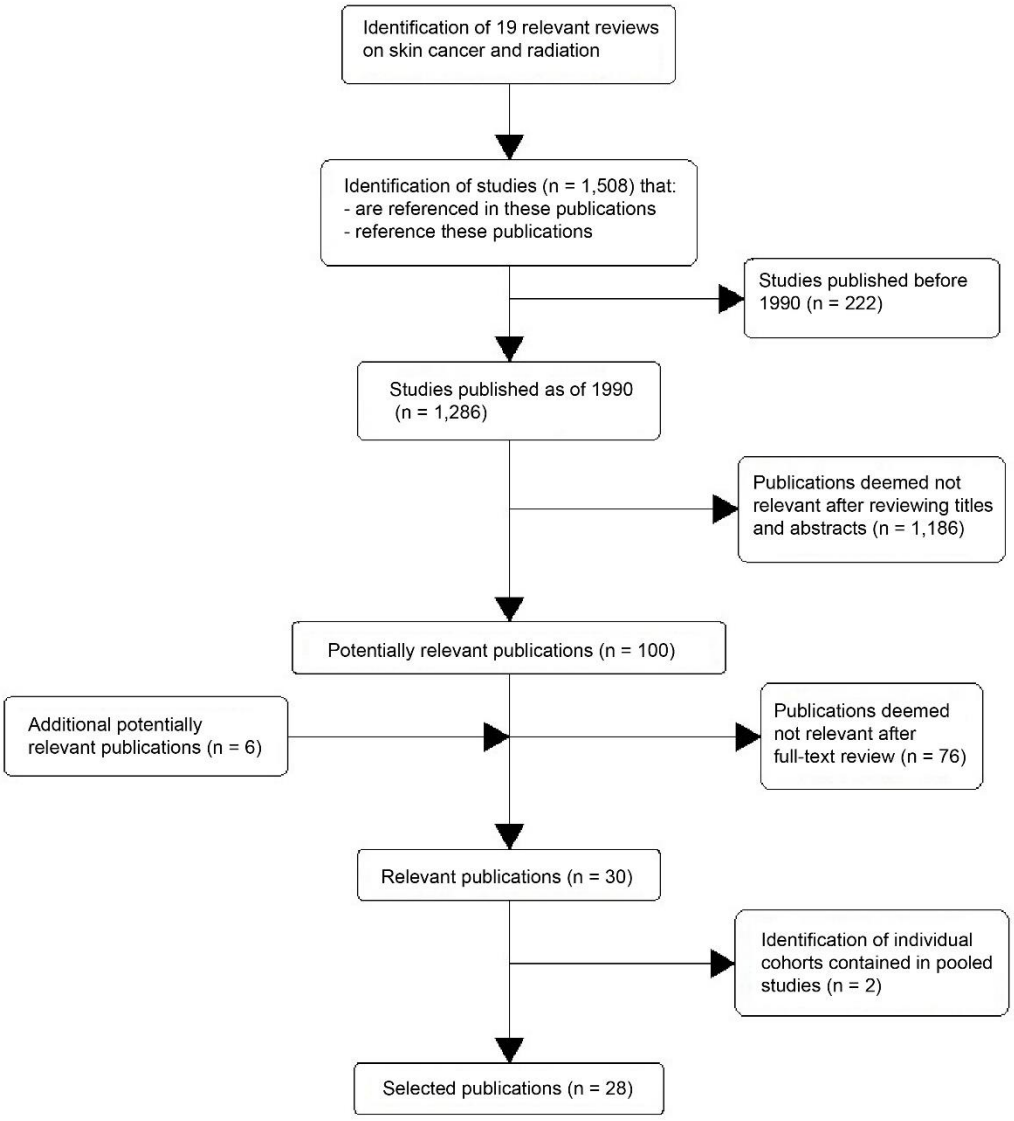

Figure 1: Literature search strategy (authors:Luca Caramenti, Michael Hauptmann)

Figure 1 shows a summary of the underlying literature search. The 28 identified articles can be subdivided into therapeutically exposed persons (n = 7), flight personnel (n = 6), occupationally exposed persons in nuclear power plants and medical facilities (n = 11), radon-exposed population (n = 3) and the LSS (n= 1). Of seven LSS publications that met the inclusion criteria and are described in more detail further below due to their overall significance and their being referenced in other studies, only the most important and more recent publication relating to skin cancer was chosen. Of the six subsequently added publications, the three publications relating to radon-exposed persons were among the 28 articles selected, while none of the three subsequently added LSS publications met the inclusion criteria, as they either presented no results for skin cancer (one study) or concerned children of atomic bomb survivors (two studies).

For each of the 28 selected publications, the most important features were extracted in the tables in Annex A-4 and the strength of the evidence for a causal relationship between radiation and skin cancer was assessed.

4 Studies on radiation-induced skin cancer

4.1 Life Span Study (LSS)

As previously mentioned, in determining the risk coefficients of the individual organs and tissues, ICRP Publication 103 (ICRP 2007) relies heavily on the results of the incidence studies of the Life Span Study (LSS) among the survivors of the atomic bombings of Hiroshima and Nagasaki. Skin cancer, however, was an important exception. Even though some of the LSS publications did, in fact, contain findings related to MM and to the non-melanoma skin cancers BCC and SCC, the ICRP did not consider these data robust enough for determining risk coefficients for skin cancer (see chapter 2).

For the present evaluation, a total of seven publications presenting results of the LSS were identified which meet the inclusion criteria (Annex Table A-3). Table A-3 lists three older evaluations of the LSS cohort (Thompson et al. 1994, Little und Charles 1997, Pierce et al. 1996) that are not further discussed here. These evaluations offer a more qualitative or an only general quantitative analysis of incidence and mortality data for skin cancer. The results are contained in the later publications that are described herein.

In an analysis of the LSS cohort for the observation period 1958 to 1987, Ron et al. (1998) report a significant increase in the radiation-induced incidence risk of BCC with a suspected ("with some suggestion") non-linear dose-response relationship. The individual DS86 kerma[5], weighted as the sum of gamma kerma plus ten times the neutron kerma, is used as a reference dose ("skin dose"). The skin dose is expressed in Sv. In the total cohort of 80,149 persons, n = 80 cases of BCC are observed. Various non-linear dependencies of ERR on dose are analysed. Of these, a linear spline (two consecutive linear segments with different slopes) with a knot at 1 Sv provides the best fit. Below 1 Sv the ERR/dose unit in this model is 0.7 Sv^{-1} (90% CI: <0.1-2.8). For a purely linear relationship, albeit with a poorer fit, the result is an ERR/dose unit of 1.9 Sv^{-1} (90% CI: 0.6-4.3). The authors report a value of 0.2 $(10^4 \text{ PY Sv})^{-1}$ (95% CI: 0.05-0.5) as the excess absolute risk EAR/dose for BCC. No statistically significant relationships are found for SCC (n = 69) and MM (n = 10).

A subsequent evaluation of the same LSS cohort by Kishikawa et al. (2005) is concerned primarily with a histological characterisation of the various skin cancer types but – unlike Ron et al. (1998) – includes the not-in-city (NIC) cohort in its estimation of the ERR, resulting in case numbers of n = 106 for BCC, n = 81 for SCC and n = 14 for MM. For a linear-no-threshold model (LNT model) the result is an ERR/dose unit of 1.9 Sv^{-1}, identical to Ron et al. (1998). To enable a comparison with UV exposure, the EAR is standardised to the skin surface area (in units $(10^5 \text{ m}^2 \text{ Sv})^{-1}$). It was shown that there is no significant difference in the EAR between areas of skin exposed to UV radiation and those protected from it.

In Preston et al. (2007) the observation period of the LSS cohort is expanded from 1958 to 1998. The individual DS02 kerma, weighted as the sum of gamma kerma plus ten times the neutron kerma like in Ron et al. (1998), is used as a reference dose (equivalent dose to the skin). However, the equivalent dose to the skin is expressed in Gy in order to show that no weighting is performed with the tissue weighting factor. The results of this study also suggest a non-linear dose-response relationship for non-melanoma skin cancer (NMSC, ICD 10: C44) (n = 330). A spline model with a knot at 1 Gy provides the best fit to the data. For this model the result is an ERR/dose unit of 0.17 Gy^{-1} (CI: 0.003-0.55) for doses below 1 Gy. When applying an LNT

[5] During the observation period, which spanned several decades, the dosimetry system on which the LSS based its evaluations was changed multiple times.

model with a poorer fit, the result is an ERR/dose unit of 0.48 Gy^{-1} (CI: 0.12-1.3). Using the Japanese background data for skin cancer and an LNT model, an EAR/dose unit of 0.35 $(10^4 PY\ Gy)^{-1}$ (CI: 0.0-1.1) is found. BCC and SCC are also analysed separately. The analysis showed a strong association for BCC (ERR/dose unit = 0.57 Gy^{-1}, 90% CI: 0.18-1.38; EAR/dose unit = 1.36 $(10^4 PY\ Gy)^{-1}$, 90% CI: 0.6-2.4), but not for SCC (ERR/dose unit = 0.17 Gy^{-1}). For MM a total of n = 17 cases was observed. These cases were not evaluated separately, but in combination with other solid tumours. Even though ICRP Publication 103 already refers to the evaluations of the LSS cohort in Preston et al. (2007) with regard to other types of cancer, this is not the case for skin cancer, as outlined above.

The most significant newer publication evaluating the LSS cohort with regard to skin cancer is the one by Sugiyama et al. (2014) for the observation period of 1958 to 1996 (Annex A-1). Therefore, the results of this study, which also includes the data of all previous studies, will be used here as an evidence base for the LSS data on skin cancer (Tab. A-4.1). The dosimetry is identical to that used by Preston et al. (2007). Of the cohort consisting of 80,158 persons (NIC excluded), BCC (n = 123), SCC (n = 114), SCC in situ (n = 64) and MM (n = 10) are identified separately and analysed pathologically and/or histologically. No statistically significant dose-response relationship is found for MM. The point estimate for (non-invasive) SCC is even negative, albeit without statistical significance.

Different models for fitting a dose-response relationship are tested for BCC (see Figure 2). For the group of 70-year-olds exposed at an age of 30 years, taking all effect modifications into account, the following is found:

1.) Spline functions with a knot between 0.5 Gy and 1.5 Gy in increments of 0.01 Gy. In these increments, a knot at 0.63 Gy (95% CI: 0.3-0.9) provides the best fit. The slope above 0.63 Gy results in an ERR/dose unit of 2.0 Gy^{-1} (95% CI: <0-4.3). For dose values below 0.63 Gy the slope is negative (-0.05 [95% CI: <-0.05-1.2]).

2.) Linear model with a threshold dose: This model provides the best fit with a threshold of 0.63 Gy (95% CI: 0.32-0.89) and a slope above that of 2.0 Gy^{-1} (95% CI: 0.69-4.3).

3.) LNT model: Using this model, the best fit results in a slope of 1.3 Gy^{-1} (95% CI: 0.44-2.8).

4.) Linear-quadratic model: The best fit provides a linear term of 0.40 Gy^{-1} (95% CI: <0-2.0).

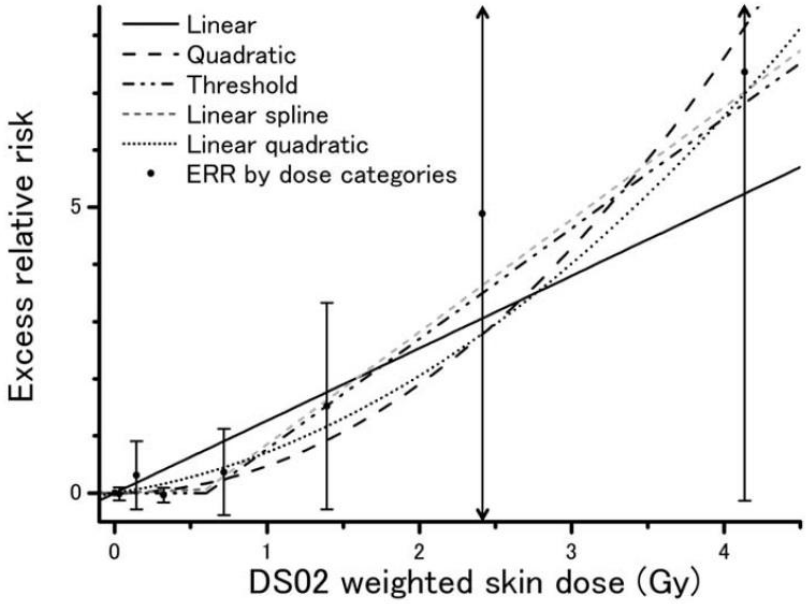

Figure 2: Dose-response relationships for basal cell carcinoma (BCC) in the LSS cohort for different fit models of excess relative risk (ERR) (from Sugiyama et al. (2014), © 2023 Radiation Research Society).

Other models, including a purely quadratic dose-response model, were additionally assessed. However, among all models, the linear threshold model (dose threshold: 0.63 Gy, slope 2 Gy^{-1}) provides the best overall fit for the dose-response relationship for BCC. Age at exposure is identified as the most significant effect modifier. A steady exponential decrease in the ERR of 11% per year after exposure is reported. Based on the background cases of BCC in the Japanese population, the best-fit model (linear with threshold) also results in an EAR at 1 Gy. This provides an estimate of 0.059 (CI: <0-0.3) cases per 10^4 person-years. This estimate is significantly lower than that reported by Preston et al. (2007). The reason for this is the significant change of the reference values in the background risk for BCC in the Japanese population (Preston et al. 2007, Ichihashi et al. 1995). Below the threshold of 0.63 Gy the EAR for this model is = 0.

As already studied in Kishikawa et al. (2005), Sugiyama et al. (2014) additionally assess the interaction of UV exposure and radiation exposure due to the atomic bombs for BCC. The EAR values standardised to skin surface area (in units $(10^5\ m^2\ Gy)^{-1}$) show differences between the skin areas exposed to UV radiation and those protected against UV exposure. The authors conclude that neither an additive nor a multiplicative interaction effect can be ruled out owing to the major statistical uncertainties.

A finding in Sugiyama et al. (2014) that is both surprising and difficult to explain is the statistically significant increase in the risk for SCC in situ, a non-invasive intra-epidermal form of SCC. Using the linear no-threshold model (LNT model), the ERR at 1 Gy was estimated as 0.71 (CI: 0.063-1.9). However, the authors emphasise that the evidence for a causal connection with radiation exposure is uncertain.

Conclusion:

In agreement with all previous analyses of the LSS cohort, no statistically significant dose-response relationships were found for SCC and MM.

For BCC, on the other hand, the findings consistently show a statistically significant non-linear and upwardly curved relationship between risk and dose. In the most recent evaluation, a linear dose-response model with a threshold provides the best fit for the LSS data (Sugiyama et al. 2014). Viewed conservatively, the lower 95% confidence interval of the threshold dose of 0.3 Gy lies within a dose range that exceeds most exposures that occur in practical radiation protection. A pure LNT model, albeit with a poorer fit, provides a very conservative estimate for the ERR/dose unit of 1.3 Gy^{-1}. Use of a dose and dose-rate effectiveness factor (DDREF) of 2, which is also used by the ICRP for the other types of cancer, would result in an ERR/dose of 0.65 Gy^{-1}. With 0.4 Gy^{-1} the linear proportion of a linear-quadratic model yields a similar estimate.

Using the model with the best fit, the absolute risk for BCC is likewise not increased below a threshold dose of 0.63 Gy. If one were to use the EAR value at 1 Gy for a very conservative estimate to extrapolate linearly to the zero point, the result would be an EAR/dose unit of 0.059 $(10^4 \text{ PY Gy})^{-1}$.

4.2 Therapeutically exposed persons

The medical literature published in the last four decades following therapeutic exposure of patients to radiation almost exclusively describes BCC with mostly low specific incidences of around 2% to 5%, while SCC is very rarely mentioned and MM only appears in case studies. An overview of the relevant studies selected can be found in Table A-4.2.

In their updated cohort study, Shore et al. (2002) compare the findings of therapeutically exposed tinea capitis[6] patients with those of non-exposed tinea capitis patients given only topical medications during childhood (mean age nine years, n = 2,224, control group n = 1,380). With a follow-up period of up to 50 years, the relative risk for BCC in the head/neck region for persons with a light complexion (Caucasians) was 3.6 (95% CI: 2.3-5.9; mean scalp dose 4.8 Gy; 124 irradiated cases and 21 control cases; in-field: ERR/dose = 1.7 Gy^{-1}; field edge: ERR/dose = 0.6 Gy^{-1}). No MM of the head and neck and only few cases of SCC were observed. Among 328 BCC cases in total, about 40% of the irradiated patients had multiple BCCs. Even though 25% of the subjects in both the irradiated and the control group had a dark complexion (African-Americans), only three BCCs were observed among African-American subjects in the irradiated group and no BCCs in the non-irradiated control group. A light complexion, severe sunburn and North European descent were predictive of the risk of BCC in the irradiated group; chronic sun exposure, however, was not. Young children exposed to radiation therapy were found to have the highest risk for BCC (age zero to nine years: ERR = 21; 90% CI: 4.1-73; age >40 years: ERR = 0.7; 90% CI: -0.05-2.2). The relative risk for BCC was more or less constant with time since exposure, suggesting that the risk could probably last a lifetime.

Another study (Ron et al. 1991) analysed the relative risk for BCC in more than 10,000 therapeutically exposed tinea capitis patients (mean age seven years, mean radiation dose 7 Gy, mean follow-up period 25 years) in comparison with around 16,000 control subjects in Israel. A total of 80 skin tumours on or in the immediate vicinity of the irradiated scalp were observed (irradiated/non-irradiated cases: total 58/22, BCC 41/13, SCC 0/2, ECC 1/0, MM 2/1, benign tumours 14/6). The relative risk for NMSC was 4.2 (95% CI: 2.3-7.6), the absolute risk was 1.2 per 10,000 person-years (PY) (95% CI: 0.8-1.7) and did not differ significantly between men and women or by time since exposure. However, the risk was greatest after exposure

[6] Tinea capitis is a fungal infection of the hairy scalp that is caused by dermatophytes and occurs primarily during childhood (AWMF-S1 Guideline (013-033)).

during early childhood. Adjusted for sex, ethnic origin and attained age, for BCC the estimated ERR/dose unit was = 1.7 Gy^{-1} and the EAR/dose unit = 0.31 (10,000 PY $Gy)^{-1}$. Similar to Shore et al. (2002) the risk per dose unit for BCC ranged between the increased risk in persons with a light complexion (Caucasian) and no risk in persons with a dark complexion (African-Americans), again suggesting a possible role of UV exposure as a co-factor for radiation-induced BCC.

Landthaler et al. (1995) retrospectively analysed the incidence of radiogenic ulcers and skin tumours in 522 patients with 612 radiation fields following soft X-ray therapy of primary skin lesions (average skin dose 80 Gy (56-184 Gy), minimum total dose ≥12 Gy, follow-up period ≥10 years). The authors considered epithelial skin tumours to be radiogenic if they occurred after more than ten years in the primarily irradiated area. The findings included 12 BCCs (2%), 9 SCCs (1.5%) and 58 ulcers (9.4%). No association was found between the total dose and the frequency of secondary skin tumours. In contrast, radiogenic ulcers increased with a higher total dose and occurred more frequently in patients who were younger at the time of irradiation.

Schwartz et al. (2009) evaluated the risk for BCC after successful haematopoietic cell transplantation (HCT) in relation to age at transplantation, attained age since transplantation, ethnic origin, total-body irradiation (TBI, total dose 7.5 Gy to 18.4 Gy, 90% to 95% dose to the first 1-3 mm of skin) for conditioning and radiation fractionation in 6,306 patients (with/without TBI: 3,870/2,436, age: 0 to 65 years, follow-up: 100 days to 36.2 years after HCT). The age-specific BCC rates in patients without TBI were higher than the natural rates reported for the general population. The general characteristics were similar: the rates increased with attained age and were eightfold lower for non-white patients. After adjusting for these effects, the risk in patients without TBI did not vary significantly with age at HCT. The additional BCC risk in patients with TBI was highest for the youngest ages at exposure to radiation, whereby the relative risks for those who underwent transplantation at less than 10 years of age exceeded 20 and decreased with increasing age at exposure until the age of 40 years. For patients aged older than 40 years, no increased risk was identified. The relative risk for BCC relative to the total dose was as follows for TBI versus no TBI: 0 Gy vs. 7.5-11.99 Gy results in an RR = 48.2; 12.0-12.99 Gy results in an RR = 143.5; 13.0-14.99 Gy results in an RR = 41.1; 15.0-19.0 Gy results in an RR = 29.1; each dose of TBI results in an RR = 62.7 (95% CI: 28.4-109.4). The relative risk for patients with TBI did not vary significantly with attained age, dose fractionation or ethnic origin. The risks per unit dose in HCT patients were similar to those of other populations therapeutically exposed to similar radiation doses under clinical settings.

Guérin et al. (2003) retrospectively analysed possible therapy-related risk factors for the development of MM after childhood cancer. The study cohort included 4,401 at least three-year survivors among 25,120 cancer registry patients (aged under 20 years) from eight French and British centres after treatment of the primary tumour. Sixteen patients developed MM as a second malignant neoplasm. In a case control study, these 16 patients were matched with three to five controls in their respective cohort according to sex, age at primary tumour, calendar year of occurrence of the primary tumour and follow-up period. Primary radiotherapy with local doses >15 Gy appeared to increase the risk of MM (OR: 13; 95% CI: 0.94-174). Following primary chemotherapy with alkylating substances and spindle inhibitors, an increased risk was also found for secondary MM (OR: 2.7; 95% CI: 0.5-14). Children treated for a primary gonadal tumour were found to have a higher risk of secondary MM (OR: 8.7; 95% CI: 0.9-86). Common genetic causes of gonadal tumours and MM are regarded as likely by the authors. The adjusted OR/dose unit for the local radiation dose was 1.07 Gy^{-1} (95% CI: 1.00-1.15), which means that primary radiotherapy may contribute to an increased risk of secondary MM, but only at very high local doses (>15 Gy) far beyond those relevant for radiation protection.

Haddy et al. (2012) retrospectively studied therapy-related risk factors for the development of MM after primary haemangioma treatment. The cohort includes 4,620 patients treated before the age of 16 years for cutaneous haemangioma in France, thirteen of whom developed MM. In a case control study, each of these 13 patients were compared with five controls of the cohort after matching for sex, age at haemangioma therapy, calendar year of occurrence of the haemangioma and follow-up period. The radiation dose applied to the site of the MM in patients and to the same site in controls was estimated and termed "local dose". A total of 13 melanomas were registered during an average follow-up of 35 years, whereby the relative risk of developing MM after haemangioma treatment was 2.5-fold higher in the total cohort (n = 4,620) than in the general population (95% CI: 1.4-4.1). In patients who did not receive radiotherapy (n = 896) the relative risk was 0.8 (95% CI: 0.05-3.6) compared to 3.0 (95% CI: 1.6-5.1) in patients after radiotherapy (n = 3,724). After adjusting for sex, age, year of treatment and follow-up period, the risk for MM in patients after radiotherapy (yttrium-90) was 11.9 times higher (95% CI: 1.4-123) than in patients who did not receive radiotherapy. The case control study found no association between the risk for MM and the local radiation dose; however, the risk increase for MM was already observed at very low local doses (<0.001 Gy: 3.9 [95% CI: 0.5-32]; > 0.01 Gy: 6.9 [95% CI: 0.5-99]). While the analysis suggests that radiation therapy of skin haemangioma increases the risk of secondary MM, no evidence was found for an association with the local dose.

In a case control study, Karlsson et al. (1998) evaluated the secondary risk of non-epithelial skin tumours (sarcoma) in women after breast cancer treatment. The cohort includes all women with breast cancer (n = 122,991) registered in the Swedish Cancer Registry between 1958 and 1992. A total of 116 secondary sarcomas were registered (SIR[7]: 1.9; 95% CI: 1.5-2.2). The absolute risk was 1.3 per 10,000 PY (expected: 0.7 per 10,000 PY). There were 40 cutaneous angiosarcomas and 76 soft tissue sarcomas of other subtypes. The sarcomas were located mainly (63%) in the breast region or on the ipsilateral arm (67/106). To evaluate the impact of radiation therapy, which was applied with very different treatment protocols (in particular conventional radiotherapy) over the study period, the authors calculated the total absorbed dose (integral dose, body weight (kg) x absorbed dose (J kg^{-1})). A relationship between the risk of secondary angiosarcoma and the integral dose of the primary radiotherapy was not found. Only a significant correlation of the risk of angiosarcoma with treatment-associated chronic lymphoedema of the arm was observed (OR: 9.5; 95% CI: 3.2-28.0). For other subtypes of secondary soft tissue sarcomas, an association with the integral dose of the primary radiotherapy was found. The dose-response relationship showed that the risk for secondary soft tissue sarcoma increased linearly with the integral dose up to 150-200 J and stabilised at higher integral doses. For an integral dose of 50 J, which corresponds roughly to the therapeutic exposure of the affected breast after breast-conserving surgery, the OR was 2.4 (95% CI: 1.4-4.2). Consequently, only treatment-associated chronic lymphoedema of the arm correlated with the risk of secondary cutaneous angiosarcoma. For other subtypes of secondary soft tissue sarcomas, the integral dose of the radiotherapy was found to be a predictor of the risk of sarcoma.

Besides the included studies on therapeutic radiation exposure and secondary skin tumours published as of 1990, there are a number of other publications which likewise show that ionising radiation can cause secondary BCC, but not a definite dose-dependent increase in SCC or MM (literature references in Annex A-2: Lichter et al. 2000, Perkins et al. 2005, Levi et al. 2006, Karagas et al. 2007). They further show that the risk of developing secondary BCC after exposure to radiation at a young age is higher than in older years (literature reference in Annex A-

[7] Standardised Incidence Ratio

2: Karagas et al. 2007) and that ethnic differences exist (very rarely BCC in irradiated persons with a dark complexion compared with light-skinned persons exposed to a comparable dose), suggesting that UV exposure cannot be ruled out as a possible co-factor for radiation-induced BCC (Shore et al. 2002, Ron et al. 1991). These publications do not, however, allow any additional statements to be made on a possible dose threshold and/or dose dependence of the risk of secondary BCC supplementing the LSS data and were therefore not considered further.

Few cohort studies following the primary treatment of cancer patients report increased risks for MM without being able to unequivocally demonstrate a dose-dependent relationship between exposure to ionising radiation and an increased risk for secondary MM (Guérin et al. 2003, Haddy et al. 2012).

Finally, secondary sarcomas are described after therapeutic exposure of breast cancer patients, in particular angiosarcoma with an incidence of around 0.5% and an average latency period of 6.0 years (two years to 57 years), without clear evidence of a dose-dependent association thus far (Karlsson et al. 1998).

4.3 Occupationally exposed persons in nuclear power plants and medical facilities

This section provides a description of the studies performed in all occupationally exposed groups except flight personnel (Table A-4.3). Studies conducted among pilots and other crew members are summarised in section 4.4. As the studies described here frequently involve larger cohorts with exclusively mortality endpoints, the results on skin cancer mostly relate to MM.

In their case control study on melanoma conducted among employees of the Lawrence Livermore National Laboratory, Moore et al. (1997) reported the results of 69 prevalent cases, diagnosed between 1969 and 1989, with 69 controls matched by sex, age, date of recruitment, years of schooling and training, duration of employment and retirement yes/no. The cumulative exposure from gamma, neutron and tritium, hand and skin dose was estimated individually from dosimeter values. The average of the sum of the five exposures was 7.6 mSv among the diagnosed cases and 7.1 mSv among the controls. Results of a formal comparison between diagnosed cases and controls were not reported.

A case control study among employees of the Lawrence Livermore National Laboratory (Austin und Reynolds 1997) with 31 melanoma cases diagnosed between 1969 and 1980 and 110 individually matched controls showed an OR of 2.3 (95% CI: 1.0-7.6) for exposed persons versus other persons, and an OR of 1.12 per year of occupational exposure ($p = 0.017$), adjusted for education, moles, familial history of skin cancer, prior NMSC diagnoses, exposure to volatile photographic chemicals, age, ethnicity and sex.

Sont et al. (2001) evaluated the incidence of melanoma among 191,333 nuclear power plant workers in the National Dose Registry of Canada. According to the cancer registry, 222 individuals were diagnosed with melanoma between 1969 and 1988. Using individual dosimeter values from 1951 to 1988, the cumulative whole-body dose was calculated (with a lag of ten years), resulting in an average dose of 6.64 mSv. After adjusting for age, sex and birth year, Poisson regression showed an ERR per dose unit of 0.43 per 100 mGy (90% CI: <0-1.96).

Freedman et al. (2003) described the incidence of melanoma among 68,588 radiologic technologists in the US. Between 1926 and 1998, 207 cases of melanoma were diagnosed during an average follow-up of 10.2 years. The duration of employment in different periods, reconstructed using self-reported work history information, was used as a surrogate for the radiation dose received at work, which was not quantified. Based on external evidence, the potential for

relevant exposure at the workplace was greatest before 1950, after which exposure was significantly reduced through occupational health measures. After adjusting for skin type, eye and hair colour, personal history of NMSC diagnoses, family history of melanoma and residential sunlight exposure, an RR of 2.4 (95% CI: 0.7-8.7) was calculated for those who worked more than five years before 1950 versus those who worked less than five years (p-trend = 0.03). No association was observed for subsequent periods.

In the 15-country study conducted by Cardis et al. (2007) among 407,391 nuclear industry workers from 15 countries, melanoma was indicated as the cause of death on 87 death certificates over an average follow-up of 12.7 years. The average cumulative whole-body dose reconstructed from dosimeter values was 19.4 mSv. The ERR/dose unit, calculated using Poisson regression and adjusted for sex, age, calendar year, socio-economic status and nuclear power plant, was -0.72 Sv^{-1} (90% CI: <0-1.93).

Using information extracted from death certificates, Samson et al. (2011) evaluated the melanoma mortality (four and twelve deaths, respectively, between 1968 and 1994) in two cohorts of French nuclear workers, 14,796 exposed only to external and 14,408 exposed to external and internal radiation. Estimates of the cumulative effective dose were calculated from individual dosimeter values. The mean dose was 3.7 mSv (cohort with only external exposure) and 12.9 mSv (cohort with external and internal exposure). Using Poisson regression and after adjusting eleven categories of the cumulative effective dose as the continuous variable, no significant dose-response relationship was observed, adjusted for age, sex, calendar year, socio-economic status and duration of employment. Numerical results were not presented.

Muirhead et al. (2009) evaluated mortality data of 174,541 workers from the National Registry for Radiation Workers (NRRW) in the United Kingdom. According to the cancer registry, 261 workers were diagnosed with MM and 326 with NMSC between 1976 and 2001 over a mean follow-up of 22 years. Individual dosimeter values showed a mean cumulative effective dose of 24.9 mSv. After adjusting for age, sex, calendar period, industrial classification and first employer, this resulted in a linear ERR/dose unit of 1.39 Sv^{-1} (95% CI: -0.65-5.6) for MM and 1.50 Sv^{-1} (95% CI: 0.05-3.85) for NMSC.

Metz-Flamant et al. (2013) studied 59,021 workers of the French Atomic Energy Commission and Nuclear Fuel Company with a mean follow-up of 25.9 years and, extracting data from death certificates, recorded 68 deaths due to melanoma and 7 deaths due to NMSC between 1968 and 2004. The whole-body dose reconstructed from individual dosimeter values was, on average, 22.5 mSv among those exposed. After adjusting for sex, age, calendar period, company and socio-economic status, Poisson regression with a log-linear dose term resulted in an ERR/dose unit of 126.5 Sv^{-1} for NMSC (90% CI: 7.03-1916); for melanoma there was a negative ERR/dose unit with a p-value of 0.72.

Extracting information from medical patient records and archives, Azizova et al. (2018) observed 60 incident cases of MM and 294 cases of NSCM among 22,377 workers of the Mayak plutonium production plant in Russia between 1948 and 2013 over an average follow-up of 25.5 years (MM) and 25.2 years (NMSC). The mean cumulative skin dose estimated by work history amounted to 0.54 Sv. After adjusting for sex, age, calendar period and neutron dose, Poisson regression resulted in an ERR/dose unit of 0.51 Sv^{-1} for NMSC (95% CI: 0.22-0.93) and 0.15 Sv^{-1} for MM (95% CI: -0.41-1.31).

In the same cohort, but with a cancer incidence up to 2018 (Azizova et al. 2021), there were 295 BCCs and 48 SCCs (mean follow-up 26.3 years for BCC and 26.4 years for SCC). The mean cumulative skin dose from gamma radiation was 0.50 Gy. After adjusting for sex, age and calendar period, Poisson regression resulted in an ERR/dose unit of 0.57 Gy^{-1} (95% CI: 0.27-1.03) for BCC and 0.14 Gy^{-1} (95% CI: -0.23-0.91) for SCC.

In the same cohort as Freedman et al. (2003), namely radiologic technologists in the US, Lee et al. (2015) evaluated the risk for BCC among 65,719 individuals, 3,615 of whom were diagnosed with BCC during an average follow-up of 17 years between 1983 and 2005. Using dosimeter readings and information about the workplace, the absorbed dose to the skin was estimated and averaged 55.8 mGy. The estimated ERR/dose unit was -0.01 Gy^{-1} (95% CI: -0.43-0.52) and was adjusted for education, income, cigarette smoking, alcohol consumption, BMI, exercise, eye colour, skin complexion, sunburn history, dental x-rays, solar UV exposure, sex, age and calendar period.

The studies outlined here are, for the most part, very complex and large cohort studies. The information on occupational radiation exposure is largely based on individual and measured values. The mean radiation dose, where indicated, was well below 100 mSv (or mGy), apart from the two Mayak cohort studies with mean doses of approx. 0.5 Gy (Azizova et al. 2018, 2021). In the risk analyses, adjustments were generally made for different confounders. However, UV radiation was only considered as a potential confounder in the two studies performed in radiologic technologists in the USA (Freedman et al. (2003), Lee et al. (2015)), and both studies used the duration of employment rather than individual dose estimates. In several studies, only mortality data were available. In these cases, the analysis was generally limited to melanoma. In summary, among the studies described here, only one study related to SCC (Azizova et al. 2021) which, however, showed no evidence of a dose-response relationship. There were two studies on BCC: one with strong evidence (Azizova et al. 2021) and one without evidence of a dose-response relationship (Lee et al. 2015). The combination of SCC and BCC (NMSC) was evaluated in two studies, one with strong evidence (Azizova et al. 2018) and one with weak evidence of a dose-response relationship (Muirhead et al. 2009). None of the nine studies on MM revealed any evidence of a dose-response relationship.

4.4 Flight personnel

In Germany, occupational exposure to ionising radiation is monitored by the German National Dose Register (*Strahlenschutzregister*, SSR). Using these data it was determined that flight personnel, with 2 mSv to 6 mSv, are subject to an increased exposure to cosmic radiation during a flight, particularly at high altitudes and near the poles (Frasch et al. 2015). Unlike exposure to ionising radiation, exposure to solar UV radiation is significantly influenced by an individual's behaviour. This applies particularly during leisure time, but also for outdoor workers and for everyday professional life. In order to minimise UV exposure in this setting, employers are obliged to take precautionary measures. Occupational exposure of flight personnel to UV radiation is not monitored systematically. Exposure of flight personnel to UV radiation during a flight is expected to be low. While an earlier study reported no UV exposure of flight personnel (Diffey 1999), a current study for which UVA exposure was measured during a flight reported erythemally weighted radiation of 0.1 SED (standard erythema dose) for pilots on flights within Europe. The lifetime occupational dose of ionising radiation and UV radiation is generally dependent on the duration of employment and often, therefore, on attained age.

In order to identify potential occupational risks from exposure to ionising radiation, numerous studies evaluating the cancer risk of flight personnel have been conducted. Often, these studies also include the risk of skin cancer, which means that evidence on the induction of skin cancer due to ionising radiation can be expected as a result. The selective literature search described in chapter 3 identified six publications on this subject (Table A-4.4). The evaluation of the standardised mortality ratio (SMR) or of the SIR showed no increase in risk for most cancer types. The risk for skin cancer was almost always an exception and was often increased, albeit not always in a statistically significant manner. All studies include data for MM, three studies

additionally include data on non-melanoma skin cancer (NMSC); of these, three studies separately evaluate data relating to BCC. In addition to cosmic radiation, a disruption of the circadian rhythm is also discussed as a reason for the increased risk of melanoma. However, increased UV exposure during leisure or in the rest times between flights is assumed in all studies and regarded as highly likely in most studies. In a study by Rafnsson et al. (2003) a survey showed that flight personnel exhibit a higher prevalence for spending their holidays in the sun compared to the general population. The increased risk for NMSC is also most likely attributable to increased UV exposure. One study discusses a potential dose effect for BCC in connection with increased exposure to ionising radiation.

A vast majority of the cohorts stems from Scandinavia (Denmark, Finland, Iceland, Norway, Sweden), a large cohort stems from Germany, and data from Italy and the US are also described. It should be noted that the data of the individual cohorts were frequently included in pooled evaluations. Furthermore, data from the individual cohorts were also evaluated and published separately. The results of the individual studies are described in more detail below.

Dreger et al. (2020) report about a large retrospective cohort study (German cohort) on the cancer mortality of flight personnel relative to exposure to cosmic radiation. The study considers data from 1960 to 2014 and includes 26,846 flight personnel (cockpit and cabin crew). One major strength of this study is the use of individual exposure data from 2004 to 2014 recorded in the German National Dose Register. These data were used to estimate the exposure data from 1960 to 2003, resulting in a median cumulative effective dose of 34.2 mSv. For nearly all cancer types studied, the result was an SMR <1. A non-significantly increased SMR of 1.88 for MM (95% CI: 0.78-3.85) was found only for male pilots. A significant dose-related increase in SMR was not observed for any of the cancer types studied. This also applies to the slightly elevated relative risk per dose unit of 1.29 per 10 mSv (95% CI: 0.78-2.4) for MM among male pilots. The authors do not rule out the influence of increased UV exposure during leisure time, which the increased values for SMR and RR may be attributable to.

Pinkerton et al. (2018) report about a retrospective cohort study (US cohort) on the incidence of cancer (MM, thyroid and gynaecological cancers) in 6,095 female flight attendants. The data were collected by questionnaire. Exposure data were calculated using flight plans. A connection between the incidence of MM and the measured values of cumulative exposure to cosmic radiation was not observed. A positive, non-statistically significant association was found for the risk of MM (Hazard Ratio HR = 1.08, 95% CI: 0.95-1.21) in connection with long-haul flights (“SSI travel”, flights with a standard sleep interval). In this regard, the authors discuss the influence of a disruption of the circadian rhythm or of increased UV exposure during leisure time.

Gudmundsdottir et al. (2017) report about a cohort study (Icelandic cohort) among 551 male pilots. Of these, 286 pilots were employed at Icelandair and regularly flew transatlantic routes (a part of the cohort is included in the study by Pukkala et al. (2002)). The remaining 265 pilots worked for other airlines and did not fly transatlantic routes. The individual cosmic exposure was determined from the air hours of the pilots and the dose rates, modelled for typical flight routes of specific types of aircraft. For the Icelandair pilots, a median cumulative dose of 22.55 (0.28-83.20) mSv was determined. The study considers data for the period 1955 to 2015. For all cancer types studied, an SIR of 0.9 was calculated (95% CI: 0.71-1.11). For all 551 pilots, the SIR was 3.31 for MM (95% CI: 1.33-6.81) and 2.49 for BCC (95% CI: 1.69-3.54). A further evaluation of the data estimated the relative risk for the Icelandair pilots versus the other pilots (reference) relative to the cumulative dose. For malignant melanoma the RR increased from 5.07 (95% CI: 0.14-201.23) at exposures to <25 mSv to 9.88 (95% CI: 1.57-86.61) at exposures to >25 mSv (p-trend 0.009). For BCC, for the same exposure categories, the RR increased from 1.92 (95% CI: 0.49-7.23) to 3.61 (95% CI: 1.64-8.84, p-trend 0.0005). Assuming similar leisure

patterns of pilots and the remaining population (Rafnsson et al. 2003), the authors believe that increased UV exposure of the pilots in their free time is not the only reason for the increased risk for MM. Regarding BCC, given the strong dose-dependent trends and the fact that some of the carcinomas occurred on the trunk, the authors consider that a connection with increased radiation exposure is possible.

Pukkala et al. (2012) report about a cohort study on the incidence of cancer (cohorts from Finland, Iceland, Norway and Sweden) among 8,507 female and 1,559 male flight attendants included in the study between 1947 and 1997. Cosmic exposure was estimated from the flight profiles and the dose rates using the EPCARD software. For female flight attendants, a significantly increased incidence was observed for MM (SIR = 1.85; 95% CI: 1.41-2.38) and an increased incidence for BCC (data only from Finland and Iceland) (SIR = 2.39; 95% CI: 1.80-3.10). For male flight attendants, a significantly increased incidence was observed for MM (SIR = 3.00; 95% CI: 1.78-4.74) and for non-melanoma skin cancer (excluding BCC) (SIR = 2.47; 95% CI: 1.18-4.53). A dose-dependent trend was not found for any of the cancer types studied. A case control study performed on the basis of the data likewise found no evidence of an influence of cosmic radiation. This also applies to other cancer types with a significantly increased incidence rate: breast cancer and leukaemia (female flight attendants), Kaposi sarcoma, laryngeal cancer and pharyngeal cancer (male flight attendants). The authors argue that the increased risk of skin cancer may be attributable to exposure to UV radiation.

Langner et al. (2004) report about a large, retrospective European cohort study (ESCAPE) (individual cohorts from Scandinavia, Germany and Italy) evaluating the connection between cancer mortality and exposure to cosmic radiation among 19,184 male pilots (in a period from 1921 to 1997). The mean lifetime dose is reported as 15.3 mSv, determined on the basis of the pilots' air hours and the dose rates, modelled for typical flight routes of specific types of aircraft. For almost all cancer types studied, a significant SMR <1 was determined, with a negative trend with increasing doses. For MM, SMRs > 1 (1.51; 95% CI: 0.48-3.6; 1.38; 95% CI: 0.28-4.19; 2.37; 95% CI: 0.77-5.7 and 0.66; 95% CI: 0.02-3.91) were determined for the dose ranges 0 mSv to 4.99 mSv, 5 mSv to 14.99 mSv, 15 mSv to 24.99 mSv and ≥25.0 mSv, albeit without statistical significance. Regarding SMR and RR, no dose-related trend was observed for MM. The authors did not rule out increased UV exposure of the pilots as the reason for the trend towards an increased SMR. Parallel recording of UV exposure data is warranted for further investigation.

Pukkala et al. (2002) report about a retrospective cohort study assessing the incidence of cancer among 10,032 male pilots from Scandinavian countries (Denmark, Finland, Iceland, Norway, Sweden). The study evaluated data of the national cancer registries from 1943 to 1997. Cosmic exposure was determined from the pilots' air hours and the dose rates, modelled for typical flight routes of specific types of aircraft. Except for skin cancer, the study did not indicate an increased cancer risk in connection with increased exposure to cosmic radiation. As pilots are assigned to the better-situated population, data from the population group with a high social status were used for the determination of the SIR. This resulted in a statistically significant SIR of 2.29 for MM (95% CI: 1.73-2.98), an SIR of 2.46 for BCC (95% CI: 1.88-3.16) and an SIR of 2.08 for other skin cancers (95% CI: 1.74-2.79). For all types of skin cancer, the relative risk increases with the cumulative dose (MM: p-trend 0.008; BCC: p-trend 0.09; other skin cancer: p-trend 0.08). For MM, the authors see a connection with increased UV exposure from sunbathing; the influence of a disruption of the circadian rhythm is also considered. This is not discussed for BCC and other types of skin cancer.

All in all, regarding SMR or SIR, the studies do not indicate an increased risk for flight personnel for most of the cancer types included. By contrast, the data on skin cancer, which were collected mainly for MM, often suggest an (albeit not always significantly) increased risk.

In order to classify this effect, it must be considered that both epidemiological studies (Arnold et al. 2018, Armstrong und Kricker 2001) and molecular biological data (Ramasamy et al. 2017) have identified UV radiation as the main risk factor for skin cancer. An increased risk of skin cancer due to increased UV exposure during leisure times and particularly during rest times of flight personnel in countries with a high UV radiation is therefore highly likely. Use of personal dosimeters to record the UV exposure of flight personnel during leisure times would help further clarify this question.

4.5 Radon-exposed population

In their study assessing the association of radon exposure with the incidence of non-lung solid cancers, Kulich et al. (2011) evaluated the relative risk (RR) in a case cohort study of 22,816 uranium miners in the Czech Republic who had worked underground between 1949 and 1975. For MM (n = 23) they found a non-significant positive association with RR = 2.92 (95% CI: 0.91-9.42) at exposures above 180 working level months (WLM)[8] compared to exposures below 3 WLM.

In a prospective ecological study, Bräuner et al. (2015) investigated the incidence of skin cancer from residential radon exposure in Denmark among 57,053 persons between 1993 and 1997. Based on the geocoded addresses of the study subjects, location-related radon activity concentrations were calculated and incidence rate ratios (IRR) determined. The results showed a weakly positive and statistically significant association for BCC (n = 3243) with IRR = 1.14 per 100 Bq m^{-3} (95% CI: 1.03-1.27), and no statistically significant associations for SCC (n = 317) with IRR = 0.90 per 100 Bq m^{-3} (95% CI: 0.70-1.37) or for MM (n = 329) with IRR = 1.08 per 100 Bq m^{-3} (95% CI: 0.77-1.50).

Using data of the Swiss National Cohort, a Swiss study investigated skin cancer mortality from residential radon exposure in 5.2 million adults (Vienneau et al. 2017). Radon concentrations in different locations and at different addresses were calculated and assigned to a total of 2,989 deaths from skin cancer. Among these, a positive and statistically significant association was found for MM (n = 1,900) with an adjusted hazard ratio (relative to an age of 60 years) of HR = 1.16 per 100 Bq m^{-3} (95% CI: 1.04-1.29). As a relevant risk factor for MM, UV exposure was also included in the study. However, inaccuracies in the estimation of both UV exposure and radon exposure and their interaction make it unclear whether the increased melanoma mortality risk observed in the study is, in fact, attributable to long-term radon exposure. Furthermore, the risk of death from MM reflects the risk of developing any type of skin cancer only to a very limited extent.

All in all, one of the three studies on the risk of skin cancer from radon exposure provides weak evidence of a positive association with MM (Vienneau et al. 2017), while another provides weak evidence for a connection with BCC (Bräuner et al. 2015). On the whole, however, the studies on the risk of skin cancer from radon provide little evidence that radon, particularly radon exposure in dwellings, increases the risk of developing skin cancer, even if an increase in skin cancer risk cannot be ruled out completely.

Details of the relevant studies are shown in Table A-4.5.

[8] Working level month (WLM) is a historic unit for the cumulative Rn-222 activity concentration that was introduced specifically for occupational safety in uranium mining. Even though WLM is not an SI unit and should therefore no longer be used, it is still widely used in the relevant epidemiological literature. Using the equilibrium factor F, it is converted into the corresponding SI unit as follows: 1 WLM = 0.64 F^{-1} MBq·h·m^{-3}.

4.6 Summary

4.6.1 Basal cell carcinoma

Of the selected studies, eleven report results on the incidence of BCC (Table A-5.1). The case numbers range from 12 to 3,615. Six studies indicate an ERR at 100 mGy, which is statistically significantly positive in five studies. The results of these five studies (Azizova et al. 2021, Sugiyama et al. 2014, Ron et al. 1991, Shore et al. 2002, Schwartz et al. 2009) are interpreted as a clear indication of a causal relationship. Three of these five studies involved medical therapeutic exposure to a mean dose in the range of several Gy (Ron et al. 1991, Shore et al. 2002, Schwartz et al. 2009). Although the mean dose was lower in the two other studies, namely those among Mayak workers (Azizova et al. 2021) and atomic bomb survivors (Sugiyama et al. 2014), these two studies leave open the question as to a relationship with doses below 100 mGy, as the mean dose in the Mayak study (Azizova et al. 2021) was around 500 mGy, and the analysis of the LSS data by Sugiyama et al. (2014), as the best-fit model, identified a threshold at 630 mGy with no evidence of an association below that. Two studies with radon exposure (Bräuner et al. 2015) or a considerably lower dose due to cosmic radiation (Gudmundsdottir et al. 2017) also indicated a dose-response relationship, while four studies (Pukkala et al. 2002, Lee et al. 2015, Landthaler et al. 1995, Pukkala et al. 2012) found no evidence of a dose-response relationship. It should be noted that of the only two studies whose results were corrected for the effect of UV radiation, one indicates a causal link (Bräuner et al. 2015), while the other does not (Lee et al. 2015). With more than 3,000 cases each, these two studies are by far the largest studies on this entity.

In summary, given the larger number of studies with a significant dose-response relationship, sufficient case numbers and a detailed characterisation of exposure, there is strong epidemiological evidence to suggest a causal relationship between radiation and BCC. However, uncertainties continue to exist regarding an association in the dose range below 100 mGy and confounding due to UV radiation.

4.6.2 Squamous cell carcinoma

Of the five selected studies with results on SCC, none showed any indication of a dose-response relationship (Table A-5.2). The largest study with 317 cases (Bräuner et al. 2015) found a non-significant negative trend following radon exposure. This was also the only study that adjusted for UV radiation.

In summary, the reviewed studies provide no epidemiological evidence suggesting a causal relationship between radiation and squamous cell carcinoma.

4.6.3 Malignant melanoma

A total of 21 studies reported results on a possible dose-response relationship between ionising radiation and MM (Table A-5.3). Of these, 15 studies investigated the incidence (14) or prevalence (1) and 6 studied the mortality. The number of cases ranged between 7 and 1,900. Sixteen studies (Freedman et al. 2003, Langner et al. 2004, Dreger et al. 2020, Austin et al. 1997, Samson et al. 2011, Bräuner et al. 2015, Moore et al. 1997, Sugiyama et al. 2014, Pinkerton et al. 2018, Azizova et al. 2018, Haddy et al. 2012, Cardis et al. 2007, Sont et al. 2001, Muirhead et al. 2009, Metz-Flamant et al. 2013, Pukkala et al. 2012) found no evidence of a causal relationship. In these studies, exposure was occupational, and the mean dose values were mostly below 100 mSv, except for one study with therapeutic exposure to local doses >15 Gy (Guerin et al. 2003). In four studies (Vienneau et al. 2017, Guerin et al. 2003, Kulich et al. 2011, Gudmundsdottir et al. 2017) there was an indication of a positive association (two of which after radon exposure), and one study strongly suggested a possible dose-response

relationship (Pukkala et al. 2002). This study among pilots with 56 incident cases showed a positive and significant trend ($p = 0.007$) of the relative risks across dose categories. However, the results were adjusted only for age and calendar period. Confounding due to UV radiation cannot be ruled out.

In summary, the numerous and partly large studies on MM predominantly show no evidence of a dose-response relationship. The influence of confounding due to UV radiation is unclear. However, should a causal relationship exist, it is considered highly unlikely that the negative results would be attributable to confounding. Therefore, the existing data is interpreted as evidence against a causal relationship.

4.6.4 Combinations of skin cancer types and other subtypes

The results on non-melanoma skin cancer showed a significant dose-response relationship in two of the four studies on this combined endpoint (Table A-5.4), namely the Mayak study by Azizova et al. (2018) with 294 incident cases and the NRRW study by Muirhead et al. (2009) with 261 cases. The mean dose among the Mayak workers was a factor 20 higher than that among the NRRW workers. The largest study by Vienneau et al. (2017) after radon exposure, with 838 cases, which is the only study in this group that adjusted for UV radiation, showed no association with NMSC.

One single study found a clear connection between exposure to radiotherapy and sarcomas in connective tissue, breast and skin (116 incident cases) (Table A-5.6).

5 Determination of the detriment for skin cancer

5.1 Estimation of the nominal risk coefficient

The main input parameter that is used in determining the detriment is the nominal risk coefficient according to ICRP Publication 103 (2007). It represents the excess absolute lifetime risk per dose, averaged across all sexes, ages and populations, if necessary applying a DDREF. The above ICRP publication specifies a nominal risk coefficient of 1,000 $(10^4\ Sv)^{-1}$ for skin cancer.

The following quantitative estimates are based mainly on the most recent evaluations of the LSS cohort with regard to skin cancer (Sugiyama et al. 2014). As the other older and newer studies have already shown, there is no evidence of a causal association between ionising radiation and MM or SCC. Therefore, risk coefficients for skin cancer relate almost exclusively, or at least mainly, to BCC: usually, the starting point for risk estimates is information either on the excess relative risk (ERR) or on the excess absolute risk (EAR). Both variables are interlinked via the background incidence rates, in this case for BCC. If details of the respective background rates are available for the population in which the investigations were carried out, the two risk variables ERR and EAR can be easily converted into one another. If, on the other hand, one of the variables is transferred to another population and a conversion is then carried out, any differences in the background rates will affect the conversion (see below).

A risk estimate based on the LSS data shows the following: For BCC, Preston et al. (2007) indicate an ERR/dose unit of 0.57 Sv^{-1} for a linear model and 0.48 Sv^{-1} for a non-linear model (for <1 Sv)[9]. Sugiyama et al. (2014), when comparing the various fit models, apply the AIC criterion (Akaike information criterion), which provides a ranking of the goodness of fit, in

[9] In the original publications, the weighted dose to the skin is expressed in Gy. For the sake of clarity, and because the risk coefficients relate to the organ equivalent dose with the unit Sv according to ICRP Publication 103, reference is made only to the unit Sv here and in the following.

order to assess the goodness of fit. If the LNT model (AIC = 1089.6) from Sugiyama et al. (2014) is taken as a basis, the result is a conservative estimate for the ERR/dose unit of 1.3 Sv^{-1}. A linear-quadratic model (AIC = 1088,8) results in 0.4 Sv^{-1} for the linear term. Taking effect modification into account, the LSS model with the best fit (linear threshold model, AIC = 1084.3) shows no dose-response relationship for low and intermediate doses up to the threshold of 0.63 Sv, i.e. the ERR = 0 and the EAR = 0 for D <0.63 Sv. For a realistic estimate of the risk coefficient, a value can be derived ranging from about 0.4 Sv^{-1} to 1 Sv^{-1}, depending on the underlying assumptions.

The LNT model, applied to the EAR per dose unit and per time interval, results in an estimate of 0.059 (10^4 PY Sv)$^{-1}$ for the Japanese population, to which the investigations relate (Sugiyama et al. 2014, cf. section 4.1). Assuming an average life expectancy of 80 years, this results in a risk coefficient of around 5 (10^4 Sv)$^{-1}$.

If the model with the best fit is used as a basis for a risk estimation, analogous to MM and SCC there is also no increase in risk for BCC below a dose threshold of 0.63 Gy. This means that, under this assumption, skin cancer would generally not be considered inducible by radiation in a dose range relevant to radiation protection.

5.2 Dose and dose-rate effectiveness factor (DDREF)

Almost all studies that allow a statement to be made on the (qualitative) course of the dose-response relationship for BCC clearly indicate a curve that deviates from a pure LNT model. This is shown in dependencies that suggest a threshold dose, contain a quadratic term or show a different upwardly curved graph. This means that estimates which are based on a linear extrapolation of high doses to lower doses lead to overestimation of the risk. In addition, non-linearities also lead to a dependence of the risk on the dose rate. To account for this, the ICRP introduced a dose and dose-rate effectiveness factor (DDREF) that was defined as 2 for almost all organs and tissues in ICRP Publication 103 (ICRP 2007). The SSK published a detailed rationale on this (SSK 2014).

The non-linear dose-response relationship is much more pronounced for BCC than for many other cancer types (cf. Figure 2). Therefore, there is a particularly strong justification for applying a DDREF for this case. Against the backdrop that the LSS model with the best fit indicates a dose threshold of 0.63 Sv, i.e. that the risk below this dose level is equal to zero, linear models tend to be very conservative, even when a DDREF is used. This would still be the case if the DDREF were significantly greater than 2.

Using a DDREF = 2 results in values of 0.2 Sv^{-1} to 0.5 Sv^{-1} for the ERR/dose unit. For the EAR/dose unit, the result is a value around 2.5 (10^4 Sv)$^{-1}$ for the Japanese population. This value is a factor 400 smaller than the nominal risk coefficient in ICRP Publication 103.

5.3 Transfer to other populations

As illustrated in chapter 2, ICRP Publication 103 (ICRP 2007) uses a mixed model with a ratio of 50% ERR and 50% EAR for almost all organs and tissues when transferring the Japanese data to the global population. For skin cancer, on the other hand, only the ERR is transferred to other populations (100% ERR to 0% EAR). In Japan there is a very low background incidence rate for BCC (and likewise for the other types of skin cancer), while the incidence rates particularly in Europe and the US are extraordinarily high, the highest even of all cancer types. This leads to a very wide variation of the nominal risk coefficients depending on the transfer model applied.

For a transfer to other populations, knowledge of the background incidence rates for BCC in these groups is indispensable. The background rates for the non-melanoma skin cancers, i.e. also for BCC, are often hard to determine, as many international cancer registries do not record non-melanoma skin cancers due to the difficult conditions of registration (multiple diagnoses, unclear classification etc.). For example, while the SEER Tables of the US Dept. of Health and Human Services (e.g. NIH|NCI 2021) contain data on mortality, they do not indicate incidence rates for BCC and SCC. For Germany, the number of new skin cancer diagnoses can be extrapolated using data of the Schleswig-Holstein Cancer Registry. These data lead to an estimate of around 160,000 new BCC cases for 2020 (Katalinic 2022). Given a life expectancy of 80 years and a total population of 80 million, this yields a lifetime incidence probability of about 0.15, which can be assumed to be the background risk for BCC in Germany.

If, using a 100% ERR transfer model, the average background incidence risk of 0.15 were multiplied by an ERR/dose unit (including DDREF = 2) of 0.2 Sv^{-1} to 0.5 Sv^{-1}, the result is an EAR/dose unit and thus a risk coefficient of 0.03 Sv^{-1} to 0.08 Sv^{-1}. The value of 0.1 Sv^{-1} for skin cancer indicated in ICRP Publication 103 is thus slightly above the range for BCC determined for Germany using this estimate.

If, on the other hand, a 100% EAR model were used to transfer the data to the global population, the risk coefficient for skin cancer – with a value of 0.00025 Sv^{-1} – would be negligibly small and skin cancer could be completely disregarded for stochastic effects in radiation protection.

If also applied to skin cancer, a mixed model like the one used by the ICRP for the other cancer types (50% ERR and 50% EAR) would result in a risk coefficient between 0.015 Sv^{-1} and 0.04 Sv^{-1} for Germany, i.e. three times lower than the value indicated in ICRP Publication 103.

5.4 Non-radiation parameters

The purpose of the ICRP detriment concept is to enable a quantitative comparison of stochastic radiation damage for the various organs. To this end, organ-specific nominal risk coefficients are weighted using a function intended to express the amount of damage or the severity of a disease. This function incorporates a variety of variables that do not depend on radiation parameters, but on characteristics of the disease itself. These include the lethality of the disease (lethality fraction k), the resulting reduction of quality of life q, the minimal reduction of quality of life $q_{\min}$ and the loss of life expectancy L.

Using these non-radiation parameters, the detriment $d(k)$ is modelled with the following equation according to ICRP Publication 103 (ICRP 2007):

$$d(k) = [(1 - q_{\min}) \cdot (2k - k^2) + q_{\min}] \cdot L \tag{1}$$

The detriment (expressed in Sv^{-1}) is determined individually for each cancer by multiplying the nominal risk coefficient assigned to the respective cancer (expressed in Sv^{-1}) with the corresponding severity of the damage d (without a unit) for each type of cancer. For more details on this approach, see SSK (2018) or Breckow (2020).

Lethality fraction

According to ICRP Publication 103, while skin cancer – with 0.1 Sv^{-1} – exhibits an exceptionally high nominal risk coefficient (greater than for all other cancers together), it is also characterised by very low lethality. The lethality fraction k is the most significant variable in estimating the detriment. The above publication indicates a value of 0.002 for skin cancer. However, ICRP Publication 103 contains barely any details of the data sources or the procedures used to determine the lethality fraction.

Breckow et al. (2018) study the temporal course of non-radiation parameters using equation (1) for all cancer types in the USA and in Germany for the period 1980 to 2012. For skin cancer in the US in 2012, for example, a lethality fraction of $k = 0.0023$ is indicated, which is approximately the same value given in ICRP Publication 103. For Germany in the year 2012, the report underlying the publication of Breckow et al. (2018) (Emami und Breckow 2016) indicates a value of $k = 0.03$ and a detriment of $d = 0.05$, which is a factor 10 higher than the ICRP value.

Minimal reduction of quality of life

The parameter for "minimal reduction of quality of life" $q_{\min}$ in equation (1) is designed to show that quality of life may be reduced to a fraction q_{min} ($\neq 0$), even for an entirely non-fatal cancer ($k = 0$).

By assigning a minimal reduction of quality of life $q_{\min} = 0$ in the detriment, ICRP Publication 103 attributes a very minor reduction of quality of life to skin cancer (according to equation (1), for $q_{\min} = 0$ and $k \neq 0$ the detriment $d(k)$ is low but not zero). Skin cancer is the only tissue with $q_{\min} = 0$. The publication offers barely any justification why this value was chosen. However, it can be assumed that it is based on the assessment that skin cancer, which can be treated easily and with little burden, is associated with hardly any reduction in quality of life. Strictly speaking, however, $q_{\min} = 0$ means that with a lethality approaching zero, *absolutely* no reduction in quality of life is assumed.

With a low lethality, the choice of the value for $q_{\min}$ has a strong impact on the amount of damage d and thus also on the resulting detriment. For a cancer type with a very low lethality k, as is the case for skin cancer, the assumption $q_{\min} = 0$ would mean that the amount of damage and thus also the detriment approach zero. If, on the other hand, $q_{\min} = 0.1$ were also valid for skin cancer, like for nearly all other types of cancer (except thyroid cancer), with the remaining values from ICRP Publication 103 skin cancer would become the second most significant radiation-inducible type of cancer after lung cancer.

Relative loss of life expectancy

The relative loss of life expectancy L is the absolute loss of life expectancy of one type of cancer relative to the value averaged across all types of cancer, in other words, the average loss of life expectancy divided by the totality of all cancers. In comparison with the lethality k and the minimal reduction of quality of life $q_{\min}$, this factor has only a minor impact on the calculation of the detriment. Therefore, this factor plays only a subordinate role in the present statement and will not be further elaborated on.

Conclusion

In the current system of organ-specific detriment values as per ICRP Publication 103 (ICRP 2007), due to the very low lethality of BCC and despite the very high nominal risk coefficient of 0.1 Sv^{-1} there is an only very low detriment of $4 \cdot 10^{-4}$ Sv^{-1}, which ultimately leads to a minor contribution of the skin of 0.7% to the total detriment and the low tissue weighting factor for the skin. If an LNT fit model were used, a DDREF = 2 were applied, a 100% ERR transfer model were used and all non-radiation parameters were kept unchanged, no significant changes would occur, even in the light of the literature published after ICRP Publication 103. This would also hold true if – like for all other types of cancer – a mixed model with 50% ERR and 50% EAR were used for skin cancer.

However, based on the more recent literature, significant changes with partly far-reaching consequences would occur under the following assumptions:

- A change of the minimal reduction of quality of life from $q_{min} = 0$ to $q_{min} = 0.1$, while keeping all other parameters unchanged, would mean a 25-fold increase in detriment. This would make skin cancer the most important single type of cancer inducible by radiation, after lung cancer.
- Use of a dose threshold model that provides the best fit to the LSS data, on the other hand, would mean that the skin could be dropped entirely from the list of organs for which tissue weighting factors are provided. This could have far-reaching consequences for the detriment model as a whole (cf. chapter 6).

6 Statements

Between 1990 and 2021 a total of 106 articles were published that met the inclusion criteria for further evaluation (cf. chapter 3). Of these, 28 publications were regarded as relevant and sufficiently reliable to draw conclusions in this statement. Considering the period of more than 30 years, this is a surprisingly small number of publications on which statements on radiation-inducible skin cancer can be made. Regarding the various types of skin cancer, the following qualitative statements can be derived from these publications:

Statement 1:

There is no scientifically reliable evidence demonstrating that either MM or SCC are caused by ionising radiation. The only type of skin cancer for which there is evidence of a causal relationship is BCC. However, this evidence relates mainly to exposures above 0.5 Gy. This is also consistent with the previously available findings. Therefore, any statements that relate to radiation-inducible "skin cancer" refer exclusively to BCC.

Quantitative statements on dose-response relationships, i.e. indications of the risk coefficient, stem mostly from the publications on studies performed in the atomic bomb survivors of Hiroshima and Nagasaki, the LSS cohort. Evaluations of medical exposure and exposure of flight personnel, on the other hand, only allow few quantitative statements to be made. The studies on skin cancer and radon show no evidence that radon exposure increases the risk of skin cancer. The available studies do not allow statements to be made on the combined effect of ionising radiation and UV radiation (the main risk factor for the induction of skin cancer). However, since this combination reflects the real exposure of the population to radiation, both epidemiological studies and radiobiological investigations are warranted.

Statement 2:

Unlike most other types of cancer or organs, ICRP Publication 103 (ICRP 2007) does not base its statements concerning radiation-inducible skin cancer on evaluations of the LSS, but on studies conducted in the early 1990s among medically exposed cohorts. Based on studies that have meanwhile been published, we are now able to make quantitative statements on dose-response relationships and on risk coefficients from the LSS evaluations. The most significant and relevant LSS study is the evaluation by Sugiyama et al. (2014) for the period 1958 to 1996.

In their study, Sugiyama et al. (2014) test different models for fitting a dose-response relationship for BCC (cf. Figure 2). The tested models include spline functions with knots from 0.5 Gy to 5 Gy in increments of 0.01 Gy, a linear threshold model, a linear no-threshold model (LNT) and a linear-quadratic model. Other models, including a purely quadratic dose-response model, were additionally tested. Of all models, the linear threshold model (dose threshold:

0.63 Gy, slope ERR/dose unit = 2 Gy^{-1}) provides the best fit for the dose-response relationship for BCC. The threshold dose of 0.63 Gy lies within a dose range that exceeds most exposures that occur in practical radiation protection. A pure LNT model, albeit with a poorer fit, provides a very conservative estimate for the ERR/dose unit of 1.3 Gy^{-1}. Use of a dose and dose-rate effectiveness factor (DDREF) of 2, which is likewise used by the ICRP in Publication 103 for the other types of cancer, would result in an ERR/dose unit of 0.65 Gy^{-1}. With 0.4 Gy^{-1} the linear proportion of a linear-quadratic model yields a similar estimate.

Statement 3:

The choice of the fitting model to describe the dose-response relationship is decisive. If the linear threshold model, which provides the best fit, is used as a basis, then BCC plays no role in dose ranges that are relevant for radiation protection. However, if the LNT model, which is used for most other cancer types and organs, is also applied for BCC, then BCC contributes significantly to the risk.

Due to the major differences between the background rates of BCC in different populations, particularly between European and Asian populations, the use of specific models to transfer the results from the Japanese data to other reference populations has a significant impact. The same applies to the choice of parameters that are included when determining the detriment. In ICRP Publication 103, both the choice of transfer model and the detriment parameters differ significantly from those used for other cancer types or organs. In this regard, they are a specific exception in comparison with all other types of cancer.

Table 1: Nominal risk coefficients R_I and detriment D for skin cancer based on the LSS (Sugiyama et al. 2014) using a DDREF = 2 and lethality fraction k = 0.002 and q_{min} = 0 from (ICRP 2007, Tab. A.4.1)

Dose-response model	**ERR/EAR mixed model**	**RI / (10 000·Sv)$^{-1}$**	**D / (10 000·Sv)$^{-1}$**
LNT ERR/D = 0.2/Sv … 0.5/Sv	0:100	2.5	0.01
	50:50 *like all other cancer types*	150 … 400	0.6 … 1.6
	100:0	300 … 800	1.2 … 3.2
Linear with threshold dose at 0.63 Gy *best fit*	Any ratio	0	0
For comparison:			
ICRP Publication 103	100:0	1,000	4

Table 1 summarises the detriment values resulting from the various models and parameter constellations. For example, if an LNT model with DDREF = 2 were used, combined with a 100:0 mixed model and a q_{min} = 0, like the one used for skin cancer in ICRP Publication 103, the detriment would only be slightly lower than that given in ICRP Publication 103 (Table 1). In a 50:50 mixed model, the detriment would be reduced by more than a factor of 2, while a 0:100 mixed model would even mean a 400-fold reduction. If the same LNT model with DDREF = 2 were used, but with q_{min} = 0.1, like for all other cancer types or organs, the detriment would be increased more than 10-fold (Table A-6.1). In yet another combination, BCC would have the second highest detriment (after lung cancer) in comparison with all other cancer types or organs.

Conversely, if the LSS dose-response model with the best fit (linear threshold model) were used, the detriment for BCC would be negligible. In this case, skin cancer as a whole would no

longer be considered inducible by ionising radiation in the dose range encountered in radiation protection.

Statement 4:

Depending on the combination of dose-response model, transfer model and detriment parameters used, the range of possible values for the detriment (ICRP 2022) and thus also of tissue weighting factors varies considerably. It ranges from the assessment that, in the dose range relevant for radiation protection, skin cancer does not contribute in any way to the risk of radiation, to the assessment that skin cancer has the second highest contribution to the total detriment after lung cancer. The tissue weighting factors associated with these assessments range between $w_T = 0$ (tantamount to dropping the skin from the list of tissue weighting factors) and $w_T = 0.12$ (group of highest tissue weighting factors). This would affect not only the tissue weighting factor for the skin, but all other tissue weighting factors as well.

The existing literature on radiation-induced skin cancer provides little guidance as to which dose-response model, which transfer model and which detriment parameters should be preferred. Choosing the dose-response model that offers the best fit according to Sugiyama et al. (2014) would, as outlined above, lead to the very far-reaching conclusion that skin cancer is not at all inducible by radiation. However, the existing literature provides only insufficiently reliable evidence to support such a far-reaching statement. This applies to an even greater extent to the choice of transfer model and detriment parameters. The literature barely provides any guidance on these questions, so that the reasoning for or against specific models or parameters must be based on other sources, such as plausibility assumptions on additive or multiplicative risk models, considerations regarding the quantification of a reduction of quality of life or general considerations regarding the radiation protection concept.

Statement 5:

Based on the existing literature on radiation-induced BCC, no sufficiently robust decision in favour of a specific dose-response model can be made, especially in the dose range below 0.5 Gy. The choice of a specific transfer model and of other detriment parameters, such as the minimal quality of life q_{min} in particular, must be based on a different foundation. The question as to how we should deal with the unclear situation of assessing the contribution of the skin cancer risk to the overall stochastic risk must be left to an international discussion.

7 List of abbreviations

BCC	Basal cell carcinoma
CI	Confidence interval
DDREF	Dose and dose rate effectiveness factor
EAR	Excess absolute risk
ERR	Excess relative risk
EPCARD	European Program Package for the Calculation of Aviation Route Dose
HCT	Haematopoietic stem cell transplantation
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IRR	Incidence rate ratio
LNT	Linear-no-threshold
LSS	Life Span Study
MM	Malignant melanoma
NIC	Not-in-city cohort group of the LSS
NMSC	Non-melanoma skin cancer
OR	Odds ratio
PY	Person years
RR	Relative risk
SCC	Squamous cell carcinoma
SED	Standard erythema dose
SEER	Surveillance, Epidemiology and End Results Program of the National Cancer Institute (NCI)
SIR	Standardised Incidence Ratio
SMR	Standardised mortality ratio
TBI	Total body irradiation

8 Glossary

Equivalent dose

The ICRP and the ICRU have both stipulated weighting factors for radiation protection purposes which make it possible to take account of the varying biological effectiveness of different radiation types and energies and different radiation sensitivities of various organs and tissues in the dose estimation. Accordingly, the dose term "equivalent dose" used in radiation protection has the general meaning of a product of an absorbed dose and either the radiation weighting factor defined by the ICRP or the quality factor defined by the ICRU. The term "equivalent dose" is used for body doses defined by the ICRP with the radiation weighting factor and for the local and personal dosimetry measurands defined by the ICRU with the quality factor. The equivalent dose is expressed in the same unit as the absorbed dose J kg^{-1}. In order to make it clear that this is a weighted dose quantity, as with the effective dose it is expressed in sieverts (Sv) and not in grays (Gy).

Occupationally exposed person

Occupationally exposed person means a person who, as a result of practices, may incur occupational exposure which

1. exceeds an effective dose of 1 millisievert (mSv) in a given calendar year,
2. exceeds an equivalent dose for the lens of the eye of 15 mSv in a given calendar year, or
3. exceeds an equivalent dose for the skin, averaged over any area of 1 cm^2, regardless of the area exposed, of 50 mSv in a given calendar year.

Occupational exposures resulting from emergency exposure situations shall not be taken into account thereby. A person who receives occupational exposure exclusively in an emergency exposure situation or other hazardous situation shall not be deemed to be an occupationally-exposed person.

Definition taken from section 5 (7) StrlSchG 2017 (Act on Protection against the Harmful Effects of Ionising Radiation (Radiation Protection Act – *Strahlenschutzgesetz*) of 27 June 2017 (Federal Gazette [BGBl.] I p. 1966), last amended by section 11 of the law of 12 December 2019 (Federal Gazette I p. 2510)

Dose and dose-rate effectiveness factor (DDREF)

The DDREF is an evaluation factor that takes into account, for certain radiation effects, the lower biological effectiveness (per unit of dose) of radiation exposures at low doses and low dose rates. It is the factor by which a dose-response relationship to be described differs from the LNT model. Whether it

should continue to be considered in malignant processes is currently under discussion.

Detriment

The detriment is also referred to as the detriment-adjusted risk. The detriment is the product of the nominal risk coefficient and the detriment quality. It is expressed in Sv^{-1}. The detriment depends on a number of parameters. In particular, the following parameters are included in the calculation for each organ or tissue: the likelihood of incidence, the lethality fraction, the reduction of quality of life and the relative loss of life expectancy.

Effective dose

The effective dose is the sum of the organ equivalent doses H_T (in relevant tissues and organs) multiplied by the corresponding tissue weighting factors w_T recommended by the ICRP and laid down in the Radiation Protection Ordinance.

$$E = \sum_T w_T \cdot H_T = \sum_T w_T \sum_R w_R \cdot D_{T,R}$$

H_T is the organ equivalent dose in a tissue or organ T; w_T is the tissue weighting factor and w_R the radiation weighting factor. The effective dose is expressed in $J\ kg^{-1}$. In order to make it clear that this is a weighted dose quantity, like the effective dose it is expressed in sieverts (Sv) and not in grays (Gy).

Erythemally weighted radiation

The erythemally weighted radiation H_{er} serves as a measure of comparison of the erythema effectiveness of UV radiation sources, relative to the “erythema reference action spectrum and the standard erythema dose”.

ISO/CIE 17166:2019-05 Erythema reference action spectrum and standard erythema dose 2019-05

Excess absolute risk (EAR)

The excess absolute risk is an expression of risk based on the assumption that the excess risk from radiation exposure adds to the underlying or background risk rises by an increment dependent on dose but independent of the background risk. The excess absolute risk is often expressed as the additive excess rate per Gy or per Sv, both in terms of incidence and mortality.

http://icrpaedia.org/Excess_absolute_risk

Excess relative risk (ERR)

The excess relative risk is an expression of the risk of an event (e.g. disease or death) in an exposed population divided by the risk of the event in an unexposed population, minus 1. In radiation epidemiological studies, the excess relative risk can be estimated from the ratio of the event rates in both populations, minus 1. In the literature, this relationship is frequently omitted and the excess relative risk is equated with the ratio of the event rates, minus 1.

Tissue weighting factor

Tissue weighting factors w_T represent an approximation of the contribution to the total health risk from radiation resulting from irradiation of a specific tissue or organ *T* after homogeneous whole-body irradiation. These factors are average values (averaged over men and women and across all age groups) and therefore do not represent specific characteristics of individuals. Tissue weighting factors are used to weight individual organ equivalent doses H_T in calculations of the effective dose *E*. These factors w_T reflect the different sensitivity of various organs, tissues or body parts *T* to stochastic radiation effects (cancer, heritable effects).

Kerma

Kerma (kinetic energy released in matter or kinetic energy released per unit mass) describes the sum of the initial kinetic energies of all secondary charged particles that are released in the irradiated medium in a volume element. It is a physical quantity dependent on the irradiated medium. Contrary to the absorbed dose, which is a measure of the energy absorbed by the material, kerma refers to the energy released in the material.

The interaction between a medium and indirectly ionising radiation leads to charged particles (secondary electrons). Secondary electrons release their energy to atoms and molecules of the material. Dose measurements only involve the energy effective in the measuring volume. Secondary electron equilibrium describes the state where the amounts of charged particles (electrons) emitted outside the measuring volume are equal to those entering the measuring volume from the surroundings.

In a state of secondary electron equilibrium, the kerma value approximates that of the absorbed dose. The kerma is expressed in gray (Gy).

Lethality fraction

The lethality fraction k_T is a component of the ICRP detriment model to quantify the harmful risk of cancers or heritable effects. It describes the fraction of a lethal disease (mortality) for an organ *T* relative to the overall probability of occurrence of the disease (incidence). The reference values are the lifetime mortality risk $r_{M,T}$ and the lifetime incidence risk $r_{I,T}$ in a specific population for the organ *T*. If the observation period and the reference groups are identical for both values, the lethality fraction k_T can be approximated using the corresponding values for the number of deaths $n_{M,T}$ and the number of incident cases $n_{I,T}$:

$$k_T = \frac{r_{M,T}}{r_{1,T}} = \frac{n_{M,T}}{n_{1,T}}$$

	The lethality fraction is expressed as a value between 0 and 1, where $k_T = 0$ means that the observed disease in organ T always has a non-fatal course and that no deaths occur as a result of this disease, while $k_T = 1$ denotes a disease that always has a fatal outcome.
Life Span Study (LSS)	The LSS Life Span Study is an epidemiological study of the health effects in survivors of the atomic bombings of Hiroshima and Nagasaki. Epidemiological investigations in this cohort play a pivotal role in radiation epidemiology. Estimates of the dose-dependent cancer risk from this study were used in developing the fundamentals of the current system of radiation protection, for example, when defining limits.
LNT model	Linear no-threshold model. As used in radiation protection, this model assumes that the frequency of stochastic effects that are observed at medium to high doses of radiation (around 0.1 to 5 Gy) can be extrapolated in a linear fashion to the zero dose (i.e. without a threshold dose).
Nominal risk coefficient	The nominal risk coefficient is a lifetime risk estimate per dose unit for a representative population, averaged for sex and age at exposure. The lifetime risk is the absolute probability per dose unit of developing a solid cancer or leukaemia (incidence risk) or of dying from cancer (mortality risk). Among other things, nominal risk coefficients are used to determine tissue weighting factors.
Odds Ratio (OR)	A ratio of two odds; in the field of radiation research these are often the odds with radiation exposure and those without radiation exposure.
Risk coefficient	The risk coefficient in radiation protection is a coefficient that is used to calculate the probability of occurrence of a stochastic effect per dose unit. A risk coefficient can be defined for the excess relative risk, the excess absolute risk or for cumulative risks. The parameter is the product of the risk coefficient and the dose. The unit is Sv^{-1}.
Standard erythema dose (SED)	The standard erythema dose (SED) is used as a measure of erythemally weighted radiation H_{er}: $H_{er} = 100\ J\ m^{-2} = 1$ SED. The SED is independent of the individual erythema sensitivity of the human skin.
Radiation exposure	Exposure to radiation is the term used for any action of ionising radiation on the human body. Whole-body exposure is the action of ionising radiation on the whole body. Partial-body exposure is the action of ionising radiation on individual or-

gans, tissues or body parts. External exposure to radiation involves radiation sources outside the body, while internal exposure to radiation involves radiation sources inside the body.

Note
This glossary uses the term radiation exposure for exposures to ionising radiation, while the radiation protection legislation uses the term “exposure” alone, since the context is clear.

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A-3 Overview of all identified studies with data of the LSS

First author:	Year of publication:	Follow-up period:	Outcomes:	Cases:	Dosimetrysystem:
Thompson	1994	1958-1987	NMSC, MM / Incidence	245 NMSC, 20 MM	DS86
Little	1997	1958-1987	NMSC / Incidence	245 NMSC, 20 MM	DS02
Ron	1998	1958-1987	BCC, SCC, MM / Incidence	80 BCC, 69 SCC, 10 MM	DS86
Kishikawa	2005	1958-1987	BCC, SCC, MM / Incidence	106 BCC, 81 SCC, 14 MM	DS86
Preston	2007	1958-1998	NMSC, BCC, SCC / Incidence	330 NMSC, 166 BCC, 131 SCC	DS02
Pierce	1996	1950-1990	NMSC / Mortality	28 Todesfälle	DS86
Sugiyama	2014	1958-1996	BCC, SCC, MM / Incience	123 BCC, 114 SCC, 10 MM	DS02

(authors:Luca Caramenti, Michael Hauptmann)

A-5 Tables with details of the study design (relative to person groups)

Tab. A-4.1 Details of the selected studies among survivors of the atomic bombing (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diag-noses	Outcome ascer-tainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
LSS / Sugiyama et al. 2014	Cohort / 80,158 / 25.2 years / Incidence	123 BCC, 114 SCC, 10 MM	1958-1996	Registries	A-bomb / Acute	Distance to center (DS02)	Dose to the skin	Not reported

Tab. A-4.2 Details of the selected studies among therapeutically exposed persons (authors:Luca Carramenti, Michael Hauptmann)

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Swedish Cancer Registry / Karlsson et al. 1998	Nested case-control / 122,991 (underlying cohort, 3 controls per case) / 7.4 years / Incidence	116 sarcoma of connective tissue, breast or skin *(angiosarcoma: 40; other sarcomas: 76)*	1959-1992	Cancer registry (Swedish cancer register)	Radiation therapy (IR) / Acute	RT 2D-treatment planning from clinical records	Integral dose in J (combination of "dose" and irradiated volume)	177 J among exposed controls
Scalp ringworm cohort / Shore et al. 2002	Cohort / 2,224 exposed and 1,380 unexposed / – / Incidence	124 exposed BCC and 21 unexposed)		Self-report with physician verification (94.4 %)	X-ray treatment for scalp ringworm / Acute	Phantom-based estimation	Cumulative scalp dose	4.8 Gy
Childhood cancer survivors / Guerin et al. 2003	Case control / 16 cases, 75 controls / – / Incidence	16 MM	1942–1987	Cancer registry	Radiotherapy / Acute	Individual simulation based on RT files	Mean local dose to MM location (case) and corresponding location (control)	mean local dose was 15.5 Gy for cases and 3.1 Gy for controls
TBI cohort Schwartz et al. 2009	Cohort / 6,306 / 100 days – 36.2 years / Incidence	282 BCC	1969–2005	Questionaires of patients	Radiotherapy / Acute	Prescribed dose from patient record	Whole body dose	12.7 Gy
German RT patients Landthaler et al. 1995	Cohort / 612 radiation sites of 522 patients / – / Incidence	12 BCC and 9 SCC	More than 10 years after treatment	Pathology records and clinical records	Radiotherapy for mostly cutaneous tumors / Acute	Treatment planning	Treatment dose	80 Gy

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Skin hemangioma cohort / Haddy et al. 2012	Cohort + nested case-control / 4,620 cohort members, case-control study with 13 cases and 5 controls per case / – / Incidence	13 MM	1986–2003	Self-report with pathological confirmation	Radiotherapy for skin hemangioma / Acute	Phantom-based	Dose to tumour location (corresponding location in controls)	1.08 Gy cases, 0.002 Gy controls
Tinea capitis cohort / Ron et al. 1991	Cohort / 27,060 / 24.5 years / Incidence	54 BCC	1950-1980	Pathology records and cancer registry	Radiotherapy for tinea capitis / Acute	Phantom-based	Cumulative absorbed scalp dose (Gy)	6.8 Gy

Tab. A-4.3 Details of the selected studies on occupationally exposed persons in nuclear power plants and medical facilities (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
USRT (1) / Freedman et al. 2003	Cohort / 68,588 / 10.2 years / Incidence	207 MM	1926-1998	Self report	Occupational X-rays (IR) / Chronic	No; work history information used instead	Years of employment in different calendar time periods as surrogate	
LLNL (1) / Austin et al. 1997	Case-control / 31 cases and 110 individually matched controls, 4 per case / – / Incidence	31 MM	1969-1980	Cancer registry (California Tumor Registry)	Occupational / Chronic	No, just occupational exposure history	Ever vs. never exposed to occupational ionizing radiation and number of exposed years	not provided, range from 7 to 27 Sv
NRRW / Muirhead et al. 2009	Cohort / 174,541 Workers / 22 years / Incidence	261 MM, 326 NMSC	1976-2001	Cancer Registry	Personal records of radiation exposure / Chronic	Individual	Cumulative effective dose (mSv)	24.9 mSv
French nuclear workers (1) / Samson et al. 2011	Cohort / 2 cohorts, external only: 14,796 ext. and int.: 14,408 / Mortality	ext. only: 4 ext. and int.: 12	1968-1994	Death certificate	Occupational / Chronic	Individual dosimeters	Cumulative effective dose from external sources (mSv)	Cohort with external exposure only: 3.7 mSv, cohort with external and internal exposure: 12.9 mSV

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
USRT (2) / Lee et al. 2015	Cohort / 65,719 / 17 years / Incidence	3,615 BCC	1983-2005	Questionaire and medical reports	Occupational / Chronic	Estimation based on batch readings and workplace information	Absorbed skin dose	55.8 mGy
Mayak workers (2) / Azizova et al. 2021	Cohort / 22,377 / BCC 26.3 years, SCC 26.4 years / Incidence	295 BCC, 48 SCC	1948-2018	Archive, medical records, patients' hospital charts	Plutonium production facility / Chronic	Individual estimation based on job records	Cumulative absorbed gamma-ray skin dose (Gy)	0.50 Gy
LLNL employees (2) / Moore et al. 1997	Case-control / 138 (69 matched controls) / – / Incidence, prevalence	69 MM	1969-1989	Skin cancer diagnoses among employees	Nuclear workers / Chronic	Individual estimates from dosimetry records	Cumulative dose for gamma, neutron, tritium, skin and hand (rem)	7.6 mSv cases, 7.1 mSv controls
Mayak workers (1) / Azizova et al. 2018	Cohort / 22,377 / MM 25.5 years, NMSC 25.2 years / Incidence	60 MM, 294 NMSC	1948-2013	Archive, medical records, patients' hospital charts	Plutonium production facility / Chronic	Individual estimation based on job records	Cumulative skin dose (Sv)	0.54 Sv
15-Country Study / Cardis et al. 2007	Cohort / 407,391 / 12.7 years / Mortality	87 MM		Death certificate	Nuclear workers / Chronic	Recorded dose	Cumulative whole body dose (mSv)	19.4 mSv

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Canadian National Dose Registry / Sont et al. 2001	Cohort / 191,333 / – / Incidence	222 MM	1969-1988	Cancer registry	Nuclear workers / Chronic	Occupational routine measurements	Cumulative whole body dose 1951-1988 (in Sv lagged by 10 years)	6.64 mSv
French nuclear workers (2) / Metz-Flamant et al. 2013	Cohort / 59,021 / 25.9 years / Mortality	68 MM, 7 NMSC	1968-2004	Death certificates	Nuclear workers / Chronic	Estimation based on individual dosimeter readings	Whole body dose	22.5 mSv among exposed (72 %)

Tab. A-4.4 Details of the selected studies among flight personnel (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Nordic airline pilots / Pukkala et al. 2002	Cohort / 10,032 / 17.7 years / Incidence	56 MM, 27 other skin excluding BCC, 61 BCC	1943-1997	National Cancer Registry (Denmark, Finland, Iceland, Norway, Sweden)	Cosmic / Chronic	Block hours, type of flight, altitude	Effective dose (mSv)	Mean dose not provided, 11 % of person years >20 mSv
ESCAPE airline pilots / Langner et al. 2004	Cohort / 19,184 (male pilots) / – / Mortality	14 MM	1921-1997	Death certificate (Denmark, Finland, Germany, Iceland, Italy, Norway, Sweden)	Cosmic / Chronic	Block hours and job exposure matrix (aircraft and calendar year specific dose rates)	Effective dose (mSv)	Mean lifetime cumulative dose: 15.3 mSv
German aircrew / Dreger et al. 2020	Cohort / 26,846 / 32 years / Mortality	10 MM	1960-2014	Death certificate	Cosmic / Chronic	Individual estimation based on Federal Radiation Protection Register data	Cumulative effective dose (Sv)	Median cumulative effective dose 34.2 mSv (Max: 116 mSv)
US flight attendants / Pinkerton et al. 2018	Cohort / 6,095 female Qx respondents / – / Incidence	125 MM	from 1970	Self-report, medical records, cancer registry	Cosmic / Chronic	Flight schedule	Cosmic radiation absorbed dose, lagged 10 years	Median 7.3 mGy

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Icelandic pilots Gudmundsdottir et al. 2017	Cohort / 551 male pilots / 31.8 years / Incidence	7 MM 31 BCC	1955-2015	Cancer registry	Cosmic / Chronic	Block hours, type of flight, altitude	Cumulative effective dose (mSv)	Median cumulative effective dose 22.6 mSv per year (for 286 Icelandair pilots)
Nordic airline cabin crew Pukkala 2012	Cohort / 8.507 female, 1.599 male/ - / Incidence	Female 59 MM, 56 BCC, 13 other skin Male 18 MM 2 BCC 10 other skin	1947-2006	Cancer registry	Cosmic / Chronic	Block-hours type of flight, altitude	Cumulative effective dose (mSv)	30% >5-14.9 mSv 29% 15-34.9 mSv 6% ≥35 mSv

Tab. A-4.5 Details of the selected studies in the radon-exposed population (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Design / Study size / Mean follow-up / Incidence or mortality	Number of cases	Period of case diagnoses	Outcome ascertainment	Exposure source / Acute or chronic exposure	Dosimetry	Exposure metric	Mean dose
Swiss population / Vienneau et al. 2017	Cohort / 5,249,467 / 7.8 years / Mortality	1,900 MM, 838 NMSC	2000-2008	Death certificate	Residential radon / Chronic	Exposure assessment	Average annual concentration at place of residence in 4.12.2000, adjusted for floor of residence (Bq m^{-3})	91.8 Bq m^{-3}
Danish cohort / Bräuner et al. 2015	Cohort / 51,445 / 13.6 years / Incidence	329 MM, 3,243 BCC, 317 SCC	1993-2011	Cancer registry	Residential radon / Chronic	Exposure assessment for residential histories	Time-dependent time-weighted average radon concentration (Bq m^{-3})	Median: 38.3 Bq m^{-3}
Czech Uranium miners/ Kulich et al. 2011	Case-cohort / 1,730 / Median: 16.5 years / Incidence	23 MM	1977-1996	Cancer registry	Occupational radon / Chronic	Exposure assessment for occupational histories	Cumulative Working Level Months (WLM)	84.0 WLM

A-5 Tables with results (relative to skin cancer subtypes)

Tab. A-5.1 Details of the selected studies on basal cell carcinoma (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Number of cases / Incidence or mortality	Confounder control	Type of dose-response analysis	Dose-response result + CI (95% if not specified otherwise)	ERR at 100 mGy + CI (95 % if not specified otherwise)
Danish cohort / Bräuner et al. 2015	3,243 / Incidence	Age, sex, skin reaction to sunlight, freckles, nevi, BMI, education, SES, outside leisure activities, outdoor occupations, mean daily hours of bright sunshine	Cox regression with loglinear time-dependent time-weighted average radon concentration	Incidence Rate Ratio (IRR) per 100 Bq m^{-3} =1.14 (1.03; 1.27)	Not provided
Icelandic pilots / Gudmundsdottir et al. 2017	31 / Incidence	Age	Poisson regression	RR = 1.92 (95 % CI 0.49; 7.23) for Icelandair pilots with > 0 to < 25 mSv, 3.61 (95 % CI 1.64; 8.48) for Icelandair pilots with >= 25 mSv vs unexposed pilots, p-trend = 0.0005	Not provided
Nordic airline pilots / Pukkala et al. 2002	61 / Incidence	Age, calendar period	Poisson regression with continuous loglinear time-dependent cumulative dose	RR for categories 3 – < 10 mSv, 10 – < 20, 20+ vs < 3: 1.8 (0.7, 4.8), 1.4 (0.6, 3.4), 1.9 (0.98, 3.5), p trend = 0.17	Not provided
USRT (2) / Lee et al. 2015	3,615 / Incidence	Education, income, smoking, alcohol, BMI, exercise, eye colour, skin complexion, sunburns, dental X-rays, solar UV exposure, gender, age, calendar year	Poisson regression with linear ERR		ERR: -0.01 per Gy (-0.43, 0.52)
German RT patients / Landthaler et al. 1995	12 / Incidence	None	Case % by dose category	No dose-response: BCC and SCC combined by dose: 1 (4.3 %) for < 30 Gy, 4 (3.9) for 31 – 60 Gy, 13 (3.0) for 61 – 90 Gy, 3 (5.0 %) for >90 Gy	Not provided

Study name / Reference	Number of cases / Incidence or mortality	Confounder control	Type of dose-response analysis	Dose-response result + CI (95% if not specified otherwise)	ERR at 100 mGy + CI (95 % if not specified otherwise)
Nordic airline pilots / Pukkala et al. 2012	106 / Incidence	Matched by country and year of birth	Conditional logistic regression of continuous (loglinear) and categorical dose	OR per 10 mSv: 0.95 (0.72; 1.25)	Not provided
TBI cohort / Schwartz et al. 2009	282 / Incidence	None	Poisson regression, linear ERR model		ERR by age: 0-9 years at treatment 1.49 (0.64; 3.17), 10-19: 0.55 (0.28; 1.00), 20-39: 0.11 (0.06; 0.18), 40-64: 0.02 (-0.01; 0.06)
Mayak workers (2) / Azizova et al. 2021	295 / Incidence	Sex, attained age, calendar period	Poisson regression with linear ERR		ERR: 0.57 per Gy (0.27-1.03)
LSS / Sugiyama et al. 2014	123 / Incidence	City, sex, attained age	Linear ERR via Poisson regression (with threshold)		0.22 (0.078; 0.29); with threshold at 0.63 (0.3; 0.9) Gy and then slope of 0.2 (0.069; 0.43) per 100 mGy fitted best
Tinea capitis cohort / Ron et al. 1991	54 / Incidence	Sex, ethnicity, age, country of birth, year of immigration, number of X-rays, time since exposure	Poisson regression with linear ERR		ERR 0.79 per Gy ($p < 0.001$), calculated from RR provided for two dose values
Scalp ringworm cohort / Shore et al. 2002	145 / Incidence	Sex, attained age, other risk factors for BCC were identified (light complexion, Caucasian, sunburns) but not adjusted for	Poisson and Cox regression	Sign elevated SIR (3.3) for exposed vs unexposed, significant elevated risk per dose	ERR 6.0 per 100 mGy (3.0; 11.0)

Tab. A-5.2 Details of the selected studies on squamous cell carcinoma (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	**Number of cases / Incidence or mortality**	**Confounder control**	**Type of dose-response analysis**	**Dose-response result + CI (95% if not specified otherwise)**	**ERR at 100 mGy + CI (95 % if not specified otherwise)**
Danish cohort / Bräuner et al. 2015	317 / Incidence	Age, sex, skin reaction to sunlight, freckles, nevi, BMI, education, SES, outside leisure activities, outdoor occupations, mean daily hours of bright sunshine	Cox regression with loglinear time-dependent time-weighted average radon concentration	Incidence Rate Ratio (IRR) per 100 Bq m^{-3} = 0.90 (0.70; 1.37)	Not provided
Mayak workers (2) / Azizova et al. 2021	48 / Incidence	Sex, attained age, calendar period	Poisson regression with linear ERR		ERR per Gy: 0.14 (-0.23; 0.91)
LSS / Sugiyama et al. 2014	114 / Incidence	City, sex, attained age	Linear ERR via Poisson regression (with threshold)		-0.012 (<-0.012; 0.025)
German RT patients / Landthaler et al. 1995	9 / Incidence	None	Case % by dose category	No dose-response: BCC and SCC combined by dose: 1 (4.3 %) for < 30 Gy, 4 (3.9) for 31-60 Gy, 13 (3.0) for 61-90 Gy, 3 (5.0 %) for >90 Gy	Not provided
Nordic airline pilots / Pukkala et al. 2002	Other skin: 27 (Skin cancer other than melanoma and excluding basal cell carcinoma and, in Denmark, all non-melanoma skin cancers diagnosed before 1979) / Incidence	Age, calendar, period	Poisson regression with continuous loglinear time-dependent cumulative dose	RR for categories 3- < 10 mSv, 10-< 20, 20+ vs < 3: other skin 0.5 (0.1; 4.3), 1.5 (0.5, 4.5), 1.9 (0.7, 5.0), p trend = 0.14;	Not provided

Tab. A-5.3 Details of the selected studies on malignant melanoma (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	Number of cases / Incidence or mortality	Confounder control	Type of dose-response analysis	Dose-response result + CI (95 % if not specified otherwise)	ERR at 100 mGy + CI (95 % if not specified otherwise)
Nordic airline pilots / Pukkala et al. 2002	56 / Incidence	Age, calendar period	Poisson regression with continuous loglinear time-dependent cumulative dose	RR for categories 3 – < 10 mSv, 10 – < 20, 20+ vs < 3: 2.1 (0.9; 4.9), 2.2 (1.0; 4.7), 2.8 (1.3; 5.9), p trend = 0.007	Not provided
USRT (1) / Freedman et al. 2003	207 / Incidence	Skin tone, eye and hair color, personal history of nonmelanoma skin cancer, family history of melanoma and indicators of residential sunlight exposure(no estimates of individual radiation doses, and no detailed information about sun exposure, sunburn history)	Cox proportional hazards regression with time dependent number of years worked in time periods	RR = 2.4 (0.7; 8.7) for 5+ years worked before 1950, p trend = 0.03	Not provided
ESCAPE airline pilots / Langner et al. 2004	14 / Mortality	Age	Poisson regression with categorical cumulative dose	RR (0 – 4.99 mSv) = 1.0, (5 – 14,99 mSv) = 0.71 (0.22; 2.18), (15 – 24.99 mSv) = 1.26 (0.45; 3.50), (= > 25mSv) = 0.33 (0.06; 1.85). p trend = 0.481	Not provided
German aircrew / Dreger et al. 2020	10 / Mortality	Age, year, employment status	Poisson regression with loglinear continuous cumulative effective dose	RR>=40 mSv vs <5: 2.37 (0.21; 26.95). RR per 10 mSv (loglinear term) in male cockpit crew: 1.29 (0.78; 2.40) for MM	Not provided
LLNL (1) / Austin et al. 1997	31 / Incidence	education, moles, skin cancer family history, previous NMSC, volatile photografic chemicals, age, race and sex	Conditional logistic regression with loglinear number of exposed years	OR ever vs never exposed = 2.3 (1.0; 7.6). RR per year exposed: 1.12 (p = 0.017)	Not provided
French nuclear workers (1) / Samson et al. 2011	ext. only: 4 ext. and int.: 12 / Mortality	Age, sex,calendar year, socioecomonic status, duration of employment	Poisson regression with continuous fit of 11 categories of cumulative effective dose	No significant dose–effect relationship observed (no results shown)	Not provided

Study name / Reference	Number of cases / Incidence or mortality	Confounder control	Type of dose-response analysis	Dose-response result + CI (95 % if not specified otherwise)	ERR at 100 mGy + CI (95 % if not specified otherwise)
Swiss population / Vienneau et al. 2017	1900 / Mortality	Sex, civil status, education, SES, outdoor occupation with UV exposure, mother tongue, UVErythemal dose	Cox regression with loglinear radon concentration	Hazard Ratio per 100 Bq m^3 = 1.16 (1.04; 1.29)	Not provided
Danish cohort / Bräuner et al. 2015	329 / Incidence	Age, sex, skin reaction to sunlight, freckles, nevi, BMI, education, SES, outside leisure activities, outdoor occupations, mean daily hours of bright sunshine	Cox regression with loglinear time-dependent time-weighted average radon concentration	Incidence Rate Ratio (IRR) per 100 Bq m^3 =1.08 (0.77; 1.50)	Not provided
Childhood cancer survivors / Guerin et al. 2003	16 / Incidence	Alcylating agents and spindle inhibitors, gonadal first primary tumours, country, gender, age at first cancer, calendar year of first cancer	Conditional logistic regression with continuous dose	OR = 13 (0.94;174), >15Gy vs no RT, unadjusted. Loglinear OR per Gy: 1.07 (1.00; 1.15), p = 0.05	Not provided
LLNL (2) / Moore et al., 1997	69 / Prevalence	Retirement status, sex, age, start of job, years of education, years of work	Paired sample t-test of dose for matched case-control pairs	No difference (p-value = 0.82)	Not provided
LSS / Sugiyama et al. 2014	10 / Incidence	City, sex, attained age	Linear ERR via Poisson regression (with threshold)		0.086 (-0.14; 0.73)
US flight attendants / Pinkerton et al. 2018	125 / Incidence	Age, year of birth, education, race	Cox regression with loglinear cumulative dose	HR=1.01 (0.88; 1.13) per 4.6 mGy absorbed dose	Not provided
Mayak workers (1) / Azizova et al. 2018	60 / Incidence	Neutron dose, sex, age, calendar year	Poisson regression with linear ERR		ERR per Sv 0.15 (-0.41; 1.31)
Skin hemangioma cohort / Haddy et al. 2012	13 / Incidence	Sex, age at treatment, calendar year	Logistic regression of categorical dose	OR vs no RT: 3.9 (0.5; 32) >0-0.001 Gy, 3.9 (0.2; 73) 0.001-0.01 Gy, 6.9 (0.5; 99) >0.01 Gy	Not provided
15-Country Study / Cardis et al. 2007	87 / Mortality	Sex, age, calendar period, facility, duration of employment, SES	Poisson regression with linear ERR		ERR -0.72 per Sv (90 %: < 0; 1.93)
Canadian National Dose Registry / Sont et al. 2001	222 / Incidence	Age, gender, birth year	Poisson regression with linear ERR	Significantly elevated SIR for MM but ERR non-significant	ERR per 100 mGy = 0.43 (90 %: < 0; 1.96)

Study name / Reference	Number of cases / Incidence or mortality	Confounder control	Type of dose-response analysis	Dose-response result + CI (95 % if not specified otherwise)	ERR at 100 mGy + CI (95 % if not specified otherwise)
Czech uranium workers / Kulich et al. 2011	23 / Incidence	Age, calendar time, smoking	Cox regression with loglinear cumulative exposure	HR for 180 vs 3 WLM = 2.92 (0.91; 9.42), RR 10 – 50 WLM = 2.16 (0.67; 6.90), RR 50 – 100 WLM = 5.55 (1.83; 16.86), RR > 100 WLM = 3.38 (0.82; 13.94), relative to <= 10 WLM, p heterogeneity = 0.002	
NRRW / Muirhead et al. 2009	261 / Incidence	Age, sex, calendar year, industrial job and first employer	Linear ERR regression with categorical cumulative dose	p-trend = 0.26	ERR per Sv = 1.39 (-0.65; 5.6)
French combined nuclear workers (2) / Metz-Flamant et al. 2013	68 / Mortality	Sex, age, calendar period, company, SES, duration of employment	Poisson regression with linear ERR model and loglinear model		ERR < 0, one-sided p-value = 0.72
Icelandic pilots / Gudmundsdottir et al. 2017	7 / Incidence	Age	Poisson regression	RR = 5.07 (0.14; 201.23) for Icelandair pilots with > 0 to < 25 mSv, 9.88 (1.57; 190.78) for Icelandair pilots with >= 25 mSv vs unexposed pilots, p-trend = 0.009	
Nordic airline pilots / Pukkala et al. 2012	68 / Incidence	Matched by country and year of birth	Conditional logistic regression of continuous (loglinear) and categorical dose	OR per 10 mSv: 0.99 (0.59; 1.66)	

Tab. A-5.4 Details of the selected studies on non-melanoma skin cancer (NMSC) (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	**Number of cases / Incidence or mortality**	**Confounder control**	**Type of dose-response analysis**	**Dose-response result**	**ERR at 100 mGy + 95 %-CI if not specified otherwise**
Swiss population / Vienneau et al. 2017	838 / Mortality	Sex, civil status, education, SES, outdoor occupation with UV exposure, mother tongue, UVErythemal dose	Cox regression with logline	Hazard Ratio = 1.14 (0.87; 1.50)	Not provided
Mayak workers (1) / Azizova et al. 2018	294 / Incidence	Neutron dose, sex, age, calendar year	Poisson regression with linear ERR		ERR: 0.51 per Sv (0.22; 0.93)
NRRW / Muirhead et al. 2009	261 / Incidence	Age, sex, calendar year, industrial job and first employer	Linear ERR regression with categorical cumulative dose	p-trend = 0.04	ERR: 1.50 per Sv (0.05; 3.85)
French combined nuclear workers (2) / Metz-Flamant et al. 2013	7 / Mortality	Sex, age, calendar period, company, SES, duration of employment	Poisson regression with linear ERR model and loglinear model		NMSC: ERR = 126.5 (90% CI 7.03; 1916)

Tab. A-5.5 Details of the selected studies on all skin cancers together (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	**Number of cases / Incidence or mortality**	**Confounder control**	**Type of dose-response analysis**	**Dose-response result**	**ERR at 100 mGy + 95 %-CI if not specified otherwise**
NRRW / Muirhead et al. 1999	30 (incl. 26 MM) / Mortality	Age, sex, calendar year, industrial job and first employer	Linear ERR regression (probably Poisson)		ERR: 2.07 per Sv (90%-CI: -1.04–15.1)

Tab. A-5.6 Details of selected studies on sarcoma (authors:Luca Caramenti, Michael Hauptmann)

Study name / Reference	**Number of cases / Incidence or mortality**	**Confounder control**	**Type of dose-response analysis**	**Dose-response result**	**ERR at 100 mGy + CI (95 % if not specified otherwise)**
Swedish Cancer Registry / Karlsson et al. 1998	116 sarcoma of connective tissue, breast or skin *(angiosarcoma: 40; other sarcomas: 76)* / Incidence	Age, year of breast cancer diagnosis, county and lymphoedema	Conditional logistic regression, continuous dose in linear and quadratic terms adjusted for oedema	Positive significant linear term and negative significant quadratic term for all soft tissue sarcoma and other sarcoma, no positive association for angiosarcome. Integral dose of RT was a predictor of the risk for other sarcomas (OR for 50 J: 2.4 (1.4; 4.2); OR for 100 J: 4.8 (1.6; 14.9); OR for 150 J: 8.0 (1.4; 46.1). All soft tissue sarcome: linear term 1.8 (0.8; 2.7), quadratic term -0.4 (-0.6; -0.1). Other sarcoma: 1.9 (0.8; 3.0), -0.4 (-0.6; -0.1)	Not provided

A-6 Risk coefficients and detriment D based on LSS data

Tab. A-6.1: Incidence risk coefficients RI and detriment D for skin cancer based on the LSS (Sugiyama et al. 2014) using a DDREF = 2 and lethality fraction k = 0.002 for qmin = 0 and qmin = 0.1 from ICRP 2007, Tab. A.4.1

Dose-response model:	**ERR/EAR-mixed model**	**R_I / (10.000·Sv)$^{-1}$**	**minimal reduction in quality of life**	**D / (10,000·Sv)$^{-1}$**
LNT ERR/D = 0.2/Sv … 0.5/Sv	0:100	2.5	q_{min} = 0	0.01
			q_{min} = 0.1	0.25
	50:50 *like all other cancer types*	150 … 400	q_{min} = 0	0.6 … 1.6
			q_{min} = 0.1	15 … 40
	100:0	300 … 800	q_{min} = 0	1.2 … 3.2
			q_{min} = 0.1	30 … 80
Linear with threshold dose at 0.63 Gy *(best fit)*	Any ratio	0	all	0
For comparison:				
ICRP Publication 103	100:0	1 000	q_{min}=0	4