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Assessment of Prospective Cancer Risks from Occupational Exposure to Ionizing Radiation

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ASSESSMENT OF PROSPECTIVE CANCER RISKS FROM OCCUPATIONAL EXPOSURE TO IONIZING RADIATION

The Agency's Statute was approved on 23 October 1956 by the Conference on the Statute of the IAEA held at United Nations Headquarters, New York; it entered into force on 29 July 1957. The Headquarters of the Agency are situated in Vienna. Its principal objective is "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

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JOINTLY PREPARED BY THE
INTERNATIONAL ATOMIC ENERGY AGENCY
AND THE INTERNATIONAL LABOUR ORGANIZATION

INTERNATIONAL ATOMIC ENERGY AGENCY
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FOREWORD

Radioactive materials and other sources of radiation are used throughout the world for a variety of beneficial purposes in industry, medicine, research, agriculture and education. The use of radioactive materials and other sources of radiation can pose health risks due to radiation exposure, which can occur in many different professions. Artificial sources of radiation are commonly used in the manufacturing and service industries, research institutions and universities, and the nuclear power industry. As a result, workers in a number of occupations can be exposed to artificial sources of radiation, such as radiologists, radiographers (both medical and industrial), and other medical and nuclear industry workers. There are also a significant number of workers exposed to naturally occurring sources of radiation, such as underground miners and aircrew.

At high enough levels of exposure, ionizing radiation can produce adverse tissue reactions, known as deterministic effects. These tissue reactions only occur above particular threshold doses and the severity of the reaction increases in line with increasing tissue doses. The biological mechanism of tissue reactions is cell killing or cell malfunction. At lower levels of exposure, radiation can also induce stochastic effects. The current understanding is that there are no threshold doses for stochastic effects and the probability of a stochastic effect increases with increasing tissue doses. The result of stochastic effects on the biological mechanism is non-lethal cell modification.

Individuals exposed to ionizing radiation in their work may have a risk of developing health problems associated with this exposure. Risks of radiation exposure need to be assessed and controlled. IAEA Safety Standards Series Nos GSR Part 2, GSR Part 3 and GSG-7 establish requirements and provide guidance on the protection of workers against exposure to radiation. Estimating radiation risk is required to evaluate potential adverse health outcomes. According to the requirements established in GSR Part 3, an employer is responsible for ensuring radiation safety in the workplace and informing employees about the risk to health due to occupational radiation exposure.

Member States have requested guidance from the IAEA on the assessment of prospective cancer risks. The Radiation Safety Standards Committee subsequently advised that a publication be developed to focus on the technical issues of assessing risk based on individual doses.

The IAEA has developed this publication, which includes relevant theory, models and a methodological framework, to provide practical information for prospectively assessing radiation induced cancer risks. It also offers practical examples of carrying out cancer risk assessments for workers subject to internal and external radiation exposure. The publication is intended for individuals and organizations working in the field of radiation safety or those with a risk of radiation exposure.

The objectives of this publication are (i) to provide information on a methodological framework for the assessment of prospective risks of cancer in individuals with occupational exposure to radiation, (ii) to provide information to assist in managerial decisions on limiting and controlling exposure and (iii) to facilitate the implementation of occupational radiation protection programmes. The publication does not discuss medical and public exposure to radiation.

This publication was developed in collaboration with the International Labour Organization. The IAEA would like to express its gratitude for the contributions made by Jie Fu (China) and R. Abutalipov (Russian Federation). The IAEA officer responsible for this publication was Jizeng Ma of the Division of Radiation, Transport and Waste Safety.

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CONTENTS

1. INTRODUCTION 1
   1.1 BACKGROUND 1
   1.2 OBJECTIVE 2
   1.3 SCOPE 2
   1.4 STRUCTURE 3
2. ASSESSMENT OF RADIATION-INDUCED CANCER RISK 5
   2.1. INTRODUCTION 5
   2.2. FACTORS INFLUENCING CANCER RISK 5
   2.3. RADIATION EFFECTS 6
   2.4. FACTORS INFLUENCING RADIATION-INDUCED CANCER RISK 7
   2.5. SHAPE OF DOSE-RESPONSE AND ITS IMPACT ON RISK ASSESSMENT 8
   2.6. CONCLUSIONS 9
3. DESCRIPTIVE CANCER RISK MODELS 11
   3.1. INTRODUCTION 11
   3.2. RADIATION DOSIMETRY AND EXPOSURE ASSESSMENT 11
      3.2.1. Doses from external exposures 12
      3.2.2. Doses from photons (gamma or X-rays) 12
      3.2.3. Doses from neutrons 12
      3.2.4. Doses from internal exposures 12
   3.3. MINIMUM LATENT PERIOD 13
      3.3.1. Dose and dose-rate effectiveness factor 13
   3.4. ADDITIVE AND MULTIPLICATIVE MODELS 14
   3.5. MAIN MODIFYING FACTORS 16
   3.6. TRANSFER OF RISK BETWEEN POPULATIONS 19
   3.7. CONCLUSIONS 20
4. METHODOLOGY FOR THE CALCULATION OF ASSESSED RADIATION RISK 21
   4.1. INTRODUCTION 21
   4.2. RISK QUANTITIES 21
   4.3. EXAMPLES OF CALCULATIONS AND INTERPRETATION OF THE RESULTS 24
   4.4. CONCLUSIONS 31
5. SOURCES OF UNCERTAINTY IN USING EXISTING METHODOLOGIES 33

5.1. INTRODUCTION 33
5.2. MODELLING UNCERTAINTIES 33
5.2.1. Statistical uncertainties 34
5.2.2. Epidemiological uncertainties 34
5.2.3. Dose-response modelling 35
5.2.4. Dose and Dose Rate effectiveness Factor (DDREF) 36
5.3. MODEL APPLICATION UNCERTAINTIES 37
5.3.1. Transfer of risk 37
5.3.2. Average radiosensitivity 38
5.3.3. Lifetime risk 39
5.3.4. Radiation quality 39
5.3.5. Radiation doses 40
5.4. INFLUENCE OF OTHER FACTORS 41
5.5. CONCLUSIONS 42
6. SUMMARY AND KEY POINTS 43
7. CONCLUSIONS AND THE WAY FORWARD 45
REFERENCES 47
ABBREVIATIONS 65
CONTRIBUTORS TO DRAFTING AND REVIEW 67

1. INTRODUCTION

1.1 BACKGROUND

Ionizing radiation is part of the human environment (for example, cosmic rays and emissions from naturally occurring radioactive materials). Ionizing radiation includes X-rays and gamma rays (electromagnetic radiation) as well as corpuscular radiation (subatomic particles, notably: alpha, beta and neutron radiation). Radioactive materials and other sources of radiation are used throughout the world for a wide variety of beneficial purposes in industry, medicine, research, agriculture and education.

The use of radioactive materials and other sources of radiation involves risks to health due to radiation exposure. Such exposure occurs in many occupations. Artificial sources of radiation are commonly used in the manufacturing and service industries, in research institutions and universities, and in the nuclear power industry. Many workers are exposed to artificial sources of radiation, such as radiologists, radiographers (medical and industrial), other medical staff and nuclear industry workers, and many workers are exposed to naturally occurring sources of radiation, such as underground miners (to radon and its decay products) and aircrew (to cosmic radiation).

At high enough levels of exposure, ionizing radiation can produce adverse tissue reactions, which are also known as deterministic effects (for example, skin burns and sterility). Tissue reactions only occur above particular threshold doses, and the severity of the reaction increases with increasing tissue dose. The underlying biological mechanism producing tissue reactions is cell killing (or malfunction). At lower levels of exposure, radiation can also induce stochastic effects (cancer and hereditary diseases). Current understanding is that there are no threshold doses for stochastic effects, and the probability (rather than the severity) of a stochastic effect increases with increasing tissue dose; the linear no-threshold dose-response model for stochastic effects remains the model underlying radiation protection. The biological mechanism underlying stochastic effects is non-lethal cell modification (conventionally, DNA mutation). Consequently, owing to these adverse health effects resulting from irradiation, radiation exposure is measured and controlled; GSR Part 2[1], GSR Part 3[2] and GSG-7[3] provide requirements and guidance on the protection of workers against occupational exposure to radiation.

In 2010, the ILO, IAEA, and WHO jointly prepared a publication entitled “Approaches to attribution of detrimental health effects to occupational ionizing radiation exposure and their application in compensation programmes for cancer: A practical guide”[4]. This guide provides advice on procedures and methodology to assess the attribution of a particular case of cancer to prior occupational exposure to ionizing radiation, and to assist decision-making regarding compensation of workers who have developed cancer. This guide is intended, in particular, for use by competent authorities, employers and workers, and persons in charge of compensation programmes for occupational diseases. However, the methodology and approaches in retrospectively assessing cancer risks due to prior occupational exposure, as set out in the guide, provide a useful source of reference for the present TECDOC, prospectively assessing cancer risks due to specific occupational radiation exposures.

The IAEA published the TECDOC-870 “Methods for estimating the probability of cancer from occupational radiation exposure” in 1996[5]. It presents the factors that are generally accepted as being causes (or material contributary causes) of cancer, examines the role of radiation as a carcinogen, demonstrates how the retrospective probability of cancer causation by radiation

may be calculated, and provides information on the uncertainties that are associated with the use of various risk factors and models in such calculations. This TECDOC-870 is also a useful source of information for the prospective assessment of cancer risks due to radiation exposure.

Some Member States have already established a methodology and tools to assess the prospective cancer risk from exposure to radiation. Although the UNSCEAR 2006 Report[6] and ICRP Publication 103[7] address specific aspects of radiation risk, a comprehensive evaluation, covering both the calculation of risk and its application to the control of occupational exposure, is not available. Recent scientific developments in radiation epidemiology and risk assessment invite the development of a publication to fill in this gap. Requests for guidance from the IAEA on assessment of prospective cancer risks were made by Member States. The Radiation Safety Standards Committee (RASSC) advised that a TECDOC be developed to focus on the technical issues of assessing risk based on individual doses, such as addressing existing methods and models of radiation-induced cancer risk rather than creating new models.

RASSC also advised that the TECDOC include information on the approaches used by Member States and address both external and internal exposures; but not discuss insurance and compensation issues (the latter already having been covered by the joint ILO/IAEA/WHO report referred to above[4]).

1.2 OBJECTIVE

The objectives of the present TECDOC are to:

- Present a methodological framework for the assessment of prospective risks of cancer incidence potentially incurred by workers from occupational exposure to radiation;
- Assist in managerial decisions on constraining or controlling exposure;
- Facilitate the implementation of occupational radiation protection programmes.

This TECDOC is not intended to be a completely comprehensive reference work on the subject, but rather to provide a methodological framework that can be updated or revised as new risk models and updated cancer incidence data for populations become available in the future.

This TECDOC can be used by:

- Utilities, owners, operating organizations, registrants and licensees;
- Regulatory bodies;
- Research and academic organizations;
- Technical support organizations;
- Radiation protection officers;
- Workers and their organizations;
- Employers and their organizations.

1.3 SCOPE

This TECDOC elaborates the current methodology in assessing prospective cancer incidence risks from occupational exposure to ionizing radiation.

This publication does not cover risks of hereditary effects or deterministic effects, or the assessment of cancer risks from factors other than radiation, except when these factors modify the radiation-induced risk of cancer. Other health effects, such as cardiovascular diseases and

eye cataracts, are also not covered here, since it has not been established that these are health effects that can be induced by low-level exposure to radiation.

Exposure due to radon is one of the principal causes of lung cancer for occupationally exposed workers. Radon is not specifically treated in this TECDOC, since the evidence on the dose from alpha-particles to sensitive lung tissue from radon and its short-live decay products and the consequent risk of lung cancer has recently been reviewed[8], and the Pooled Uranium Miner Analysis (PUMA)[9] is being undertaken and results from this large international study are awaited. The publication addresses only occupational exposure as defined in the IAEA Safety Glossary: "Exposure of workers incurred in the course of their work"[10] and is limited to normal operation under planned exposure situations. The publication does not deal with medical and public exposure, exposures *in utero* (including to embryos and foetuses of female radiation workers), exposures from environmental sources of radiation (naturally occurring or artificial) outside an occupational context, or exposures to non-ionizing radiation (e.g. ultraviolet radiation and microwave radiation).

1.4 STRUCTURE

The TECDOC is divided into six main sections. Section 2 provides an overview of the assessment of radiation-induced cancer risk. Section 3 describes existing descriptive (empirical) cancer risk models. Section 4 focuses on the methodology for calculations of different risk measures based on these descriptive models. Section 5 describes sources of uncertainty and their influence on risk assessment. Section 6 summarizes the publication and gives the key points of each section. Section 7 presents conclusions and the way forward.

Annex I provides a brief review of a software package that could be an example of a system used for monitoring of radiation risk from occupational exposure.

Annex II presents comparative analyses of risk estimations performed for different national populations using existing software tools.

2. ASSESSMENT OF RADIATION-INDUCED CANCER RISK

2.1. INTRODUCTION

There is strong epidemiological and biological evidence that moderate- and high-level exposure of humans to ionizing radiation leads to an increased risk of cancers in many organs or tissues. Ionizing radiation is classified by the International Agency for Research on Cancer (IARC) as a Group 1 Carcinogen ("carcinogenic to humans"). However, cancer risks associated with low-level radiation exposure – either low dose (less than 100 mGy of low-LET radiation) or low dose rate (less than 0.1 mGy/min of low-LET radiation when averaged over about one hour)[11] – which is the predominant exposure for workers and the general public, are difficult to detect definitively because of the difficulty of distinguishing a small radiation signal from the relatively large variations in background cancer risks. Therefore, cancer risk assessment for workers is often based on extrapolations from data of effects at moderate and high acute doses. However new direct evidence is accumulating from epidemiological studies for risks at low doses[12]. This section summarizes the current knowledge on biological and epidemiological aspects of cancer, the factors known to cause cancer, including ionizing radiation, and the key points of radiation-related risk assessment. In this report, risk is defined to be the probability that a certain adverse event, e.g., a particular disease, will occur within a specific period, e.g., the remaining lifetime of an individual.

2.2. FACTORS INFLUENCING CANCER RISK

Cancer is the second leading cause of death globally and was responsible for an estimated 9.6 million deaths in 2018 which accounts for almost 1 in 6 deaths in the WHO Fact sheets[13]. Currently, approximately one third of deaths from cancer are due to five leading behavioural and dietary factors: tobacco smoking, high body mass index, low fruit and vegetable intake, lack of physical activity, and alcohol consumption in the WHO fact sheets[13].

Tobacco smoking is one of the most important risk factors for cancer and is responsible for approximately 20% of cancer deaths worldwide[14]; the corresponding value is 30% for the US population[15], and 23% for the Japanese population[16]. Infections, such as hepatitis, human papilloma virus (HPV) and Helicobacter pylori, are also major risk factors for some types of cancer such as liver cancer, cervical cancer and stomach cancer, and responsible for 15% for cancer cases globally, rising to 25% in low- and middle-income countries[17]. Ionizing radiation is also classified as a universal carcinogen due to its ability to induce most types of cancer[18]. Cancer may also result from other environmental and occupational factors, but contributions of these factors seem to be relatively small compared with behavioural and dietary factors.

About four out of ten persons in the general population are expected to develop cancer during their lifetime. The five most common types of cancer diagnosed among men globally are, in descending order: lung, prostate, colorectum, stomach, and liver; while among women, the five most common sites of cancer are, in descending order: breast, colorectum, lung, cervix, and stomach[19]. The development of a cancer is a complex process, consisting of a number of stages. An initiating phenomenon, most probably affecting a single stem cell, appears to start the process, but a series of other events seem to be necessary before the cell becomes malignant and the tumour develops. Most cancers become evident only a long time after the initial cellular damage occurs, the intervening period being the latent period.

2.3. RADIATION EFFECTS

Radiation-induced cancer may occur a long time after the initiating exposure. The occurrence of radiation-induced cancer is DNA (deoxyribonucleic acid) mutations induced in normal cells by radiation exposure, although the overall process is a complex one that is likely to involve epigenetic components. While the exact mechanisms leading to the development of cancer are not properly understood, it is believed that the underlying biological process involves a series of steps, occurring over long periods. Other possible biological mechanisms such as epigenetic effects and non-targeted effects may play a role in carcinogenesis, but are less clear. Leukaemia and thyroid cancer can first appear a few years after exposure to radiation, while most other types of cancer are not observed until at least 5 to 10 years, and often several decades, after exposure. Mutations can occur either spontaneously or as a result of exposure to ionizing radiation or other mutagens. Despite recent advances in molecular biological knowledge and technology, there are no unique biomarkers for radiation-induced cancers currently identified. Further, no specific type of cancer is caused only by radiation exposure, and it is currently impossible to distinguish radiation-induced cancer cases from those arising from other causes. Nevertheless, methodology has been developed to estimate the probability of a particular case of cancer being attributable to certain doses of radiation, either retrospectively or prospectively.

Epidemiological studies of people exposed to ionizing radiation for a number of reasons (e.g., occupationally or for medical reasons) are used to estimate risks of radiation-induced cancer and to generate risk models in the UNSCEAR 2008 Report[6]. To achieve dependable findings, these studies have to be carefully designed and conducted, include a large number of individuals who received a wide range of radiation doses and who were followed up for cancer incidence and/or mortality over long periods. Of particular importance in this respect is the Life Span Study[1](LSS) of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, not least because of the considerable effort that has been expended on this study since it was established in October 1950. The LSS includes a large population of both sexes, a wide range of ages-at-exposure, individual dose estimates covering low to high dose, and follow-up is long and effectively complete. A series of LSS reports have clearly demonstrated significantly increased risks for many types of cancer, including cancers of the stomach, lung, liver, colon, bladder, female breast, ovary, thyroid, and non-melanoma skin, as well as for leukaemia. Studies of other populations exposed to ionizing radiation have also shown a strong link of such cancers with radiation exposure. For some cancer types, such as chronic lymphocytic leukaemia, Hodgkin lymphoma and skin melanoma, there is limited evidence of an excess risk after radiation exposure among the atomic bomb survivors and other exposed groups. However, there are considerable variations in radiation sensitivity for cancer induction according to which organs/tissues of the body are irradiated.

Although strong evidence of the carcinogenic effect of radiation comes from studies of atomic-bomb survivors who were mainly exposed to external gamma radiation, information also exists on the effects of internal exposures following intakes of radionuclides for several types of cancer among various populations. In particular, there is clear evidence of an increased lung cancer risk among underground hard-rock miners (e.g., uranium miners) who had been exposed to substantial levels of radon and its decay products. In addition, there is strong evidence for an increased risk of thyroid cancer among those exposed as children or adolescents following intakes of radioactive iodine after the Chernobyl nuclear power plant accident. Although it is difficult to directly compare the effects of

[1] The Life Span Study (LSS) is a research programme (rerf.or.jp) investigating life-long health effects based on the epidemiologic study of a cohort of Japanese atomic bomb survivors. Its major objective is to investigate the long-term effects of atomic bomb radiation on the risk of various causes of death and incidence of cancer.

internal and external exposures, particularly under certain circumstances such as the irradiation of upper lung tissues by short-range alpha-particles from radon progeny, current assessments suggest that, once radiation quality and distribution of tissue dose are taken into account, there are no substantial differences in carcinogenic risks from external and internal exposures[20].

Although ionizing radiation is an established cause of cancer, information on the magnitude of the cancer risk associated with low doses of radiation or doses received protractedly or repeatedly over an extended period is still limited and uncertain. Direct information about the consequences of exposures that workers and the general public routinely experience is growing from epidemiological studies of workers and general public which support excess cancer risks from low-dose radiation[21], but reliable inferences are currently not possible. Uncertainties associated with estimates based on low-dose and low-dose rate studies are still considerable, so we really do not know what the risks are. The UNSCEAR has evaluated, in its 2017 report, the quality of epidemiological studies of cancer associated with exposure at low dose rates from environmental sources[11]. The overall results of those studies do not provide evidence of a higher cancer risk per unit dose than that derived from high dose-rate studies, but do not rule out a lower risk per unit dose because there is considerable uncertainty in the estimates owing to both limited statistical power and limitations in other respects.

2.4. FACTORS INFLUENCING RADIATION-INDUCED CANCER RISK

Several factors are known to influence the relationship between radiation exposure and cancer risk. Clearly, the dose received by the "target tissue" (i.e., the tissue in which a particular type of cancer originates) is fundamental to the risk of a given type of cancer, but the tissue absorbed dose will have an associated relative biological effectiveness (RBE) that depends upon the types of radiation (and sometimes its energy) involved. The RBE may depend on the energy of the radiation, as occurs for neutrons and beta-particles (for example, the RBE for neutrons depends on the energy of the neutron, and the low energy beta-particles emitted by tritium have a larger RBE than high energy electrons). The RBE weighted absorbed dose is used for cancer risk assessment in this publication in a broader sense than mentioned in the IAEA Safety Glossary[10].

The Dose and Dose-Rate Effectiveness Factor (DDREF) is an important concept in the prediction of cancer risks associated with low-level exposure to radiation. The DDREF modifies the risk per unit dose from that at moderate-to-high acute doses when dealing with low doses or low dose-rates of low-LET radiation; the DDREF does not apply to high-LET radiations. If DDREF>1 then the effect per unit dose at low doses or low dose-rates is less than that at moderate-to-high acute doses and implies an underlying sub-linear dose-response. For the purposes of radiation protection, the International Commission on Radiological Protection has adopted a DDREF of 2 for use for doses <100 mGy or dose-rates <0.1 mGy/min (when averaged over about an hour). Evidence for a DDREF>1 is derived from both epidemiological and experimental data, but substantial efforts are now in progress to review the evidence[22][23][24][25].

Age-at-exposure is another important factor influencing radiation-induced cancer risk. Epidemiological studies have generally demonstrated that lifetime cancer risks are higher if exposure occurs at a younger age. Dependency of cancer risk on age at exposure is most marked for thyroid and brain cancers as well as for leukaemia, but less apparent for some types of cancer including lung cancer. There is also a difference in cancer risk between the sexes, with females tending to have a higher risk per unit dose than males, although the nature of variation in risk between males and females depends on whether cancer risk is expressed on an absolute or relative scale. For example, mortality data for the atomic bomb survivors show the excess relative risk of all solid cancer for females is almost twice of that for males[26], but excess absolute risks are similar for males and

females in the LSS, as would be expected from considering the ERRs applied to background cancer rates in Japan which are for females about half of those for males. It is of particular interest that a recent study of the atomic bomb survivors showed a significant modifying effect of age at menarche on radiation-related breast cancer risk, with higher excess relative and absolute risk for those with earlier age at menarche[27].

Carcinogens other than ionizing radiation are also likely to influence, to a greater or lesser extent, the relationship between radiation exposure and cancer risk. Joint effects of ionizing radiation and smoking on lung cancer have been investigated in a number of studies including those of atomic bomb survivors, patients received radiotherapy, uranium miners, and residential radon. The results are mixed, varying from a complicated joint effect in the Japanese atomic bomb survivors[28][29] to multiplicative joint effect among patients who received radiotherapy[30]. A multiplicative joint effect between smoking and radon on lung cancer has been clearly demonstrated among uranium miners[31]. Histories of cigarette smoking need to be taken into account when estimating lung cancer risk. Reproductive factors have also been investigated for their effect on breast cancer risk, but again results are generally inconsistent[32].

Hereditary genetic factors are potentially important for estimating cancer risk from radiation exposure. The impact of genetic susceptibility on cancer risk has been extensively studied especially for medically irradiated populations, including patients with retinoblastoma and breast cancer cases with BRCA mutations, which is a known genetic factor for breast and ovarian cancers. Strongly expressing cancer-predisposing mutations in humans are judged to be too rare to appreciably distort population-based estimates of radiation-associated cancer risk[33][7]. Although recent advances in molecular biological knowledge and techniques have enabled researchers to evaluate the effect of genetic susceptibility on cancer risk, no clear findings have been obtained so far.

2.5. SHAPE OF DOSE-RESPONSE AND ITS IMPACT ON RISK ASSESSMENT

The studies of the Japanese atomic bomb survivors have contributed fundamental information about the nature of the dose-response between cancer and radiation exposure. The simplest shape for dose-response is a linear no-threshold (LNT) in which the dose-response is based on the assumption that radiation dose greater than zero will increase the cancer risk in a simple proportionate manner. The studies of atomic bomb survivors have not generally found a significant departure from a linear dose-response at low-doses for solid cancers combined, while the dose-response for leukaemia is linear-quadratic, with the dose-responses being consistent with the absence of a threshold dose. The shape of the dose-response is less clear for site-specific cancers, and for some cancer types such as non-melanoma skin cancer (NMSC) there are suggestions of a threshold dose. For example, the study of atomic bomb survivors in Japan showed an estimate of threshold dose of about 0.6 Gy for basal cell carcinoma of the skin, the most common type of NMSC[34].

The slope of LNT model is a measure of cancer risk per unit dose, corresponding to either excess relative risk (ERR) per unit dose on a relative scale or excess absolute risk (EAR) per unit dose on an absolute scale. For radiation epidemiological studies, ERR per unit dose is often calculated and evaluated in comparison with that from atomic bomb survivor data as a “gold standard”.

Cancer risk is the probability of a cancer occurring under defined circumstances (e.g., during a particular period). This publication addresses the assessment of the prospective cancer risk for a cancer-free occupationally exposed worker who has received a given dose of radiation. The association between radiation and cancer can also be assessed retrospectively in terms of probability of causation for an individual who has already developed a cancer. The methodology and implications

of such a retrospective assessment have been described elsewhere[5] and are not within the scope of this publication.

2.6. CONCLUSIONS

This section summarized the scientific information on radiation risk assessment, including a summary of the current knowledge on biological and epidemiological aspects of cancer, the factors known to cause cancer, including ionizing radiation, and the key points of radiation-related risk assessment. The LSS has long been a major source of information on dose-response relationship and on the age and sex patterns of radiation-related risks. For the purposes of radiation protection, the LNT model is adopted for exposures to low doses or low dose rates. For solid cancers generally a linear dose-response fits the LSS data best while a linear-quadratic model provides the best fit for leukaemia to the LSS incidence and mortality data.

3. DESCRIPTIVE CANCER RISK MODELS

3.1. INTRODUCTION

The purpose of this section is to present the types of currently available descriptive (empirical) models for assessing the prospective cancer incidence risk to workers which arises from their individually determined external and internal occupational doses of ionizing radiation incurred during the course of their work. Cancer incidence risk models and consequent central estimates of radiation risks form the basis of the current system of radiation protection introduced in the ICRP Publication 103[7] so the emphasis in this TECDOC is in cancer incidence rather than mortality. Cancer mortality models could be used for modelling risks, if this is thought appropriate, and cancer incidence cases can be weighted by the health detriment associated with a particular type of cancer, if desired.

The focus is on methods suitable for application in occupational radiation protection against stochastic health effects in the exposed individual (cancer). Methodological issues related to other health effects, such as hereditary effects, deterministic effects or potential stochastic effects other than cancer (e.g., cardiovascular diseases or cataracts) or to compensation and insurance claims, will not be considered here. Other sources of radiation exposures such as medical, environmental (naturally occurring or artificial), in utero (including to embryos and foetuses of female radiation workers) or non-ionizing radiation, will also not be considered.

3.2. RADIATION DOSIMETRY AND EXPOSURE ASSESSMENT

Cancer risk assessments are usually based on the organ/tissue doses relevant to the types of cancer being considered. However, in most occupational settings, only dosimetric monitoring data is available. Such monitoring data are collected for the purposes of radiation protection and regulatory control and need to be converted into the organ/tissue doses for use in cancer risk assessment. The choice of conversion method depends on whether the organ/tissue doses arise from external exposures to penetrating radiation or internal exposures. If the organ/tissue doses come from external sources of radiation, then it may be appropriate to consider that all organs/tissues receive the same dose due to a high level of homogeneity in the external dose distribution throughout the organs/tissues of the human body. Nonetheless, there may be circumstances when this is not appropriate, such as when external exposure involves a beam of radiation that has preferentially exposed particular organs/tissues. Further, even for homogeneous external irradiation there will be some shielding by body tissues, so that deep-seated organs/tissues receive lower doses than organs/tissues closer to the surface of the body, and there is the question of what organ/tissue dose is most representative for the grouping of all solid cancers combined (and the colon dose is often used in this respect). However, if the organ/tissue doses come from internal doses, it may be more appropriate to consider site-specific cancers separately as suitable outcomes in risk assessments due to heterogeneity in internal dose distributions throughout the organs/ tissues of the body – for example, radioisotopes of iodine deliver their dose predominantly to the thyroid gland whereas radioisotopes of caesium deliver their dose throughout soft tissues.

General and specific guidance on appropriate monitoring programs to assess radiation doses to workers from exposures to external sources of radiation and from exposures from intakes of radionuclides, for radiation protection purposes, has recently been given the GSG-7 of the IAEA[3]. Definitions for all dosimetric quantities relevant to radiation protection in occupational settings have recently been assembled and published together[3] and so are not given explicitly in this TECDOC.

3.2.1. Doses from external exposures

The choice of a personal dosimeter for monitoring exposure depends on the type of radiation and on the information that is necessary for determining the RBE- (Relative Biological Effectiveness-) weighted absorbed dose that is relevant for the tissue/organ considered in cancer risk assessment. A comprehensive set of recommendations for monitoring procedures and application of conversion factors for use in assessment of occupational external doses has recently been given in the GSG-7[3].

3.2.2. Doses from photons (gamma or X-rays)

External gamma or X-ray doses to an individual worker are often monitored with dosimeters such as thermoluminescent dosimeters (TLDs) or optically stimulated luminescent (OSL) dosimeters. The operational quantity for individual monitoring is the personal dose equivalent $H_p(d)$. Any statement of personal dose equivalent has to include a specification of the reference depth from the surface of the body, d. For strongly penetrating radiation, the reference depth is 10 mm. For weakly penetrating radiation, the reference depth is 0.07 mm. The measured results of dosimeters may be converted into $H_p(10)$ using conversion factors provided by ICRP in its publications in 1987, 1997 and 2010[35][36][37]. However, for the purposes of cancer risk assessment, it is the absorbed dose received by the particular organ/tissue that is used (or the representative whole-body absorbed dose), and dosimeter readings need to be converted into organ/tissue doses. If the radiation exposure is photons with a radiation weighting factor of 1, then equivalent doses to organs/tissues (in Sv) may be closely approximated by absorbed doses (in Gy). However, it is important to be borne in mind that low energy photons may have a higher RBE than high energy photons[38].

3.2.3. Doses from neutrons

In some occupational settings, doses from neutrons can contribute to the total organ/tissue doses. The RBE for neutrons is greater than one but depends on the energy of the neutron. For the purposes of radiation protection, the radiation weighting factor for neutrons increases with neutron energy from 2.5 to 20 (at ~1 MeV) and then decreases to 2.5, forming a bell-shaped distribution. For assessed effective doses for air-crew, for example, neutrons may contribute 40–80% of the effective doses, where this percentage depends on altitude, latitude and the stage in the solar cycle; other particles, such as protons, also contribute to the total effective dose for air-crew. Some nuclear workers are also exposed to neutrons as indicated in the INWORKS dosimetry paper in 2007[39]. For assessing radiation fields including high energy neutrons or particles in accelerator facilities, dosimeters calibrated for doses at different depths below the body surface are necessary. Current recommendations state that photon dosimeters should always be worn together with neutron dosimeters, because gamma radiation is always present in neutron fields[3].

3.2.4. Doses from internal exposures

Different occupational settings and job types may involve exposures to various radionuclides such as tritium, fission products, uranium, plutonium and other actinide elements. Doses from radionuclide intakes are usually specific to certain organs, but this is not always so. Tritium, for example, delivers uniform whole-body low-energy beta-particle irradiation. Estimation of organ/tissue doses involves knowledge of the chemical form of the radionuclide, and properties such as particle size ranges, solubility levels and the mode of intake (inhalation, ingestion, skin contamination). For intakes of radionuclides emitting gamma and higher-energy X-rays, direct monitoring using external whole-body or partial-body counters may be appropriate. Other monitoring methods are based on measurements from: excretion analyses of urine and/or fecal samples; exhalation air samples; and

static or personal air sampling. A comprehensive guidance for monitoring and assessment of occupational internal doses has recently been given[3][38].

3.3. MINIMUM LATENT PERIOD

Radiation-related cancer genesis is a process that develops with time after the first radiation exposure, such that any cancers developing very soon after exposure cannot be regarded as related to that particular exposure. Just how soon after exposure a radiation-related cancer may be clinically manifest can be quantified by a minimum latent period, which is usually a time period of several years. There are good reasons for assuming a minimum latency L of 2 years for leukaemia[40], 3 years for thyroid cancer and[41] 5 years for all other solid cancers[6][42].

3.3.1. Dose and dose-rate effectiveness factor

It is currently unclear whether the excess cancer risk per unit dose for low doses or doses accumulated over a protracted period at a low dose rate differ notably from the cancer risk per unit dose from a single acute exposure to a moderate or high dose of radiation. A report from the United Nations Scientific Committee on the Effects of Atomic Radiation in 1958[43] gave early advice that only results from high doses and dose-rates could be used to estimate the effects of low levels of radiation. This type of estimation approach, assuming a particular shape of dose-response, e.g., a linear no-threshold (LNT) dose response model, is often necessary for estimating low dose or low dose rate risks[44][45][46]. The dose and dose-rate effectiveness factor (DDREF) concept was developed subsequently in the UNSCEAR 1977 Report[47] to allow for the perceived inadequacies in low dose or low dose rate risk estimates from epidemiological studies, mainly because radiobiological data provided evidence of non-linear effects at low doses or dose-rates. DDREF is a factor that aims to provide a general estimate of the ratio of cancer risk per unit of acute exposure at moderate to high levels to the cancer risk per unit of chronic or low-dose exposure. DDREF may be perceived as a combination of a low dose effectiveness factor (LDEF) to extrapolate from moderate and high doses to low doses, and a dose-rate effectiveness factor (DREF) to extrapolate from high to low dose-rates. In the currently recommended dose limits for occupational exposures in the ICRP Publication 103 [7], it has been assumed that solid cancer risk coefficients for a low-level exposure are a factor of two lower than for the Japanese A-bomb survivors receiving doses >100 mGy (i.e., DDREF=2.0). The US National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations in its Seventh Report (BEIR VII)[33] has presented evidence and arguments for a DDREF of 1.5. The German Commission on Radiological Protection (SSK) has recommended that a DDREF not be applied[48] (i.e., an implicit assumption here is a DDREF=1) and WHO did not apply a DDREF greater than unity in their published lifetime attributable radiation risks for assessing the health effects after the Fukushima accident[49], although an application of DDREF was carefully discussed in the report and it was acknowledged that the risks presented in the tables could easily be scaled to account for DDREF values over unity, if necessary. Because of this disparity in recommendations, ICRP are currently reviewing the usefulness of this concept and the weight of evidence for various numerical values of estimates for DDREF[50][51]. Recent research has investigated the strength of direct epidemiological evidence for DREF magnitudes with a meta-analysis[23] that included 22 low-dose and/or low dose rate solid cancer studies (19 mortality studies and 3 incidence studies). The overall meta-analysis estimate of the DREF was 3.0 (95% CI: 1.9; 7.7)[23]. However, the result after the exclusion of the Mayak worker cohort[52], which exerted a large influence on the combined DREF, was 1.9 (95% CI: 1.0; 11).

3.4. ADDITIVE AND MULTIPLICATIVE MODELS

Additive and multiplicative models representing the situation where a radiation effect may either add to or multiply the baseline cancer rates (i.e., the cancer rates in the absence of the specific exposure to radiation under consideration) are often used to apply radiation risks obtained from one population to another population. These additive and multiplicative models are discussed in greater detail below.

Table 1 lists the main current sources of descriptive (empirical) radiation risk models available in the literature.

TABLE 1. CURRENT SOURCES OF USEFUL DESCRIPTIVE (EMPIRICAL) EXCESS CANCER RISK MODELS AVAILABLE IN THE LITERATURE.

Radiation risk models	Reference and Link
UNSCEAR solid cancers and leukaemia (incidence and mortality)	UNSCEAR 2006 Report (2008)[6] http://www.unscear.org/docs/publications/2006/UNSCEAR_2006_Annex-A-CORR.pdf
Radiation Effects Research Foundation (RERF) solid cancers incidence	Preston et al. 2007[53] http://www.rrjournal.org/doi/abs/10.1667/RR0763.1
Radiation Effects Research Foundation (RERF) all solid cancers and leukaemia mortality	Ozasa et al. 2012[54]
RERF leukaemia, lymphoma and multiple myeloma incidence	Hsu et al. 2013[55] http://www.rrjournal.org/doi/abs/10.1667/RR2892.1
ICRP solid cancers and leukaemia incidence	ICRP Publication 103 (2007)[7] http://www.icrp.org/publication.asp?id=ICRP%20Publication%20103
BEIR VII solid cancers and leukaemia (incidence and mortality)	BEIR VII 2006[42] https://www.nap.edu/catalog/11340/health-risks-from-exposure-to-low-levels-of-ionizing-radiation US NCI enhancement of BEIR VII 2012: http://iopscience.iop.org/article/10.1088/0952-4746/32/3/205 (plus website: https://radiationcalculators.cancer.gov/radrat/)
US EPA solid cancers and leukaemia	US EPA 2011[56] https://www.epa.gov/radiation/blue-book-epa-radiogenic-cancer-risk-models-and-projections-us-population

Radiation risk models	Reference and Link
German ProZES solid cancers and leukaemia	Ulanowski et al. 2020 [57]

Most radiation risk models reported in the literature and cited in Table 1 employ a linear no-threshold (LNT) model for the risk to dose response relationship for solid cancers. There is broadly medium to strong weighting of evidence towards the LNT model[58][59][60] from a wide variety of modern radiation epidemiological studies. Generally, in the analysis of radiation epidemiological data, and particularly in fitting the data from the Life Span Study (LSS) of the Hiroshima and Nagasaki A-bomb survivors, use is made of a general rate (hazard) model of the form

$$\lambda(d,a,e,s,c,nic) = \lambda_0(a,e,s,c,nic) * [1 + ERR(a,e,s,d)] \quad (1)$$

$$\lambda(d,a,e,s,c,nic) = \lambda_0(a,e,s,c,nic) + EAR(a,e,s,d)] \quad (2)$$

for the excess relative risk (*ERR,* called a multiplicative model because the radiation risk multiplies the baseline risk) or excess absolute risk (*EAR,* called an additive model because the radiation risk adds to the baseline risk), where $\lambda_0(a,e,s,c,nic)$ is the baseline cancer incidence rate, at attained age, a, age at exposure, e (used in the baseline model as a surrogate for birth-year for modelling secular trends), with indicator variables for sex, s (M=male, F=female), city, c (H=Hiroshima, N=Nagasaki) and "not in either city at the time of the bombings", *nic*. Organ/tissue doses, d, are from γ-rays and neutrons, $d = d_r + RBE * d_n$, i.e., the organ/tissue absorbed doses weighted by the relative biological effectiveness (*RBE*) of neutrons relative to gammas. The evaluation of neutron RBEs is an inherently difficult problem. An *RBE* value of 10 has generally been adopted in the past for weighting the organ/tissue doses from neutrons, but there are indications for larger values[61][62][63][64].

The *ERR* and *EAR* models for solid cancers derived from the LSS are usually considered in the same parametric form, although the fit parameters have very different central estimates.

$$(1 + t * s) * k_d * d * \exp\ [-g_e * (e - 30) + g_a * \ln\,(a/70)] \quad (3)$$

i.e., a linear dose response with adjustments in the *ERR* and *EAR* for age-related explanatory covariables, as defined above, and sex, where s = -1 for males or +1 for females. The four fit parameters of each model are either the ERR central estimate, k_d (ERR/Gy) or the EAR central estimate, k_d (EAR/Gy – in cases per 10,000 person-years), and the effect modifiers of these central risk estimates by sex, s, age at exposure, g_e, and age attained, g_a. However, other models may contain a time since exposure term or be semi-parametric in form (e.g., in modelling the outcome leukaemia).

Most risk to dose response models in terms of excess relative risk (*ERR*) and excess absolute risk (*EAR*) for many cancer incidence site groupings considered in the literature have similar forms to those given above. These models generally have: the form of a linear no-threshold risk to dose-response function for all solid cancers, thyroid cancer, female breast cancer and other solid cancer sites (oesophagus, stomach, colon, liver, lung, bone, skin, ovary, bladder); a linear-quadratic dose-response function for leukaemia (or leukaemia excluding CLL); and include risk effect modification by age-at-exposure (e), sex (s) and attained age (a). For example, in ICRP calculations of lifetime risks[7], similar models to those above were applied for solid cancers (see Table 2): oesophagus, stomach, colon, liver, lung, breast (EAR only), ovary, bladder, thyroid (ERR only) and all other sold cancers combined; but for leukaemia, a semi-parametric EAR model was applied based on earlier incidence data[65] and is given in Table 2. (ICRP Publication 103 also adopted nominal risk models for bone and skin cancers, which were not based on LSS data.)

TABLE 2. RISK MODELS USED TO CALCULATE LIFETIME CANCER RISKS AND AS APPLIED IN THE EXAMPLES OF LIFETIME CANCER RISK QUANTITIES IN CALCULATIONS PRESENTED IN SECTION 4.

Cancer Site	Model	
Solid cancers incidence (Preston et al. 2007)[53] (fit parameters from www.rerf: filename:- lss07sitemod.log).	$ERR(d,a,e,s) = (1 + t * s) * k_d * d * \exp\ [-g_e * (e-30) + g_a * \ln(a/70)]$ fit parameters for all solid cancer incidence with standard errors are: $t = 0.2465 \pm 0.06762$, $k_d = 0.4666 \pm 0.04413$, $g_e = 0.01849 \pm 0.00636$, $g_a = -1.621 \pm 0.3058$, (deviance=14736.0, degrees of freedom, df=25551).	$EAR(d,a,e,s) = (1 + t * s) * k_d * d * \exp[-g_e * (e-30) + g_a * \ln(a/70)]$ fit parameters for all solid cancer incidence with standard errors are: $t = 0.1622 \pm 0.06988$, $k_d = 51.63 \pm 4.982$, $g_e = 0.02805 \pm 0.006215$, $g_a = -2.406 \pm 0.2731$, (deviance =14739.9, df=25551).
Leukaemia incidence (Preston et al. 1994)[65] (Fit parameters from Appendix 2 of Preston et al 1994)	Risk model is categorical in sex and age at exposure, with parametric risk effect modification by time since exposure, *tsx*. $\mathrm{EAR}(d,tsx) = 0.33 * (d + 0.79 * d^2) * exp(-0.17 * (tsx - 25))$, for males, e=0-19 years $= 0.66 * (d + 0.79 * d^2) * exp(-0.07 * (tsx - 25))$ for females, e=0-19 years $= 0.48 * (d + 0.79 * d^2) * exp(-0.13 * (tsx - 25))$ for males, e=20-39 years $= 0.97 * (d + 0.79 * d^2) * exp(-0.03 * (tsx - 25))$ for females, e=20-39 years $= 1.31 * (d + 0.79 * d^2) * exp(-0.07 * (tsx - 25))$ for males, e > 40 years $= 2.64 * (d + 0.79 * d^2) * exp(0.03 * (tsx - 25))$ for females, e > 40 years	

In the most recent LSS solid cancers incidence analysis, based on the largest number of LSS solid cancer incidences to date, Grant et al[66] demonstrated significant upward curvature in the ERR risk to dose response for all solid cancers combined for males with little indication of non-linearity for females. This is in contrast to previous papers on the LSS solid cancer incidence data which reported linear ERR dose responses, as the best fits to the data, for both males and females. However, Grant et al[66] urge caution in interpreting the curvature findings and drawing conclusions from this follow-up because of several evolving issues. These issues include: whether or not curvature in the female ERR dose response will emerge in future follow-ups; whether or not the sex difference in the shape of dose response for solid cancer incidence reflects the heterogeneity of dose responses among different cancers for specific organs/tissues and distribution of these cancers in males and females; and whether or not a deeper exploration of the effect of the updated dosimetry will change the impact of the zero-dose comparison group on the risk estimates.

3.5. MAIN MODIFYING FACTORS

Some factors can influence the risk from ionizing radiation and lead to systematic variability in the risk, often quantified as systematic differences in the dose-response relationships. These main risk-influencing factors are called risk effect modifiers and are applied to quantify heterogeneity of effect

in radiation epidemiology. However, in order to adequately determine joint effects of radiation and other factors in epidemiological studies, adequate statistical power is necessary (i.e., a substantial study size is needed, indicated, among other factors, by the number of radiation-related cases and the range of doses received). For this reason, the Life Span Study of Hiroshima and Nagasaki A-bomb survivors has been a major source of information on risk effect modifiers in the past and will continue to be an important study for quantifying risk effect modifiers.

In the most recent follow-up period (1958-2009) for solid cancer incidence among the LSS of atomic bomb survivors[66], sex, attained age and age at exposure were found to be significant modifiers of the main risk to dose response and time since exposure was also considered. Furthermore, this recent LSS analysis[66] succeeded in removing a surveillance bias on the age-at-exposure effect, induced from cases diagnosed solely by autopsy. The most recent analysis of LSS leukaemia incidence among atomic bomb survivors[55] reported that the types of risk effect modifiers indicated by the model fitting were: sex, attained age, time since exposure. However, for the large INWORKS study of nuclear workers from USA, France and UK, the results from all solid cancer analysis[67] showed that no risk effect modifiers were indicated by the model fitting, but this may have been due to insufficient statistical power in INWORKS.

Sex

In a paper reporting solid cancer incidence risks among atomic bomb survivors, the ERR/Gy for women was found to be a factor of 1.6 larger than that for men (ERR= 0.35/Gy for men and 0.58/Gy for women)[53]. The EAR/Gy for women was found to be a factor of 1.4 larger than that for men (60 versus 43 excess cases per 1000 person-years per Gy) and this factor was found to further decrease, if breast, prostate and gynecological cancers are excluded from all solid cancer grouping under analysis. It was further demonstrated by Walsh and Zhang (2015)[68] using the LSS data applied in the paper of Preston et al. (2007) that the EAR and ERR effect modifications by sex are not statistically significant for the outcome ‘‘all solid cancer other than thyroid and breast cancer’’. A recent analysis by Cologne et al. (2019)[69], aimed to shed some light on the unexpected differences in the shapes of sex-specific dose response reported by Grant et al. (2017*)* and already mentioned above. However, none of the results from Cologne et al. (2019), lead to an alleviation of the current lack of definitive conclusions on the shape of the male and female LSS all solid cancer incidence dose response. Until an improved all solid cancer model is made available, the results reported by Grant et al. (2017) on different curvature in the dose response for males and females obtained from the recent cancer incidence data of atomic bomb survivors are supposed to be interpreted with care[70][71].

In the LSS cancer site-specific risks given by Preston et al (2007)[53], the largest differences by sex were, for ERR/Gy, lung and bladder cancers and for EAR/Gy, thyroid, lung and stomach cancers (see Table 3 with examples for non-sex-specific sites). No strong differences in leukaemia incidence risks by sex have been reported by Preston in 1994 and Hsu et al in 2013[65][55], although borderline statistical significance was reported for a sex difference in the EAR model for leukaemia other than CLL or ATL[55].

TABLE 3. SEX RATIOS IN EXCESS CANCER RISKS

Cancer site	**F/M ratio** (Preston et al 2007)	
	ERR	EAR
All solid	1.6	1.4
Bladder	3.1	0.7

Cancer site	**F/M ratio** (Preston et al 2007)	
	ERR	EAR
Colon	0.5	0.2
Liver	0.9	0.3
Lung	4.8	1.5
Skin	2.2	0.8
Stomach	2.3	1
Thyroid	1.3	3.6
Leukaemia*	1	0.7

*Leukaemia results are from Hsu et al 2013

Age at exposure

In common with past analyses of the LSS data, the all solid cancer incidence analysis by Grant et al. (2017)[66] reported risk effect modification by age-at-exposure. For a linear ERR model without adjustment for smoking, the sex-averaged ERR/Gy for all solid cancers at attained age of 70 years after exposure at age 30 years was reported to decrease by 28.6% per decade increase of age at exposure (compared to the decrease of 17% per decade increase of age at exposure reported by Preston et al (2007)[53]. Other cancer sites were also fitted with age at exposure risk effect modifiers and the results for the non-sex-specific sites are given as examples in Table 4.

TABLE 4. THE PERCENTAGE CHANGE IN THE EXCESS CANCER RISK PER UNIT DOSE FOR EACH DECADE INCREASE IN AGE AT EXPOSURE

Cancer site	**Change in risk per decade increase of age at exposure (%)** (Preston et al 2007)	
	ERR	EAR
All Solid	-17	-24
Bladder	-3	-19
Colon	1	-56
Liver	3	-21
Lung	20	2
Skin	-73	-61
Stomach	-13	-2
Thyroid	-31	-46
Leukaemia*	Not given	-59

* Leukaemia results are from Hsu et al 2013[55].

Attained age

The LSS all solid cancer incidence analysis by Grant et al. reported risk effect modification by attained age. For a linear ERR model without adjustment for smoking, the sex-averaged ERR/Gy for all solid cancers at attained age of 70 years after exposure at 30 years, was found to decrease with age to the power of –2.02 (compared to the previous decrease with age to the power of –1.65 reported in Preston et al in 2007, see Table 5. Other cancer sites were also fitted with attained age risk effect modifiers and the results for the non-sex-specific sites are given as examples in in Table 5.

TABLE 5. THE POWER OF ATTAINED AGE IN THE EXCESS CANCER RISK EFFECT MODIFICATION

Cancer site	**Attained age (power)** (Preston et al 2007)	
	ERR	EAR
All Solid	-1.7	2.4
Bladder	0.3	6.3
Colon	-2.7	6.9
Liver	-2.7	3.6
Lung	-1.9	4.2
Skin	0.3	4.4
Stomach	-1.5	1.9
Thyroid	-1.5	0.6
Leukaemia*	1.1	-1.5

*Leukaemia results are from Hsu et al 2013[55].

3.6. TRANSFER OF RISK BETWEEN POPULATIONS

All quantities needed for a radiation risk assessment are supposed be pertinent to the population of interest for that risk assessment, i.e., for the current TECDOC, a particular group of workers occupationally exposed to ionizing radiation. However, these quantities are mostly derived from results reported in epidemiological cohort studies on particular populations or groups exposed to radiation in the past. The populations of interest in specific risk assessments may differ in age, ethnicity, geographical location, sex, occupation, life-style factors and secular lifetime ranges, from epidemiologically studied cohorts. For these reasons, risk from epidemiological studies need to be transferred to the population of interest in any particular risk assessment e.g., nuclear workers. Appropriate transfer of risks can be approximately achieved by: applying an additive model (transferring the EAR) when the excess absolute rate in the population under consideration is assumed to be the same as the excess absolute rate in the studied cohort, i.e., the radiation-related excess risk is assumed to be independent of the baseline risk (which is the usual assumption for female breast cancer risk), or applying a multiplicative model (transferring the ERR) when the proportional increase in risk in the population is assumed to be the same as the proportional increase in risk in the studied cohort, i.e., the radiation-related excess risk is dependent on the baseline risk (which is the

usual assumption for thyroid cancer risk). In most instances, the transfer of risk is assumed to be a mixture of the transfer of the ERR and EAR, and then the combined excess risk model, *ER*(*d*, *e*, *a, s*), is given by

$$ER(d,e,a,s) = w * EAR(d,e,a,s) + (1-w) * ERR(d,e,a,s) * m(a,s) \quad (4)$$

where: *w* is the weighting factor between an absolute (*EAR*) and a relative (*ERR*) transfer of risk. Expert choices for values of the weighting factors that are usually applied in radiation protection risk assessments are: *w*= 0.5 for most types of solid cancer and leukaemia; *w*= 0.7 for lung cancer; *w*= 1.0 for breast cancer; and *w* = 0 for thyroid cancer. The *m*(*a*, *s*) are the age- and sex-specific baseline cancer incidence rates relevant to the population under consideration in the specific risk assessment. Section 4 gives more details about these population rates.

3.7. CONCLUSIONS

The characteristics of currently available descriptive (empirical) models suitable for application in the calculation of prospective cancer incidence lifetime risk for occupationally exposed individuals have been reviewed. Such models provide central estimates for the risk per unit RBE-weighted absorbed dose, with risk-effect modification by sex, attained age and age at exposure or time since exposure. Although many different models exist and are being regularly updated in new scientific publications, some emphasis is placed here on the excess risk models used to calculate radiation related lifetime cancer risks in ICRP Publication 103 [7]. These risk models were applied in the examples of lifetime cancer risk quantities in calculations presented in the next section and this choice was based on achieving consistency with the current radiation protection guidelines from ICRP

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4. METHODOLOGY FOR THE CALCULATION OF ASSESSED RADIATION RISK

4.1. INTRODUCTION

A methodology is presented describing the various terms related to the risk quantities relevant to assessing the likelihood that employees could develop a cancer, attributed to their individual radiation exposure, during a certain period of time after exposure, including over their remaining lifetime.

4.2. RISK QUANTITIES

Basic values

The person-time incidence rate of a cancer, hereinafter referred to as the "cancer incidence rate", is a common measure of the frequency of cancer occurrence in a population. It is the number of newly diagnosed cancer cases identified in a given population during a specified period of observation divided by the sum of the time each person being observed was at risk of cancer. Usually, the cancer incidence rate is expressed as the number of newly diagnosed cases of cancer per 10,000 person-years. Baseline cancer incidence rates (the rate in the absence of the specific radiation exposure under consideration) are derived from population health statistics. As mentioned in Section 3.7, these rates vary with attained age and sex, and for a particular period are denoted as $m_i\,(a, s)$, where i designates a specific cancer site, a is the attained age (in years) and s is the sex. Baseline cancer incidence rates also vary by population and year of birth, and when the ERR is transferred between populations or different periods it is important that assessed radiation-related excess cancer risks are derived from the appropriate population from which the group being assessed is drawn (and it may be that other circumstances have to be taken into account, such as the level of cigarette smoking in the assessed group of workers).

Exposure of a population to radiation causes an excess cancer incidence rate above the baseline by an additional value of $M_i\,(d_i, e, a, s)$, where i designates a specific cancer site (the tissue or organ i), d_i is the absorbed dose in the tissue or organ i (weighted as necessary to account for the biological effectiveness of the radiations involved), e is the age at exposure, a is the attained age. For the leukaemia model (Table 2, All leukaemia incidence) time since exposure $tsx = a\text{-}e$.

For practical calculations, it is assumed that the total excess of cancer incidence rate related to radiation exposure is the sum of excess incidence rates by specific sites of cancer, accounting for the relevant latent periods and DDREFs.

$$M(d_i, e, a, s) = \sum_{i=1}^{N} M_i(d_i, e, a, s) = \sum_{i=1}^{N} L_i(a - e) \times ER_i(d_i, e, a, s)/DDREF_i \qquad (5)$$

where i is the index of specific cancer site (the tissue or organ i), N is the number of specific cancer sites relevant to radiation risk calculations; d_i is the (weighted) absorbed dose in a tissue or organ i; $(a\text{-}e)$ is the time since exposure; $L_i\,(a\text{-}e)$ is the time-response function accounting for the latent period, monotonically increasing from 0 to 1, either as a S - shaped or stepped function; ER_i is the excess cancer incidence rate for a specific cancer site i; $DDREF_i$ is the appropriate dose and dose-rate effectiveness factor for the i-th risk model. For ease of calculation, for uniform whole-body exposure of gamma radiation the total increase in cancer incidence rate can be calculated using only two risk models ($N = 2$): for all solid cancer incidence and for all leukaemia incidence (Table 2). Examples of calculations are given in the next section.

The current system of radiation protection recommended by the ICRP in its 2007 Recommendations[7] was justified using radiation risk models derived mainly from the Life Span Study of the Hiroshima and Nagasaki A-bomb survivors (Section 3.5), that is, for an acute exposure. In occupational exposure, an employee is generally exposed to radiation for a protracted period of possibly several or even many

years, especially in the case of internal exposure to radionuclides, which can reside for many years in the body after intake. Here an assumption has to be made on how to use available risk models derived from a single acute radiation exposure in order to predict the prospective cancer risk from protracted radiation exposure. The key assumption is that the excess cancer incidence rates, associated with different radiation doses, accumulated over different periods of time by an employee, are additive at any future point of time (although the risk consequent to any particular dose may be modified by factors such as age at exposure and time since exposure).

For prospective cancer risk assessment, the protracted radiation exposure of employees can be represented by a set of annual radiation doses. Assuming that an employee's radiation dose accumulated over one year from age (*e*-1) to age *e* as the dose accumulated from a single exposure, then the excess cancer incidence rate for a specific cancer site (***i***) associated with protracted radiation exposure is calculated using the following formula:

$$M_i(\{d_{i,e}\},\{e\},a,s) = \sum_{e=e_1}^{e_{max}} M_{i,e}(d_{i,e},e,a,s) \quad (6)$$

where $d_{i,e}$is the weighted absorbed dose in a tissue or organ *i*, accumulated over one year from age (*e*-1) to age *e*; {*e*}: [$e_1 \ldots e_{max}$] is a set of ages at exposure. For the internal exposure $\boldsymbol{d_{i,e}}$ can represent annual doses (dose rates) after single radionuclide intake at age (e_1-1). These dose rates for ingestion and inhalation of various radionuclides can be obtained using special software[72][73].

In order to calculate the risk per year, or risk density, for cancer incidence at a given attained age *a* in future, the probability of survival without cancer from age ***e*** to age ***a*** has to be known. This probability accounts for the probability of death from all causes and the probability of a new cancer case occurring.

For the unexposed population it is defined on the basis of the exponential survival function ***S*(*a, s*)**, that is, the probability of survival from 0 to age a:

$$S(a,s) = exp\left[-\int_0^a \mu_{total}(\tau,s)d\tau\right] \quad (7)$$

where ***a*** is the attained age; $\boldsymbol{\tau}$ is the current age, *s* is the sex; $\boldsymbol{\mu}_{\text{total}}$ is the baseline all-cause mortality rate (age- and sex-specific).

Accounting for the probability of a new case of a specific cancer site ***i*** provides the following survival function:

$$S_i(a,s) = exp\left[-\int_0^a [\mu_{total}(\tau,s) - \mu_i(\tau,s) + m_i(\tau,s)]d\tau\right] \quad (8)$$

where $\boldsymbol{\mu_i}$ is the baseline cancer mortality rate for the cancer site *i*; m_i. is the baseline cancer incidence rate for the cancer site *i*.

The conditional survival function $S_i(a|a_{min}, s)$ is the probability of surviving cancer-free to age *a*, adjusted for cancer-free survival, with the condition that the probability equals one at the age at the beginning of risk (a_{min}), corresponding to age-at-exposure for exposed people. Replacing the integrals in the previous formulas by summation over age, we obtain an approximate expression:

$$S_i(a|a_{min},s) = \frac{S_i(a,s)}{S_i(a_{min},s)} \approx exp\left[-\sum_{\tau=a_{min}}^{a} [\mu_{total,}(\tau,s) - \mu_i(\tau,s) + m_i(\tau,s)]\right] \quad (9)$$

This survival function does not depend on radiation doses, and all baseline rates usually are derived from population statistics.

Since the dose-dependent probability of survival is expected to be less than the dose-independent one, the use of dose-independent survival function provides the conservative estimation (overestimation) of the radiation risk per year (radiation risk density) for cancer incidence:

$$AR_i(\{d_{i,e}\},\{e\},a|a_{min},s) = M_i(\{d_{i,e}\},\{e\},a,s) \times S_i(a|a_{min},s) \quad (10)$$

For adults and weighted absorbed doses less than 0.5 Gy, the aforementioned overestimation of risk density does not lead to contradictions, such as probabilities above unity, when the lifetime radiation-related risk of cancer incidence is calculated.

The baseline risk per year for cancer incidence is

$$BR_i(a|a_{min},s) = m_i(a,s) \times S_i(a|a_{min},s) \quad (11)$$

The percentage of radiation risk per year to the total risk, including the baseline one, is known as a risk fraction attributable to radiation, or "attributable risk fraction" (ARF):

$$ARF_i(\{d_{i,e}\},\{e\},a|a_{min},s) = \frac{AR_i(\{d_{i,e}\},\{e\},a|a_{min},s)}{AR_i(\{d_{i,e}\},\{e\},a|a_{min},s)+BR_i(a|a_{min},s)} \times 100\% = \frac{M_i(\{d_{i,e}\},\{e\},a,s)}{M_i(\{d_{i,e}\},\{e\},a,s)+m_i(a,s)} \times 100\% \quad (12)$$

Lifetime risk

A lifetime cancer risk is the probability that a cancer occurs at some time in the future in an exposed person. There are several estimates of lifetime radiation-related cancer risk. The simplest one is the conventional lifetime attributable risk, *LAR*[74][75].

For protracted exposure of a tissue or organ ***i*** with a dose $d_{i,e}$ in ages $\{e\}$: $[e_1 \ldots e_{max}]$ it is calculated as follows:

$$LAR_i(\{d_{i,e}\},\{e\},a_{min},s) = \sum_{a=a_{min}}^{a_{max}} AR_i(\{d_{i,e}\},\{e\},a|a_{min},s) \quad (13)$$

The maximum age of survival, a_{max}, is for practical purposes about 100 years. *LAR* is approximately equivalent to the risk of radiation-induced incidence of cancer and to other similar measures[76] at the doses relevant to occupational exposure (less than about 0.5 Gy).

Applying the same notation as for the definition of *LAR,* thelifetime baseline risk of cancer, *LBR,* is calculated as:

$$LBR_i(a_{min},s) = \sum_{a=a_{min}}^{a_{max}} BR_i(a|a_{min},s) \quad (14)$$

The percentage of lifetime radiation-related cancer cases to the total cancer cases, including the baseline cases, is known as a “lifetime attributable risk fraction” (LARF):

$$LARF_i(\{d_{i,e}\},\{e\},a_{min},s) = \frac{LAR_i(\{d_{i,e}\},\{e\},a_{min},s)}{LAR_i(\{d_{i,e}\},\{e\},a_{min},s)+LBR_i(a_{min},s)} \times 100\% \quad (15)$$

The duration of any lifetime at-risk segment under consideration, depends on the age at exposure (i.e., the higher the ages at initial exposure the shorter the lifetime segment up to the expected age at death). This causes complications in any comparisons of results among different ages at exposure. Therefore, the cumulative risks over, for example, 20 years-at-risk after the initial exposure (or any other time period) may also be calculated. Such cumulative risks can be a suitable representation to satisfy interest in early risks of cancer from a short-term occupational health perspective and also for comparisons between calculated risks and risks potentially provided by any epidemiological studies of nuclear workers[77][78]. This is particularly relevant for cancer types such as leukaemia where the

relative increase in risk is expected to be stronger during the first few decades after occupational exposures.

An important consideration here is that risk quantities, although they may be based on individual doses, cannot represent a particular individual's risk accurately, mainly due to missing information on other important co-factors that influence a particular individual's cancer risk and how these co-factors might influence radiation-related risk. Such co-factors include: any genetic pre-disposition to cancer development; individual radiation sensitivity; lifestyle factors such as smoking status and alcohol intake; other occupational risk factors; and past medical conditions that may have been treated with chemotherapy or radiation. Furthermore, population-based incidence and survival curves, used in the integration of risks over time, only represent average values for the particular population under consideration. Hence, LAR and AR are supposed to be interpreted as an average risk for specific ages, sexes and populations.

4.3. EXAMPLES OF CALCULATIONS AND INTERPRETATION OF THE RESULTS

When performing "direct" tasks (i.e., calculating risk from dose records), the following sequence of actions ought to be followed.

1. Task statement, including:
    - choice of risk quantities to calculate;
    - preparation of personal dose records, in a format of linked pairs "age at radiation exposure" (e) - "annual weighted absorbed dose in a tissue or organ" i ($d_{i,e}$): $\{e, d_{i,e}\}$;
    - preparation of necessary data from relevant population health statistics: age-, sex- and population-specific rates for all-cause mortality, cancer mortality and cancer incidence for a specific cancer site, i.
2. Selection of mathematical models for excess cancer incidence rates, including the time-response function to account for the latent period L_i (and any variation of risk with time since exposure), the weights w between absolute (EAR) and relative (ERR) risk transfer for calculating the combined excess risk model ER_i, and any values of $DDREF_i$.
3. Calculation of risks.
4. Interpretation of results.

Example 1. Informing employees about occupational radiation risk

In order to inform an interested person, such as an employee about a risk arising from a particular occupational exposure to radiation, the *LAR* or *AR* values may be compared with limits, constraints or reference values, or with the risk that would have been experienced by that person in the absence of the particular occupational exposure. It is often of value to also use the relative measures *LARF* and *ARF*, so that the additional risk from the particular occupational exposure may be expressed as, say, a percentage of the background risk that would have been experienced anyway. It may also be of relevance that workers employed in the particular job that led to the occupational exposure may have background risk below that experienced by general population (the so-called "healthy worker effect"), although this would be difficult to quantify.

Example 1a. A man has not been occupationally exposed to ionizing radiation before the age of 20 years. Then, during the course of his work, he is annually exposed at low dose-rates to uniform whole-body gamma radiation at doses of 20 mGy/y. What are his consequent assessed radiation risks for the incidence of all types of cancer from 1 year or 5 years of occupational exposure?

To answer the question, we calculate the following risk quantities: *LAR* and *LARF* and maximum by attained age values of *AR* and *ARF*. We use only two risk models for this purpose: for all solid cancer incidence and for all leukaemia incidence (Table 2). The time-response functions for each annual

exposure, accounting for the latent periods in these models, is assumed to vary stepwise from 0 to 1 exactly 5 years and 2 years after exposure, for solid cancers and leukaemia, respectively. The weighting factor between an absolute (EAR) and a relative (ERR) transfer of risk (***w***) equals 0.5 for all solid cancers and for leukaemia (see Subsection 3.7 above) and *DDREF* value is assumed to be 1.0 (i.e., no reduction in risk from low-level exposure). From Table 6 we use the following data on health statistics for the hypothetical population from which this worker is drawn:

- sex- and age-specific all-cause mortality rates;
- sex- and age-specific all-cancer mortality rates (for cases with ICD-10 codes C00–C96);
- sex- and age-specific all-cancer incidence rates (for cases with ICD-10 codes C00–C96);
- sex- and age-specific all-solid cancer incidence rates (for cases with ICD 10 codes C00–C89).)

The age- and sex-specific cancer morbidity and mortality rates for this hypothetical population were assumed to be the average of the equivalent rates for the Euro-American and Asian composite populations presented in ICRP Publication103 (Tables A.4.10 - A.4.17)[7] and are given in Table 6.

The results of the calculations are given in Table 7.

Example 1b is the same as Example 1a, but for a 20-year-old woman. The results of the calculations are shown in Table 7.

Example 1c is the same as Example 1a, but for a 40-year-old man. The results of the calculations are shown in Table 8.

Example 1d is similar to Example 1b, but for 40-year-old woman. The results of the calculations are shown in Table 8.

TABLE 6. HEALTH STATISTICS FOR THE HYPOTHETICAL POPULATION (AS DEFINED IN THE TEXT) WHICH IS USED FOR CALCULATIONS IN THE EXAMPLES; MORTALITY AND INCIDENCE RATES ARE SCALED PER 100 000 PERSON-YEARS

Age group, y	**Male**				**Female**			
	Mortality rate		**Incidence rate**		**Mortality rate**		**Incidence rate**	
	All causes	All cancers	All cancers	All solid cancers	All causes	All cancers	All cancers	All solid cancers
20-24	72.6	4.4	17.4	15.2	30.4	3.4	19.5	17.9
25-29	79.5	6.4	27.4	24.7	36.7	5.9	36.9	35.2
30-34	102.4	11.4	41.5	38.3	50.2	12.7	68.5	66.5
35-39	137.7	22.1	66.9	63.6	72.1	24.5	121.4	118.5
40-44	206.5	45.6	118.0	113.8	115.2	46.4	200.4	196.5
45-49	299.1	81.8	198.2	192.1	177.7	77.0	298.5	294.1
50-54	452.8	144.7	347.7	338.4	273.5	121.7	408.3	401.5
55-59	733.9	254.9	604.2	591.2	444.6	190.2	532.7	524.7
60-64	1317.6	466.0	1055.9	1036.5	770.7	291.3	721.1	708.7
65-69	2174.3	738.7	1589.2	1560.2	1261.7	418.7	913.1	896.6
70-74	3570.2	1059.0	2108.3	2066.6	2141.2	576.1	1150.1	1127.2
75-79	5692.0	1387.5	2480.3	2430.8	3544.7	721.5	1303.6	1277.4

Age group, y	Male				Female			
	Mortality rate		Incidence rate		Mortality rate		Incidence rate	
	All causes	All cancers	All cancers	All solid cancers	All causes	All cancers	All cancers	All solid cancers
80-84	9392.4	1762.2	2738.5	2679.5	6222.1	878.5	1454.3	1422.5
85-89	13339.5	1965.7	3264.5	3194.0	9400.4	942.6	1567.1	1534.3
90+	23198.2	2139.9	3592.9	3516.5	18596.3	1031.7	1728.0	1680.0

Figure 1 and Figure 2 illustrate some intermediate points in the calculations. Figure 1 shows the annual cancer-free survival functions for men and women with a work duration of 5 years, from the age of 20 years to the age of 24 years, with the cancer-free survival functions equal to unity at the age of 24 years. These plots also confirm that the survival for women is better than that for men: the median age of cancer-free survival equals 79 years for women and 74 years for men.

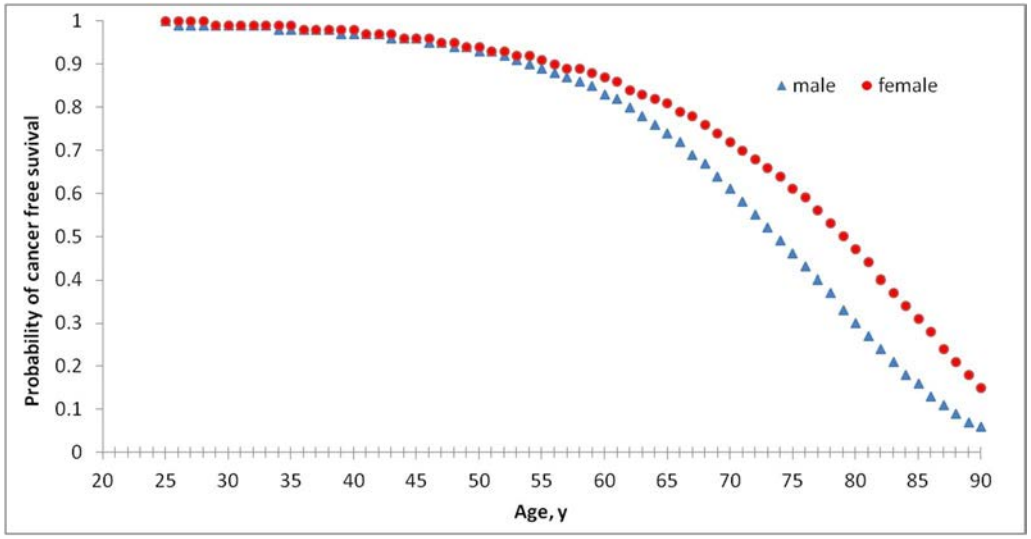

Fig. 1. Cancer free survival functions for 24-year-old men and women who have worked for 5 years, starting at the age of 20 years (Examples 1a and 1b)

Figure 2 shows the baseline probability for 24-year-old men and women to develop a cancer at the attained age of ***a***, that is, the baseline risk per year of attained age (baseline risk density) for cancer incidence:

$$BR(a|24,s) = m(a,s) \times S(a|24,s) \qquad (16)$$

where baseline rates are used from the hypothetical population as defined in the text above (see Table 6).

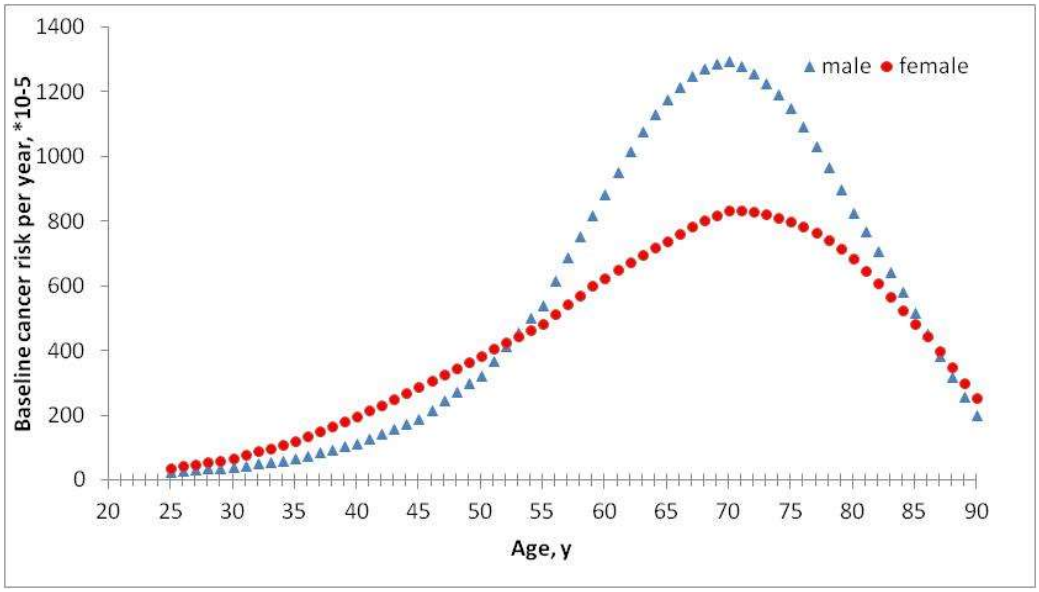

Fig. 2. The baseline risk per year of attained age (baseline risk density) for cancer incidence, BR $(a|24, \boldsymbol{s})$*, for 24-year-old men and women who have worked for 5 years, starting at the age of 20 years (Examples 1a and 1b).*

Figure 2 can be easily verified using the data from Table 6 and Figure 1. For example, for a 70-year-old man m (70, *male*) = 2108.3*10^{-5} (Table 6: 70-74 years attained age group, third column), $S(70|24,$ *male)* $\approx$ 0.6. Hence $BR(70|24, male) = m(70, male) \times S(70|24, male) \approx 2100 \times 0.6 \times 10^{-5} = 1260 \times 10^{-5}$, which agrees well with the data in Figure 2. Further, the lifetime baseline risk (*LBR*) is the area under the curve of baseline risk density, and *LBR*(24, *male*) ≈ 1260*(90 - 40) * 0.5 * 10^{-5}=31500*10^{-5}. Thus, the lifetime probability of a 24-year-old man developing cancer is ~31.5%.

Figure 3 shows the radiation-related excess risk per year of attained age (radiation risk density) for cancer incidence, AR $(a|24,$ s), for 24-year-old men and women who have worked for 5 years, starting at the age of 20 years, exposed to gamma radiation doses of 20 mGy/y.

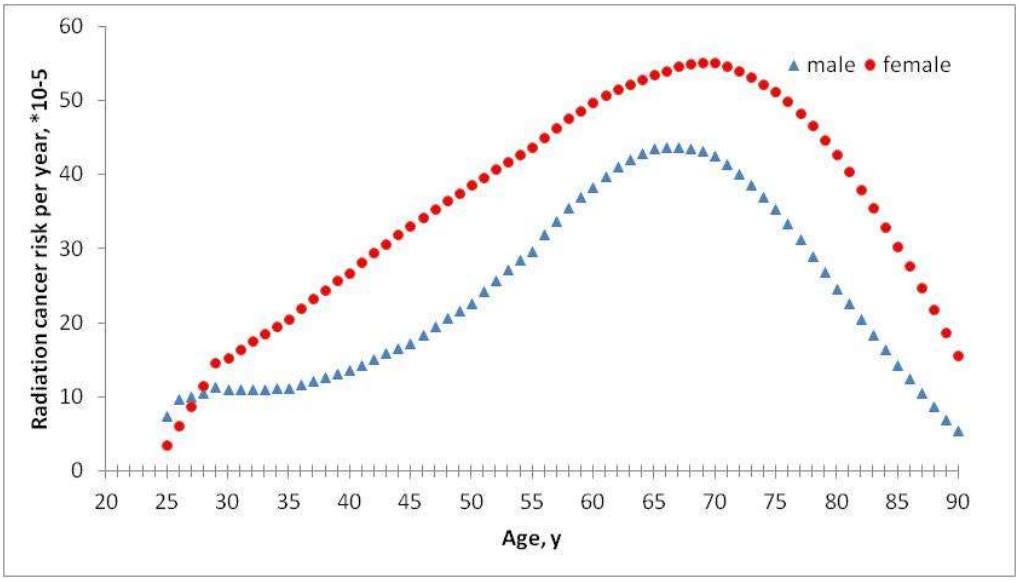

Fig. 3. The radiation-related excess risk per year of attained age (radiation risk density) for cancer incidence, AR ($a|24, \boldsymbol{s}$), for 24-year-old men and women who have worked for 5 years, starting at the age of 20 years, exposed to gamma radiation doses of 20 mGy/y (Examples 1a and 1b)

Figure 2 and Figure 3 demonstrate that, within the scope of Examples 1a and 1b, the risks of cancer attributable to occupational radiation exposure are about ten to twenty times less than the baseline cancer risks. In Figure 3, the radiation-related excess risk for women is about 1.5 times higher than that for men, with the exception of ages younger than 28 years, when the latent period of 5 years for solid cancers affects the radiation risks (within the scope of Examples 1a and 1b).

TABLE 7. CALCULATED RISK QUANTITIES FOR EXAMPLES 1a and 1b

Example number		**1a**	**1b**
Sex		Male	Female
Age at start of work, y		20	20
Annual whole-body dose of gamma radiation, mGy		20	20
1 year of work	LAR	$332*10^{-5}$	$501*10^{-5}$
	LARF, %	0,9	1,7
	max AR (attained age, y)	$9*10^{-5}$ (*66*)	$12*10^{-5}$ (*68*)
	max ARF, % (attained age, y)	8 (*23*)	5,9 (*25*)
5 years of work	LAR	$1576*10^{-5}$	$2376*10^{-5}$
	LARF, %	4.1	7.4
	max AR (attained age, y)	$44*10^{-5}$ (*66*)	$55*10^{-5}$ (*69*)
	max ARF, % (attained age, y)	24 (*26*)	19 (*29)*

TABLE 8. CALCULATED RISK QUANTITIES FOR EXAMPLES 1c and 1d

Number of Example		**1c**	**1d**
Sex		Male	Female
Age at start of work		40	40
Annual whole-body dose of gamma radiation, mGy		20	20
1 year of work	LAR	$198*10^{-5}$	$283*10^{-5}$
	LARF, %	0.5	1,0
	max AR (attained age, y)	$6*10^{-5}$ (*65*)	$8*10^{-5}$ (*69*)
	max ARF, % (attained age, y)	1.7 (*45*)	1.6 (*45*)

5 years of work	LAR	$933*10^{-5}$	$1319*10^{-5}$
	LARF, %	2,5	4,5
	max AR (attained age, y)	$30*10^{-5}$ (*66*)	$38*10^{-5}$ (*69*)
	max ARF, % (attained age, y)	5.6 (*49*)	6.4 (*49*)

Example 1e. A man has not been occupationally exposed to ionizing radiation before the age of 40 years. Then, at the age of 40 years and in the course of his work, he is internally exposed to radiation due to the inhalation of 1000 Bq of ^{234}U. The inhaled radioactive particles are characterized by the activity median aerodynamic diameter of 1 μm, a slow lung absorption type (S) and a gut absorption factor (f1) of 0.02. What are his risks for the incidence of all types of cancer arising from this intake of ^{234}U?

To answer the question, we calculate the following risk quantities: *LAR* and *LARF* and maximum by attained age values of *AR* and *ARF*.

To calculate radiation risks the annual RBE-weighted organ/tissue absorbed doses are defined and we assume here that they can be approximated by organ/tissue equivalent doses, i.e., for RBE weighting factors we use ICRP Publication 103 radiation weighting factors, w_R. Table 9 comprises committed equivalent dose coefficients (Sv/Bq) to organs/tissues following inhalation of ^{234}U under the conditions of Example 1e[73].

TABLE 9. COMMITTED EQUIVALENT DOSE COEFFICIENTS TO ORGANS/TISSUES FOLLOWING INHALATION OF **^{234}U** UNDER THE CONDITIONS OF EXAMPLE 1E (*), SV/BQ

Organs/tissues	**Time after intake**					
	1 year	5 years	10 years	20 years	30 years	45 years
Bladder Wall	2.5E-10	1.2E-09	2.6E-09	5.7E-09	8.9E-09	1.3E-08
Bone Surface	2.6E-08	1.1E-07	1.9E-07	3.0E-07	3.8E-07	4.5E-07
Breast	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08
Oesophagus	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08
St Wall	5.6E-10	1.6E-09	3.0E-09	6.0E-09	9.2E-09	1.4E-08
Colon	9.2E-09	1.1E-08	1.3E-08	1.6E-08	1.9E-08	2.4E-08
Liver	1.2E-09	9.2E-09	2.1E-08	3.9E-08	5.1E-08	6.2E-08
Ovaries	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08
Red Marrow	2.8E-09	1.3E-08	2.2E-08	3.3E-08	4.0E-08	4.6E-08
Lungs	3.5E-05	5.4E-05	6.1E-05	6.7E-05	6.9E-05	7.0E-05
Skin	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08
Testes	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08
Thyroid	2.4E-10	1.2E-09	2.6E-09	5.7E-09	8.8E-09	1.3E-08

Organs/tissues	Time after intake					
	1 year	5 years	10 years	20 years	30 years	45 years
Remainder	6.9E-09	1.9E-08	2.3E-08	2.6E-08	3.0E-08	3.4E-08

(*) [ICRP Database of Dose Coefficients: Workers and Members of the Public; Ver. 3.0; URL: http://www.icrp.org/page.asp?id=402]

Table 9 shows that 99% of the total committed equivalent dose to all organs/tissues is to the lungs, therefore, to simplify the calculation of radiation risks in this example, we use radiation risk models only for lung cancer incidence in ICRP Publication 103[7]:

$$ERR(e, a, male) = 0.29 * d * exp\,[0.0157 * (e - 30) - 1.65 * ln(a/70)] \quad (17)$$

$$EAR(e, a, male = 6.47 * 10^{-4} * d * exp\,[0.001 * (e - 30) + 4.25 * ln(a\,/\,70)] \quad (18)$$

One year after inhalation of 1000 Bq of ^{234}U, the cumulative equivalent dose to the lungs is 35 mSv or ~50% of the committed equivalent dose after 45 y (70 mSv). One can see from Table 8 that annual equivalent doses decrease from 35 mSv for the first year after intake to ~1 mSv at the tenth year, ~0.5 mSv – at the 20th year and ~0.1 mSv – after the 40th year. As in the previous examples, we use age-specific all-cause mortality rates from Table 6. Age-specific lung cancer mortality and incidence rates (for cases with ICD-10 codes C34) for men in the hypothetical population (see text above) are given in Table 10. The results of the radiation risk calculations are shown in Table 11.

TABLE 10. LUNG CANCER MORTALITY AND INCIDENCE RATES FOR THE HYPOTHETICAL MALE POPULATION (AS DEFINED IN THE TEXT), WHICH IS USED FOR CALCULATIONS IN EXAMPLE 1E. RATES ARE SCALED PER 100 000 PERSON-YEARS

Age group, y	Lung cancer mortality	Lung cancer incidence
40-44	8,5	12,1
45-49	18,5	23,3
50-54	38,2	50,4
55-59	74,2	94,5
60-64	146,3	182,8
65-69	245,4	310,6
70-74	344,6	420,1
75-79	415,4	483,0
80-84	455,5	500,3
85-89	421,2	543,1
90+	363,4	473,3

TABLE 11. RADIATION RISK QUANTITIES FOR EXAMPLE 1e

Number of Example		**1e**
Sex		Male
Age at intake (years)		40
Internal exposure	nuclide	^{234}U
	Activity inhaled, Bq	1000
After intake	LAR	$141*10^{-5}$
	LARF, %	1.8
	max AR (attained age, y)	$5.2*10^{-5}$ (*70*)
	max ARF, % (attained age, y)	2.3 (*47*)

Example 2. Exposure planning

Existing radiation risks and their temporal changes ought to be taken into account for exposure planning and optimization of radiation protection. The ICRP Publication 103[7] recommended the annual dose limit 20 mSv per year on average over five executive years. Below this limit, additional constraints may be set for planned occupational exposure situations to implement the IAEA fundamental safety principles "Optimization of protection" and 'Limitation of risks to individuals"[79]. These constraints are intended to minimize radiation risks as low as reasonably achievable in order to provide the best achievable protection of the individual worker under the circumstances.

Example 2a. A man was externally exposing to gamma radiation at his workplace from 20 to 32-years-old, with the annual doses of 18 mSv. What would be the dose of external exposure at the age of 33, so that the radiation cancer risk per year does not exceed 10^{-3} during his life?

We use risk models and statistics data the same as in Example 1a.Calculations show that after this employee has worked for 13 years, maximum $AR = 95*10^{-5}$(at the attained age of 66), and at the next year of work, his dose of external gamma exposure would not exceed 15 mSv.

Example 2b. A woman was externally exposing to gamma radiation at his workplace from 20 to 29-years-old, with the annual doses of 18 mSv. What would be the dose of external exposure at the age of 30, so that the radiation cancer risk per year does not exceed 10^{-3} during her life?

We use risk models and statistics data the same as in Example 2a. Calculations show that after this employee has worked for 10 years, maximum $AR = 94*10^{-5}$(at the attained age of 68), and at the next year of work, her dose of external gamma exposure would not exceed 12 mSv.

4.4. CONCLUSIONS

Assessment of prospective radiation risks is essential for implementation of several fundamental safety principles in the SF-1[79], in particular, principles of "Justification of facilities and activities", "Optimization of protection" and 'Limitation of risks to individuals".

The justification principle invites the comparison between prospective radiation risks and supposed benefits from facilities or activities. The collective or average risk estimates are needed in this case, because justification decisions are taken at the level of government or regulatory authorities.

Risk estimates based on the individual doses are important for implementation of principals of optimization and limitation of risks to individuals. The IAEA emphasizes that these two principles have to be used concurrently: "because dose limits and risk limits represent a legal upper bound of acceptability, they are insufficient in themselves to ensure the best achievable protection under the circumstances, and they therefore have to be supplemented by the optimization of protection. Thus, both the optimization of protection and the limitation of doses and risks to individuals are necessary to achieve the desired level of safety[79].

The examples in Section 4 show how dose constraints can be derived from the given risk constraints.

Informing personnel about radiation risks, planning exposures and optimizing radiation protection are important components of the overall risk management process. For these purposes, an example is briefly described in Annex I of use by the Russian nuclear industry of the ARMIR computer system.

5. SOURCES OF UNCERTAINTY IN USING EXISTING METHODOLOGIES

5.1. INTRODUCTION

Descriptive (empirical) risk models are derived from appropriate epidemiological data that meet certain quality criteria in order to produce valid results[11]. To some extent, these empirical models may be guided by an incomplete knowledge of biological mechanisms, but this guidance is a matter of judgement as to the degree to which existing radiobiological evidence can be used to influence empirical modelling[80].

George Box summarised statistical modelling thus: "All models are wrong, but some are useful"[81]. In other words, and for our purposes, no model is going to be a *perfect* description of the way a particular exposure to ionizing radiation affects the consequent risk of the development of cancer, but models of radiation-related cancer can provide *valuable* tools for predicting the risk of cancer arising from a given exposure to a particular individual or group of people, provided uncertainties are properly taken into account.

The sources of uncertainty in any estimation of the risk of radiation-related cancer are many and various, and the influence of these sources will vary from case to case, depending on the specific circumstances. In this section the sources of uncertainty will be examined, supplemented by a more detailed treatment in appendices. Uncertainties in radiation risk estimates have been addressed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), especially in the UNSCEAR 2012 Report, Annex B[40] and in the UNSCEAR 2017 Report, Annex A [11]. This section relies heavily on the detailed discussions to be found in these two UNSCEAR reports.

Two broad categories of uncertainties will be examined: those inherent in the risk models themselves and those related to the application of risk models to specific circumstances. There will be uncertainties associated with any particular model of radiation-related cancer because the model is derived from a certain set (or sets) of epidemiological data, so that statistical and systematic errors are present in the parameters that define the model. These intrinsic model uncertainties will inevitably contribute to the overall uncertainty in a risk estimate when a particular model is applied to any given set of circumstances, but other uncertainties will then arise because the model has been derived from particular epidemiological conditions and applied to other circumstances that will differ to a greater or lesser extent. The treatment of uncertainties may differ when risk models are applied either to a population or to an individual, since more information of relevance to a risk model may be available for an individual (e.g., their smoking status).

The quantitative assessment of uncertainty is an essential aspect of a proper understanding of risk modelling[40][40][11]. Without a quantitative indication of uncertainty, it would not be possible to distinguish between the reliance that could be placed upon two risk predictions with more or less the same point value of radiation-related risk, but with very different associated uncertainties – much more dependability would be placed in a risk prediction with a relatively low associated uncertainty than in a prediction with a relatively large associated uncertainty. Examples of how uncertainties can be quantified for particular models applied to particular circumstances are given in the Annexes.

5.2. MODELLING UNCERTAINTIES

Statistical models describing how the future additional risk of a particular type of cancer varies with the absorbed dose of radiation received by the relevant target tissue, and how this risk is modified by factors such as sex, age-at-exposure and time-since-exposure, are derived from the experience of certain populations exposed to radiation. One such population is the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, and the Life Span Study (LSS) of the survivors is the primary

source of information for the construction of risk models. However, even for a study as large as the LSS, the numbers of incident cases or deaths upon which models are built are limited, particularly for the less common cancer types, and this is an inevitable source of uncertainty. Then there are other sources of uncertainty, such as the accommodation in the models of the doses from biologically more damaging neutrons received by the survivors, the shape of the dose-response at low doses, and the treatment of variations in background incidence/mortality due to, for example, socioeconomic status or cigarette smoking habits that could distort the dose-response. In this section, the various sources of uncertainty that are introduced into risk models by the observational data upon which they are based will be examined critically.

5.2.1. Statistical uncertainties

As with any scientific study, epidemiological studies will produce findings that are subject to statistical uncertainties, arising because some underlying parameter, such as radiation-related risk, is being estimated using data that is limited in quantity, to a greater or lesser extent. Hence, there are statistical errors associated with any estimate of risk in any study, due to random fluctuations in the data – the less data available to make an estimate the greater are the relative fluctuations around the "true" value. The statistical uncertainties in a study are usually quantified using a confidence interval (usually a 90% or 95% confidence interval) – were it to be possible to repeat the exactly the same study many times, and assuming that the study produces accurate results (i.e., results that centre on the true value of the parameter being estimated), then the percentages (e.g., 90% or 95%) equal the proportion of intervals expected to contain the true value of the parameter being estimated[82]. Statistical uncertainties are inevitable and can only be reduced by having more data available in a study, but statistical uncertainties are an inherent feature of risk models based on epidemiological findings. In general, statistical uncertainties are smallest for studies with a large number of subjects and a large number of cases of the disease of interest distributed over a wide range of exposures of interest.

5.2.2. Epidemiological uncertainties

The vast majority of epidemiological studies are observational in nature – observational studies are non-experimental, and epidemiology relies almost entirely upon data generated by the largely uncontrolled conditions of everyday life[83][84]. Therefore, in observational studies randomization of study subjects is not possible, and the elimination of systematic background differences between individuals who have received different levels of exposure cannot be achieved through this means, as is done in randomised controlled clinical trials. This poses difficulties in the design, conduct and interpretation of epidemiological studies because the statistical errors that are inevitably present when data are analysed are supplemented by systematic errors that are often difficult to identify and consequently eliminate or adjust for, leading to bias in risk estimates and risk modelling. This also poses difficulties for the replication of study results.

Biases (systematic errors) can take many forms and are frequently subtle, and they can produce results that have the potential to be seriously misleading. Sources of bias range from misidentification of study subjects, misdiagnosed diseases and differential loss of cases from the study, to erroneous exposure estimates, preferential inclusion of cases with high/low exposures and mistaken recall of past events. Related to biases are confounding factors, which are correlated with both the disease under study and the exposure of interest and have the potential to distort associations. An example of a confounding factor is cigarette smoking in the study of radon and lung cancer – if the frequency of smoking is associated with the level of exposure due to radon then the major influence of smoking on the risk of lung cancer can produce a misleading degree of association between radon exposure and lung cancer.

The generation of misleading results through bias and confounding is particularly prone in studies of low-level exposures that are predicted to produce excess risks that are comparable with, or less than, variations in background risks produced by other factors. Under these circumstances it is easy to attribute such background variations to an effect of the exposure of interest. This gives rise to a subtle bias in the reporting of results because researchers are more likely to report, and to have published in journals, notable associations that they attribute to the exposure of interest when these are, in fact, the results of background variations. For further discussion see Berrington de Gonzalez et al.[12] and subsequent papers in this JNCI Monograph.

In radiation epidemiology, researchers are supposed to strive to minimise the chance of obtaining unreliable results by achieving in a study, among other things: sound case ascertainment, an appropriate comparison (reference) group, sufficiently long follow-up, a proper accounting for confounding factors and well-characterised[85][85][6]. Some epidemiological studies largely meet these objectives, but others fail to do so in one or more respects. Consequently, the degree of overall epidemiological uncertainty varies from study to study. It is important to quantify the various sources of epidemiological uncertainty in the derivation of risk models from an epidemiological study or studies. These uncertainties are supposed to flow through the application of radiation risk models to particular circumstances and be accounted for in the final overall uncertainty in a specific risk calculation.

5.2.3. Dose-response modelling

Based on epidemiological data, statistical models of risk may be constructed, generally expressed in terms of the Excess Relative Risk (ERR, the proportional increase in risk relative to the background risk) or the Excess Absolute Risk (EAR, the additional risk over background), as discussed in Section 3. The most important aspect of this modelling is the nature of the dose-response – how the risk of cancer varies with the dose of radiation received. Risk modelling is not usually straightforward because different statistical models can often be produced using the same set of data, and expert judgement is necessary to select the most appropriate model under particular sets of conditions. Scientific parsimony ("Occam's razor") is frequently applied to select the simplest model to adequately describe the data, but other considerations may be applied, such as guidance based upon the currently incomplete understanding of biological mechanisms of radiation carcinogenesis.

The upshot is that several risk models may be produced to describe how the risk of a certain type of cancer varies with the dose of radiation received by the tissue in which the cancer has its origin. These models may differ in a number of respects, such as whether cancer-specific models are generated for each sex, and how the excess risk is assumed to vary with different combinations of age-at-exposure, time-since-exposure, and attained age. A contributor to this uncertainty is incomplete follow-up in an epidemiological study upon which a model is based, so that not all members of a study cohort have died, and certain assumptions have to be made about the evolution of the excess risk beyond the end of follow-up. Under these circumstances, a pragmatic approach is to determine how much variation in risk is obtained by using different models, and in this way estimate the modelling uncertainties.

For example, one of the ways risk models may differ is in the manner in which the latent periods for given cancer types are accounted for. It is known from the studies of the Japanese atomic-bomb survivors, among others, that a radiation-related cancer may occur many years after exposure. It is also known that there exists a minimum latent period following exposure during which no excess risk due to the exposure will be apparent. Therefore, in any cancer risk estimate the minimum latent period has to be taken into account such that no excess risk is predicted during this period following a given exposure. The minimum latent period will to some extent be dependent on the type of cancer under consideration – it is usually assumed to be 2 years for leukaemia, 3-4 years for thyroid cancer

and 5 years for other solid cancers – but the period will not be known with certainty. The LSS provides only limited information on minimum latency, since the follow-up began in 1950 (five years after the bombings) for cancer mortality and the incidence of lymphopoietic malignancies, and not until 1958 for solid cancer incidence.

One particular aspect of risk modelling is that risk estimates are most usually obtained from moderate or high doses received at a high dose-rate (although high acute doses may also lead to substantial cell killing and a consequent downturn in the cancer dose-response, so the doses considered ought not to be too high). These exposure circumstances lead to relatively high excess risks that are better quantified than those received from lower levels of exposure. The question then arises as to how these risk models may be generalised for application to low doses or low dose-rates, because assumptions have to be made about the nature of the dose-response following low-level exposure (although the shape of the dose-response will be constrained to some extent by the available epidemiological data for low-level exposures). In other words, how is the risk to be interpolated between the reasonably well characterised risks at high-to-moderate doses and a zero excess risk at a zero excess dose. It is usual to make an initial assumption of a linear no-threshold (LNT) dose-response model, because this is the simplest (most parsimonious) model that is compatible with the data[86][87], but this assumption is challenged by some, and a linear model may turn out not be the best fit to the data for some types of cancer. Inevitably, therefore, there is uncertainty associated with risk modelling at low doses or low dose-rates, the uncertainty increasing in relative terms as the doses become lower.

There are epidemiological studies that directly address risks at low doses or low dose-rates, and these studies have now increased in statistical power to an extent that direct estimates of risks at low levels of exposure can reasonably be made[88]. For example, large studies of children exposed to radiation during computed tomography (CT) scanning are being conducted that examine risks following a dose (or a series of doses) of ~10 mGy of X-rays. Similarly, large studies of nuclear industry workers investigate risks among adults who may have received moderate or even high cumulative occupational doses, but as a series of many low doses received at low dose-rates. At present, the epidemiological uncertainties inherent in such studies preclude their use to generate reliable risk models, but these uncertainties may soon be overcome so that they offer a window to directly assess risks at low levels of exposure. Nuclear worker studies are especially valuable in confirming that the assumptions that have to be made in applying risk models derived from the Japanese atomic-bomb survivors to occupational exposure circumstances are broadly correct, as they have done to date[89][80].

5.2.4. Dose and Dose Rate effectiveness Factor (DDREF)

Based on an incomplete and broad knowledge of radiobiological mechanisms of carcinogenesis, upward curvature of the dose-response for cancer at moderate-to-high doses beyond the low dose region is often assumed for low-LET radiations (if received at a high dose-rate). Hence, even though the best statistical fit to the data over the entire dose range may be linear, a dose and dose-rate effectiveness factor (DDREF) is applied to risk estimates obtained from a linear fit to data at moderate-to-high doses and high dose-rates (i.e., from the assumed region of underlying upward curvature) to reduce the slope of the linear dose-response at low doses or low dose-rates. The DDREF is used in radiation protection from an implicit belief (based upon experimental studies and simplified radiobiological reasoning) in the underlying upward curvature of a dose-response at higher doses of low-LET radiation received at a high dose-rate, rather than being derived directly from risk modelling using epidemiological data, although for some cancers (such as leukaemia) a non-linear model curving upwards at moderate-to-high acute doses of low-LET radiation provides the best fit to the epidemiological data. However, a DDREF derived from radiobiological data are not supposed to be

in conflict with epidemiological evidence, and the values of DDREF that are currently used in risk modelling are compatible with the findings of epidemiological studies. Clearly, there is uncertainty in any estimate of the DDREF, to the extent that some expert groups have concluded that for the purposes of radiation protection the DDREF is supposed to be 1.0 (i.e., there is no reduction of the slope of the dose-response following low-level exposure). Usually in risk modelling, the dose-response is derived directly from the best fit to the available epidemiological data, without any consideration of an explicit DDREF. If the modelled dose-response for a particular cancer type contains curvature then the slope varies with the dose (although possibly only at moderate-to-high acute doses), whereas if a linear fit is the best fit then there is no variation of the slope with dose, but in neither instance is an explicit DDREF needed for the modelling. However, the source of uncertainty associated with any fitted dose-response at low doses remains and is substantial.

It ought to be noted, however, that the radiobiological reasoning behind the application of an explicit DDREF only applies to low-LET radiations. This is due to the sparsely ionizing nature of low-LET radiations, such that moderate and high doses received at a high dose-rate are needed to produce a sufficiently high ionization density from multiple tracks crossing a cell nucleus to cause DNA damage (double-strand breaks in DNA) that is particularly difficult for natural DNA repair mechanisms to deal with effectively (and hence the assumed upward curvature of the dose-response – a greater effect per unit absorbed dose – under these conditions of exposure). However, for high-LET radiations, sufficiently high ionization density occurs along a single track to cause such DNA damage and so upward curvature at higher doses is not assumed to occur – high-LET radiations are assumed to have linear dose-responses from low doses to moderate-to-high doses (at all dose-rates) with slopes that are greater than those for low absorbed doses of low-LET radiations by a factor that reflects the relative biological effectiveness (RBE) of the particular high-LET radiation under these conditions of exposure (see discussion below on radiation quality).

5.3. MODEL APPLICATION UNCERTAINTIES

Statistical models derived from the findings of epidemiological studies are applied to particular sets of exposure circumstances, and inevitably, this will introduce uncertainties because these exposure circumstances will differ, to some extent or other, from those experienced by the population(s) used to generate the models. The Japanese atomic bomb survivors were acutely exposed to (mainly) gamma radiation in 1945, so when the models obtained from the experience of the survivors are applied to other conditions of exposure, such as a present-day nuclear workforce, the uncertainties introduced by doing so must be taken into account. These uncertainties include differences in background rates of incidence/mortality in as much as these affect the predicted radiation-induced excess risk, differences in dose-rates, and differences in radiation types, among others. In this section we examine the various uncertainties that arise when risk models are applied to a particular set of exposure conditions

5.3.1. Transfer of risk

Risk models are generally expressed in terms of the ERR or the EAR. For any particular exposed group upon which the models are based, it doesn't matter too much whether the risk model is expressed in terms of the ERR or EAR if the statistical modelling is sufficiently sophisticated. However, the application of the risk models to groups of people with background risks of cancer that differ from those of the population providing the data for the production of the models poses a difficulty in that this depends upon the assumptions made about the nature of the interactions between radiation and background risk factors[90]. Background risks of cancer incidence will be dictated by a number of intrinsic (inherited) and extrinsic (environmental) factors, and their possible interaction, and how radiation interacts with these background factors to produce an excess radiation-related risk

is complex and frequently unknown. An example of when the transfer of risk between populations is important is stomach cancer in a mid-20th century Japanese papulation and in a 21st century European population, because stomach cancer incidence was much higher in the former than in the latter. In contrast, female breast cancer incidence is much higher in the latter than in the former. Transfer of the excess relative risk or excess absolute risk obtained from the experience of radiation exposure of a mid-20th century Japanese population will clearly have notably different effects on the predicted radiation-related excess risks of stomach cancer incidence and female breast cancer incidence in the 21st century European population.

The application to a particular population of an EAR model derived from another population means that the number of radiation-related excess cases in the second population is independent of the background cancer rates experienced by that population – the radiation-related risk just adds on to the background risk. However, this is not so if an ERR model is applied to the second population because then the number of radiation-related excess cases depends on the background rates of cancer – the radiation-related risk is a multiple of the background risk. Whether the EAR or ERR, or some combination of the two, is more appropriate to transfer between populations is uncertain, the degree of uncertainty varying between cancer types. Basically, this is due to an absence of biological knowledge about how radiation interacts with other factors that affect the risk of cancer (such as tobacco smoke). This source of uncertainty needs to be taken into account in any estimation of radiation-related risk, and a sensitivity analysis to determine how much the excess risk varies under different assumptions about the transfer of risk may be appropriate.

A further aspect of uncertainty when transferring risks between populations is the quality of the cancer incidence and mortality data available for these populations. For some source populations, such as the Japanese atomic-bomb survivors, cancer incidence and mortality data are good because of the effort that has been expended on the construction of the databases (although the data are still not without associated uncertainties), but this might not be the case for a population to which the risk model is applied. Indeed, for some populations reliable cancer incidence registration data are not available, or have only been available for a limited time. A further potential difficulty is that cancer classifications have varied over time so that what constitutes a particular type of cancer during the period in which a model is constructed is different from that during the period in which the model is applied. If cancer mortality data are available, using these may be a reasonable alternative to incidence data under some circumstances, but difficulties are presented for cancer types with a low lethality, such as thyroid cancer, and this source of uncertainty has to be borne in mind. Further, the accuracy of the certification of cause of death needs to be taken into account.

Baseline cancer rates for the population from which a certain sub-population has been drawn, such as a workforce in a particular country, might not be directly applicable to the modelling of risk in that group. In many instances, it has been found that workforces are healthier than the general population because, for example, they smoke less; this is known as the “healthy worker effect”. Therefore, if some component of the ERR is transferred between populations, the healthy worker effect will lead to additional uncertainty in risk assessments of occupational groups, which will be more important for some types of cancer than others, because of the difference between the baseline rates for workers compared to the general population (for example, lung cancer because of different smoking habits).

5.3.2. Average radiosensitivity

The application of risk models to individual circumstances makes the implicit assumption that the individual responds to radiation in the same way as does an individual in the population from which the risk model is derived, after allowing for potential risk modifying factors such as sex and age-at-exposure (which vary between cancer types) and the assumed effect of different baseline cancer rates. It is known that people with certain rare hereditary conditions are more sensitive to cancer induced

by exposure to radiation, but it is not known how much the sensitivity to radiation-induced cancer varies in the general population[7].

In some respects, individual radiosensitivity can be seen as an aspect of the transfer of radiation-related risk derived from one population to an individual drawn from another population having different baseline cancers risks, in that this will depend on the extent of the interaction between radiation and background risk factors. Therefore, to some extent, the uncertainty in individual radiosensitivity is addressed in the assessment of the uncertainty in transferring risks between different populations. Particular sensitivity to radiation-induced cancer among people with rare hereditary conditions is an example of an intrinsic sensitivity because it may be assumed that this sensitivity arises from the genetic make-up of an individual at conception. However, factors arising from lifestyle and environmental exposures can lead to the modification of the genome throughout life, an example being tobacco smoking. A person who smokes cigarettes has a higher risk of lung cancer than a person who does not smoke, but a smoker is likely to have a higher risk of lung cancer from exposure due to radon decay products than a non-smoker experiencing the same level of exposure due to radon decay products. This is because of an interaction between the effects of tobacco smoke and radon decay products, and is an example of extrinsic sensitivity (which may interact with intrinsic sensitivity – there are individuals who may be inherently more sensitive to cancer induction consequent to exposure to tobacco smoke and/or radiation). If interactions exist between radiation and risk factors such as exposures to other carcinogenic agents (such as the use of solvents in the workplace), then a lack of information on the levels of the presence of such factors in a population or individual will lead to additional uncertainty about the overall radiation risk. Further, there are likely to exist factors affecting the risk experienced by an individual from exposure to radiation (and other exposures) that could be important, but remain unknown[91].

5.3.3. Lifetime risk

Frequently, the lifetime risk associated with radiation exposure needs to be assessed. This will entail determining the evolution of the radiation-related risk following a given exposure, or temporal pattern of exposures, for an individual or group of people. Clearly, the lifetime risk will depend on the variation of excess risk with certain risk modifying factors such as time-since-exposure, but it will also depend upon future baseline cancer rates if the radiation-related risk depends to some extent on background risk factors (i.e., the ERR is relevant to future risk), and baseline cancer rates change with time. Also pertinent is the life expectancy of an individual or group, and how this changes with time: most radiation risk models assume that some excess risk persists throughout the remaining lifetime so the longer a person lives the more opportunity there is for radiation-related excess risk to be expressed. Life expectancy will depend upon a number of factors, such as whether an individual smokes or not, and the socio-economic conditions and medical treatment available in a country, and these factors can be complex and change quickly under certain circumstances (e.g., a pandemic), adding to the uncertainty surrounding lifetime risk estimates. Lifetime risk, therefore, depends not only on the structure of the assumed risk model (such as the dependency of risk upon age at exposure and time since exposure), but also on how the risk from radiation exposure interacts with other risks and the expected length of life over which the risk is expressed[92].

5.3.4. Radiation quality

Risk models are mainly derived from the studies of the Japanese atomic-bomb survivors, who were briefly exposed to mainly gamma radiation, but with a relatively small component of neutrons. In addition to considerations on how risk estimates obtained from these acutely exposed survivors may be applied to protracted exposures to low dose-rates of gamma radiation is the question of how these models are applied to circumstances of exposure to different radiations, for example, high-LET

radiations such as neutrons and alpha particles. Certain assumptions have to be made about the relative biological effectiveness (RBE) of these different radiations, which may differ between different cancer types. For the purposes of radiation protection, the radiation weighting factor, w_R, for a particular radiation (of a particular energy) is applied to an absorbed dose to derive the equivalent dose, but w_R might not be appropriate for modelling the RBE for certain combinations of radiations and tissues if better information is available than a blanket application of w_R (such as the RBE of the low-energy beta-particle emitted by tritium, which may be greater than 1.0 when compared to reference high-energy gamma radiation). Risk models derived from populations exposed principally to gamma radiation, such as the Japanese atomic-bomb survivors, may be used to obtain the risks from absorbed doses of other radiations through weighting the dose by an appropriate effectiveness factor relative to exposure to gamma radiation (i.e., by weighting the absorbed dose by an appropriate RBE). However, the assumptions concerning the RBE of particular radiation types in the context of particular target tissues inevitably introduce uncertainty into risk estimates.

In addition to radiation quality affecting the excess risk per unit tissue absorbed dose is the matter of whether different radiations may have different shapes of dose-response and/or different degrees of modification by factors such as age-at-exposure. From the discussion above on the DDREF it will be appreciated that although a dose-response for a particular cancer (e.g., leukaemia) might be assumed to curve upwards at moderate-to-high doses of low-LET radiation, this curvature is also assumed to be absent in the dose-responses for high-LET radiations because of considerations of radiobiological mechanisms at the microscopic level. Consequently, for a given type of cancer, the shape of the dose-response may differ between low-LET and high-LET radiations. Indeed, this is relevant to the RBE (and w_R) for a certain radiation because this will be dependent on the shape of the dose-response of the reference radiation – if the shape of the dose-response for the reference radiation (usually taken to be acutely delivered high-energy gamma radiation) is linear-quadratic then the RBE of a high-LET radiation with a linear dose-response will depend on the reference radiation dose. For the radiation weighting factor, w_R, the reference gamma radiation dose-response is assumed to be linear at low doses, and is related to the $RBE_{MAX,}$ that is, the maximum value of the RBE (that at low doses or low dose rates of the reference gamma radiation).

For particular exposures, such as inhaled radon and its alpha-particle-emitting decay products in underground mines, risk models have been developed directly from epidemiological studies of underground hard-rock miners (e.g., uranium miners), which reduces some of the uncertainty associated with applying a RBE between different types of radiation exposure. However, studies that produce reliable data from such exposures are rare.

5.3.5. Radiation doses

To estimate cancer risks the relevant dose of radiation received have to be known. Further, if the exposure is a protracted one then the simple cumulative dose might not be appropriate for the risk model if this depends on, say, time-since-exposure, when the distribution of the doses received over time is needed. Further, the risk prediction has to take into account the minimum latent period following a particular exposure during which an excess risk arising from that exposure will not be apparent.

Beyond these general considerations for risk modelling are the uncertainties associated with the doses received by an individual when applying risk models. A worker may have been monitored for exposure to radiation through, say, wearing a dosimeter, but the doses recorded from this monitoring are unlikely to be completely accurate, and this uncertainty will have varied with time. So, for example, neutron exposure in earlier years of operations in the nuclear industry might not have been

monitored, or not monitored accurately. This may involve the need for doses to be reconstructed, which will be an uncertain procedure to an extent that will vary depending on the circumstances[93].

One particular aspect of dose uncertainty involves internal doses received from intakes of radionuclides. For short-range radiations emitted from deposited radionuclides, direct measurement of doses is not usually possible and tissue-specific doses have to be inferred from bioassay measurements such as urinalysis. For some exposures, such as the dose to the lung received from short-lived radon decay products, doses have to be reconstructed from an assessment of how much radioactive material has been inhaled. For other circumstances, such as an insoluble compound of long-lived plutonium deposited in the lung, urinalysis is of limited direct value because the lung dose will then depend upon the assumed solubility of the compound in the lung and therefore what fraction of the deposited material has passed into blood, potentially deposited in other (systemic) tissues, and is then being excreted in urine.

An important distinction between radiation doses received from sources external to the body and those received from internally deposited radionuclides is that the former may be received briefly, such as during an atomic-bomb explosion, whereas the latter may be received protractedly if the radionuclide is physically long lived and also resides for some characteristic time within the body. Therefore, following the intake of a given quantity of a radionuclide, the dose accumulated will depend on the length of the period following the intake, and risk modelling has to take account of the dose actually received over time from deposited radionuclides, which is an uncertain estimate. Note, therefore, that radiation protection quantities such as effective dose and committed dose are of limited value to the prediction of future risk in an exposed worker because it is the actual absorbed (and possibly RBE-weighted) doses to organs/tissues of relevance to the specific cancer under consideration that need to be estimated (along with modifying factors such as the age at which the dose was received).

A further difficulty with the doses received from internal emitters is that the radioisotopes of some elements distribute themselves heterogeneously between the tissues of the body, so that different tissues receive different doses from the intake. An example is plutonium, which if inhaled delivers a dose to the lung (that will depend upon the residence time in the lung and hence the solubility of the compound), and then preferentially deposits in the liver and bone surfaces, and is only slowly excreted from the body. It is the tissue-specific doses that are relevant to the risk of cancer consequent to the dose received from an internally deposited radionuclide, and these tissue-specific doses (and potentially the distribution of dose within a tissue) will possess various components of uncertainty.

Such considerations of dosimetry indicate that the uncertainties that are associated with dose assessments are greater under certain circumstances, and, in particular, when doses are received from radioactive materials taken into the body and irradiating tissues internally. These uncertainties have to be assessed when estimating the risks arising from intakes of radionuclides, and under certain circumstances these uncertainties can be considerable.

5.4. INFLUENCE OF OTHER FACTORS

Important co-factors, other than radiation, that may influence a particular individual's cancer risk are known to exist. Such co-factors include: any genetic pre-disposition to cancer development; lifestyle factors such as smoking status and alcohol intake; other occupational risk factors such as asbestos, chemicals, UV, biological agents, shift work; medical risk factors such as increased Body Mass Index(BMI), lack of exercise; and past medical conditions that may have been treated with chemotherapy or radiation, and diagnostic radiation procedures. Hereditary factors such as the

hereditary form of retinoblastoma, mutations in the ataxia telangiectasia gene are both associated with higher radio-sensitivity to cancer development.

The influence of smoking on solid cancer incidence among the LSS of atomic bomb survivors for the most recent follow-up period (1958-2009) has recently been published[66]. In this study, the joint effect of radiation and smoking were considered by applying multiplicative and additive ERR models and an additive excess rate (or excess absolute risk – EAR) model, but smoking level adjustment was found to exert little or no impact on the shape of the radiation related risk to dose response. Considering the LSS lung cancer risk however, a sub-multiplicative joint effect of smoking and radiation has been reported, i.e., the rate ratios for those with both smoking and radiation was reported to be less than the product of the main effects[94]. A latest analysis, however, provided evidence of an interaction for light to moderate smokers, which increased for moderate smokers and then decreased for heavy smokers[95].

5.5. CONCLUSIONS

This section has examined the uncertainties arising both from the production of the radiation-related cancer risk models and from the application of these risk models to particular circumstances of exposure. The assessment of uncertainties is complex because they derive from various sources in many ways. Uncertainties need to be estimated in any given evaluation of risk, but this process is unlikely to be straightforward. However, it is important to identify the major sources of uncertainty in any risk assessment so that at least a broad quantified estimate of uncertainty can be generated.

6. SUMMARY AND KEY POINTS

This section briefly reviews the material presented so far and summarises the key points.

Risk factors for cancer are summarised with special emphasis on radiation effects. The Japanese Life Span Study (LSS) has long been a major source of information to characterize the age, sex and other patterns of radiation-related risk. Importantly, the accuracy of lifetime risk projections will profit from a longer follow-up of the LSS in terms of how the risk varies with time since exposure for those exposed at younger ages. The shape of the dose response for cancer risk in different organs/tissues is best characterised by modelling the risk in the dose range from moderate to high acute doses because here the radiation-related excess risk of cancer is best distinguished from variations in the background risk. For the purposes of radiation protection, the linear no-threshold (LNT) dose-response model is adopted for exposures to low doses or low dose rates, which is a prudent and plausible model that appears to be a reasonable approximation to the underlying dose-response. For leukaemia a linear-quadratic response provided the best fit to LSS incidence and mortality data, while for solid cancers generally a linear dose-response fits the data best for most types of cancer (although radiobiological, and some epidemiological, evidence introduces the concept of the DDREF for solid cancers). Descriptive (empirical) models based on the LSS data have been developed by expert groups. A wealth of experimental knowledge on molecular and biological radiation effects continues to provide guidance, but still does not provide comprehensive knowledge for their roles in risk assessment.

Epidemiological evidence shows that there is a minimum latent period of about 2 years for leukaemia or about 5 years for solid cancers before a radiation-related cancer risk can be observed. To derive risk estimates at low doses or low dose rates a DDREF has been introduced to adjust downwards by an appropriate factor the estimates obtained from moderate-to-high acute doses. However, national and international expert committees provide different guidance on the preferred approach to adjustment. Results of examples that are presented can be adjusted to different DDREF values. Currently available descriptive models for radiation risk assessment have been published by various expert groups, and in the present TECDOC the models adopted are fitted to the LSS data for the incidence of solid cancers and of leukaemia (as carried out in ICRP Publication 103. Expert groups have yet to generate models based on the most recent leukaemia incidence data[55], and the recently published incidence data for all solid cancers combined have not been used because the issues surrounding the differences in the dose responses for males and females have yet to be resolved. Effect modifiers of the slope of the dose response include classical radio-epidemiological co-variables of sex, age at exposure and time since exposure/attained age, with the impact varying markedly between cancer sites. For lifetime risk projection the end-point of the incidence of all cancers, including all solid cancers (other than skin cancers) and all types of leukaemia, has been chosen; cancer mortality would have been an alternative end-point, but most current risk models are expressed in terms of cancer incidence, and weighting incidence by health detriment is a possibility. To transfer risk estimates from the LSS (a mid-20^{th} century Japanese population) to a hypothetical example population of a specified composition, a linear combination of equally weighted multiplicative and additive transfers has been used.

As a risk measure the attributable radiation risk per year (AR) has been chosen which can be converted into a lifetime attributable risk (LAR) after summation over a reasonably long time period. For comparison, the risk measures are also expressed as fractions of the baseline risk. The example calculations are based on scenarios of occupational exposure pertaining to two

relevant topics. The first set of examples is dedicated to employees who wish to be informed about their occupational radiation risk. In this case the recorded exposure history is applied to predict future risk expressed either as AR in each year after last exposure or as LAR. This set of examples includes the case of internal exposure to inhaled insoluble ^{234}U for which an excess cancer risk is only to be expected for the lung. To calculate estimates of LAR and maximal annual AR for lung cancer an LSS model is applied which, for simplicity, does not account for smoking behaviour. To obtain the radiation dose to the lung for this example dose conversion coefficients relating inhaled activity concentrations of ^{234}U to radiation dose have to be applied which are available online from the ICRP database. The second set of examples involves exposure planning and addresses questions of risk limitation for experienced employees with a given exposure history. Under a constraint of not exceeding a specified AR limit in any future year the appropriate radiation dose for the next year may be calculated for the purpose of the optimization.

The sources of uncertainties which can influence risk estimates based on the proposed methodology have been fully discussed and a quantitative consideration of the impact on risk estimates is considered in Annex II. In the main part of the publication, risk estimates in the example calculations are given as point values without confidence intervals. Risk estimates are inherently influenced by unavoidable statistical fluctuations of case counts in epidemiological studies. Assumptions about the shape of the dose response and the application of risk-effect modifiers can have a large influence on central risk estimates. However, incomplete understanding of radiobiological mechanisms may suggest the formulation of more complex dose responses. For low LET radiation the application of a DDREF is still under discussion and will contribute to risk uncertainties. Often epidemiological studies are not directly available for assessments of the target population and risk estimates have to be transferred from models based on the LSS. Transfer of risk between populations includes a number of implicit assumptions on the homogeneity of baseline cancer rates and dose responses which are approximations to reality. For personalized risk projections individual radio-sensitivity might play a role but is not taken into account by descriptive risk models applied to populations. In the definition of AR and LAR future baseline rates are included which are in principle not predictable. Although all different types of ionizing radiation are expected to raise cancer rates, for some types of radiation, epidemiologically based risk estimates for some cancer sites are not currently available. In order to produce dose responses for such radiation types without direct risk estimates, RBE factors are applied to obtain weighted absorbed doses applicable for risk modelling. The RBE values appropriate for some radiation types for some circumstances of exposure remain uncertain. Finally, radiation doses are themselves measured with various uncertainties, which differ for a number of reasons – for example, the measurement of neutron doses has improved with time because of improved dosimeters.

7. CONCLUSIONS AND THE WAY FORWARD

For workers exposed to different fields of ionizing radiation at their workplace prospective assessment of excess health risks is implicit in the application of ALARA to comply with principles of radiation protection. The health of workers is an important element of the management system of safety. Assessment of prospective radiation risks is essential for implementation of several fundamental safety principles of the IAEA[79], in particular, the principles of "Justification of facilities and activities", "Optimization of protection" and 'Limitation of risks to individuals". The main results and conclusions of the TECDOC are summarized below.

The TECDOC concludes that the LSS is a major source of information on dose-response relationship and on the age and sex patterns of radiation-related risk. For solid cancers generally a linear dose-response fits the LSS data best while a linear-quadratic model provided the best fit for leukaemia to LSS incidence and mortality data, although recent findings for solid cancer incidence are more equivocal and difficult to interpret[66].

The characteristics of currently available descriptive (empirical) models suitable for application in the calculation of prospective cancer incidence lifetime risk for occupationally exposed individuals have been reviewed. Such models provide estimates for the excess risk per unit dose, with risk effect modification by sex, attained age and age at exposure or time since exposure. Although many different models exist and are being regularly updated in new scientific publications, some emphasis is placed here on the excess risk models used to calculate radiation related lifetime cancer risks in ICRP Publication 103. These risk models were applied in the examples of lifetime cancer risk quantities in calculations presented here and this choice was based on the purpose of achieving consistency with the current radiation protection guidelines from ICRP. For the purposes of radiation protection, it is recommended here to adopt the ICRP recommendation of applying the LNT model for low doses or low dose rates.

The justification principle suggests the comparison between prospective radiation risks and supposed benefits from facilities or activities. Because justification decisions are taken at the level of government or regulatory body, the collective or average risk estimates are needed in this case.

Risk estimates based on individual doses are important for implementation of principles of optimization and limitation of risks to individuals. The IAEA emphasizes that these two principles have to be used concurrently: "because dose limits and risk limits represent a legal upper bound of acceptability, they are insufficient in themselves to ensure the best achievable protection under the circumstances, and they therefore have to be supplemented by the optimization of protection. Thus, both the optimization of protection and the limitation of doses and risks to individuals are necessary to achieve the desired level of safety "[79]. The examples in Section 4 show how dose constraints can be derived from given risk constraints.

The TECDOC has also examined the uncertainties arising both from the production of radiation-related cancer risk models and from the application of these risk models to particular circumstances of exposure. The assessment of uncertainties is complex because they derive from various sources in many ways. It is concluded that uncertainties need to be identified and estimated in any given evaluation of risk, but it is acknowledged that this process is unlikely to be straightforward.

Prospective cancer risk assessment for workers occupationally exposed to ionizing radiation is a useful tool to assist employers, registrants and licensees and others in making decisions on occupational radiation protection and in controlling the exposures of workers. The management of radiation and nuclear facilities is encouraged to choose an appropriate methodology and tools to assess the prospective cancer risk from exposure to radiation.

Individual exposure data of workers are essential for cancer risk assessment. It is important to establish a national system for individual monitoring of occupational exposure and record keeping in accordance with the requirements in GSR Part 3 to ensure their proper use in radiation protection and safety and to avoid potential misuse of these data.

The assessment results need to be handled with prudence and sensitivity to avoid misinterpretation and discrimination.

Further research on the mechanism of causation for radiation induced cancer, development or improvement of the methodologies and risk models will generally tend to reduce the uncertainty in the risk assessment. Most importantly, more coordinated national, regional and global epidemiological studies on cancer risk due to ionizing radiation are encouraged to be conducted to provide sound scientific basis for the assessment.

Development and use of the easily accessible tools based on ICRP recent publications for calculating the absorbed dose rates of different organs due to internal exposure or external exposure will be helpful for the risk assessment.

In conclusion, the present TECDOC outlines a methodology for prospective assessment of cancer risk for workers occupationally exposed to radiation. The methodology is based on radiation risk modelling according to experts and as considered by various other expert groups. This publication provides a flexible framework, which can be updated according to new insights in radiobiology, risk models and epidemiological data, and a tool for the management of occupational exposure and the assessment of potential risks arising from exposure to radiation in the workplace.

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ANNEX I. THE ARMIR SYSTEM FOR MONITORING RADIATION RISK OF OCCUPATIONAL RADIATION EXPOSURE

The ARMIR system is used to assess cancer risks due to occupational exposure in the Russian nuclear industry. It was developed by the State Corporation "ROSATOM" together with the Russian National Commission on Radiological Protection[I-1][I-2][I-3].

The ARMIR system is designed on the basis of principles and methods for calculation of radiation risk, described in this publication. When creating the system, the applicability of risk models based on the Japanese cohort of atomic bomb survivors for Russian nuclear workers was substantiated. Algorithms for calculation of various radiation risk metrics for occupational exposure have been developed.

The first version of the system was commissioned in 2006 at the Production Association "Mayak". Currently, the system covers more than a hundred organizations of "ROSATOM". Radiation safety services of these facilities use specialized website ARMIR+ or stand-alone software (Fig. A-1) in their work.

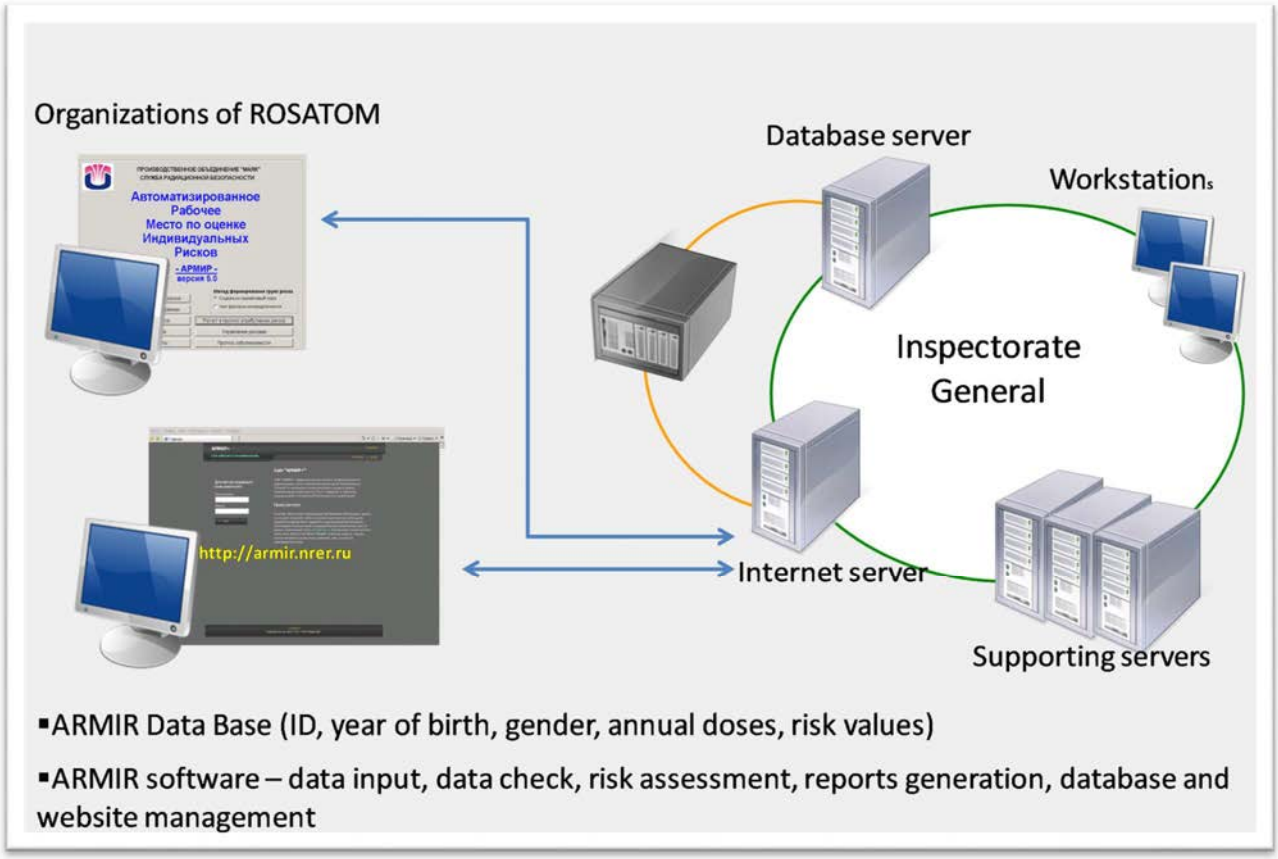

Fig. A-1. The ARMIR system structure

ROSATOM Inspectorate General provides management of the ARMIR system. One of the important functions of management is to ensure the quality and completeness of the input data, primarily individual dosimetry data.

Every year, the system receives information about more than sixty thousand employees of ROSATOM. The absolute majority of employees work in conditions of acceptable

occupational risk. For 1.21% of the number of employees individual risk exceeded the regulatory level of 10^{-3}. The high-risk group comprises mainly veterans of the industry, whose average age is more than 60 years[I-4].

Over the last years, the average individual radiation risk across ROSATOM did not exceed 8% of the regulatory limit (Table A-1), while the maximum individual risk has been decreasing steadily.

TABLE A-1. RESULTS OF RADIATION RISK MONITORING

ROSATOM's divisions	**2015**	**2016**	**2017**
Power Engineering Division	$1.2*10^{-4}$	$1.2*10^{-4}$	$1.1*10^{-4}$
Fuel Division	$3.1*10^{-5}$	$2.8*10^{-5}$	$2.7*10^{-5}$
Fuel Division	$5.0*10^{-5}$	$4.4*10^{-5}$	$4.5*10^{-5}$
Mining Division	$2.0*10^{-5}$	$2.0*10^{-5}$	$2,3*10^{-5}$
Life Cycle Back-End Division	$6.8*10^{-5}$	$4.3*10^{-5}$	$4.4*10^{-5}$
Innovation Management Unit	$1.0*10^{-4}$	$9.2*10^{-5}$	$9.1*10^{-4}$
Mechanical Engineering Division	$8.5*10^{-5}$	$6.2*10^{-5}$	$5.1*10^{-5}$
Engineering Division	-	$6.0*10^{-6}$	$2.4*10^{-5}$
ROSATOM	$7,9*10^{-5}$	$7,0*10^{-5}$	$7,0*10^{-5}$

Employees are informed about their occupational risks in line with established in Russia terms and ethical standards. Statistical data on the current radiation risks in nuclear industry are published in the Annual Public Report of "ROSATOM" and in other media.

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ANNEX II. THE ARMIR SYSTEM FOR MONITORING RADIATION RISK OF OCCUPATIONAL RADIATION EXPOSURE

Three different software tools have been applied here to illustrate the types of uncertainties inherent in the calculation of LAR and LBR for the following specific example: male or female adults exposed to a single uniform whole-body equivalent dose of high-energy gamma radiation of 20 mGy, assumed to be received at the age of 40 years in the early 21st century.

The European Union-CONFIDENCE tool

The European Union-CONFIDENCE (Coping with uncertainty for improved modelling and decision making in nuclear emergencies) project ended in December 2019 and funded the development of a health risk assessment (HRA) software (the EU-CONFIDENCE software tool) designed to be immediately available after a nuclear accident. The tool is based on the HRA methodological framework for assessing cancer risks after the Fukushima accident as developed and recommended by a WHO expert group[II-1][II-2] and by the German software tool ProZES[II-3][II-4]. This EU-CONFIDENCE tool has already been described in detail in the papers of Walsh et al in 2019 and in 2020[II-5][II-6].

The tool calculates the incidence risks of all solid cancers, leukaemia, breast cancer and thyroid cancer, per unit relevant organ dose, from contemporary models of radiation risk and for some modern European populations, currently Germany, four Nordic countries and Switzerland and can be extended to include other countries.

An important feature of the tool is that the calculated risks can now be given with confidence intervals from a full mathematical treatment of the following uncertainties in:

1. Radiation excess risk model parameters; sampled from a multivariate normal distribution using best estimates of all the model fit parameters, including those for the model baseline, and parameter covariance matrices.

2. A factor for apportioning additive and multiplicative radiation risk contributions; sampled from a uniform distribution.

3. Dose rate effects; sampled from a lognormal distribution with a geometric mean of 1.0 and geometric standard deviation varying as a linear function of dose rate with value of 1.5 at dose rate 1.5 mGy d^{-1} and value of 1 at dose rate equal to or higher than 6 mGy h^{-1}. Correspondingly, the median dose rate correction factor does not change but results in a higher variance at lower dose rates.

4. Minimum latency periods of 2 years for leukaemia and 5 years for all solid cancer; with uncertainties sampled from a sigmoid distribution.

5. Age specific cancer incidence rates; sampled from Poisson distributions.

6. Doses; sampled from a choice of different mathematical distribution forms.

The CONFIDENCE tool has been applied here to illustrate the types of uncertainties inherent in the calculation of LAR and LBR for the specific example mentioned above. For the purposes of this application, fixed doses of 20 mSv organ dose were considered without uncertainty. The results are given in Table 1 and Figure A-2 below.

TABLE A-2. LIFETIME BASELINE RISK (%) AND LIFETIME ATTRIBUTABLE RISK (%) FOR ALL SOLID CANCER AND LEUKAEMIA FROM THE EU-CONFIDENCE PROJECT TOOL.

Country	Gender	All solid cancer	All solid cancer	Leukaemia	Leukaemia	All cancer
		LBR (%) (95% CI)	LAR (%) (95% CI)	LBR (%) (95% CI)	LAR (%) (95% CI)	LAR (%)
Germany	male	40.03 (38.84 - 41.23)	0.24 (0.13 - 0.34)	1.51 (1.26 - 1.80)	0.03 (0.00 - 0.07)	0.27 (0.16 - 0.38)
Germany	female	34.42 (33.29 - 35.54)	0.33 (0.25 - 0.44)	1.10 (0.90 - 1.34	0.02 (0.00 - 0.05)	0.35 (0.25 - 0.45)
Denmark	male	42.97 (38.40 - 47.85)	0.25 (0.13 - 0.35)	1.14 (0.50 - 2.36)	0.02 (0.00 - 0.07)	0.27 (0.15 - 0.39)
Denmark	female	38.08 (33.56 - 42.90)	0.34 (0.24 - 0.48)	0.80 (0.28 - 1.86)	0.02 (0.00 - 0.05)	0.36 (0.24 - 0.48)
Finland	male	42.97 (38.33 - 47.94)	0.25 (0.13 - 0.35)	1.14 (0.49 - 2.39)	0.02 (0.00 - 0.07)	0.27 (0.15 - 0.39)
Finland	female	38.08 (33.64 - 42.81)	0.34 (0.25 - 0.48)	0.81 (0.30 - 1.83)	0.02 (0.00 - 0.05)	0.36 (0.24 - 0.48)
Norway	male	46.20 (40.81 - 52.00)	0.26 (0.14 - 0.37)	1.23 (0.48 - 2.70)	0.02 (0.00 - 0.07)	0.28 (0.16 - 0.40)
Norway	female	40.00 (34.79 - 45.59)	0.36 (0.26 - 0.50)	0.85 (0.26 - 2.10)	0.02 (0.00 - 0.05)	0.38 (0.26 - 0.50)
Sweden	male	46.70 (42.94 - 50.60)	0.27 (0.14 - 0.37)	1.28 (0.69 - 2.21)	0.03 (0.00 - 0.07)	0.30 (0.18 - 0.42)
Sweden	female	40.04 (36.39 - 43.83)	0.36 (0.26 - 0.50)	0.88 (0.41 - 1.67)	0.02 (0.00 - 0.05)	0.38 (0.26 - 0.50)
Switzerland	male	39.82 (35.88 - 44.00)	0.25 (0.13 - 0.37)	1.40 (0.73 - 2.51)	0.03 (0.00 - 0.07)	0.28 (0.16 - 0.41)
Switzerland	female	31.04 (27.50 - 34.79)	0.33 (0.24 - 0.42)	0.93 (0.42 - 1.84)	0.02 (0.00 - 0.05)	0.35 (0.26 - 0.44)

The population data pertains to the years 2010-2016 for the Nordic countries, 2010-2014 for Germany and 2015 for Switzerland. NOTE the all cancer results are not calculated directly in the tool but the all solid cancer and leukaemia tool results have been added together post tool application, with error propagation to determine the 95% confidence intervals.

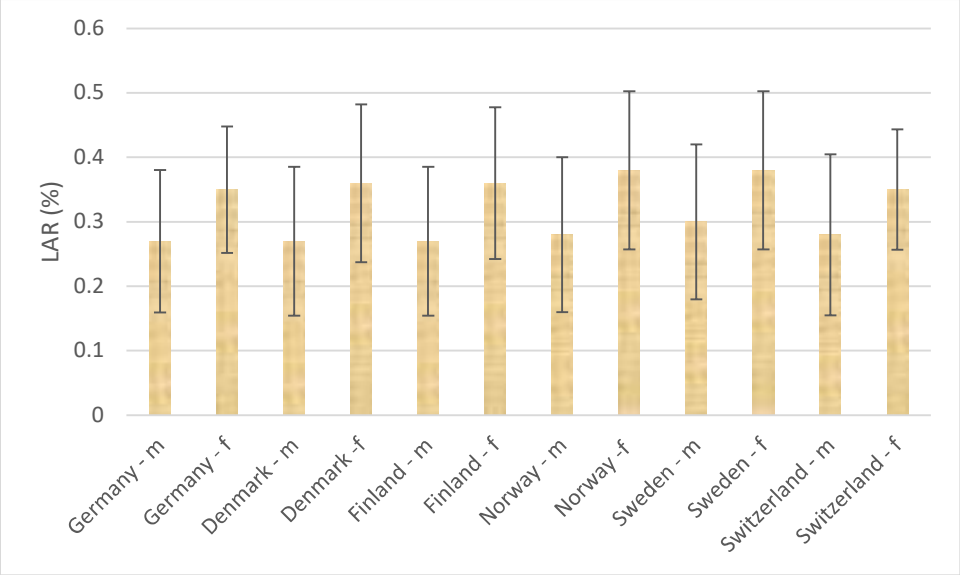

Fig. A-2. LAR (%) with 95% confidence intervals for all solid cancer + leukaemia, for several European populations calculated with the CONFIDENCE tool.

Note: The tool does not automatically give the all cancer LAR which has been calculated here from the all solid cancer LAR attributable to 20 mGy colon dose plus the leukaemia LAR attributable to 20 mGy red bone marrow dose, and added together assuming that these two organ doses are equal (error bars were calculated post tool results, from the all solid cancer errors and leukaemia errors from the actual tool results, using error propagation).

The Radiation Risk Assessment Tool (RadRAT)

The Radiation Risk Assessment Tool (RadRAT) has been developed by the US National Cancer Institute (NCI) https://radiationcalculators.cancer.gov/radrat/[II-7]. The online RadRAT module calculates the lifetime excess risk of cancer incidence following the receipt of user-specified absorbed doses of high-energy gamma radiation to particular organs/tissues, received acutely or chronically. (Note that it would be possible to input absorbed doses of other types of radiation suitably weighted by appropriate relative biological effectiveness values with high-energy gamma radiation as the reference radiation.) The RadRAT user specifies the sex of the exposed person and the age-at-exposure in particular calendar years, and a number of population baseline mortality and cancer incidence rates can be selected. The excess and baseline risks of cancer incidence over the remaining lifetime from a specified calendar year are output.

The risk models used by RadRAT are slight modifications of the cancer-site-specific risk models presented in the BEIR VII Report published by the US National Academies in 2006[II-8] (see https://radiationcalculators.cancer.gov/radrat/diff/). The modifications include the replacement of a step function to represent the minimum latent period of a cancer by an S-shaped function; the mid-points of the S-shaped functions are 2.25 years for leukaemia, 5 years for thyroid cancer and 7.5 years for other solid cancers. In addition to the eleven cancer-site-specific (slightly modified) BEIR VII models, RadRAT includes a further eight cancer-site-specific risk models developed by the US NCI from the same Japanese LifeSpan Study (LSS) cancer incidence database as used by the BEIR VII Committee.

As well as mean lifetime excess cancer risks, RadRAT also generates 90% uncertainty intervals for the lifetime risks. This is achieved by using the uncertainty distributions of the parameters

defining the cancer-site-specific risk models (e.g., the dependence of risk on sex and age-at-exposure) presented in the BEIR VII Report and the additional models generated by the NCI, to produce an overall uncertainty distribution on the risk under consideration. Further, uncertainty distributions are adopted for the minimum latent period, the transfer of risk from an exposed mid-20th century Japanese population to another population (i.e., the mixture of cancer-site-specific ERR and EAR risk models derived from the LSS), and for the Dose and Dose Rate Effectiveness Factor (DDREF) – note that the central value of the DDREF for solid cancers is taken to be 1.5, as inferred by the BEIR VII Committee, rather than the fixed DDREF for solid cancers of 2 used by the ICRP in its 2007 Recommendations (see https://radiationcalculators.cancer.gov/radrat/diff/). It is possible for a user to input uncertainty distributions associated with the doses input to RadRAT, and these dose uncertainty distributions are incorporated in the overall uncertainty output by RadRAT.

The RadRAT module is designed principally for computations based upon US population mortality and cancer incidence rates for recent years. However, a limited number of other population data are available as user-specified selections. RadRAT cannot explicitly address the uncertainty arising from the nature of the risk models themselves – using the same database, the BEIR VII Committee and, for example, UNSCEAR derived different cancer-site-specific risk models. This indicates a source of uncertainty, i.e., uncertainty associated with the form of the risk models, that is not directly derived by RadRAT, but could be assessed by running different risk models for the same input conditions.

The figure below illustrates the central estimates and 95% uncertainty intervals associated with lifetime cancer risks output by RadRAT. The RadRAT runs are based on a male or female from a number of different populations, born in 1980 and exposed to 20 mGy penetrating gamma radiation at the age of 40 years in 2020, although to illustrate the effect of age-at-exposure, RadRAT runs have also been conducted for a US male or female born in 2000 and exposed to 20 mGy at the age of 20 years in 2020. An acute exposure is assumed, although the difference in acute or chronic exposure at a dose of 20 mGy of gamma radiation is very small, but not zero in RadRAT because of the uncertainty distribution assumed for the DDREF (which has a point estimate of 1.5). The exposure is assumed to be a uniform whole-body exposure so that all tissues receive the same dose, and the dose is assumed to be a fixed value (i.e., 20 mGy) with no associated uncertainty. The lifetime excess risk attributable to the exposure is expressed in RadRAT output as the number of excess cases of cancer per 100,000 persons, but is shown in the figure below as the number of excess cases per 100 persons, i.e., the LAR expressed as a percentage, where the cases of cancer are for all types of cancer. Uncertainties are expressed as 95% uncertainty intervals (generated by multiplying the widths of the 90% uncertainty intervals output by RadRAT by a factor of 1.19). The various examples presented in the figure show the variation of lifetime risk with different population mortality and cancer incidence data (for the USA, Japan, Brazil and France). An example for a US population is also given for a male and female born in 2000 and receiving an acute dose of radiation of 20 mGy at the age of 20 years in 2020, to illustrate the influence of age-at-exposure on lifetime risk estimates, i.e., by comparing with the results for a US male or female exposed at the age of 40 years in 2020.

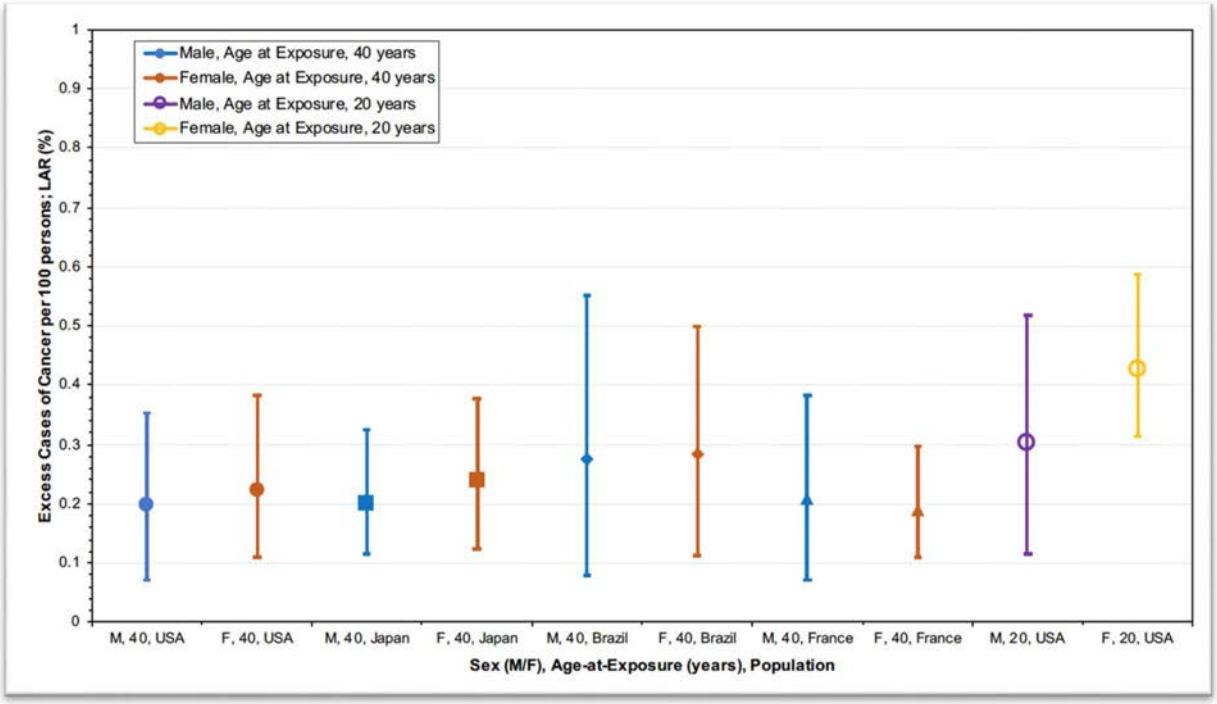

Fig. A-3. Lifetime risk of developing cancer following the receipt of an acute uniform whole-body absorbed dsoe of 20 mGy gamma radiation in 2020 by a person of a specific sex, age-at-exposure and population. Error bars are 95% uncertianity intervals. RadRAT Version.

The ARMIR system estimates

Table A-3 and Table A-4 present lifetime radiation and baseline risks (Eq. 4.9 and 4.10) of cancer incidence for Russian males and females exposed to one whole body dose of 20 mSv at the age of 40 years. The ICRP risk models in the ICRP Publication 103 for all solid cancers and leukaemia were used for calculations, with the DDREF=1 and Russian baseline rates for the 2017 year, averaged over all subjects of the Russian Federation. Latency periods in risk models were defined as 2 years and 5 after exposure, for leukaemia and solid cancers, respectively. Confidence intervals (95% CI) for lifetime attributable risk (LAR) represent uncertainty propagation from coefficients of risk models (excluding DDREF, latency period and risk transfer weighting factors), geographical variations (over all subjects of the Russian Federation) in cancer baseline rates and dose uncertainties defined by lognormal distributions with different geometric coefficients of variation (GCV).

TABLE A-3. LIFETIME ATTRIBUTABLE RISK (LAR, %) AND LIFETIME BASELINE RISK (LBR, %) OF CANCER INCIDENCE FOR RUSSIAN MALES EXPOSED TO ONE WHOLE BODY DOSE OF 20 MSV AT THE AGE OF 40 YEARS.

Risk of cancer incidence, %	**Dose uncertainty (GCV), %**	**Mean value**	**95% CI**	
LAR	0	0.164	0.158	0.171
LAR	15	0.164	0.126	0.208
LAR	30	0.164	0.098	0.256

Risk of cancer incidence, %	Dose uncertainty (GCV), %	Mean value	95% CI	
LAR	50	0.164	0.067	0.313
LBR		28.230	26.793	29.652

TABLE A-4. LIFETIME ATTRIBUTABLE RISK (LAR, %) AND LIFETIME BASELINE RISK (LBR, %) FOR CANCER INCIDENCE FOR RUSSIAN FEMALES EXPOSED TO ONE WHOLE BODY DOSE OF 20 MSV AT THE AGE OF 40 YEARS.

Risk of cancer incidence, %	Dose uncertainty (GCV), %	Mean value	95% CI	
LAR	0	0.283	0.273	0.294
LAR	15	0.283	0.217	0.361
LAR	30	0.283	0.166	0.441
LAR	50	0.283	0.115	0.548
LBR	-	27.730	25.910	29.570

In average, the estimated LAR values for Russian males and females are considerably lower than corresponding quantities for European and American populations. This result can be explained by the comparatively lower survival time in Russia.

Summary

The results from the different software tools applied here illustrate the sources of uncertainties inherent in the calculation of LAR and provide broadly consistent central estimates for the risks. The example calculations are for a male and female born in 1980 and receiving a whole-body dose of 20 mGy (of low-LET radiation) in 2020 at the age of 40 years. The EU-confidence tool central LAR estimates range between 0.27 and 0.30% and 0.35 and 0.38% for males and females respectively. The corresponding RadRAT risks ranged between 0.20 and 0.28% and 0.23 and 0.29% for males and females respectively. Similarly, the equivalent ARMIR results (without including dosimetric uncertainties) were 0.16 and 0.28% for males and females respectively.

The EU-confidence results were generally systematically higher than the RadRAT results, primarily due to the application of different choices in central estimates for the DDREF of 1 in EU-CONFIDENCE tool and ARMIR system and 1.5 in RadRAT. The variation in risks and the sizes of their confidence intervals in the tables and figures given above, illustrate the variations obtained for different choices of: populations (with their variability in life expectancy and differences in characteristic patterns of cancer incidence), the risk models adopted, and which uncertainties to include and their treatment (e.g., the central estimate of DDREF and the associated uncertainty distribution). Note that for simplicity, in the examples used the doses are taken to be fixed with no associated uncertainties, which will not occur in

real life. Under some circumstances, such as the heterogeneously distributed doses received over protracted periods from intakes of radionuclides, the uncertainties on doses can be substantial.

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ABBREVIATIONS

ARF	Attributable Risk Fraction
BEIR	Committee on the Biological Effects of Ionizing Radiation
BR	Baseline risk
BRCA	Breast cancer susceptibility protein
CLL	Chronic lymphocytic leukaemia
CT	Computed tomography
DDREF	dose and dose-rate effectiveness factor
DREF	dose-rate effectiveness factor
EAR	excess absolute risk
EAR	Excess absolute risk
ER	Excess risk
ERR	excess relative risk
Gy	Gray
HPV	Human papilloma virus
ICD10	10th revision of the International Statistical Classification of Diseases
ICRP	International Commission on Radiological Protection
ILO	International Labour Organization
INWORKS	Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers
LAR	Lifetime Attributable Risk
LARF	Lifetime Attributable Risk Fraction
LBR	Lifetime Baseline Risk
LDEF	low dose effectiveness factor
LET	Linear energy transfer
LNT	Linear no-threshold (model)
LSS	life span study of Hiroshima and Nagasaki survivors of the A-bombs

NCI	National Cancer Institute of United States of America
NMSC	Non-melanoma skin cancer
PUMA	Pooled uranium miners analysis
RASSC	Radiation Safety Standards Committee
RBE	Relative biological effectiveness
RERF	Radiation Effects Research Foundation
ROSATOM	Atomic State Corporation of Russian Federation
SSK	German Commission on Radiological Protection
Sv	Sievert
TLD	Thermoluminescent dosimeters
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WHO	World Health Organization

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