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D2.2 EURADOS SRA topics relevant to medical radiation protection research

Lead partner:	Ruđer Bošković Institute, RBI
Author(s):	Željka Knežević (RBI), M. Majer (RBI), Filip Vanhavere (SCK CEN), Lara Struelens (SCK CEN), Jean Francois Bottellier (IRSN)
Contributing AB members and external experts:	Elefteria Carionu (EEAE), Werner Ruhm (Helmholtz Zentrum)
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Introduction

The aim of task 2.2, led by RBI, was to summarise the ideas from the EURADOS platform and from the EURADOS SRA in the context of medical applications of ionising radiation and the corresponding radiation protection. The goal was to prioritise research topics and identify missing topics linked with medical radiation protection research. The summary of challenges and research lines from EURADOS will feed into the EURAMED rocc-n-roll SRA and the roadmap to be established in WP6. Priorities and missing research topics from EURADOS and other relevant stakeholders will serve for creating document on future research needs integrating views and identifying synergies in the fields for medical application of ionizing radiation and radiation protection.

The work in Task 2.2 was carried out by a panel who analysed the EURADOS SRA. The panel had several meeting and discussions of the EURADOS SRA in order to identify dosimetry aspects and related research topics important for medical applications of ionizing radiation and medical radiation protection research.

In order to collect views from the broader community, in April 2021, the panel organized a voting of the Challenges and Research Lines described in EURADOS Report 2020-04 on "Visions for Radiation Dosimetry over the Next Two Decades - Strategic Research Agenda of the European Radiation Dosimetry Group: Version 2020" in order to identify topics linked with medical radiation protection research. The voting involved EURADOS Voting Members (VMs), EURADOS Council Members (CMs) and EURADOS Working Group (WG) Chairs.

Based on a joint evaluation of the votes, a ranked list was established by the panel members.

A document reflecting the resulting synthesis of the EURADOS priorities was prepared by the panel. The following document summarises the ranked 'Challenges' and corresponding 'Research Lines' with special emphasis on their relevance for medical applications. And radiation protection.

Challenge 1: To improve patient and ambient dosimetry in radiotherapy

Approximately half of all cancer patients will receive external beam radiotherapy at some point in their illness. The development of dosimetry techniques and the measurement of doses, particularly to radiosensitive organs, is an important prerequisite for providing robust dosimetry data for epidemiological studies and, ensuring that patients receive optimum treatment.

This challenge applies to the developing array of radiation types used in modern radiotherapy, including photons, protons, other particle/ion beams and boron neutron capture therapy (BNCT).

Research Line 1.1 Dosimetry for proton and ion beam radiotherapy

Research and development of dosimetry methods and novel dosemeters; new 2D and 3D detectors and associated electronics and instrumentations for high dose rate scanning beams and ultra-high dose rates in FLASH therapy and laser induced proton beams are needed. Future dosimetry of particle beams should be based on the capabilities to individually determine the position of each primary particle e.g., proton or carbon ion and its LET (energy) for realistic beam intensities.

New dosimetric techniques to measure discrimination between neutron and photon components of the secondary irradiation fields should be developed.

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Research Line 1.2: Dosimetry during treatment and for quality assurance of the treatment process, including inter-centre audit programmes

On-line validation of dosimetry during treatment and to support Quality Control (QC) and in vivo dosimetry (IVD) requires the development of dosimetry techniques for checks at all stages of the radiotherapy dosimetry chain.

In the area of small field and edge-of-field dosimetry there is a need to investigate the performance characteristics of new detectors for both photon and ion RT and also to compare codes of practice and inter-centre applications.

Further development of realistic anthropomorphic phantoms, especially paediatric, is still needed for dosimetric verifications.

Harmonisation of the RT dosimetry throughout Europe should be improved through development of inter-centre audit and intercomparison programmes for emerging treatments (e.g., proton and ion beam radiotherapy) to complement existing programmes for photon radiotherapy.

With the development of clinical MRI-Linac combinations, work on the performance of detectors in a magnetic field and effects of magnetic fields in both reference and relative radiotherapy dosimetry is needed.

Research Line 1.3: Dosimetry in support of radiation effect research and epidemiological studies

For more accurate input to epidemiological studies, it is necessary to develop and harmonize dosimetry techniques for the measurement and estimation of the total dose to critical organs from all radiation sources (therapeutic and diagnostic) to patients receiving radiotherapy. A metrological framework for dose additivity from different radiation sources needs to be developed.

Challenge 2: Establishment of reliable patient dosimetry in CT and interventional radiology examinations

To correctly estimate the doses and risks an improved system of dose calculation including dose distributions within organs is needed based on actual patient anatomy for adult and paediatric patients.

A reliable dose estimation is needed to improve the use of diagnostic reference levels (DRLs), achievable dose levels (ADLs) and skin dose alert (trigger) levels for optimization of patient doses, improved accuracy of skin and other organ doses, and improved accuracy of population dose estimation.

Research Line 2.1: Patient-specific dose estimates in CT imaging

Due to the advances in detector technology (e.g., single-photon counting, spectral acquisition with pixelated detectors, new detector materials) approaches to image quality assessment and dose optimization together with personalized patient dosimetry must be reconsidered in cooperation with medical, dosimetry and metrology experts.

For patient-specific dose estimates (near) real-time solutions to computationally assess and store the patient's organ doses and dose distributions in anatomically realistic settings must be developed and standardized so that the data is available across systems. Comprehensive phantom libraries are needed to complete the computational phantom outside the imaged region. Also, uncertainty estimates for the computed organ doses should be considered.

Research Line 2.2: Skin and organ doses in interventional radiology and cardiology

To prevent skin injuries in interventional radiology and cardiology skin dose mapping software packages are needed to show a real-time dose distribution at patient's skin and to provide

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more user-friendly and accurate setting of alert levels than presently available. Independent, scientific validation of software is largely missing and needed.

There is still a need to harmonize nomenclature and investigate the feasibility of trigger levels for maximum skin dose during fluoroscopically guided interventional procedures. The use of online and offline software for dose recording will provide help in setting ADLs and DRLs.

Obtaining organ doses that should be implemented in any dose mapping software will be the first step to evaluate the overall exposure of a patient (by all modalities) and therefore its corresponding risk.

Research Line 2.3: Multidisciplinary data collection for personalized dosimetry

Big data, deep learning, increased computational power and availability of comprehensive patient imaging data steer toward personalized dosimetry and consideration for individual radiation sensitivity. New approaches are needed to optimize the imaging protocols on an individual patient basis and to assess the reliability and relevance of the data in a multidisciplinary environment.

Challenge 3: To develop more accurate and real-time external personal dosimetry for workers

Currently, more than one million workers are exposed to ionising radiation in Europe, many of which are working in medical applications. The exposure situations are very diverse in terms of type and energy of radiation, as well as regarding the location and size of the body part being exposed (whole body, part of the body, extremities, eye lens). The challenge is to provide reliable, accurate and real-time personal dosimetry for workers occupationally exposed.

Research line 3.1: "Real-time" dose monitoring of workers

Recently, new dosemeters associated with connected technologies have become available opening up new opportunities in the field of on-line (real time) personal dosimetry. Such systems should be more developed and adapted to the needs and constraints of personal monitoring. In addition, the research in the domain of fast Monte Carlo calculations applicable to individual monitoring should be more developed. The development of real-time individual dosimetry applications based on computer simulations and tracking devices, in addition to conventional "physical" individual dosimetry, would be of great interest.

Research line 3.2: Development of more accurate dosimetry for specific tissues and organs, especially in case of heterogeneous field or partial shielding

Eye lens dosemeters should be further developed taking into account particular ergonomic aspects. Moreover, from an operational point of view, there is a need to propose correction factors for the position of the dosemeter and for the attenuation of the eye protection, when used. Data are still needed for eye lens doses of workers in different fields such as those present in medical applications.

Extremity dosemeters currently available on the market for extremity monitoring do not show sufficient performance at low energies, are not sufficiently ergonomically adapted and, to date, there is no active system that meets the requirements of regulatory dosimetry monitoring. Besides, the exposure of the extremities in nuclear medicine is an ongoing topic of research. The introduction and/or increased use of new radionuclides (such as Lu-177 or Ga-68) poses additional problems for personal dosimetry and in particular with regard to extremity doses. The impact of such new radionuclides on the adequate assessment of extremity doses, as well as on practices from the radiation protection point of view, should be investigated.

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In the case of a heterogeneous field or partial shielding, like in interventional radiology, the operator's head, trunk, waist, upper and lower extremities are exposed to different scattered radiation fields. This implies that the position of the dosemeter on the neck, the trunk, the shoulder, or waist, when employed for the whole-body dose assessment, can have an effect on the accuracy of the evaluated doses. A study investigating the sensitivity of the dose assessment with respect to the dosemeter positioning and the influence of potential partial shielding can provide relevant information on the dose accuracy.

Challenge 4: To quantify correlations between track structure and radiation damage

Track structure has been proven to show a strong correlation with the induction of early biological effects, particularly the occurrence of DNA single and double strand breaks. As later biological endpoints also show dependence on radiation quality, there should also be a correlation of track structure characteristics and the probability of inducing these later effects, such as chromosomal aberrations or cell death. This fundamental knowledge will have a direct impact in addressing current optimization criteria in diagnostics, radiation therapy and radioprotection, such as "biologically weighted" doses delivered in hadron therapy and dose calculation in inhomogeneous irradiations such as those of short-range α-and β-emitters used in nuclear medicine.

Research line 4.1: Studies on the geometrical correlation of energy deposition and cellular damage

These studies aim at overlaying particle tracks with cells under controlled geometrical conditions in combination with radiobiological assays to quantify a chosen biological endpoint performed on the irradiated cells for a particular radiation quality. Statistical cross-analysis would then be carried out to identify, for instance, correlations between results for a particular biological endpoint for different radiation qualities and nanodosimetric probability distributions for various target sizes.

Research line 4.2: Improvement of risk estimation models

The challenge of risk estimation for low dose exposures requires not only the initial track structure calculations, chemical and effect simulations: the cancer development processes should also be considered in the modelling to obtain an estimation of low dose risk. This can be optimized by combining track structure-based nano-dosimetry and biologically based mechanistic modelling and epidemiological data. This can provide insight into molecular dosimetry for understanding the dose-response relationship at low doses and low dose rates.

Research line 4.3: Research related to the use of high-Z nanoparticles in radiotherapy

Gold nanoparticles (GNPs) have been used as radiosensitizers in preclinical targeted radiotherapy. The enhanced absorbed doses in the vicinity of multiple GNPs at the cellular and molecular level need quality assurance that is often performed by Monte Carlo simulations. Furthermore, the radiobiological effects of GNPs shown in in vitro and in vivo experiments need extended Monte Carlo simulations with chemical effect modules as implemented, e.g., in the codes Geant4-DNA and PARTRAC. Another challenge is the observation of X-ray fluorescence released from GNPs irradiated by kilo-voltage x-ray.

Research line 4.4: Research on chemical aspects of the ionising radiation interactions with biological matter

The initial energy deposited by individual inelastic interactions of ionising radiation in biological targets results in early radio-induced damage following a series of complex chemical reactions. It is necessary to promote experiments and the development of simulation techniques that investigate issues, such as the role of oxygen in DNA damage enhancement and the

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identification and/or quantification of different scavenging species in the cell nucleus or cell environment and their impact on radiation damage.

Research line 4.5: Studies of temporal correlations of radiation interaction events

Physical and chemical interactions at the basis of biological radiation damage have different reaction times and, therefore, in the case of ionising radiation at low fluence rate, different events can be considered as independent: in other words, the physical and chemical interactions of one event are finished when the next event happens in the same volume. However, when high fluence rates are used, or in the case of photon irradiation at high dose rates or flash irradiations (Flash-RT), this simplified description has to be modified. While experiments quantifying the protective effect on normal tissue of Flash-RT can bring insight into such questions, they need to be performed using accurate dosimetry, which is non-trivial as current radiotherapy dosimetry protocols are not designed for such conditions.

Challenge 5.: Improving patient dosimetry in nuclear medicine

There is an increased development and use of radiopharmaceuticals (RPs) in Europe for treating cancer in the last few years and the number of molecular radiotherapy (MRT) clinical trials is expected to continue to rise in the future. Although an accurate knowledge of the radiation absorbed dose to critical tissues would provide a more effective targeted use of MRT, most treatments still follow the historical practice of administering a nominal activity of the RP (the “one size fits all” approach). It is essential that this problem is addressed, as there is an important focus to move towards personalised medical treatment.

Research Line 5.1: Internal dosimetry within pre-clinical development and evaluation of RPs emitting alpha, beta, and Auger radiation

As targeted alpha therapy (TAT) is gaining a lot of interest, there is an important need to further elaborate dosimetry models that are more representative for the realistic TAT applications. A non-uniform distribution of the radionuclides (e.g., due to heterogeneous target expression among cells) in combination with the short path length and high-LET of alpha (and Auger) radiation results in a non-uniform dose distribution even at cellular level. Accurate dosimetry on sub-organ level will tackle the issue of accurate quantitative imaging at different time intervals at sub-organ level and can be complemented with non-imaging methods, such as activity determination in, for example, blood samples. Currently, there is a lack of standardised protocols for pre-clinical testing and quantitative imaging. Additionally, accurate dosimetry requires the development of appropriate and new computational models of organs/tissues of interest, using imaging modalities (e.g., µCT and µMRI) with appropriate image contrast and spatial resolution to distinguish between the different organ substructures.

In the case of using RPs labelled with alpha emitters, the recoil energy of recoiling daughters is so high that the chemical bonds of the daughter molecule with the targeting vehicle will be lost. Imaging of the parent nuclide is usually based on imaging the gamma-emitting daughter molecules, but the difference in biokinetics is an important concern hampering accurate dosimetry.

Tumour and normal tissue dose-responses for radionuclide therapy have not been studied as extensively as within external beam radiotherapy, the latter one generally described by a linear-quadratic (LQ) model. As the relationship between administered activity, the absorbed dose and biological effects are not yet well understood, more work is needed on the determination of dose-response relationships within radionuclide therapy. This requires both good biology and dosimetry research and will provide fundamental data that might help treatment planning in NM.

Research Line 5.2: Optimization of patient dose in diagnostic nuclear medicine

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The patient dose to diagnostic radiopharmaceuticals is estimated according to the MIRD/ICRP formalism schema for internal dose calculations by use of the biokinetic data and S-values for reference persons. However, the biokinetic data of many radiopharmaceuticals commonly used are obsolete, and the S-values are calculated by the stylized computational phantoms. With the advanced development of image acquisition by PET and SPECT, new precise biokinetic data, especially the rare data for children and adolescents at optimal time points can be acquired and can be used for dose optimization in paediatric nuclear medicine. In addition, compartmental models based on the relevant physiology may be developed in comparison to the fitting and integration procedures for dose quantification and further risk estimation for age-independent reference persons.

Research Line 5.3: Implementation of internal dosimetry in clinical MRT

The European Association of Nuclear Medicine (EANM) has issued guidelines for absorbed dose uncertainty assessment in nuclear medicine. However, the EANM guidelines do not provide guidance how to identify the influential parameters in the dose calculation chain. Therefore, development of a global sensitivity analysis (GSA) approach is needed to assess the crucial parameters influencing the uncertainties and then to work on improvement of protocols. Furthermore, development of a Bayesian network approach is needed to incorporate a priori knowledge taking into account ill-defined parameters.

Patient tailored dose assessment certainly needs detailed knowledge of patient specific biokinetics of RPs. This biokinetic information can be improved by quantitative imaging, namely increasing the number of pre-therapeutic imaging examinations, but also by better calibration protocols. For that purpose, development of new, more realistic calibration phantoms with varying shapes and sizes using 3D printing tools makes it possible to obtain more realistic calibration factors. Research is needed to set-up appropriate protocols for each specific radionuclide and to investigate the challenge in relating macroscopically determined image-based activity to small-scale absorbed doses to sub-organ structures, in particular for short-range particles.

Internal dosimetry within nuclear medicine, entirely relates to the calculation of organ doses, based on analytical models, dose kernels or Monte Carlo calculations. To improve the accuracy in the calculation of dose from activity-time distributions the comparison between the different dosimetry approaches, as well as the experimental validation of the computational approaches is needed. The use of 2D and 3D experimental techniques, such as for example gel and film dosimetry in combination with anthropomorphic phantoms is worthwhile investigating.

Research Line 5.4: Accuracy of radionuclide activity measurements with radionuclide calibrators

Traceability established by a systematic calibration of the radionuclide calibrator for each relevant nuclide is recommended to comply with the growing need for quantitative accuracy in nuclear medicine and the upcoming more exotic radioisotopes with more complex decay schemes, used within radionuclide therapy. Moreover, the uncertainty in activity measurements of clinical radioisotopes needs to be assessed, which is caused by source geometry effects. To improve the traceability between primary standards and the accuracy of activities administered to patients and used in pre-clinical research based on radionuclide calibrator measurements, the organisation of intercomparison exercises of activity measurement capabilities in pre-clinical centres and hospitals could be performed.

Challenge 6: To Improve the protection and operational quantities used in dosimetry

The system of radiological protection employs two sets of dose quantities, the protection quantities defined by ICRP, and the operational quantities defined by ICRU. Recently, a change in the operational quantities has been proposed. Because the protection and the

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operational quantities are closely related to each other, the consequences of any change in these quantities and their use (e.g., for patients) requires careful consideration.

Research line 6.1: To investigate the effects of any change in the protection quantities

Effective dose defined by ICRP relates radiation effects to radiation dose. Effective dose may be used as an approximate indicator of possible radiation-induced risk, also in the context of medical applications. Any decisions on potential additional health outcomes of relevance (e.g., cardiovascular diseases) to be used in detriment calculation, or any changes in the numerical values of radiation weighting factors and tissue factors used to calculate effective dose, should be complemented by considerations on consequences for the definition of operational quantities.

Research line 6.2: To investigate the effects of a change in operational quantities

With the new ICRU operational quantities published recently, there will be a need to evaluate their impact across a wide range of outcomes. In this effort, the full range of exposure situations and applications including medical exposures of all types as well as the full range of radiations and energies should be considered. Main differences of the new with the existing quantities must be explored, given for example that there are significant differences for diagnostic-energy X-rays. Furthermore, any impact on dosemeter and instrument design, and associated standards, needs to be assessed, as well as that on dosemeter and instrument calibration.

Challenge 7: To develop neutron dosimetry techniques

The increasing use of accelerators for medical and research purposes generates neutrons with higher energies than is typical of most nuclear sites. Current dosemeters are not properly characterized for such high energies and are expected to perform poorly in those fields.

Research Line 7.1: To evaluate and improve, if necessary, the response of neutron personal dosemeters in high-energy fields

The rapid expansion of hadron therapy brings high-energy radiation fields with a strong neutron component into the medical area, exposing both workers and the public with neutrons. Research into the radiation fields that people are exposed to, and the correct calibration of dosemeters used in those fields, is needed to ensure that doses to people in such facilities are not underestimated. The development of new personal dosimetry methods for high-energy fields may be extensible to air crew, who are currently not accurately monitored for extreme space weather events.

Challenge 8: To improve biokinetic and dosimetric models for internal emitters

Internal doses can occur when individuals handle unsealed radionuclides, e.g., in the biomedical sector and research, and in nuclear medicine departments. In such cases, the potential health risk due to incorporated radionuclides is indicated by the assessed committed effective dose. Because this dose cannot be directly measured it must be assessed through measurements of radionuclide activities and the applications of models describing the metabolic behaviour of the contaminants inside the human body.

Measurements include in vivo monitoring (measurements of radiation emitted from the body by incorporated radionuclides), in vitro monitoring (measurements of radionuclides in the

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excreta) or workplace monitoring (measurements of radionuclides in the air). Models include biokinetic and dosimetric models that describe the spatial and temporal distribution of radionuclides in the body and their excretion, and the absorption of energy emitted following their decay.

Research line 8.1: Improvement of biokinetic and dosimetric models

Biokinetic and dosimetric models can still be improved to describe the effect of perturbations such as decorporation therapies. For example, following accidental incorporation of actinides DTPA can be administered to accelerate the removal of the radionuclides from the body. There has been considerable theoretical and experimental work on this subject but no consensus on therapy protocols, monitoring, and dose assessment, has so far emerged. Consequently, an experimental program that would produce data to enable the identification of a good general model is needed, perhaps involving animal models that would allow application of modern techniques including laser ablation and micro-XRF-imaging to provide information on the tissue/cellular level about the physico-chemical characteristics of the actinides and the DTPA. This knowledge can also be useful in the design and development of novel and targeted decorporation agents for targeted radiopharmaceuticals used in radiation therapy.

For short-range non-penetrating radiation emitters (alpha-, beta-, Auger emitters) any heterogeneity of activity distribution within tissues would directly translate into heterogeneity in doses. Investigating any direct mechanistic relationship between dose and effects then becomes challenging, or even irrelevant. Thus, the radionuclide distribution at the multi-cellular scale should be studied, using laser ablation, and SIMS and SR-XRF coupled with imaging techniques. Such techniques would need to be applied to autopsy samples of contaminated animals. Tissue Banks with human tissues, such as the United States National Human Radiobiology Tissue Repository (NHRTR) maintained at USTUR (US Transuranium and Uranium Registries), could also be utilized in these studies. This would allow production of dose maps revealing the heterogeneity of doses among cells.

Research line 8.2: Improvement of in vivo measurement

In vivo measurement systems are calibrated with reference radiation sources implemented in physical models representing the human body or a part of it (phantoms). As recent work has shown, 3D printing technology facilitates the production of more realistic calibration phantoms which should be explored further. Phantom development should include production of lung phantoms including overlying breast tissue of various thicknesses, reference head phantoms for bone-seeking radionuclides, and realistic wound models.

An alternative to physical calibration is numerical calibration employing mathematical models of the source/detector geometry and Monte Carlo methods to estimate detector efficiency. Such efforts should consider, (i) the activity distribution in the body at several time intervals after intake, and (ii) variations in body shape, to obtain calibration factors that can be compared with reference physical calibration factors. Studies might benefit from the use of the new generation of deformable phantoms (in MESH or NURBS formats), to include various monitoring positions (sitting, recumbent, reclining in a dedicated monitoring chair).

Efforts to develop physical and numerical calibration should be pursued jointly since both techniques offer complementary advantages.

Individuals exposed to short-lived radionuclides such as those used in nuclear medicine departments (handled for example by nuclear medicine staff; or comforters, carers and relatives who may be exposed to patients injected with radiopharmaceuticals such as ^{131}I), need to be monitored very frequently depending on the radionuclide. Because in vitro bioassay is often not an adequate technique, these individuals should be monitored in situ using existing

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monitoring equipment (e.g., contamination monitors, dose rate meters or even gamma cameras) available at the site/hospital. These instruments need to be characterized and qualified for this task, and sets of reference conversion factors need to be developed.

Research line 8.3: Dose and uncertainty assessment for epidemiology studies in workers

Dose assessment for cohorts of workers including those working in the medical sector brings several specific challenges. Firstly, dose must be assessed for thousands, tens of thousands or even more workers. Secondly, life-long dose reconstruction for periods with varying exposure conditions, varying monitoring data (inter or intra cohorts) is required. Thirdly, the information needed (type of compounds, value of the detection limits, exposure conditions) is often lacking. Fourthly, a significant percentage of measurements are usually below detection limits. Whatever the quality of the dose data for each worker may have, hundreds or even thousands of pieces of information are associated with them (measurement dates, results of measurements, exposure type/route/time, and exposure compound types).

Consequently, also for workers in the medical sector who can be exposed internally and externally, harmonized protocols for life-long dose assessment are needed including strategies to deal with measurement results below the detection limit. Software must be developed for life-long dose assessment including the definition of dataset standards. Consideration of dose uncertainties is generally important. For retrospective dose assessment involving internal emitters, specific attention must be placed on dose uncertainties due to the choice of biokinetic models, imprecise knowledge of historical working conditions (e.g., unclear chemical specification of incorporated radioactive substances), and incomplete recollection of previous workers.

Challenge 9: To estimate uncertainties and validate dose results

Within epidemiological studies the assessment of dose uncertainty distribution is expected to account for risk estimates especially when stochastic model sets are concerned. A well-established methodology is required to decrease the sources of uncertainty and subsequently the biases in risk estimates.

Research line 9.1: Validation of calculated doses by using methods for retrospective dosimetry

In order to validate dose calculations, independent or alternative measurements have proven to be a key challenge for benchmarking the evaluation of uncertainties. Regarding dose calculations for patients and/or workers in medical radiological facilities and in case of uniform external exposure situation, biological dosimetry is a well-established and validated methodology. However, for partial body or internal exposures research is focused on retrospective dosimetry and, more specifically, on electron paramagnetic resonance (EPR) on tooth enamel as well as, for internally deposited radionuclides, on the fluorescent situ hybridization (FISH) on circulating lymphocytes especially.

Research line 9.2: Uncertainty analysis in the calculated doses and estimation of their influence on the radiation-risk coefficients

Quantification of dose uncertainty is an essential parameter of radiation-induced risk assessment because it is impossible to achieve a deterministic estimate of the “true” dose for each person. The uncertainty budget includes components such as uncertainty on dose measurements, data about working conditions, or patient exposures. The uncertainty analysis of dose estimates should always distinguish between uncertainty that is specific to each subject (i.e., unshared errors), and uncertainty of doses that are present due to a lack of knowledge about parameter values that are shared to varying degrees by many subjects (or subsets) within the study cohort (i.e., shared errors). The influence of each uncertainty component on each result should be identified and the highest uncertainty should be reduced so as to have a reduced overall uncertainty of the dose estimate. Advanced statistical methods

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should be elaborated and employed to account for the complex error structures in risk analyses.

Challenge 10: To improve understanding of spatial correlations of radiation interaction events.

The dependence of biological effectiveness on radiation quality is commonly believed to be related to the differences in the energy deposition pattern on a microscopic and nanoscopic scale. Identification and quantification of the relevant statistical characteristics of the microscopic spatial pattern of interactions are essential prerequisites for the improvement of present dose concepts. Micro-and nanodosimetry have provided experimental and computational techniques for the microscopic and nanoscopic characterization of the track structure.

The overarching objective of Challenge 1.1 is the development of a novel, unified concept of radiation quality as a general physical characteristic of the radiation field that would allow separating the physical and biological components contributing to the eventual biological effects of radiation. Achieving the overall goal will require further investigation into the physical characteristics of particle track structure to identify relevant statistical features that can be exploited for defining the new radiation quality concept and related measurement quantities.

Also in the medical field, an improved understanding of the biological effects is needed, especially for new treatment modalities, such as proton and hadron therapy, as well as targeted radionuclide therapy.

Research line 10.1: Research on experimental track structure characterization

In principle, nanodosimetry enables a three-dimensional characterization of the particle track structure including the statistical correlations between different target volumes which may be decisive for biological effects of different radiation qualities. Further progress in the field will need track structure imaging techniques, which require the development of novel instruments capable of measuring nanodosimetric track structure information for a complete set of targets along a section of a track. The research on experimental track structure characterization also provides a benchmark for the validation of track structure simulation codes.

Research line 10.2: Investigation of experimental scaling relations for micro-and nanodosimetry and further characterization of existing detectors

The generic multi-scale approach for characterizing particle track structure by a combination of both microdosimetry and nanodosimetry at different length scales has so far only been studied with a prototype detector integrating one of the nanodosemeters in Europe and a silicon microdosemeter. With the ongoing endeavours to extend gas-counter based microdosimetry to target sizes of few 100 nm and even to target sizes below 100 nm and the significant progress made with silicon-based detectors with truly micrometric target sizes, the further investigation of the link between these novel types of microdosimetric information on track structure and its nanodosimetric characteristics is mandatory. This also applies to novel interpretations of nanodosimetric measurands when multiple targets are considered, e.g., in the frame of a potential application of nanodosimetry in radio-oncology treatment planning.

Research line 10.3: Uncertainty estimation for measured track structure quantities

The establishment of uncertainty budgets for measured track structure quantities is a still ongoing challenge that has become even more relevant with the aforementioned novel approaches in microdosimetry and nanodosimetry.

Research line 10.4: Further development of computational methods for track simulations

Deriving estimates of the uncertainty of nanodosimetric characteristics of track structure is also a major task for the computational methods used for numerical simulation of particle tracks.

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These numerical methods are, in principle, well suited for studying track formation and for obtaining the probability distributions for micro-or nanodosimetric quantities. The 'multi-scale' characterization of particle track structure and the link between nanodosimetry and microdosimetry strongly rely on such simulations. There are, however, still several issues and challenges to resolve, regarding the use of such track structure codes. All these issues associated with simulations of microdosimetric and nanodosimetric quantities call for the development of a 'gold standard' for Monte Carlo simulations of track structure with a robust quality assurance scheme based on evaluated databases of cross sections with ascertained uncertainties, implementation in the codes and investigation of uncertainty propagation from cross sections to the final simulation results. This should be complemented by a set of high-quality benchmark experiments that provide a reference for the assessment of the quality of simulation results.

Challenge 11: To anticipate future epidemiological studies

Epidemiological studies are usually retrospective in nature. However, prerequisites for future studies to be launched in the near future should be designed, especially for health effects caused by advanced developing technologies such as ion beam therapy or new radiopharmaceuticals in nuclear medicine (therapy and diagnosis).

Research line 11.1: Molecular epidemiological studies

A completely new class of radiation epidemiological studies are the molecular studies, which take advantage of the fact that the final results of radiation can be expressed at molecular level, i.e., DNA, rather than tissue, organ, or organism level. In these developing epidemiological studies, the harmonization of dosimetry and scoring method techniques as well as the dose reconstruction techniques are of outmost importance, especially, nowadays, that these studies are in their early stages.

Research line 11.2: Prepare future epidemiological studies

For the preparation of future epidemiological studies, the specifications for recording all the relevant data in a harmonized way is a challenge. Dosimetrists, epidemiologists, medical physicists, and data managers should form the basis for the collection and archive of the dosimetry parameters, personal data, data on the involved practices and equipment, radiopharmaceuticals, and all the relevant information which will be used for future studies. Special effort is needed to build registers for arrangements that are not known yet such as theranostics, or the use of newly implemented practices, such as proton therapies. Finally, attention shall be given for personal data protection issues.

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