Abou-Elkacem L, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, Lederle W.
Regorafenib inhibits growth, angiogenesis and metastasis in a highly aggressive, orthotopic colon cancer mModel.
Mol Cancer Ther (2013) 12: 1322-1331.

The combination of target-specific drugs like bevacizumab with chemotherapeutics has improved treatment efficacy in advanced colorectal cancer (CRC). However, the clinical prognosis of metastatic CRCs is still poor, and novel drugs are currently assessed with respect to their efficacies in patients with CRCs. In a phase III study, the multikinase inhibitor regorafenib (BAY 73-4506) has recently been shown to prolong survival of patients with CRCs after standard therapies failed. In the present study, the activity of regorafenib was investigated in comparison with the angiogenesis inhibitor DC101 in the highly aggressive, murine CT26 metastatic colon cancer model. While a treatment for 10 days with DC101 given at a dose of 34 mg/kg every third day significantly delayed tumor growth compared with vehicle-treated animals, regorafenib completely suppressed tumor growth at a daily oral dose of 30 mg/kg. Regorafenib also induced a stronger reduction in tumor vascularization, as longitudinally assessed in vivo by dynamic contrast-enhanced MRI (DCE-MRI) and confirmed by immunohistochemistry. In addition, regorafenib inhibited the angiogenic activity more strongly and induced a three times higher apoptosis rate than DC101. Even more important, regorafenib completely prevented the formation of liver metastases, whereas in DC101-treated animals, the metastatic rate was only reduced by 33% compared with the vehicle group. In addition, regorafenib significantly reduced the amount of infiltrating macrophages. These data show that the multikinase inhibitor regorafenib exerts strong antiangiogenic, antitumorigenic, and even antimetastatic effects on highly aggressive colon carcinomas indicative for its high potential in the treatment of advanced CRCs.

Ainsbury E, Al-Hafidh J, Bajinskis A, Barnard S, Barquinero JF, Beinke C, de Gelder V, Gregoire E. Jaworska A, Lindholm C, Lloyd D, Moquet J, Nylund R, Oestreicher U, Roch-Lefèvre S, Rothkamm K, Romm H, Scherthan H, Sommer S, Thierens H, Vandevoorde C, Vral A, Wojcik A.
Inter- and intra -laboratory comparison of a multibiodosimetric approach to triage in a simulated, large scale radiation emergency.
Int J Radiat Biol (2013) (Epub ahead)

PURPOSE: The European Union's Seventh Framework Programme-funded project 'Multi-disciplinary biodosimetric tools to manage high scale radiological casualties' (MULTIBIODOSE) has developed a multiparametric approach to radiation biodosimetry, with a particular emphasis on triage of large numbers of potentially exposed individuals following accidental exposures. In November 2012, an emergency exercise took place which tested the capabilities of the MULTIBIODOSE project partners. The exercise described here had a dual purpose: Intercomparison of (i) three biodosimetric assays, and (ii) the capabilities of the seven laboratories, with regards to provision of triage status for suspected radiation exposed individuals.
MATERIALS AND METHODS: Three biological dosimetry tools - the dicentric, micronucleus and gamma-H2AX (the phosphorylated form of member X of histone H2A, in response to DNA double-strand breaks) foci assays - were

tested, in addition to provision of the triage status results (low exposure: < 1 Gy; medium exposure: 1-2 Gy; high exposure: > 2 Gy) by the MULTIBIODOSE software. The exercise was run in two modes: An initial triage categorisation of samples (based on the first dose estimates for each assay received from each laboratory) followed by collation of the full set of estimated doses (all the results from all modes of each assay carried out by the participating laboratories) calculated using as many modes of operation as possible of the different assays developed during the project. Simulated acute whole body and partial body exposures were included.
RESULTS: The results of the initial triage categorisation and the full comparison of assays and methods within and between laboratories are presented here.
CONCLUSIONS: The data demonstrate that the MULTIBIODOSE approach of applying multiparametric tools to radiation emergencies is valid and effective.

Bannik K, Rössler U, Faus-Kessler T, Gomolka M, Hornhardt S, Dalke C, Klymenko O, Rosemann M, Trott KR, Atkinson M, Kulka U, Graw J.
Are mouse lens epithelial cells more sensitive to c-irradiation than lymphocytes?
Radiat Environ Biophys (2013) 52(2): 279-86.

In this pilot study we compared for the firsttime the radiation sensitivity of mouse lens epithelial cells (LECs) and mouse lymphocytes. We freshly prepared LECs andlymphocytes and irradiated them with c-rays (137Cs; doses ranging from 0.25 to 2 Gy). DNA damage and repair were evaluated by alkaline comet assay and cH2AX foci assay. Using the comet assay, we observed adose-dependent increase in DNA damage in both celltypes. The faster formation of single- and double-strandbreaks in LECs of C57BL/6 mice at doses below 1 Gy to be confirmed in other mouse strains. Immunofluorescence for cH2AX foci showed a higher degree of lesions in LECs from C57BL/6J mice compared to those of JF1 mice and to lymphocytes of both strains. Correspondingly, repair of DNA damage proceeded faster in LECs of C57BL/6J mice compared to LECs of JF1 mice and lymphocytes of both strains. It is obvious that the lymphocytes of both strains repaired DNA lesions more slowly than the corresponding LECs. In conclusion, our results demonstrate that LECs of C57Bl/6 mice show a steeper dose–response than lymphocytes in both types of experiments. It shows that both test systems are able to be used also at doses below 0.25 Gy. The observed difference in DNA repair between the LECs from C57BL/6J mice compared to the LECs from JF1 mice and to the lymphocytes of both strains warrants further experiments to identify the underlying molecular mechanisms.

Beinke C, Barnard S, Boulay-Greene H, De Amicis A, De Sanctis S, Herodin F, Jones A, Kulka U, Lista F, Lloyd D, Martigne P, Moquet J, Oestreicher U, Romm H, Rothkamm K, Valente M, Meineke V, Braselmann H, Abend M.
Laboratory intercomparison of the dicentric chromosome analysis assay.
Radiat Res (2013) 180:129-137.

The study design and obtained results represent an intercomparison of various laboratories performing dose assessment using the dicentric chromosome analysis (DCA) as a diagnostic triage tool for individual radiation dose assessment. Homogenously X-irradiated (240 kVp, 1 Gy/min) blood samples for

establishing calibration data (0.25–5Gy) as well as blind samples (0.1–6.4 Gy) were sent to the participants. DCA was performed according to establishedprotocols. The time taken to report dose estimates was documented for each laboratory. Additional information concerning laboratory organization/characteristics as well as assay performance was collected. The mean absolute difference (MAD) was calculated and radiation doses were merged into four triage categories reflecting clinical aspects to calculate accuracy, sensitivity and specificity. The earliest report time was 2.4 days after sample arrival. DCA dose estimates were reported with high and comparable accuracy, with MAD values ranging between 0.16–0.5 Gy for both manual and automated scoring. No significant differences were found for dose estimates based either on 20, 30, 40 or 50 cells, suggesting that the scored number of cells can be reduced from 50 to 20 without loss of precision of triage dose estimates, at least for homogenous exposure scenarios. Triage categories of clinical significance could be discriminated efficiently using both scoring procedures.

Berg HP.

Critical infrastructure and resilience goals

Journal of Polish Safety and Reliability Association 4 (2013) Nr. 2: 147-154

Critical infrastructure risks pose a special problem for all countries. The companies that own these infrastructures operate in competitive and regulated environments. However, it is neither practical nor possible to protect critical infrastructures from all hazards. For the government, the continuity of these infrastructures is critical to many of its fundamental missions: economic stability and growth, national security, public safety, and quality of life. In that context resilience has become an important factor to fulfil the task of the critical infrastructure protection. Thus, the development of a framework to establish resilience goals could be helpful.

Berg HP, Fritze N.

Risk and consequences of transformer explosions and fires in nuclear power plants

Journal of KONBIN 23 (2013) Nr. 1: 5-16

The high failure frequency and the resulting reliability and safety implications in recent years of transformers, in particular at nuclear power plants (NPP), required an in-depth assessment. Fires of main transformers are considered as critical because of the large quantity of oil in contact with high voltage elements. Therefore, these phenomena have been investigated in more detail using the information from the OECD FIRE Database for NPP. 12.8 % of all fires and, thus, the most frequent fire source in this database are transformer fires, mainly fires of high voltage oil-filled transformers. Thus, possible diagnostic measures to avoid such events and enhance the reliability currently discussed in Germany are shortly described. Moreover, consequences of transformer failures with respect to a reliable electric power supply are addressed.

Berg HP, Krauß M.

External hazards - in focus after the Fukushima accident

Kerntechnik Volume 78 (2013) Nr. 2: 84-91

International experience has shown that external hazards can be safety significant contributors to the risk of industrial plants with a high potential of damage to the environment; this has become evident after the Fukushima accident. As a consequence main focus has been set on adequate design measures against external hazards and appropriate assessment methods. Possible methods to analyse existing plants systematically regarding the adequacy of their existing protection equipment against hazards can be deterministic as well as probabilistic. On international level, new recommendations regarding external hazards are recently issued. In that context, in particular earthquakes and flooding scenarios have been re-evaluated to some extent. Also in Germany, a revised guideline on probabilistic safety analyses (PSA) and corresponding technical documents are issued in 2005 addressing external hazards. As a reaction to the accidents in Japan in March 2011, the German Reactor Safety Commission has issued a catalogue of requirements for plant-specific reviews of German nuclear power plants, and the status of the plants have been evaluated with respect to these requirements. The results of these investigations have been the basis for the German report in the frame of the European stress tests; the results with respect to natural external hazards are presented.

Bossew P.

Anthropogenic Radionuclides in Environmental Samples from Fukushima Prefecture

Radiation emergency medicine 2 (2013), Nr.1, 69-75

Four environmental samples from Fukushima prefecture, taken in March 2012, were analysed with gamma and alpha spectrometry. The aim was determining radionuclide ratios. The estimated ratio of ^{134}Cs / ^{137}Cs equals 1.062, with standard deviation (indicating variability between samples) 0.024. The ratio seems to be somewhat higher than what is mostly reported in the literature, namely between <0.9 and about 1. The only other long-lived gamma radionuclide which could be identified is 110mAg, whose ratio to ^{137}Cs equals $(2.3 \pm 0.2)\ 10^{-3}$. The ratios of $^{239+240}$Pu and ^{137}Cs in Fukushima fallout are below 10^{-6}, calculated under the assumption that the only Pu sources are global and Fukushima fallout. More samples would be needed to improve the statistical reliability of the results, and to investigate the reason for the found slight discrepancy of Cs ratios with those reported in literature.

Bossew P.

Small-scale Variability of the Gamma Dose Rate in the Urban Environment of Fukushima City

Radiation emergency medicine 2 (2013), Nr.1, 64-68

Local variability of external gamma dose rate has been measured in the centre of Fukushima City, Japan, in March 2012. The arithmetic mean in the monitored zone was 0.48 µSv / h and the coefficient of variation, 27%. Small-scale variability is very high and the observations revealing no local autocorrelative structure. The reasons are probably locally very different effects of redistribution, accumulation and depletion of the fallout, as well as shielding of gamma rays. These effects are typical for urban environments. Spatial median smoothing allows identifying an autocorrelative structure of local means, which may be interpreted as mid-scale differences in deposition levels. The result is however uncertain, given the low number of observations and the small area which has been sampled.

Bossew P.
Hot spots as random objects.
Radiation emergency medicine 2 (2013), Nr.1, 35-42

Among the most important tasks in quantifying spatial phenomena in environmental assessment is delineation and quantification of zones of high values of a response variable, for beneficial cases (resources) like for detrimental situations (pollutants). If no exhaustively known physical control variable is available, such as geology in some cases, assessment of “excursion sets” (Adler) or “hot spots” is often based on geostatistical procedures, like simulation. Often the estimation procedure has to rely on only few “anomalously” high, amidst many “background” observations with point support. A common definition of such zone is a connected set of mapping units (pixels, grid cells, estimation supports) in each of which the estimated expectation of the investigated variable exceeds a threshold. However the resulting area of a “patch”, as geometrical object, is different from the expectation of areas of many patches each resulting from a realization of the field through simulation. This is demonstrated on the example of observed 131I concentrations over Europe after the Fukushima accident. It is found that the difference in estimated size of hot spots between the two approaches can be considerable, and may have to be taken into account in cases of importance, e.g. if for radioprotection reasons a conservative estimate is needed. The effect adds to the uncertainty budget of quantified properties of the object (like its size), but conceptually differently from other uncertainty components related to geostatistical estimation procedures, such as uncertainty of histogram, distribution tail modelling and variogram.

Brix G, Berton M, Nekolla E, Lechel U, Schegerer A, Süselbeck T, Fink C.
Cumulative radiation exposure and cancer risk of patients with ischemic heart diseases from diagnostic and therapeutic imaging procedures.
Eur J Radiology (2013) 82: 1926-32.

Objectives: To present a detailed analysis of the cumulative radiation exposure and cancer risk of patients with ischemic heart diseases (IHD) from diagnostic and therapeutic imaging. Methods: For 1219 IHD patients, personal and examination data were retrieved from the information systems of a university

hospital. For each patient, cumulative organ doses and the corresponding effective dose (E) resulting from all imaging procedures performed within 3 months before and 12 months after the date of the diagnosis were calculated. The cumulative lifetime attributable risk (LAR) of the patients to be diseased by radiation-related cancer was estimated using sex-, age-, and organ-specific risk models. Results: Among the 3870 procedures performed in the IHD patients, the most frequent were radiographic examinations (52.4%) followed by coronary catheter angiographies and percutaneous cardiac interventions (41.3%), CT scans (3.9%), and perfusion SPECT (2.3%). 87% of patient exposure resulted from heart catheter procedures. E and LAR were significantly higher in males than females (average, 13.3 vs. 10.3 mSv and 0.09 vs. 0.07%, respectively). Contrary to the effective dose, the cancer risk decreased markedly for both sexes with increasing age. Conclusions: Although IHD patients were partially exposed to considerable amounts of radiation, estimated LARs were small as compared to their baseline risk to develop cancer in the remaining life.

Brix G, Nekolla EN, Borowski M, Noßke D.

Radiation risk and protection of patients in clinical spect/ct. (Invited review).

Eur J Nucl Med Mol Imag (2013), doi:10.1007/s00259-013-2543-3

Clinical studies have demonstrated that hybrid SPECT/CT for various diagnostic issues has an added value as compared to SPECT alone. However, the combined acquisition of functional and anatomical images can substantially increase radiation exposure to patients, in particular when using a hybrid system with diagnostic CT capabilities. It is, therefore, essential to carefully balance the diagnostic needs and radiation protection requirements. To this end, the evidence on health effects induced by ionising radiation is outlined. In addition, the essential concepts for estimating radiation doses and life-time attributable cancer risks associated with SPECT/CT examinations are presented taking into account both the new recommendations of ICRP Publication 103 as well as the most recent radiation risk models of the BEIR VII report. Representative values of effective dose and life-time attributable risk are reported for 10 frequently used SPECT radiopharmaceuticals and 5 fully-diagnostic partial-body CT examinations. A diagnostic CT scan acquired as part of a combined SPECT/CT examination contributes considerably to, and for some applications even dominates, the total patient exposure. For the common SPECT and CT examinations considered in this study, the life-time attributable risk of developing a radiation-related cancer is less than 0.27 % / 0.37 % for males / females older than 16 years, respectively, and decreases markedly with increasing age at exposure. Since there is no clinical indication for a SPECT/CT examination unless an emission scan has been indicated, the issue on justification comes down to the question of whether it is necessary to additionally acquire a low-dose CT for attenuation correction and anatomical localization of tracer uptake or even a fully-diagnostic CT. In any case, SPECT/CT studies have to be optimised, e.g. by adapting dose reduction measures from state-of-the-art CT practice, and exposure levels should not exceed the national diagnostic reference levels for standard situations.

Chaisan K, Smith JT, ***Bossew P, Kirchner G,*** *Laptev GV.*
Worldwide isotope ratios of the Fukushima release and early-phase external dose reconstruction
Scientific reports 3 (2013) doi:10.1038/srep02520

Measurements of radionuclides (RNs) in air made worldwide following the Fukushima accident are quantitatively compared with air and soil measurements made in Japan. Isotopic ratios RN:^{137}Cs of ^{131}I, ^{132}Te, ^{134,136}Cs, are correlated with distance from release. It is shown, for the first time, that both within Japan and globally, ratios RN:^{137}Cs in air were relatively constant for primarily particle associated radionuclides (^{134,136}Cs; ^{132}Te) but that ^{131}I shows much lower local (<80 km) isotope ratios in soils relative to ^{137}Cs. Derived isotope ratios are used to reconstruct external dose rate during the early phase post-accident. Model "blind" tests show more than 95% of predictions within a factor of two of measurements from 15 sites to the north, northwest and west of the power station. It is demonstrated that generic isotope ratios provide a sound basis for reconstruction of early-phase external dose rates in these most contaminated areas.

Dufey F, Walsh L, Sogl M, Tschense A, Schnelzer M, Kreuzer M
Radiation dose dependent risk of liver cancer mortality in the German uranium miners cohort 1946–2003
J. Radiol. Prot. (2013) 33: 175–185

An increased risk of mortality from primary liver cancers among uranium miners has been observed in various studies. An analysis of the data from a German uranium miner cohort (the 'Wismut cohort') was used to assess the relationship with ionising radiation. To that end the absorbed organ dose due to high and low linear energy transfer radiation was calculated for 58 987 miners with complete information on radiation exposure from a detailed job-exposure matrix. 159 deaths from liver cancer were observed in the follow-up period from 1946 to 2003. Relative risk models with either linear or categorical dependence on high and low linear energy transfer radiation liver doses were fitted by Poisson regression, stratified on age and calendar year. The linear trend of excess relative risk in a model with both low and high linear transfer radiation is -0.8 (95% confidence interval (CI): -3.7, 2.1) Gy^{-1} and 48.3 (95% CI: -32.0, 128.6) Gy^{-1} for low and high linear energy transfer radiation, respectively, and thus not statistically significant for either dose. The increase of excess relative risk with equivalent liver dose is 0.57 (95% CI: -0.69, 1.82) Sv^{-1}. Adjustment for arsenic only had a negligible effect on the radiation risk. In conclusion, there is only weak evidence for an increase of liver cancer mortality with increasing radiation dose in the German uranium miners cohort considered. However, both a lack of statistical power and potential misclassification of primary liver cancer are issues.

Farah J, Struelens L, Dabin J, Koukorava C, Donadille L, Jacob S, Schnelzer M, Auvinen A, Vanhavere F, Clairand I.
A correlation study of eye lens dose and personal dose equivalent for interventional cardiologists.

Radiat Prot Dosimetry (2013) 157(4): 561-9

This paper presents the dosimetry part of the European ELDO project, funded by the DoReMi Network of Excellence, in which a method was developed to estimate cumulative eye lens doses for past practices based on personal dose equivalent values, H(p)(10), measured above the lead apron at several positions at the collar, chest and waist levels. Measurement campaigns on anthropomorphic phantoms were carried out in typical interventional settings considering different tube projections and configurations, beam energies and filtration, operator positions and access routes and using both mono-tube and biplane X-ray systems. Measurements showed that eye lens dose correlates best with H(p)(10) measured on the left side of the phantom at the level of the collar, although this correlation implicates high spreads (41 %). Nonetheless, for retrospective dose assessment, H(p)(10) records are often the only option for eye dose estimates and the typically used chest left whole-body dose measurement remains useful.

Fenech M, Kirsch-Volders M, Rossnerova A, Sram R, Romm H, Bolognesi C, Ramakumar A, Soussaline F, Schunck C, Elhajouji A, Anwar W, Bonassi S.
HUMN project initiative and review of validation, quality control and prospects for further development of automated micronucleus assays using image cytometry systems.
Int J Hyg Environ Health (2013) 216: 541-552.

The use of micronucleus (MN) assays in in vitro genetic toxicology testing, radiation biodosimetry and population biomonitoring to study the genotoxic impacts of environment gene-interactions has steadily increased over the past two decades. As a consequence there has been a strong interest in developing automated systems to score micronuclei, a biomarker of chromosome breakage or loss, in mammalian and human cells. This paper summarises the outcomes of a workshop on this topic, organised by the HUMN project, at the 6th International Conference on Environmental Mutagenesis in Human Populations at Doha, Qatar, 2012. The aim of this paper is to summarise the outcomes of the workshop with respect to the set objectives which were: (i) Review current developments in automation of micronucleus assays by image cytometry; (ii) define the performance characteristics of automated MN scoring using image cytometry and methods of assessment for instrument validation and quality control and (iii) discuss the design of inter-laboratory comparisons and standardisation of micronucleus assays using automated image cytometry systems. It is evident that automated scoring of micronuclei by automated image cytometry using different commercially available platforms [e.g. Metafer (MetaSystems), Pathfinder™ (IMSTAR), iCyte(®) (Compucyte)], particularly for lymphocytes, is at a mature stage of development with good agreement between visual and automated scoring across systems (correlation factors ranging from 0.58 to 0.99). However, a standardised system of validation and calibration is required to enable more reliable comparison of data across laboratories and across platforms. This review identifies recent progress, important limitations and steps that need to be taken into account to enable the successful universal implementation of automated micronucleus assays by image cytometry.

Gering F, Gerich B, Wirth, E, Kirchner, G.
Potential consequences of the Fukushima accident for off-site nuclear emergency management: a case study for Germany.
Radiation protection dosimetry 155 (2013), Nr.2, 146-154
doi:10.1093/rpd/ncs323

The Fukushima accident led to high radionuclide releases into the atmosphere for more than 3 weeks. This situation has not been assumed when the concepts of nuclear emergency preparedness were developed internationally. The results of simulations studying potential implications of Fukushima-like source terms on nuclear emergency preparedness are presented. Two hypothetical source terms are considered. Radiological consequences are assessed with the decision support system RODOS. Atmospheric dispersion calculations are based on meteorological monitoring data from June and December 2010, respectively, to study potential seasonal effects. Simulations are performed for two nuclear power plant sites in Northern and Southern Germany, respectively. These sites are chosen due to their differing meteorology and topography. Predicted radiation doses of members of the population are compared with dose reference levels actually recommended for initiating protective measures in Germany. Potential implications of general interest for nuclear emergency planning are discussed.

Grosche B.
***Der* Reaktorunfall von Fukushima: Folgen für Japan und für uns.**
Gesundheitswesen (2013) 75: 179-183.

Der Reaktorunfall von Fukushima war die Folge einer vorangegangenen doppelten Naturkatastrophe, nämlich eines Erdbebens am 11. März 2011 und dem daraus entstandenen Tsunami. Aufgrund günstiger Windverhältnisse und von Evakuierungsmaßnahmen war die Strahlenbelastung für die Allgemeinbevölkerung in Japan insgesamt und mit Ausnahmen auch in den Regionen außerhalb der Evakuierungszone gering. In diesem Beitrag wird versucht, auf der Basis der Expositionsabschätzung der WHO, von Erkenntnissen im Zusammenhang mit dem Reaktorunfall von Tschernobyl, den oberirdischen Atombombentests in Kasachstan und zum Risiko von Leukämien im Kindesalter nach niedriger Strahlenexposition eine Einschätzung möglicher gesundheitlicher Folgen zu geben. Für Deutschland bestand keine gesundheitsrelevante Gefährdung durch die radioaktiven Freisetzungen, gleichwohl haben die Ereignisse in Japan zu der Erkenntnis geführt, dass die Regelwerke, die für Kernkraftwerksunfälle erarbeitet wurden, einer Ergänzung bedürfen.

*Gruber V, **Bossew P**, De Cort M, Tollefsen T.*
The European map of the geogenic radon potential.
Journal of radiological protection 33 (2013), Nr.1, 51-60
doi:10.1088/0952-4746/33/1/51

As part of its projected European Atlas of Natural Radiation (EANR), the Joint Research Centre (JRC) of the European Commission, in cooperation with research institutions and radioprotection authorities all over Europe, is currently developing a map of the geogenic radon potential. In an accompanying report the state of knowledge, mapping approaches and problems are discussed. We explain the rationale and the legal situation in Europe and present an overview on the main problems stemming from the heterogeneity of input datasets between participating countries and from the definition of input variables and their differently implemented sampling procedures or protocols. Further topics are definition of the target variable which quantifies the geogenic radon potential and its estimation from heterogeneous input and proxy variables, as well as problems specific to mapping, such as choice of mapping support and resolution.
The geogenic map was preceded by a European map of indoor radon concentrations, which is still growing as ever more countries decide to participate, and which served as training for harmonisation problems occurring in the European data realm. We shall also briefly discuss its main results and implications for the geogenic map.

Gruber V, Tollefson T, ***Bossew P****, De Cort M.*
The European indoor radon map and beyond.
Carpathian journal of earth and environmental sciences 8 (2013), Nr.2, 169-176

Started six years ago, the European map of indoor radon concentrations has evolved to includedata from 25 countries, covering a fair part of Europe. As of October 2012, the map is composed of morethan 18,000 non-empty grid cells with data, based on more than 800,000 individual measurements. Thenumber of measurements per cell ranges from one up to nearly 24,000. The coverage of territory varieswidely between the countries: from less than 20% for some up to more than 100% for others (due to aborder effect). While the arithmetic mean for all non-empty cells in Europe (for all participating countries) is 100 Bq/m^3, the median is 65 Bq/m^3. In parallel, a European map of geogenic radon potentialis under development, with a first, trial map having been published. These and other maps will eventuallyform parts of a planned European Atlas of Natural Radiation.

Gürtler A, Kunz N, Gomolka M, Hornhardt S, Friedl AA, McDonald K, Kohn JE, Posch A.
Stain-free technology as a normalization tool in Western blot analysis.
Anal Biochem. (2013) 433(2): 105-11.

Western blots are used to specifically measure the relative quantities of proteins of interest in complex biological samples. Quantitative measurements can be subject to error due to process inconsistencies such as uneven protein transfer to the membrane. These non-sample-related variations need to be compensated for by an approach known as normalization. Two approaches to data normalization are commonly employed: housekeeping protein (HKP) normalization and total protein normalization (TPN). In this study, we evaluated the performance of Stain-Free technology as a novel TPN tool for Western blotting experiments in comparison with glyceraldehyde-3-phosphate

dehydrogenase (GAPDH) as a representative of the HKP normalization strategy. The target protein (TP) used for this study was MCM7, a DNA licensing replication factor, which was shown previously to be down-regulated by 20% in irradiated lymphoblastoid cell lines (LCLs). We studied the regulation of MCM7 with a multiplex Western blotting approach based on fluorescently labeled secondary antibodies and found that Stain-Free technology appears to be more reliable, more robust, and more sensitive to small effects of protein regulation when compared with HKP normalization with GAPDH. Stain-Free technology offers the additional advantages of providing checkpoints throughout the Western blotting process by allowing rapid visualization of gel separation and protein transfer.

Hansmann J, Schoeppler GM, Henzler T, Brix G, Meyer M, Attenberger UI, Schoenberg SO, Fink C.

Ct of urolithiasis: comparison of image quality and diagnostic confidence using filtered back projection and iterative reconstruction techniques.

Acad Radiol (2013) 20: 1162-7.

Rationale and objectives: To compare the image quality and diagnostic confidence of low-dose computed tomography (CT) of urololithiasis using filtered back projection (FBP) and iterative reconstruction techniques (IRT). Materials and methods: A 4.8 × 4.3 × 5.2 mm^3 uric acid ureteral stone was placed inside an anthropomorphic Alderson phantom at the pelvic level. Fifteen scans were performed on a 64-row dual-source CT system using different tube voltages (80, 100, and 120 kV) and current-time products (8, 15, 30, 70, and 100 mAs). Image reconstruction using FBP and IRT (iterative reconstruction in image space) resulted in 30 data sets. Objective image quality was evaluated by noise measurements. Effective doses were estimated for each data set with use of an established dosimetry program. Subjective image quality and confidence level were rated by two radiologists. Results: Noise was systematically lower for images reconstructed with IRT compared to FBP (55 ± 30 vs 65 ± 26 Hounsfield units; P = .004) for volume CT dose index values above about 0.6 mGy (or an effective dose of about 0.4 mSv for both sexes). For the 14 scans rated to have diagnostic image quality, the estimated effective doses ranged from 0.3 to 2.5 mSv for males and from 0.4 to 3.1 mSv for females. Subjective image quality and diagnostic confidence for IRT was not significantly better than those for FBP. Conclusions: In a phantom study for CT of urolithiasis, IRT improves objective image quality compared to FBP above a certain dose threshold. However, this does not translate into improved subjective image quality or a higher degree of confidence for the diagnosis of high-contrast urinary stones.

Hellmich, M.

Semi-Markov embeddable reliability structures and applications to load-sharing k-out-of-n systems

International Journal of Reliability, Quality and Safety Engineering 20 (2013) 1350007: 21 pages

This paper deals with the application of nonhomogeneous semi-Markov processes in reliability modeling. The notion of a semi-Markov embeddable reliability structure is introduced and discussed. As an example, load-sharing k-

out-of-n :G systems of equal components with arbitrary life distributions under the equal load-sharing rule are treated in the context of semi-Markov embeddable systems. Besides some discussion about load-life models, the case of repairable components is to some extent treated as well.

Hellmich, M, Berg, H.P.
On the construction of component importance measures for semi-Markov systems
Mathematical Methods of Operations Research 77 (2013): 15-32

In this paper we consider semi-Markov reliability models of systems with discrete state space in a setup general enough to cover systems with maintenance and repair. The systems are assumed to consist of several components which can either be up or down in each state. In this framework we propose two different types of component importance measures which are based on transition rates and interval availability, respectively. For these importance measures we study both the time-dependent and the steady state situation, and express them in terms of quantities easily calculated from the building blocks of the semi-Markov process.

Hinton TG, Garnier-Laplace J, Vandenhove H, Dowdall M, Adam-Guillermin C, Alonzo F, Barnett C, Beaugelin-Seiller K, Beresford NA, Bradshaw C, Brown J, Eyrolle F, Fevrier L, Gariel JC, Gilbin R, Hertel-Aas T, Horemans N, Howard BJ, Ikäheimonen T, Mora JC, Oughton D, Real A, Salbu B, Simon-Cornu M, ***Steiner M****, Sweeck L, Vives i Batlle J.*
An invitation to contribute to a strategic research agenda in radioecology.
Journal of environmental radioactivity 115 (2013), 73-82
doi:10.1016/j.jenvrad.2012.07.011

With intentions of integrating a portion of their respective research efforts into a trans-national programme that will enhance radioecology, eight European organisations recently formed the European Radioecology ALLIANCE (www.er-alliance.org). The ALLIANCE is an Association open to other organisations throughout the world with similar interests in promoting radioecology. The ALLIANCE members recognised that their shared radioecological research could be enhanced by efficiently pooling resources among its partner organizations and prioritising group efforts along common themes of mutual interest. A major step in this prioritisation process was to develop a Strategic Research Agenda (SRA). An EC-funded Network of Excellence in Radioecology, called STAR (Strategy for Allied Radioecology), was formed, in part, to develop the SRA. This document is the first published draft of the SRA. The SRA outlines a suggested prioritisation of research topics in radioecology, with the goal of improving research efficiency and more rapidly advancing the science. It responds to the question: "What topics, if critically addressed over the next 20 years, would significantly advance radioecology?" The three Scientific Challenges presented within the SRA, with their 15 associated research lines, are a strategic vision of what radioecology can achieve in the future. Meeting these challenges will

require a directed effort and collaboration with many organisations the world over. Addressing these challenges is important to the advancement of radioecology and in providing scientific knowledge to decision makers. Although the development of the draft SRA has largely been a European effort, the hope is that it will initiate an open dialogue within the international radioecology community and its stakeholders. This is an abbreviated document with the intention of introducing the SRA and inviting contributions from interested stakeholders. Critique and input for improving the SRA are welcomed via a link on the STAR website (www.star-radioecology.org).

Hunter N, Muirhead CR, Tomasek L, Kreuzer M, Laurier D, Leuraud K, Schnelzer M, Grosche B, Placek V, Heribanova A, Timarche M.

Joint analysis of three European nested case-control studies of lung cancer among radon exposed miners: exposure restricted to below 300 WLM.

Health Phys. (2013) 104 (3): 282-92

Analyses of lung cancer risk were carried out using restrictions to nested case-control data on uranium miners in the Czech Republic, France, and Germany. With the data restricted to cumulative exposures below 300 working-level-months(WLM) and adjustment for smoking status, the excess relative risk (ERR) per WLM was 0.0174 (95% CI: 0.009-0.035), compared to the estimate of 0.008 (95% CI:0.004-0.014) using the unrestricted data. Analysis of both the restricted and unrestricted data showed that time since exposure windows had a major effect; the ERR/WLM was six times higher for more recent exposures (5-24 y) than for more distant exposures (25 y or more). Based on a linear model fitted to data on exposures <300 WLM, the ERR WLM of lung cancer at 30 y after exposure was estimated to be 0.021 (95% CI: 0.011-0.040), and the risks decreased by 47% per decade increase in time since exposure. The results from analyzing the joint effects of radon and smoking were consistent with a sub-multiplicative interaction; the ERR WLM was greater for non-smokers compared with current or ex-smokers, although there was no statistically significant variation in the ERR WLM by smoking status. The patterns of risk with radon exposure from the combined European nested case-control miner analysis were generally consistent with those based on the BEIR VI Exposure-Age-Concentration model. Based on conversions from WLM to time weighted averaged radon concentration (expressed per 100 Bq m), the results from this analysis of miner data were in agreement with those from the joint analysis of the European residential radon studies.

Ingwersen M, Drabik A, Kulka U, Oestreicher U, Fricke S, Krankenberg H, Schwencke C, Mathey D

Physicians´ radiation exposure in the catheterization lab: does the type of procedure matter?

JACC Cardiovasc Interv (2013) 6: 1095-102.

This study evaluated the effect of different types of cath lab procedures on operators' radiation exposure by using real-time dosimetry. We found a 1.6-2.5 fold increased effective radiation dose to the body from pelvic, upper limb and

below the knee procedures compared to coronary angiography. Operators' eye doses from these peripheral procedures were significantly higher than from coronary angiography. Hands were exposed to the highest radiation doses during pelvic procedures. We conclude that endovascular peripheral procedures are accompanied with a significantly higher radiation exposure of cath lab operators than coronary procedures. Protection devices should be used wherever applicable.

Kabai E, Beyermann M, Seeger J, Savkin BT, *Stanglmaier S, Hirsche L.*
Separation technique for the determination of ^{99}Tc in milk and dairy products in case of emergency.
Applied radiation and isotopes 81 (2013), 36-41
doi:10.1016/j.apradiso.2013.03.031

A method for the determination of (99)Tc ($T_{1/2}$: 2.1 × 10^5 a) in milk and dairy products is presented in detail. The method includes the separation of fat and proteins from milk, the separation of Tc by anion exchange from other metals and the purification of Tc by extraction chromatography with subsequent measurement using LSC. A recommendation is given on how to use rhenium as a carrier for this particular matrix. The full analysis is done in 24h. The detection limit for milk is 0.2 Bq/l.

Kaiser JC and Walsh L
Independent analysis of the radiation risk for leukaemia in children and adults with mortality data (1950-2003) of Japanese A-bomb survivors.
Radiat Env Biophys. (2013) 52 (1): 17-27

A recent analysis of leukaemia mortality in Japanese A-bomb survivors has applied descriptive models, collected together from previous studies, to derive a joint excess relative risk estimate (ERR) by multi-model inference (MMI) (Walsh and Kaiser in Radiat Environ Biophys 50:21-35, 2011). The models use a linear-quadratic dose response with differing dose effect modifiers. In the present study, a set of more than 40 models has been submitted to a rigorous statistical selection procedure which fosters the parsimonious deployment of model parameters based on pairwise likelihood ratio tests. Nested models were consequently excluded from risk assessment. The set comprises models of the excess absolute risk (EAR) and two types of non-standard ERR models with sigmoidal responses or two line spline functions with a changing slope at a break point. Due to clearly higher values of the Akaike Information Criterion, none of the EAR models has been selected, but two non-standard ERR models qualified for MMI. The preferred ERR model applies a purely quadratic dose response which is slightly damped by an exponential factor at high doses and modified by a power function for attained age. Compared to the previous analysis, the present study reports similar point estimates and confidence intervals (CI) of the ERR from MMI for doses between 0.5 and 2.5 Sv. However, at lower doses, the point estimates are markedly reduced by factors between two and five, although the reduction was not statistically significant. The 2.5 % percentiles of the ERR from the preferred quadratic-exponential model did not fall below zero risk in exposure scenarios for children, adolescents and adults at very low doses down to 10 mSv. Yet, MMI

produced risk estimates with a positive 2.5 % percentile only above doses of some 300 mSv. Compared to CI from a single model of choice, CI from MMI are broadened in cohort strata with low statistical power by a combination of risk extrapolations from several models. Reverting to MMI can relieve the dilemma of needing to choose between models with largely different consequences for risk assessment in public health.

Kletting P, Schimmel S, Kestler HA, Hänscheid H, Luster M, Fernández M, Bröer JH, Nosske D, Lassmann M, Glatting G.

Molecular radiotherapy: The NUKFIT software for calculating the time-integrated activity coefficient.

Med Phys (2013) 40: doi: 10.1118/1.4820367.

Purpose: Calculation of the time-integrated activity coefficient (residence time) is a crucial step in dosimetry for molecular radiotherapy. However, available software is deficient in that it is either not tailored for the use in molecular radiotherapy and/or does not include all required estimation methods. The aim of this work was therefore the development and programming of an algorithm which allows for an objective and reproducible determination of the time-integrated activity coefficient and its standard error.
Methods: The algorithm includes the selection of a set of fitting functions from predefined sums of exponentials and the choice of an error model for the used data. To estimate the values of the adjustable parameters an objective function, depending on the data, the parameters of the error model, the fitting function and (if required and available) Bayesian information, is minimized. To increase reproducibility and user-friendliness the starting values are automatically determined using a combination of curve stripping and random search. Visual inspection, the coefficient of determination, the standard error of the fitted parameters, and the correlation matrix are provided to evaluate the quality of the fit. The functions which are most supported by the data are determined using the corrected Akaike information criterion. The time-integrated activity coefficient is estimated by analytically integrating the fitted functions. Its standard error is determined assuming Gaussian error propagation. The software was implemented using MATLAB.
Results: To validate the proper implementation of the objective function and the fit functions, the results of NUKFIT and SAAM numerical, a commercially available software tool, were compared. The automatic search for starting values was successfully tested for reproducibility. The quality criteria applied in conjunction with the Akaike information criterion allowed the selection of suitable functions. Function fit parameters and their standard error estimated by using SAAM numerical and
NUKFIT showed differences of <1%. The differences for the time-integrated activity coefficients were also <1% (standard error between 0.4% and 3%). In general, the application of the software is user-friendly and the results are mathematically correct and reproducible. An application of NUKFIT is presented for three different clinical examples.
Conclusions: The software tool with its underlying methodology can be employed to objectively and reproducibly estimate the time integrated activity coefficient and its standard error for most time activity data in molecular radiotherapy.

Kreuzer M, Dufey F, Sogl M, Schnelzer M, Walsh L.
External gamma radiation and mortality from cardiovascular diseases in the German WISMUT uranium miners cohort study, 1946-2008.
Radiat Environ Biophys (2013) 52(1): 37-46

It is currently unclear whether exposure of the heart and vascular system, at lifetime accumulated dose levels relevant to the general public (<500 mGy), is associated with an increased risk of cardiovascular disease. Therefore, data from the German WISMUT cohort of uranium miners were investigated for evidence of a relationship between external gamma radiation and death from cardiovascular diseases. The cohort comprises 58,982 former employees of the Wismut company. There were 9,039 recorded deaths from cardiovascular diseases during the follow-up period from 1946 to 2008. Exposures to external gamma radiation were estimated using a detailed job-exposure matrix. The exposures were based on expert ratings for the period 1946-1954 and measurements thereafter. The excess relative risk (ERR) per unit of cumulative gamma dose was obtained with internal Poisson regression using a linear ERR model with baseline stratification by age and calendar year. The mean cumulative gamma dose was 47 mSv for exposed miners (86 %), with a maximum of 909 mSv. No evidence for an increase in risk with increasing cumulative dose was found for mortality from all cardiovascular diseases (ERR/Sv = -0.13; 95 % confidence interval (CI): -0.38; 0.12) and ischemic heart diseases (n = 4,613; ERR/Sv = -0.03; 95 % CI: -0.38, 0.32). However, a statistically insignificant increase (n = 2,073; ERR/Sv = 0.44; 95 % CI: -0.16, 1.04) for mortality from cerebrovascular diseases was observed. Data on smoking, diabetes, and overweight are available for subgroups of the cohort, indicating no major correlation with cumulative gamma radiation. Confounding by these factors or other risk factors, however, cannot be excluded. In conclusion, the results provide weak evidence for an increased risk of death due to gamma radiation only for cerebrovascular diseases.

Kreuzer M, Sogl M, Brüske I, Möhner M, Nowak D, Schnelzer M, Walsh L.
Silica dust, radon and death from non-malignant respiratory diseases in German uranium miners.
Occup Environ Med (2013) 70(12): 869-75

OBJECTIVE: To quantify the relationship between death from non-malignant respiratory diseases (NMRD) and exposure to silica dust or radon in a cohort of 58,690 former German uranium miners. METHODS: In the follow-up period from 1946 to 2008, a total of 2336 underlying deaths from NMRDs occurred, including 715 deaths from chronic obstructive pulmonary diseases (COPD) and 975 deaths from silicosis or other pneumoconiosis. Exposure to respirable crystalline silica and radon was individually assessed by means of a comprehensive job-exposure matrix. Risk analyses were based on a linear Poisson regression model with the baseline stratified by age, calendar year and duration of employment. RESULTS: There was no increase in risk of death from COPDs or any other NMRDs in relation to cumulative exposure to silica (mean=5.9, max=56 mg/m(3)-years), except in the group of deaths from silicosis or other pneumoconiosis. Here, a strong non-linear increase in risk was observed.

Cumulative radon exposure (mean=280; max=3224 Working Level Months) was not related to death from COPDs or any other NMRDs. CONCLUSIONS: The present findings do not indicate a relationship between mortality from COPD with silica dust or radon. However, validity of cause of death and lack of control for smoking remain potential sources of bias.

Lassmann M, Noßke D.
Dosimetry of 223Ra-chloride: dose to normal organs and tissues.
Eur J Nucl Med Mol Imaging (2013) 40: 207-212.

Purpose: ^{223}Ra-Chloride (also called Alpharadin®) targets bone metastases with short range alpha particles. In recent years several clinical trials have been carried out showing, in particular, the safety and efficacy of palliation of painful bone metastases in patients with castration-resistant prostate cancer using ^{223}Ra-chloride. The purpose of this work was to provide a comprehensive dosimetric calculation of organ doses after intravenous administration of ^{223}Ra-chloride according to the present International Commission on Radiological Protection (ICRP) model for radium.
Methods: Absorbed doses were calculated for 25 organs or tissues.
Results: Bone endosteum and red bone marrow show the highest dose coefficients followed by liver, colon and intestines. After a treatment schedule of six intravenous injections with 0.05 MBq/kg of ^{223}Ra-chloride each, corresponding to 21 MBq for a 70 kg patient, the absorbed alpha dose to the bone endosteal cells is about 16 Gy and the corresponding absorbed dose to the red bone marrow is approximately 1.5 Gy.
Conclusion: The comprehensive list of dose coefficients presented in this work will assist in comparing and evaluating organ doses from various therapy modalities used in nuclear medicine and will provide a base for further development of patient-specific dosimetry.

Merk R, Kröger H, Edelhäuser-Hornung L, Hoffmann B.
PENELOPE-2008 Monte Carlo simulation of gamma exposure induced by 60Co and NORM-radionuclides in closed geometries
Applied radiation and isotopes 82 (2013), 20-27
doi:10.1016/j.apradiso.2013.07.006

We present Monte Carlo simulations of the gamma exposure in closed rooms made of steel or concrete and contaminated by ^{60}Co or NORM radionuclides. The computer code PENELOPE-2008 (Salvat et al., 2009) was used. Our simulations for ^{60}Co suggest considering detailed Monte Carlo simulations in future recommendations on clearance and exemption of materials with low radioactivity. For NORM nuclides our calculations suggest that Monte Carlo simulations are a possible alternative in case a material fails the dose rate criteria by using the RP 112 screening method.

Preischl, W, Hellmich, M.
On the construction of component importance measures for semi-Markov systems
Reliability Engineering and System Safety 109 (2013): 150-159

We report about a project aimed to collect human reliability data from the operational experience of German nuclear power plants. Its objective is the validation and extension of existing human reliability databases (in particular, the THERP database). A method utilizing the German licensee event report system to gather the data is described. For certain tasks with specific attributes this method allows to determine the number of times the task was performed in the past, as well as the number of errors that occurred. A statistical method to estimate the corresponding human error probability (HEP) based on these numbers is provided. We have applied this method to the reportable events stored in the database collecting the reportable events in German nuclear installations. In this way up to now 37 HEPs for a wide variety of tasks were obtained, together with information about relevant performance shaping factors. We discuss these HEP estimates and compare them to the THERP database if it provides a HEP for the task in question. In all except three cases we find an agreement within the uncertainty bounds. Moreover, we contribute 21 HEP estimates for which the THERP handbook provides no data, so they serve to extend the THERP database, among them a number of memory related errors. Therefore, this data may serve as an input for the discussion of second generation HRA methods.

Pressyanov D, ***Foerster E****, Georgiev S, Dimitrova I, Mitev K.*
Traceability of CDs/DVDs used as retrospective 222Rn detectors to reference STAR laboratory
Radiation measurements 59 (2013), 165-171
doi:10.1016/j.radmeas.2013.06.002

The practical applications of the method for retrospective ^{222}Rn measurements by home stored CDs/DVDs need a proper metrological assurance. The specific feature of this method, as compared to other methods for retrospective ^{222}Rn measurements is the possibility for an individual a posteriori calibration of the used CD/DVD-detectors. This paper describes a procedure to ensure the traceability of this method to a reference STAR laboratory. A set of 7 groups of CDs/DVDs were exposed to 4 reference ^{222}Rn exposure levels. After that they were treated in the etching laboratory as ”real” detectors and the ^{222}Rn concentrations were determined by applying an individual a posteriori calibration, correction for high track density and correction for depth at which the alpha tracks were etched. The results from all 7 groups of exposed detectors demonstrated relative variation from the reference values in the interval 3.4–23.4%. The results provide evidence that the routine measurements by the CD/DVD method warrant measurements with a relative uncertainty better than 25% and therefore this method is acceptable for large-scale applications.

Richter M, Jann O, Kemski J, Schneider U, Krocker C, ***Hoffmann B.***
Determination of radon exhalation from construction materials using VOC emission test chambers
Indoor air 23 (2013), Nr.5, 397-405
doi: 10.1111/ina.12031

The inhalation of (222) Rn (radon) decay products is one of the most important reasons for lung cancer after smoking. Stony building materials are an important

source of indoor radon. This article describes the determination of the exhalation rate of stony construction materials by the use of commercially available measuring devices in combination with VOC emission test chambers. Five materials - two types of clay brick, clinker brick, light-weight concrete brick, and honeycomb brick - generally used for wall constructions were used for the experiments. Their contribution to real room concentrations was estimated by applying room model parameters given in ISO 16000-9, RP 112, and AgBB. This knowledge can be relevant, if for instance indoor radon concentration is limited by law. The test set-up used here is well suited for application in test laboratories dealing with VOC emission testing.

Rimpler A, Barth I.

Strahlenexposition und Strahlenschutz des Personals in der Nuklearmedizin – Ergebnisse des EU-Projekts ORAMED.

Der Nuklearmediziner (2013) 36(04): 263-269 doi: 10.1055/s-0033-1354404.

Staff performing the preparation and administration of radiopharmaceuticals in nuclear medicine runs the risks of receiving skin exposures to the hands, which may exceed the annual limit of 500 mSv. Within the EU project ORAMED (Optimization of Radiation Protection in Medicine) a comprehensive investigation of skin exposures in diagnostics using Tc-99 m and F-18 and during radionuclide therapies by means of Y-90 labelled pharmaceuticals were performed. The survey measurements, involving 124 staff members in 32 nuclear medicine departments from 7 countries, provided numerous data on individual skin doses. The mean of the maximum skin dose, normalised to the activity, $H_p(0.07)_{max}/A$, covered a wide range, from 0.23 mSv/GBq during Tc-99 m administration up to 11 mSv/GBq for technicians during the preparing of Y-90/Zevalin®. Generally, the radiation exposure of staff when preparing radiopharmaceuticals and syringes was found to be higher than during its administration to the patients. Various parameters that characterise the exposure conditions at workplaces were analysed. Appropriate shielding and the use of tools to increase the distance are the most effective protective means. Investigations of the pattern of skin exposure across the hands give reason to revise common practice of wearing extremity dosemeters for routine monitoring. The base of the index finger of the non-dominant hand is most suitable to fix a ring dosemeter, with the detector in palmar direction. But even if a dosemeter is worn in such a manner, the skin dose maximum is underestimated by a factor of 5 on average. The study made clear that there is sufficient potential to further optimise the radiation protection standard and to decrease exposure of staff.

Rogits B, Jungnickel K, Löwenthal D, Kropf S, Nekolla EA, Dudeck O, Pech M, Wieners G, Ricke J.

Prospektive Evaluation der Handdosis des Radiologen im Rahmen von CT-gestützten Interventionen.

RöFo (2013) 185: 1081-1088.

Im Rahmen unterschiedlicher computertomografisch (CT-)gestützter Interventionen wurden die Handdosis des durchführenden Arztes ermittelt und Einflussfaktoren auf die Höhe der Handdosis evaluiert. Mit einem sofort ablesbaren Dosimeter EDD-30 (Unfors, Schweden) wurde die Handdosis für

Stanzbiopsien, Drainageeinlagen, periradikuläre Therapie sowie Truncus coeliacus Neurolyse ermittelt. Alle Interventionen wurden an einem 16-Zeilen-CT (Aquilion 16, Toshiba, Japan) in CT-Fluoroskopie-Technik durchgeführt, wobei die Standard-Parameter 120 kV-Röhrenspannung, 90 mA-Röhrenstrom sowie 4 mm-Schichtdicke waren. Es wurden Tumorgröße, Schwierigkeitsgrad (1–3), Erfahrungsgrad des Interventionalisten, Nadeldurchmesser und die Geräteparameter (mAs, Dosis-Längen-Produkt sowie die Scanzeit) dokumentiert. In die Auswertung gingen 138 CT-gestützte Interventionen (Lokalisationen: Lunge n=41, Retroperitoneum n=53, Leber n=25 und Wirbelsäule n=19) mit 3 verschiedenen Prozeduren (Biopsien n=99, Drainagen n=23 und Schmerztherapien n=16) ein. Die zu biopsierenden Läsionen hatten eine Größe von 4–240 mm (Median 23 mm). Die Fluoroskopiezeit pro Intervention lag zwischen 4,6 und 140,2 s (Median 24,2 s). Die mit dem EDD-30 gemessene Handdosis reichte von 0,001–3,02 mSv (Median 0,22 mSv). Die Handdosiswerte für Lungenpunktionen (n=41) bewegten sich auf einem höheren Niveau (Median 0,32 mSv; p=0,01) im Vergleich zu Interventionen an Leber, Retroperitoneum und Wirbelsäule. Neben den physikalischen Einflussgrößen zeigten der Schwierigkeitsgrad (p=0,001) und die summierte Stichtiefe (p=0,004) einen signifikanten Einfluss auf die Handdosis. Schlussfolgerung: Bei den evaluierten Eingriffen wurde eine mediane Handexposition von lediglich 0,22 mSv festgestellt, sodass theoretisch über 2000 Interventionen pro Jahr von einer Person durchgeführt werden können, bevor der Handdosis-Grenzwert von 500 mSv erreicht wird.

In CT-guided interventions, the radiologist's hand dose was assessed and influencing factors were determined. The following CT guided interventions were included: Core biopsy, drainage, periradicular therapy, and celiac plexus neurolysis. Hand dose was measured with an immediately readable dosimeter (EDD-30, Unfors, Sweden). The default parameters for CT fluoroscopy were 120 kV, 90 mA and a 4mm slice thickness. All interventions were performed on a 16-slice CT unit (Aquilion 16 Toshiba, Japan). Tumor size, degree of difficulty (1 – 3), level of experience and device parameters (mAs, dose-length product, scan time) were documented. 138 CT-guided interventions (biopsy n = 99, drainage n = 23, pain therapy n = 16) at different locations (lung n = 41, retroperitoneum n = 53, liver n = 25, spine n = 19) were included. The lesion size was 4 – 240mm (median: 23 mm). The fluoroscopy time per intervention was 4.6 – 140.2 s (median: 24.2 s). The measured hand dose ranged from 0.001 – 3.02mSv (median: 0.22mSv). The median hand dose for lung puncture (n = 41) was slightly higher (median: 0.32mSv, p = 0.01) compared to that for the liver, retroperitoneum and other. Besides physical influencing factors, the degree of difficulty (p = 0.001) and summed puncture depth (p = 0.004) correlated significantly with hand dose. Conclusion: The median hand dose for different CT-guided interventions was 0.22mSv. Therefore, the annual hand dose limit would normally only be reached with about 2000 interventions.

Romm H, Ainsbury E, Barnard S, Barrios L, Barquinero JF, Beinke C, Deperas M, Gregoire E, Koivistoinen A, Lindholm C, Moquet J, Oestreicher U, Puig R, Rothkamm K, Sommer S, Thierens H , Vandersickel V, Vral A, Wojcik A.
Automatic scoring of dicentric chromosomes as a tool in large scale radiation accidents.

Mutat Res (2013) 756: 174-183.

Mass casualty scenarios of radiation exposure require high throughput biological dosimetry techniques for population triage in order to rapidly identify individuals who require clinical treatment. The manual dicentric assay is a highly suitable technique, but it is also very time consuming and requires well trained scorers. In the framework of the MULTIBIODOSE EU FP7 project, semi-automated dicentric scoring has been established in six European biodosimetry laboratories. Whole blood was irradiated with a Co-60 gamma source resulting in 8 different doses between 0 and 4.5Gy and then shipped to the six participating laboratories. To investigate two different scoring strategies, cell cultures were set up with short term (2-3h) or long term (24h) colcemid treatment. Three classifiers for automatic dicentric detection were applied, two of which were developed specifically for these two different culture techniques. The automation procedure included metaphase finding, capture of cells at high resolution and detection of dicentric candidates. The automatically detected dicentric candidates were then evaluated by a trained human scorer, which led to the term 'semi-automated' being applied to the analysis. The six participating laboratories established at least one semi-automated calibration curve each, using the appropriate classifier for their colcemid treatment time. There was no significant difference between the calibration curves established, regardless of the classifier used. The ratio of false positive to true positive dicentric candidates was dose dependent. The total staff effort required for analysing 150 metaphases using the semi-automated approach was 2 min as opposed to 60 min for manual scoring of 50 metaphases. Semi-automated dicentric scoring is a useful tool in a large scale radiation accident as it enables high throughput screening of samples for fast triage of potentially exposed individuals. Furthermore, the results from the participating laboratories were comparable which supports networking between laboratories for this assay.

Romm H, Barnard, S, Boulay-Greene H, De Amicis A, De Sanctis S, Franco M, Herodin F, Jones A, Kulka U, Lista F, Martigne P, Moquet J, Oestreicher U, Rothkamm K, Thierens H, Valente M, Vandersickel V, Vral A, Braselmann H, Meineke V, Abend M, Beinke C.

Laboratory intercomparison of the cytokinesis-block micronucleus assay.

Radiat Res (2013) 180: 120-128.

The focus of the study is an intercomparison of laboratories' dose-assessment performances using the cytokinesis-block micronucleus (CBMN) assay as a diagnostic triage tool for individual radiation dose assessment. Homogenously X-irradiated (240 kVp, 1 Gy/min) blood samples for establishing calibration data (0.25–5 Gy) as well as blind samples (0.1–6.4 Gy) were sent to the participants. The CBMN assay was performed according to protocols individually established and varying among participating laboratories. The time taken to report dose estimates was documented for each laboratory. Additional information concerning laboratory organization/characteristics as well as assay performance was collected. The mean absolute difference (MAD) was calculated and radiation doses were merged into four triage categories reflecting clinical aspects to calculate accuracy, sensitivity and specificity. The earliest report time was 4 days after sample arrival. The CBMN dose estimates were reported with

high accuracy (MAD values of 0.20–0.50 Gy at doses below 6.4 Gy for both manual and automated scoring procedures), but showed a limitation of the assay at the dose point of 6.4 Gy, which resulted in a clear dose underestimation in all cases. The MAD values (without 6.4 Gy) differed significantly (P = 0.03) between manual (0.25 Gy, SEM = 0.06, n = 4) or automated scoring procedures (0.37 Gy, SEM = 0.08, n = 5), but lowest MAD were equal (0.2 Gy) for both scoring procedures. Likewise, both scoring procedures led to the same allocation of dose estimates to triage categories of clinical significance (about 83% accuracy and up to 100% specificity).

Rothkamm K, Beinke C, Romm H, Badie C, Balagurunathan Y, Barnard S, Bernard N, Boulay-Greene H, Brengues M, De Amicis A, De Sanctis S, Greither R, Herodin F, Jones A, Kabacik S, Knie T, Kulka U, Lista F, Martigne P, Missel A, Moquet J, Oestreicher U, Peinnequin A, Poyot T, Roessler U, Scherthan H, Terbrueggen B, Thierens H, Valente M, Vral A, Zenhausern F, Meineke V, Braselmann H, Abend M.

Comparison of established and emerging biodosimetry assays.

Radiat Res. (2013) 180(2): 111-119.

Rapid biodosimetry tools are required to assist with triage in the case of a large-scale radiation incident. Here, we aimed to determine the dose-assessment accuracy of the well-established dicentric chromosome assay (DCA) and cytokinesis-block micronucleus assay (CBMN) in comparison to the emerging γ-H2AX foci and gene expression assays for triage mode biodosimetry and radiation injury assessment. Coded blood samples exposed to 10 X-ray doses (240 kVp, 1 Gy/min) of up to 6.4 Gy were sent to participants for dose estimation. Report times were documented for each laboratory and assay. The mean absolute difference (MAD) of estimated doses relative to the true doses was calculated. We also merged doses into binary dose categories of clinical relevance and examined accuracy, sensitivity and specificity of the assays. Dose estimates were reported by the first laboratories within 0.3-0.4 days of receipt of samples for the γ-H2AX and gene expression assays compared to 2.4 and 4 days for the DCA and CBMN assays, respectively. Irrespective of the assay we found a 2.5-4-fold variation of interlaboratory accuracy per assay and lowest MAD values for the DCA assay (0.16 Gy) followed by CBMN (0.34 Gy), gene expression (0.34 Gy) and γ-H2AX (0.45 Gy) foci assay. Binary categories of dose estimates could be discriminated with equal efficiency for all assays, but at doses ≥1.5 Gy a 10% decrease in efficiency was observed for the foci assay, which was still comparable to the CBMN assay. In conclusion, the DCA has been confirmed as the gold standard biodosimetry method, but in situations where speed and throughput are more important than ultimate accuracy, the emerging rapid molecular assays have the potential to become useful triage tools.

Rothkamm K, Horn S, Scherthan H, Rössler U, De Amicis A, Barnard S, Kulka U, Lista F, Meineke V, Braselmann H, Beinke C, Abend M.

Laboratory intercomparison on the γ-H2AX foci assay.

Radiat Res. (2013) 180(2): 149-155.

The focus of the study is an intercomparison of laboratories' dose-assessment performances using the γ-H2AX foci assay as a diagnostic triage tool for rapid individual radiation dose assessment. Homogenously X-irradiated (240 kVp, 1 Gy/min) blood samples for establishing calibration data (0.25-4 Gy) as well as blinded test samples (0.1-6.4 Gy) were incubated at 37°C for 2 and 24 h (repair time) and sent to the participants. The foci assay was performed according to protocols individually established in participating laboratories and therefore varied. The time taken to report dose estimates was documented for each laboratory. Additional information concerning laboratory organization/characteristics as well as assay performance was collected. The mean absolute difference (MAD) of estimated doses relative to the actual doses was calculated and radiation doses were merged into four triage categories reflecting clinical relevance to calculate accuracy, sensitivity and specificity. First γ-H2AX based dose estimates were reported 7 h after sample receipt. Estimates were similarly accurate for 2 and 24 h repair times, providing scope for its use in the early phase of a radiation exposure incident. Equal accuracy was achieved by scoring 20, 30, 40 or 50 cells per sample. However, MAD values of 0.5-0.7 Gy and 1.3-1.7 Gy divided the data sets into two groups, driven mainly by the considerable differences in foci yields between calibration and blind samples. Foci yields also varied dramatically between laboratories, highlighting reproducibility issues as an important caveat of the foci assay. Nonetheless, foci counts could distinguish high- and low-dose samples in all data sets and binary dose categories of clinical significance could be discriminated with satisfactory accuracy (mean 84%, ±0.03 SEM). Overall, the results suggest that the γ-H2AX assay is a useful tool for rapidly screening individuals for significant exposures that occurred up to at least 24 h earlier, and may help to prioritize cytogenetic dosimetry follow-up.

Saey PRJ, Ringbom A, Bowyer T W, ***Zähringer M****,* ***Auer M****, Faanhof A, Labuschagne C, Al-Rashidi M S, Tippawan U, Verboomen B.*

Worldwide measurements of radioxenon background near isotope production facilities, a nuclear power plant and at remote sites: the "EU/JA-II" Project

In: Journal of radioanalytical and nuclear chemistry 296 (2013), Nr.2, 1133-1142
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The Comprehensive Nuclear-Test-Ban Treaty (CTBT) specifies that radioxenon measurements should be performed at 40 or more stations worldwide within the International Monitoring System (IMS). Measuring radioxenon is one of the principle techniques to detect underground nuclear explosions. Specifically, presence and ratios of different radioxenon isotopes allows determining whether a detection event under consideration originated from a nuclear explosion or a civilian source. However, radioxenon monitoring on a global scale is a novel technology and the global civil background must be characterized sufficiently. This paper lays out a study, based on several unique measurement campaigns, of the worldwide concentrations and sources of verification relevant xenon isotopes. It complements the experience already gathered with radioxenon measurements within the CTBT IMS programme and focuses on locations in Belgium, Germany, Kuwait, Thailand and South Africa where very little information was available on ambient xenon levels or interesting sites offered

opportunities to learn more about emissions from known sources. The findings corroborate the hypothesis that a few major radioxenon sources contribute in great part to the global radioxenon background. Additionally, the existence of independent sources of ^{131m}Xe (the daughter of ^{131}I) has been demonstrated, which has some potential to bias the isotopic signature of signals from nuclear explosions.

Salehi Ravesh M, Brix G, Laun FB, Puderbach M, Ley-Zaporozhan J, Ley S, Fieselmann A, Schranz W, Semmler W, Risse F.

Quantification of pulmonary microcirculation by dynamic contrast-enhanced magnetic resonance imaging: comparison of four regularization methods.

Magn Reson Med (2013) 69: 188-99.

Tissue microcirculation can be quantified by a deconvolution analysis of concentration-time curves measured by dynamic contrast-enhanced magnetic resonance imaging. However, deconvolution is an ill-posed problem, which requires regularization of the solutions. In this work, four algebraic deconvolution/regularization methods were evaluated: truncated singular value decomposition and generalized Tikhonov regularization (GTR) in combination with the L-curve criterion, a modified LCC (GTR-MLCC), and a response function model that takes a-priori knowledge into account. To this end, dynamic contrast-enhanced magnetic resonance imaging data sets were simulated by an established physiologically reference model for different signal-to-noise ratios and measured on a 1.5-T system in the lung of 10 healthy volunteers and 20 patients. Analysis of both the simulated and measured dynamic contrast-enhanced magnetic resonance imaging datasets revealed that GTR in combination with the L-curve criterion does not yield reliable and clinically useful results. The three other deconvolution/regularization algorithms resulted in almost identical microcirculatory parameter estimates for signal-to-noise ratios > 10. At low signal-to-noise ratios levels (<10) typically occurring in pathological lung regions, GTR in combination with a modified L-curve criterion approximates the true response function much more accurately than truncated singular value decomposition and GTR in combination with response function model with a difference in accuracy of up to 76%. In conclusion, GTR in combination with a modified L-curve criterion is recommended for the deconvolution of dynamic contrast-enhanced magnetic resonance imaging curves measured in the lung parenchyma of patients with highly heterogeneous signal-to-noise ratios.

Salomaa S, Prise KM, Atkinson MJ, Wojcik A, Auvinen A, Grosche B, Sabatier L, Jourdain JR, Salminen E, Baatout S, Kulka U, Rabus H, Blanchardon E, Averbeck D, Weiss W.

State of the art in research into the risk of low dose radiation exposure-findings of the fourth MELODI workshop.

J Radiol Prot (2013) 33: 589-603.

The fourth workshop of the Multidisciplinary European Low Dose Initiative (MELODI) was organised by STUK—Radiation and Nuclear Safety Authority of Finland. It took place from 12 to 14 September 2012 in Helsinki, Finland. The meeting was attended by 179 scientists and professionals engaged in radiation

research and radiation protection. We summarise the major scientific findings of the workshop and the recommendations for updating the MELODI Strategic Research Agenda and Road Map for future low dose research activities.

Schmid E, Wagner FM, Canella L, Romm H, Schmid TE.
RBE of thermal neutrons for induction of chromosome aberrations in human lymphocytes.
Radiat Environ Biophys 2013; 52:113-121.

The induction of chromosome aberrations in human lymphocytes irradiated in vitro with slow neutrons was examined to assess the maximum low-dose RBE (RBE(M)) relative to (60)Co γ-rays. For the blood irradiations, cold neutron beam available at the prompt gamma activation analysis facility at the Munich research reactor FRM II was used. The given flux of cold neutrons can be converted into a thermally equivalent one. Since blood was taken from the same donor whose blood had been used for previous irradiation experiments using widely varying neutron energies, the greatest possible accuracy was available for such an estimation of the RBE(M) avoiding the inter-individual variations or differences in methodology usually associated with inter-laboratory comparisons. The magnitude of the coefficient α of the linear dose-response relationship (α = 0.400 ± 0.018 Gy(-1)) and the derived RBE(M) of 36.4 ± 13.3 obtained for the production of dicentrics by thermal neutrons confirm our earlier observations of a strong decrease in α and RBE(M) with decreasing neutron energy lower than 0.385 MeV (RBE(M) = 94.4 ± 38.9). The magnitude of the presently estimated RBE(M) of thermal neutrons is-with some restrictions-not significantly different to previously reported RBE(M) values of two laboratories.

*Stojanovska Z, **Bossew P**, Tokonami S, Zunic ZS, Bochicchio F, Boev B, Ristova M, Januseski J.*
National survey of indoor thoron concentration in FYR of Macedonia (continental Europe - Balkan region)
In: Radiation measurements 49 (2013), 57-66
doi:10.1016/j.radmeas.2012.11.023

As a part of the national survey of natural radioactivity in The Former Yugoslav Republic of Macedonia, indoor thoron gas concentration was measured in 300 dwellings during one year, from December 2008 till December 2009 using passive discriminative radon–thoron detectors. Detectors were deployed at a distance of >50 cm from walls in order to be less sensitive to distance from walls. Altogether 532 measurements were performed: 53 in winter, 57 in spring, 122 in summer and 300 in autumn. The frequency distribution is well described by a log-normal function. The geometric means of indoor thoron concentration (with geometric standard deviations in brackets) in winter, spring, summer and autumn were obtained to be: 39 Bq m^{-3} (3.4), 32 Bq m^{-3} (2.8), 18 Bq m^{-3} (2.8), 31 Bq m^{-3} (2.9), respectively. Seasonal variations of thoron appear lower than those of radon. The seasonal corrected annual mean concentration ranges between 3 and 272 Bq m^{-3} with a geometric mean of 28 Bq m^{-3} (2.12). A detailed statistical analysis of the geogenic and building factors which influence the indoor thoron concentration is also reported. This survey represents the first national survey on indoor thoron in continental Europe.

Theuring P, ***Jha A, Kirchner G,*** *Behrens S, Rode M.*

Identification of fluvial sediment sources in the Kharaa River catchment, Northern Mongolia

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doi:10.1002/hyp.9684

Fine-grained sediments constitute a major stressing factor for the aquatic ecosystem in the 15 000 km^2 Kharaa River catchment in Northern Mongolia. The objectives of this study were to identify the suspended sediment (SS) sources and quantify the sediment budget of the basin. Sediment sources were identified with the help of sediment tracing methods utilizing Be-7, Cs-137 and Pb-210 radionuclides. High-resolution discharge data were used in combination with daily suspended solid measurements to calculate the SS budget. These calculations were compared with the monthly archive data on SS and discharge to investigate temporal load variations. In addition, the sediment budget model SedNet was used to estimate the SS budget and test its applicability in a cold semi-arid region. Results of the sediment tracing showed that riverbank erosion generates 74.5% of the suspended sediment load, whereas surface erosion contributes 21.7% and gully erosion only 3.8%. In the most intensely used agricultural tributary catchment Zagdelin Gol, upland erosion contributed only 12.7% to the total SS losses. The calculated mean annual sediment load for the years 1990–2002 was 20.3 $kt \cdot a^{-1}$. The SedNet model computed SS export from the catchment in the same order of magnitude as measured data (16.2 $kt \cdot a^{-1}$). The results help to identify effective management measures to reduce sediment loads and mitigate its impact on the aquatic environment. Copyright © 2012 John Wiley & Sons, Ltd.

Walsh L and Schneider U

A method for determining weights for excess relative risk and excess absolute risk when applied in the calculation of lifetime risk of cancer from radiation exposure.

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Radiation-related risks of cancer can be transported from one population to another population at risk, for the purpose of calculating lifetime risks from radiation exposure. Transfer via excess relative risks (ERR) or excess absolute risks (EAR) or a mixture of both (i.e., from the life span study (LSS) of Japanese atomic bomb survivors) has been done in the past based on qualitative weighting. Consequently, the values of the weights applied and the method of application of the weights (i.e., as additive or geometric weighted means) have varied both between reports produced at different times by the same regulatory body and also between reports produced at similar times by different regulatory bodies. Since the gender and age patterns are often markedly different between EAR and ERR models, it is useful to have an evidence-based method for determining the relative goodness of fit of such models to the data. This paper identifies a method, using Akaike model weights, which could aid expert judgment and be applied to help to achieve consistency of approach and quantitative evidence-based results in future health risk assessments. The results of applying this method to recent LSS cancer incidence models are that the relative EAR weighting by cancer solid cancer site, on a scale of 0-1, is zero for breast and colon, 0.02 for all solid, 0.03 for lung, 0.08 for liver, 0.15 for thyroid, 0.18 for bladder and 0.93 for stomach. The EAR

weighting for female breast cancer increases from 0 to 0.3, if a generally observed change in the trend between female age-specific breast cancer incidence rates and attained age, associated with menopause, is accounted for in the EAR model. Application of this method to preferred models from a study of multi-model inference from many models fitted to the LSS leukemia mortality data, results in an EAR weighting of 0. From these results it can be seen that lifetime risk transfer is most highly weighted by EAR only for stomach cancer. However, the generalization and interpretation of radiation effect estimates based on the LSS cancer data, when projected to other populations, are particularly uncertain if considerable differences exist between site-specific baseline rates in the LSS and the other populations of interest. Definitive conclusions, regarding the appropriate method for transporting cancer risks, are limited by a lack of knowledge in several areas including unknown factors and uncertainties in biological mechanisms and genetic and environmental risk factors for carcinogenesis; uncertainties in radiation dosimetry; and insufficient statistical power and/or incomplete follow-up in data from radio-epidemiological studies.

Walsh L.

Neutron relative biological effectiveness for solid cancer incidence in the Japanese A-bomb survivors: an analysis considering the degree of independent effects from γ-ray and neutron absorbed doses with hierarchical partitioning

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It has generally been assumed that the neutron and γ-ray absorbed doses in the data from the life span study (LSS) of the Japanese A-bomb survivors are too highly correlated for an independent separation of the all solid cancer risks due to neutrons and due to γ-rays. However, with the release of the most recent data for all solid cancer incidence and the increased statistical power over previous datasets, it is instructive to consider alternatives to the usual approaches. Simple excess relative risk (ERR) models for radiation-induced solid cancer incidence fitted to the LSS epidemiological data have been applied with neutron and γ-ray absorbed doses as separate explanatory covariables. A simple evaluation of the degree of independent effects from γ-ray and neutron absorbed doses on the all solid cancer risk with the hierarchical partitioning (HP) technique is presented here. The degree of multi-collinearity between the γ-ray and neutron absorbed doses has also been considered. The results show that, whereas the partial correlation between the neutron and γ-ray colon absorbed doses may be considered to be high at 0.74, this value is just below the level beyond which remedial action, such as adding the doses together, is usually recommended. The resulting variance inflation factor is 2.2. Applying HP indicates that just under half of the drop in deviance resulting from adding the γ-ray and neutron absorbed doses to the baseline risk model comes from the joint effects of the neutrons and γ-rays-leaving a substantial proportion of this deviance drop accounted for by individual effects of the neutrons and γ-rays. The average ERR/Gy γ-ray absorbed dose and the ERR/Gy neutron absorbed dose that have been obtained here directly for the first time, agree well with previous indirect estimates. The average relative biological effectiveness (RBE) of neutrons relative to γ-rays, calculated directly from fit parameters to the all solid cancer ERR model with both colon absorbed dose covariables, is 65 (95 %CI: 11; 170). Therefore, although the 95 %

CI is quite wide, reference to the colon doses with a neutron weighting of 10 may not be optimal as the basis for the determination of all solid cancer risks. Further investigations into the neutron RBE are required, ideally based on the LSS data with organ-specific neutron and γ-ray absorbed doses for all organs rather than the RBE weighted absorbed doses currently provided. The HP method is also suggested for use in other epidemiological cohort analyses that involve correlated explanatory covariables.