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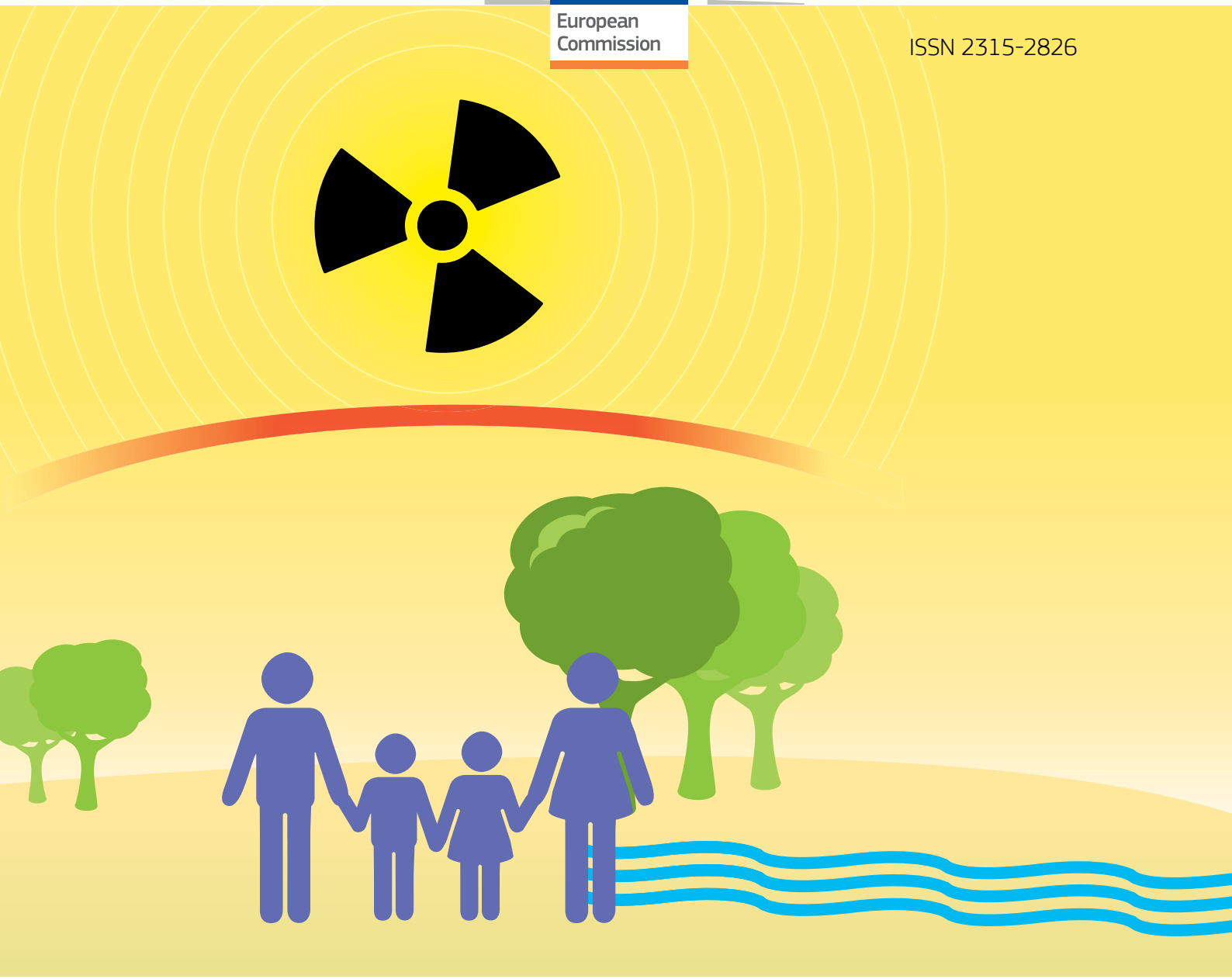

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N° 187

EU Scientific Seminar May 2017

"Emerging issues with regard to organ doses"

Energy

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RADIATION PROTECTION N° 187

EU Scientific Seminar May 2017

"Emerging issues with regard to organ doses"

Proceedings of a scientific seminar held in Luxembourg on 17 May 2017

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts

Directorate-General for Energy
Directorate D — Nuclear Energy, Safety and ITER
Unit D.3 — Radiation Protection and Nuclear Safety
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FOREWORD

Luxembourg, September 2018

The European Commission organises every year, in cooperation with the Group of Experts referred to in Article 31 of the Euratom Treaty, a Scientific Seminar on emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend research, regulatory or legislative initiatives. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts' conclusions are valuable input to the process of reviewing and potentially revising European radiation protection legislation.

In May 2017, the EU Scientific Seminar covered the issue *Emerging issues with regard to organ doses*. Internationally renowned scientists presented latest developments in the evaluation of radiation risks to organs:

- Cognitive and cerebrovascular effects induced by low dose ionising radiation (CEREBRAD)
- Radiation-induced cardiovascular disease: Is it time for a new biology?
- Issues related to the concept of organ dose
- New data regarding the lens of the eye (for radiation protection purposes)
- Evaluation of the risk of organ exposure - risk related approach versus effective dose approach

The presentations were followed by a round table discussion, in which the speakers and additional invited experts discussed potential *policy implications and research needs*.

The Group of Experts discussed this information and drew conclusions that are relevant for consideration by the European Commission and other international bodies.

CONTENTS

1 COGNITIVE AND CEREBROVASCULAR EFFECTS INDUCED BY LOW DOSE IONIZING RADIATION 'CEREBRAD'

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Summary

Up to now, the direct effects of ionizing radiation (IR) on the central nervous system remain elusive and are subject to many debates and uncertainties, especially concerning low doses of irradiation (LD-IR). In the context of the FP7 CEREBRAD (Cognitive and Cerebrovascular Effects Induced by Low Dose Ionizing Radiation, grant agreement n°295552) project, we set the stage to answer these questions by means of two approaches: (1) a direct health assessment through epidemiological studies on exposed individuals and (2) an investigation of dose-dependent and radiation-type dependent biological effects using a mouse model. Furthermore, to correctly inform on the risk estimates, we compared internal and external exposure paradigms and evaluated a possible synergistic effect of radiation with other environmental pollutants. This multidisciplinary approach was achieved by the joint effort of a European consortium including radiobiologists, epidemiologists, neurobiologists, bio-informaticians, paediatricians and dosimetrists.

1.1 Introduction

In 1929, Goldstein and Murphy reported on mental retardation and microcephaly resulting from prenatal radiation exposure, as revealed from 38 case reports of children born to mothers that received pelvic radiotherapy [1]. Decades later, this awareness was further strengthened and quantitative data was provided through the follow-up of the health of atomic bomb survivors, primarily performed and published by M. Otake and W.J. Schull [2]. Their study involved 1500 individuals exposed in utero to the radioactive fallout of the atomic bombs in Hiroshima and Nagasaki (mainly γ-radiation). Apart from an excess cancer risk [3], a higher incidence in generalized growth retardation and microcephaly, mental disability and seizures, as well as a decreased school performance and scoring on intelligence tests were observed [2]. These defects were all relatively linearly dose-dependent, with an increased risk for mental retardation of 43% and a decline of 25-29 points in IQ values per Gy [4]. No dose threshold has been proposed for these observations, except for mental retardation, for which symptoms were detected at doses as low as 0.06 to 0.31 Gy [5]. Important to note from these studies is that the developing brain is particularly sensitive to irradiation when exposure occurred between weeks 8 and 15 of pregnancy, and to a lesser extent between weeks 16 and 25 [4, 6]. Hence, the brain appears especially vulnerable for such radiation-induced risks during the period characterized by a massive neuron production and differentiation/migration.

The fallout of the Chernobyl accident in 1986 has exposed many people to radioiodine (^{131}I) and radiocaesium (^{137}Cs). Also here, prenatally irradiated subjects were followed over time, but findings are much less consistent and are subject to debate due to inconsistent dosimetry

[1] On behalf of CEREBRAD an EU FP7 project Grant Agreement 295552. Coordination by Dr. M. Abderrafi Benotmane.

[7, 8]. This might be due to the fact that people in the surrounding areas of the catastrophe were exposed to relatively low doses (between 0.01 and 0.25 Sv). Other limitations of these epidemiological studies were the potential confounding variables that could not be taken into account, the lack of accurate dose measures per individual, and the fact that cohorts were considerably smaller than those of the atomic bomb survivors [9, 10]. Nevertheless, an increased occurrence of mental retardation and decrease in (verbal) IQ scores could be noted in children and adolescents in utero exposed [9, 11-13]. Neuropsychiatric problems were also reported, but might as well be associated with the mother's health and stress [13].

In summary, the information about occurrence of late cognitive and cerebrovascular diseases due to exposure to radiation early in life (in utero or during childhood) is scarce. However, A-bomb survivor data indicate a linear dose-response curve with a threshold around 200 mGy. This raises once more the concern regarding the uncertainty of low-dose radiation. This is in part due to the lack of sufficiently large cohorts to estimate the expected mild effects from low radiation doses, combined with a lack of understanding of the underlying mechanisms. Nevertheless, the increasing use of radiation in medical diagnostics urges the need for appropriate research to define precisely the effect of low dose radiation on the brain. The aim of the FP7 CEREBRAD project (GA n°295552) contributed thus to gather sufficient scientific evidence to increase the statistical power of epidemiological data. On the other hand, the project attempts to illustrate the related cellular and molecular events modulated after exposure and most probably responsible for possible late cognitive and cerebrovascular diseases.

1.2 Human data

1.2.1 Cognitive effects of low doses

1.2.1.1 Medical irradiation during childhood

The study cohort consisted of the ANGIO cohort or haemangioma cohort. These subjects were treated in the vast majority before the age of one year. This cohort was established between 1985 and 1995 by IGR/INSERM team in France to study radiation-induced pathologies [14-17]. One hundred sixty-seven individuals who received radiation dose estimates less than 1 Gy to the brain have been identified. A total of 115 subjects were interviewed, the average age at time of questionnaire tests being 50 (from 42 to 63). Neurocognitive assessments of participating subjects based on an initial interview including 7 standardized questionnaires. Doses of ionizing radiation received by all organs of the body were estimated for all these children, regardless of the original location of the haemangioma. Well validated cognitive tests have been used to evaluate the cognitive capabilities many years after exposure.

Among the cognitive tests used:

The RAVLT test and particularly the “delay recall” task is a specific test to evaluate the episodic memory. Our finding concerning the role of the maximum brachytherapy dose to the temporal lobes in the RAVLT test scores seems relevant since the episodic memory uses neural networks in the hippocampus and more broadly in the inside of the temporal lobes. Indeed, the hippocampus appears to play a central role in the temporary and more durable storage explicit information related to different cortical structures [18].

The MoCA test involved many cognitive domains (executive function, language, memory) and most of patients lost points in memory task. It could explain the relationship between the temporal dose and the MoCA test score but this test is too general and uses several brain structures to conclude a causal relationship. A higher total radiation dose (Brachytherapy and X-rays) to the cerebral hemispheres was significantly associated to a lower education

(p=0.035). Nevertheless the total radiation dose received in cerebral hemispheres, whatever the structure considered was not significantly linked to any of the neurocognitive test used in our study, at the exception of a near from significant result when evaluating depression based on HAD-D score when considering left hemisphere. A higher average radiation dose to cerebral hemisphere was also significantly or nearly significantly associated to a degradation in the value of most of neurocognitive tests we used.

The RALVT Decay recall and Montreal Cognitive Assessment (MOCA) scores were more impacted by average radiation doses to the temporal lobes.

The HAD-D test showed a trend for increasing scores with increasing dose to the thyroid and with the maximum brachytherapy dose to the hemispheres from thresholds equal to 0.12 Gy and 0.054 respectively. Approximately the same threshold (0.059 Gy) of the radiation dose to the left hemisphere lobe is obtained to show a significant increase of the FactCog (Perceived cognitive impairments) scores. RALVT delay recall scores according the years schooling (threshold = 3 years). The maximum brachytherapy dose to the temporal lobes was also significantly associated to this test scores above 0.054 Gy.

1.2.1.2 Chernobyl studies

The cognitive function is influenced by the radiation dose and age at exposure. The level of subjective distress caused by a traumatic event is higher in young adults exposed in utero. There is some increase of somatoform symptoms and levels of anxiety, insomnia and social dysfunction. Subjects exposed in utero during the check at age of 25–27 years exhibit an excess of the disorders of autonomic nervous system (ICD-10: G90). Neurological microsymptoms as well as neurotic, stress-related and somatoform disorders (F40–F48) dominate.

Subjects exposed to ionizing radiation at adulthood as cleanup workers exhibit symptoms of mild cognitive impairment according to the operational criteria of the MMSE (mean group scores range =24–27). The cleanup workers have significantly higher level of mental disorders according to the BPRS in dose-related manner, than young adults. This could be the effect of the age and radiation dose. Cleanup workers exposed to doses over 250 mSv and, especially, 500 mSv demonstrate significant cognitive deficit in comparison with exposed below 250 mSv and non-exposed patients. In comparison with previous studies an excess of cognitive dysfunction was significant at doses of 250 mSv and higher.

COGNITIVE FUNCTION GROUPS	Mini-Mental State Examination (MMSE)	Other criteria	N	%
Normal	28 or more	No cerebrovascular disease, confirmed by neurologist	77	25
Mild Cognitive Impairment (MCI)	24-27	Cerebrovascular disease, confirmed by neurologist	183	60
Dementia (VaD, mainly vascular)	23 or less	Cerebrovascular disease, confirmed by neurologist	46	15
Total			306	100

1.2.2 Cerebrovascular effects of low doses

We set up a case-control study; the cohort included 233 cases of strokes having occurred 5 years or more following a childhood cancer radiotherapy and 233 matched controls for gender, age and date of childhood cancer, and length of follow-up. Detailed radiation dose estimation in any brain sub structure and in cerebral arteries were evaluated. In a linear model, the Excess of Odds risk 'EOR' of stroke, all types together, per Gy of average radiation dose to the cerebral arteries, was equal to EOR/Gy=0.49 (95%CI: 0.22 to 1.17). To add an exponential or a quadratic term did not improve the fit of the data. The radiation dose received to brain structure other than brain arteries did not play any role.

Our findings strongly differed according to the type of stroke, ischemic or haemorrhagic of the cerebrovascular diseases. When considering haemorrhagic strokes, an exponential model fitted better the data. Therefore the risk due to low doses was low (EOR/1GY=0.13 (95%CI: 0.07 to 0.21). At the opposite, when considering ischemic strokes, a linear exponential model was the best model. In this linear model the risk for low dose was very high: EOR/1GY=2.64 (95%CI: 0.39; 17.18).

Considered together, the EOR/1Gy we evidenced for cerebrovascular diseases (EOR/Gy=0.49 (95%CI: 0.22 to 1.17)) is coherent with the ones observed in most of the other studies. In Hiroshima Nagasaki survivors, in whom the EOR/1Gy was equal to 0.09 (95%CI: 0.01 to 0.17) when considering stroke as underlying cause of death and EOR/1Gy=0.12 (95%CI: 0.05 to 0.19) when considering stroke as underlying or contributing cause of death [19], but, in the A-Bomb survivors cohort the EOR/1GY was equal to 0.36 in survivors who were less than 10 years old at time of atomic bomb [19], similar to the age of most of the children at time of radiotherapy in our cohort. In a meta-analysis of several cohort studies, including the international nuclear workers study and the Hiroshima-Nagaski cohort, the EOR/1Gy has been estimated to 0.27 (95%CI:0.20 to 0.34) for stroke [20, 21]. Lastly, in Mayak workers, the EOR/1GY for external radiation has recently been estimated as being 0.33 (95C%I: 0.19 to 0.50) [22].

At our knowledge, up to now, no other study focused on ischemic strokes. In our study, we did not evidence any impact of radiation dose in brain structures or organs, the only risk factor being the radiation dose to the cerebral arteries. In particular, we did not evidence an impact of the radiation dose received to the kidneys, which is known to induce hypertension. This finding is coherent with the one of the cerebrovascular disease mortality study previously published by IGR/INSERM team in France [23].

All these results are nevertheless based on average radiation dose to the cerebral arteries. It has to be considered that the very strong gradients of dose near to edges of the radiation therapy fields, have as a consequence a very strong heterogeneity of dose within the cerebral arteries, whatever the average radiation dose.

1.3 Animal studies

For all animal studies, mice were exposed to prenatal irradiation at embryonic day 11 (E11) or to irradiation after birth at postnatal day 10 (PND10) or at postnatal week 10 (W10). Different modes of radiation were used, including whole-body irradiation (pre- and young postnatal IR) or local cranial irradiation (adult postnatal IR).

1.3.1 Cognitive defects

1.3.1.1 Single radiation exposure

To address persistent effects of external/internal irradiation at the embryonic or early postnatal stage, we subjected animals to a battery of behavioural tests (neuromotor, exploration and learning tests). Mice externally irradiated with 1 Gy were overall less active when compared to other groups. Further, this group showed an increased sociability and a declined spatial learning. Of interest, for internal exposure, the increased sociability/decreased anxiety could be observed in the lower activities, while irradiated animals also took longer to find a hidden platform in the Morris water maze. Thus, these data clearly indicate persistent dose-dependent aberrations in cognition and learning as a result of prenatal exposure to irradiation starting from a dose of 0.33 Gy X-rays. Even more importantly, for more subtle functions such as swim strategies in the Morris water maze, a low dose of external IR (0.1 Gy) already showed difficulties in finding the hidden platform.

In contrast, mice **neonatally exposed** to external radiation only displayed differences in behaviour starting from 0.5 Gy of gamma-irradiation, while showing a clear dose-response at 1.0 Gy. This discrepancy might be explained by the use of different behavioural paradigms (Morris water maze strategies vs. spontaneous behaviour), addressing different aspects of behaviour. Importantly, by performing behavioural tests on both males and females, we could rule out a possible gender effect that could be attributable to the radiation exposure.

Even though slight differences in dose-responses were observed, we still can conclude that behaviour is similarly affected in *in utero* and PND10 exposed animals. Therefore, we need to address this issue of LD-IR induced persistent cognitive effects in our community, to improve health assessment

1.3.1.2 Combined exposure to radiation and toxicants

As a second main aim, based on the high risk for consequences of exposure to IR and toxic agents of the developing nervous system, we characterized the (synergistic) effect of radiation and toxicants such as PBDE, methylmercury, paraquat and nicotine on mouse behaviour at the adult age of 2 and 4 months, preceded by irradiation at PND10.

The results obtained within CEREBRAD indicate a synergistically defective spontaneous behaviour in IR+PBDE exposed mice, suggestive for an altered cognitive function in adult mice neonatally exposed to gamma irradiation at doses where the sole compounds did not cause any effect. The effects on single exposure are in agreement with earlier published reports on IR [24] [25, 26] and PBDE99 [27].

In agreement with earlier published work [28], we additionally showed an interaction between IR and 0.4 mg/kg MeHg [25] as well as with paraquat and nicotine in a dose-dependent way.

1.3.1.3 Dose-Response curve

In CEREBRAD we were able to propose a shift in the dose-response curve when such environmental toxicants are combined with IR exposure, resulting in a lowering of the threshold dose of about 300 mGy (Figure 1). In addition the slope of the curve seems to be more important for combined exposure indicating severe cognitive effect with lower radiation doses.

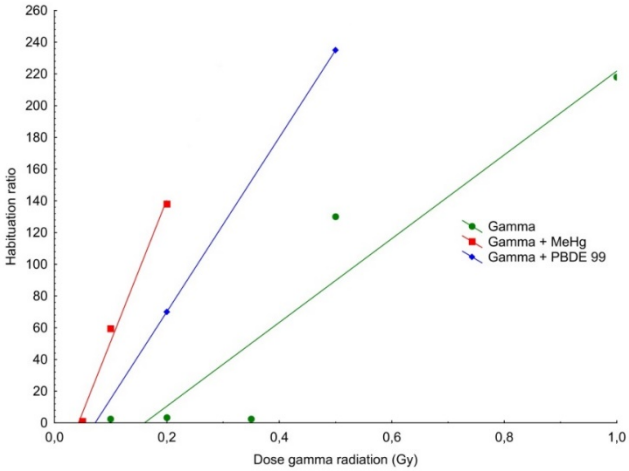

Figure 1: Habituation capability is the ratio between performance in spontaneous behaviour in a novel home environment taken from period 40-60 min and 0-20 min in 2-month-old NMRI male mice exposed on PND 10 to a single external dose of gamma-radiation (0, 0.02, 0.1, 0.35, 0.5 and 1.0) (green), a combination dose of gamma radiation and PBDE 99 or a vehicle (20% fat emulsion), a combination dose of gamma radiation (0, 0.2 and 0.5 Gy) and PBDE 99 (0.8 mg/kg bw) (Blue), a combination dose of gamma radiation (0, 0.05, 0.1 and 0.2 Gy) and MeHg (0.4 mg/kg bw) (Red).

Based on this finding, and since we are living in a mixed environment combining different physical and chemical agents, a threshold theory cannot be adopted. Future research needs to focus on combining more than two agents to be more in line with our real life. Additionally, extrapolation of this research to investigate life style would emphasize other elements of our modern society that might contribute to radiation risk estimate.

1.3.1.4 Brain morphology

We investigated brain regional differences via a voxel-based MRI morphometric approach. From this, we revealed a clear decline in total brain volume, accompanied by enlarged ventricles and a relative decrease in volume of the prefrontal cortex in 1.0 Gy irradiated animals, which indeed indicates a correlation with the Morris water maze results. Yet, other factors might be in play, since behaviour was also affected at doses below 1.0 Gy (figure 2). As such, additional analyses need to be performed to unveil all causes leading to an aberrant learning and cognition, e.g. by focusing on other brain regions or on more subtle effects as compared to a reduction in brain size [24, 29].

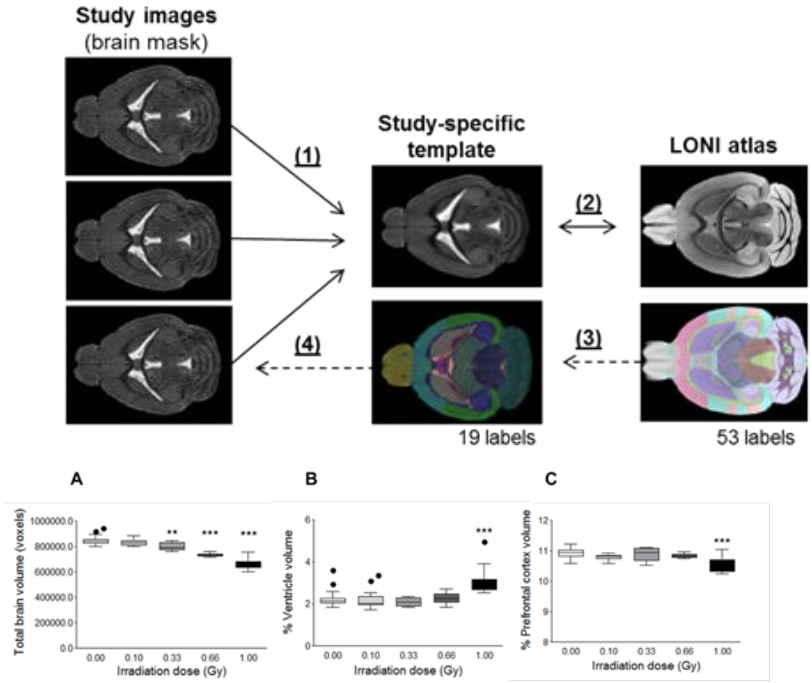

Figure 2: Brain weight changes induced by in utero exposure to radiation. (A) The total brain volume was decreased significantly from a dose of 0.33 Gy onwards. (B) When corrected for total brain volume, the volume of the ventricles was increased in the animals irradiated with the highest dose. (C) Decrease in relative frontal cortex volume in 1 Gy-exposed mice as compared to controls.

1.3.2 Cerebrovascular effect

To assess whether prenatal/neonatal radiation exposure exerts an effect on the brain vasculature, we studied the effect of local head irradiation on blood-brain barrier (BBB) damage and repair, known to contribute to a proper brain functioning and related to an increased cell ageing. To this end, whole-brain irradiation of animals and humans has indeed been reported to lead to late delayed vascular damage[30].

Local brain irradiation induced acute endothelial cell activation in the cortex, hippocampus and cerebellum in W10 irradiated mice, and in the cerebellum in PND10 irradiated mice, indicating a higher sensitivity of older mice to radiation induced acute inflammatory reactions compared to young mice. Next, a very important finding was the chronic radiation-induced BBB damage in the hippocampus and cerebellum of W10 IR animals and in the hippocampus of PND10 IR animals, which was induced both by low and high doses. Yet, it should be noted that only a small number of animals could be used for these experiments, leading to a relatively high standard deviation. As such, the trend towards a radiation-induced BBB damage, which is present even 1 month after irradiation, is very promising but will need further confirmation.

In any case, our data are of particular importance, since they are corroborated by previous research results but also contradict findings from other studies. A radiation-induced blood–brain barrier (BBB) breakdown has been supposed to explain the acute radiation syndrome and the delayed brain radiation injury, but it has been clearly demonstrated only at high doses. This study has shown that 20 Gy and 40 Gy brain irradiation produced an early permanent increase in BBB permeability in rats, while 10 Gy had no effect at all [31]. Finally, Mao and colleagues demonstrated a time- and dose-dependent loss of the vasculature following gamma and proton radiation exposure in rodents, and decrements in vessel growth

were found and could be observed as long as 12 months after a single 8- or 28-Gy exposure [32].

1.3.3 Underlying cellular and molecular mechanisms

To explain the observed cognitive and cerebrovascular defects that result from pre/neonatal radiation exposure, we investigated early and late cellular and molecular events that might be at the origin of these anomalies.

1.3.3.1 Early effects

Neurogenesis & corticogenesis

In the developing neocortex, we noted an impact of prenatal LD-IR on different aspects of brain development as well as on brain cytoarchitecture, as demonstrated by a defective hippocampal neurogenesis and differentiation. Our data also demonstrate that the developing neocortex is, next to the hippocampus, highly susceptible to LD-IR. Further studies will have to be designed to investigate permanent defects in this anatomical region following prenatal irradiation. In any way, these first indications could potentially explain the observed permanent behavioural changes that cannot solely be attributed to hippocampal aberrations.

Early genetic changes after pre- and postnatal radiation that are linked to a deviant neurogenesis and cortical development might be attributed to a p53-mediated DNA damage signaling and apoptosis, which is probably cell-type specific. Besides, we showed a dose-dependent alternative transcription of shorter isoform for several genes in the irradiated embryonic brain 2 h after X-irradiation, for which p53 was shown to bind the promotor sequence of this short isoform. On these premises, we believe that the exact mechanisms explaining LD-IR long-term effects at the organism level can be unraveled only by achieving a better understanding of the early effects (hours to days) and at the level of the different neuronal populations, of which we provided first important insights

Radiation-induced microcephaly

The observation of microcephaly already within days after *in utero* radiation exposure is believed to be largely attributable to the massive radiation-induced apoptosis (Fig. 2), but direct evidence linking the acute apoptosis with long-term brain anomalies is missing. Reduction of cortical thickness was already revealed 24 h after 1.0 Gy exposure at E11 [29]. However, a thorough gene expression analysis suggested that *in utero* irradiation triggers a p53-dependent induction of genes associated to neuronal differentiation and mitotic spindle assembly [33], hinting for a possible premature differentiation following radiation exposure. This hypothesis was further strengthened by the very strong overlap between gene expression profiles of irradiated brains and that of a genetic mouse model of microcephaly showing premature neuronal differentiation [33, 34].

In all, microcephaly as a result of prenatal irradiation is starting to be further explored, with a growing awareness of similarities between radiation-induced and microcephaly disease genes that might converge to related mechanisms.

1.3.3.2 Long-lasting structural and functional effects

Depletion of cells in the in utero irradiated brain

The prenatal radiation-induced microcephaly, as established both in humans and animals, is mostly accompanied by an overall growth retardation. This effect appears to be induced from a dose of 0.3 Gy on [35]. Whether the reduction in brain size is associated with an overall decrease in the number or density of neurons, remains however disputed. The majority of animal studies are in agreement with a reduced cell number, for instance evidenced for the

E15 irradiated rat brain by means of MRI analyses and histology [36, 37], and further substantiated for the irradiated rodent hippocampus, corpus callosum, cerebellar Purkinje cells and primary visual cortex [38-43].

A disturbed neural circuit formation after prenatal irradiation

As mentioned before, the observed disruption of neuronal migration following irradiation causes the introduction of ectopic cells spread throughout the brain. Such a disorganization of neurons can be accompanied by a defective neuronal orientation, morphology and arborisation, resulting from an improper and disturbed maturation. Evidently, such a disturbed dendritic organization might also entail an improper neural circuit formation and synaptic communication. On the other hand, a proteomic study on hippocampal samples from 6 month old prenatally irradiated mice revealed an enhanced expression of postsynaptic density protein 95 (PSD95) after 1.0 Gy exposure, suggesting a pronounced effect of moderate doses of irradiation on synaptic plasticity in hippocampal dendrites [44].

Thus, these findings demonstrate the necessity to further explore neuronal communication after prenatal irradiation, and to investigate synaptogenesis and inhibitory neuron development at multiple time points following irradiation, using a broad range of irradiation doses.

Brain structure and function deficits after prenatal irradiation

Rodent behavioural testing is a valuable tool to evaluate radiation-induced defective brain functionality. However, up to now, animal studies suggested a threshold dose of around 0.30 Gy below which no behavioural alterations can be observed, while human studies hinted at late defects after exposure to doses as low as 0.10 Gy. Here, we acutely irradiated pregnant mice at embryonic day 11 with doses ranging from 0.10 to 1.00 Gy. A thorough investigation of the dose-response relationship of altered brain function and architecture following in utero irradiation was achieved using a behavioural test battery and volumetric 3D T2-weighted magnetic resonance imaging (MRI). We revealed dose-dependent changes in cage activity, social behaviour, anxiety-related exploration and spatio-cognitive performance, of which both emotionality and higher cognitive abilities were affected in mice exposed to 0.10 Gy. Microcephaly was apparent from 0.33 Gy onwards and accompanied by deviations in regional brain volumes as compared to controls. Of note, relative ventricle and frontal cortex volume were most strongly correlated to altered behavioural parameters. Taken together, we present conclusive evidence for persistent low-dose effects after prenatal irradiation in mice and provide a better understanding of the correlation between their brain size and performance in behavioural tests. In all, we have thoroughly studied the dose-response relationship of mouse brain function and structure following prenatal irradiation, which unveiled effects at doses previously assumed to be harmless.

Notably, these high doses have been shown to produce such a large spectrum of defects in the postnatal, juvenile and/or (young) adult brain, with structural changes that completely disrupt the brain's integrity. As such, it is not surprising that animals irradiated with doses ≥1.0 Gy display a severely affected behaviour.

Other alterations that have been observed and that might contribute to persistent structural and functional deficits after *in utero* radiation exposure are, for instance, inflammation and vascular modifications. In other studies, irradiation of rats at E11 with 1.3 Gy or at E15 with 1.5 Gy was shown to induce astrogliosis and astrocyte proliferation in the hindbrain [45] and in the whole brain [36] respectively. Furthermore, a dose of 1.5 Gy resulted in an underdevelopment of the microvasculature, responsible for a decreased cerebral blood flow and angioarchitectonic abnormalities. To note, most research on radiation-induced BBB permeability has been focused on high doses, in the context of radiotherapy research where an increased permeability is desirable for the delivery of chemotherapeutics to the brain [46]. As such, due to the poor amount of data, effects on BBB permeability after lower doses of irradiation might be overlooked and should be further explored. Besides, since the blood-

brain barrier is still immature in the developing embryo and more prone to drugs, toxins and pathological conditions, special attention should be directed to effects of prenatal irradiation on BBB formation and associated neurological disorders later in life.

Similar effects to IR have been observed for maternal alcohol intake on the neuropsychological development of the offspring known as Foetal Alcohol Spectrum Disorders (FASD) or Alcohol-Related Neuro-developmental Disorder (ARND). Similarly, Infectious exposure during pregnancy is associated with schizophrenia, epilepsy or autism and cerebral palsy in the progeny. Maternal immune activation is an environmental risk factor for brain and behaviour change relevant to schizophrenia, causing marked enlargement of lateral ventricles in adulthood as observed in our study with IR. In addition, our transcriptomic changes in prenatal radiation exposed brain showed high similarities to Zika virus 'ZIKV' infection, including induction of p53 gene and its target genes involved in premature neuron differentiation. In summary, early stress during brain development can be translated by late cognitive outcome at adult age.

1.4 Conclusions

In conclusion

- Epidemiological investigations in CEREBRAD used accurate dosimetry calculations and assessed childhood cancer survivors' population for cerebrovascular diseases. Moreover, a Chernobyl cohort of *in utero* exposed individuals and clean-up workers as well as a haemangioma cohort treated with radiation below the age of 18 months were assessed and showed mostly mild cognitive impairments. Additional human cognitive and cerebrovascular studies will be appreciated to increase the statistical power of risk estimate following exposure to radiation in utero or at childhood to provide accurate recommendations to the public.
- Co-exposure experiments with environmental toxicants in CEREBRAD showed a reduction in the threshold dose for induction of cognitive impairments. Future co-exposure research needs to focus on combining multiple agents/stressors (more than 2) to be more in line with real life exposure conditions. Additionally, extrapolation of this research to investigate the impact of life style would emphasize other elements of our modern society that might contribute to radiation risk estimates.
- The molecular and cellular findings in CEREBRAD are in high correlation with the observed cognitive deficits in pre- and neonatally irradiated mice. In particular, the defective cortical development that was observed together with a disturbed hippocampal neurogenesis nicely links to the decreased thickness of the prefrontal cortex at the long term. This thus urges for more experiments investigating higher cognitive functions related to the prefrontal cortex in irradiated animals.
- CEREBRAD analysed molecular and cellular changes up to 24 weeks after irradiation. The presence of alterations at this time point strongly suggests that LD-IR might influence natural ageing. However, it is still unclear whether LD-IR could promote senescence and, eventually, in which neuronal cell type. In this regards, animal models for neurodegenerative diseases could be a valuable model to assess neuro-related ageing processes.
- Blood Brain Barrier studies in animal models in CEREBRAD showed an increase of brain permeability highly correlated with age at exposure and radiation dose, although additional investigations are highly required to fully understand the underlying mechanisms.

- Development of dedicated mathematical models based on CEREBRAD data will allow to describe precisely the biological mechanisms of radiation exposure, to be used to fit both new and available epidemiological and animal data for cognitive and cerebrovascular diseases.

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2 RADIATION-INDUCED CARDIOVASCULAR DISEASE: IS IT TIME FOR A NEW BIOLOGY?

Michael J Atkinson

Summary of the main findings of ProCardio[2]

1) The initial analysis of an epidemiological cohort of 222 childhood cancer survivors with cardiovascular disease and matched controls revealed a significant risk associated with exposure to doses of 1Gy and more (Haddy et al 2016 Circulation **133**:31-381).
2) An RBE for cardiovascular effects of high LET irradiation of between 4 and 10 was indicated using in vitro cellular models (Helm et al 2016).
3) Dose rate influences the risk of cardiovascular disease in a mouse model. A correction factor ($DDREF_{CVD}$) is thus appropriate for cardiovascular tissue (Mancuso M et al 2015)
4) There is evidence for existence of an abscopal effect, where partial body exposure avoiding the heart protects against atherosclerotic plaque formation in vessels of the non-irradiated heart.
5) Cell-cell interactions contribute to the development of radiation-induced atherosclerosis. Radiation accelerates the process by stimulating both monocyte adhesion to, and the infiltration of lipids through, the endothelium (Baselet et al 2017, Lowe & Raj 2015).
6) MicroRNAs, de-acetylated and mitochondrial respiration complex proteins are potential biomarkers of radiation-induced heart disease. (Azimzadeh et al 2017, Barjaktarovic et al 2017, Subramanian et al 2017)
7) Radiation dose dependent changes in heart energy metabolism persist months after exposure in mice and are associated with cardiovascular disease in human subjects (Azimzadeh et al 2017b).
8) New mathematical models fitted to A-Bomb survivor data indicate non-linearity of the dose response relationship towards higher doses (Christoforo et al 2017). They also indicate that plaque initiation and not plaque expansion is the key process in radiation-induced heart disease.

2.1 Foreword

The ProCardio project (November 2011 – April 2015) was conceived to address a series of unknowns relevant for the protection of the cardiovascular system from low dose/dose rate radiation. The final report of the project was submitted in 2015. In the intervening years a number of the studies started under ProCardio have been completed, providing additional evidence for radiation protection decision-making. This report encompasses and extends the final ProCardio report.

[2] Cardiovascular risk from exposure to low dose and low dose rate ionizing radiation: A follow-up interpretation of results of the ProCardio EURATOM FP7 project. (Grant Number 295823)

2.2 Background

The cardiovascular system has only recently been recognized as a relevant organ for radiation protection at low doses. Historically, the heart has been considered to be susceptible to damage only at high doses, with the tolerance dose suggested to be around 40 – 60 Gy. At these high doses the long-term damage is held to be deterministic and to primarily result from tissue fibrosis, damage to endothelial cells, electrophysiological disturbances and compensatory changes to the myocardium. As a consequence of this the risks from low doses were believed to have no relevance, falling below a supposed threshold. Indeed, macroscopic changes are not seen at the low doses relevant to radiological protection. However, more recent epidemiological evidence from exposed worker cohorts, recent evaluations of A-Bomb survivor data, medically exposed cohorts and from animal studies all consistently point to a risk of detriment that follows an LNT dose response, with a limit of sensitivity lying between 100 and 1000 mGy.

2.3 Goals of the ProCardio project

Exposure of the heart to low doses has become almost unavoidable with the development of society, with exposures from medical imaging (CT, PET, and X-rays), tumour therapy, and from workplace and environmental sources. The potential risk of adverse health effects in the dose range under 500mGy demands immediate attention to resolve uncertainties. We identified key questions impacting on assessments of cardiovascular risk from low dose/dose rate exposures:

- *Can an additional epidemiological cohort based upon childhood cancer survivors provide greater sensitivity in the analysis of risk at low doses?*

The basis for this study is that the doses to the different areas of the heart are relatively low and can be retrospectively quantified. There is a very long follow-up due to the early age at exposure, and nested case-control studies are possible within larger pan-European cohorts of childhood cancer survivors.

- *What are the mechanisms behind cardiovascular disease?*

The cellular changes causing and accompanying cardiovascular disease affect different cell populations. However, unlike cancer, there is no gene mutation driving the diseases and no clonal expansion is required. Clearly a process is operating that is not related to radiation-induced DNA damage and misrepair.

- *What are the consequences of dose rate and of radiation quality for cardiovascular disease?*

Although dose fractionation studies exist these all involve very high therapeutic doses. Thus there is almost no information available on the existence (or not) of a dose rate effect ($DREF/DDREF_{CVD}$). The same situation applies to the influence of different radiation qualities, with no defining analysis of effects of different LETs (RBE_{CVD}).

- *Do cell-cell interactions drive the radiation-induced cardiovascular disease?*

In a multi-tissue organ such as the cardiovascular system cell communication plays a significant role in regulating function. Thus, local (adrenergic and NO signalling), paracrine (e.g. atrial naturetic peptide) and systemic (e.g. vasopressin, angiotensin) all influence the system. Given the recent discovery of exosomal signalling as a mediator of cell-cell communications in the radiation response this question must be addressed.

- Is the LNT model applied to epidemiological data the appropriate means to determine the risk of cardiovascular disease?

Given the uncertainties in the mechanism and shape of the dose response relationship it is important to reconsider the use of LNT models to define cardiovascular disease risk following radiation exposure.

2.4 The ProCardio consortium

The ProCardio project coordinator was Mike Atkinson (Radiation biologist), Helmholtz Zentrum München. The scientific teams included:

Omid Azimzadeh and Soile Tapio (proteomics specialists) and Helmut Schollenberger (mathematician) from the **Helmholtz Zentrum München**; Elisabeth Pernot and Elisabeth Cardis (epidemiologists) from **CREAL (ISGlobal Barcelona)**; Florent de Vathaire, Nadia Haddy (epidemiologists) and Ibrahim Diallo (radiation physicist) from **Institut Gustav Roussy, Villejuif**; Mike Hawkins (epidemiologist) from the **University of Birmingham**; Marco Durante (radiation physicist), Sylvia Ritter and Claudia Fournier (radiation biologists) from **GSI Darmstadt**; Ken Raj (radiation biologist) from **Public Health England**; Anna Saran, Simonetta Pazzaglia and Mariatherese Mancuso (radiation biologists) from **ENEA Rome**; Rafi Benotmane (radiation biologist) from **SCK-CEN Mol**; Tamara Azizova (radiation biologist) from **SUBI Ozyorsk**; Leontin Kramer and Cecile Roenkers (radiation oncologists) from **Academic Medical Centre Amsterdam**; Harmen Bijwaard and Fieke Dekkers (mathematicians) from **RIVM Utrecht**; and Ignacia Braga Tanaka and Satoshi Tanaka (pathologists) from **IES Rokkasho.**

2.5 Results of ProCardio

2.5.1 Epidemiological study of childhood cancer survivors treated with radiation

An epidemiological case-control study of the risks of cardiovascular disease in childhood cancer survivors was initiated with a cohort of 222 cases with cardiovascular disease (130 cases from France, 82 from the UK and 10 from Spain) and an equal number of age matched control cancer survivors with no disease, matched by country, gender, age at first diagnosis, year of diagnosis and length of follow-up. Each individual was evaluated to determine the radiation doses during therapy distributed over 14 substructures (ca. 100 000 $2mm^3$ voxels) of the heart. This was done by measurements of the performance of 30+ different types of irradiation machines using appropriate anatomical phantoms and the individual therapy plans. This ProCardio cohort will contribute to a larger study of childhood cancer survivors (PanCareSurF) to generate over 900 matched cases and controls.

An initial analysis of the ProCardio case control study was performed to validate the data quality and influence of known cardiotoxic anthracyclines. A multivariate conditional logistic regression analysis revealed that as expected the treatment with anthracycline increased the incidence of heart diseases. No interaction was observed between radiation exposure and anthracycline administration. In terms of radiation dose the best modelling fit was an exponential dose response (note this is consistent with an interpretation of the most recent A-Bomb solid cancer data). This treatment produced Excess of Odds Risk (EOR) at 1Gy average heart radiation dose of 0.083 (95%CI: 0.051-0.12). The EOR was essentially unchanged if only ischaemic heart disease or heart failure plus ischaemic heart disease were considered (Haddy et al 2016).

In conclusion, the ProCardio epidemiological cohort has proven that the study of childhood cancer survivors provides essential information on the risks to the heart of radiation at low doses.

2.5.2 What are the mechanisms behind cardiovascular disease?

We have confirmed earlier studies that mitochondrial activity is associated with long-term metabolic adaptation following a single acute radiation dose in the mouse. Using a 300mGy dose we detected changes as early as 15 days that persisted until 300 days. Affected were fatty acid oxidation and the TCA cycle, both of which were up-regulated indicating adaptation to permanent stress situation. At the later time points the respiratory chain complexes were down-regulated as were a number of other cellular processes, including damage to cytoskeletal structures, all of which centre on a persistent stress response(Azimzadeh et al 2017a, Subramanian et al 2017). A possible mechanistic explanation for these changes can be alterations in protein modification through acetylation/deacetylation of lysine residues (Barjaktarovic et al 2017).

2.5.3 Does the radiation quality influence the cardiovascular effects?

Exposure to high-energy nuclei and subatomic particles is a concern for radiation protection in special situations (workplace, low earth orbit and increasingly from cancer treatments). Although the RBE for the carcinogenic effects of high LET radiation is experimentally documented it is tacitly assumed that the same RBE will apply when other biological endpoints are considered. In order to provide an evidence base for such an assumption ProCardio conducted in vitro studies on cells derived from the cardiovascular system. Thus, we compared the biological responses to Fe ions (HZE particles) and photons in both cardiomyocytes and immortalized endothelial cells derived from the human coronary artery. We tested a range of biological endpoints indicative of cardiovascular disease. These were the release of cytokines, transcriptional activity, protein expression, DNA damage and electrophysiology.

The electrophysiological studies of high and low LET exposures did not show changes in electrical activity of cardiomyocytes, suggesting that for the (0.5 Gy) doses tested, high LET radiation has no effect on electrophysiology (Helm et al 2016). We cannot exclude the possibility of an RBE at much higher doses however. In endothelial cells the changes in transcriptional activity evoked by a 2 Gy gamma exposure were most closely matched by a high LET dose of 0.5 Gy, suggesting an RBE of around 4. Changes in the patterns of gene expression were similar, irrespective of radiation quality. Analysis of the changes in protein expression yielded similar differences in response.

Cytokine release was highly dose dependent, with the response to high LET occurring at a ten-fold lower dose than that to low LET. These studies place the RBE_{CVD} of Fe ions between 4 and 10 times that of photons.

2.5.4 What are the consequences of dose rate and of radiation quality for cardiovascular disease?

There is a lack of evidence for or against a dose rate effect of cardiovascular disease. Earlier work established that fractionated radiation therapy was less damaging to heart, albeit at very high therapeutic doses causing deterministic damage. Together with the Institute of Ecological Sciences, Rokkasho, Japan, we have studied the effects of chronic low dose

gamma exposures using the ApoE-/- mouse model, with atherosclerotic lesions as the end point. Animals receiving 0.3 Gy delivered at a low dose rate showed significantly lower levels of atherosclerosis lesions in the aortic arch than mice receiving a single 0.3 Gy acute dose Mancuso et al 2015). This provides evidence for a dose-rate effect of radiation on cardiovascular health. Analysis of the proteomic and transcriptomic changes in the heart tissue of these animals also indicated a dose rate effect (Azimzadeh et al 2017a). These studies showed that the changes caused by the same dose given as either an acute or chronic exposure differed considerably. We take this as further subjective evidence for the existence of a dose rate effect.

Each comparison between animals exposed to either low or high doses exposures indicated non-linearity in translational and transcriptional changes (Baselet et al 2017). This is seen as evidence for dose and dose rate effects, suggesting that the concept of $DDREF_{CVD}$ for cardiovascular disease may be required.

Most significantly our recently completed study of human heart tissue in collaboration with the Southern Ural Biophysics Institute, Chelyabinsk, Russian Federation identified dose-dependent changes in proteomic and microRNA transcriptomic profiles. The biological pathways that are influenced by these chronic exposures were qualitatively identical to those seen in acute exposed mice (Azimzadeh et al 2017b, Subramanian et al 2017).

2.5.5 Do cell-cell interactions drive the radiation-induced cardiovascular disease?

The cardiovascular system is composed of multiple cell types whose interactions are defined by signals from local and distant sources. Local interaction between cells within this system involves myocardial cells, vascular smooth muscle, fibroblasts and endothelial cells, and probably also local immune cells such as macrophages and mast cells. The influence of irradiation on these processes is not well understood, even though it may make a contribution to disease following exposure.

More complex cell communications exist within irradiated organisms, with effects of local irradiation being transmitted to distant tissues as abscopal effects. Here the contribution to radiation injury affecting the cardiovasculature is unknown.

Using a macrophage/endothelial cell co-culture model system we show that recruitment of immune cells to the endothelial surface occurs in response to low dose irradiation of the endothelial cells. As this is also a precursor of atherosclerotic plaque formation we suggest that the stimulated recruitment promotes radiation-induced plaque formation and growth Lowe & Raj 2014).

Exposure of distant tissues (rump and hind legs) of ApoE-/- mice was able to reduce the extent of sporadic plaque formation in the aortic arches.

These two studies confirm that local and distant pathways of cell communication are able to modify the extent of radiation-induced cardiovascular disease. There is no evidence available to establish the overall contribution of the two pathways, nor to identify dose dependency of the different processes.

2.5.6 Is it possible to improve upon existing mathematical descriptions of the dose-response relationship?

Estimation of the risks at low doses is made by extrapolating from epidemiological data obtained from the study of radiation effects at high doses. Current mathematical models used

for this fitting of epidemiological data use a two-hit clonal expansion model that assumes an LNT dose response. Cardiovascular disease is not the result of a mutated cell undergoing clonal expansion, and as such the current risk estimates are unconvincing.

We have studied two different areas of cardiovascular disease to model potential effects of radiation on the cardiovasculature. The first incorporates the biological processes that have been identified as part of ProCardio, whilst the other was derived by fitting multiple modelling scenario to epidemiological data to improve the fit of the dose response estimates.

The de novo model of plaque formation is a system of ordinary differential equations describing the concentration of low-density lipoproteins, the total capacity of macrophages to take up these low-density lipoproteins, and the resulting development of plaque size with time. The model was tested using historical data for high-dose exposures from Prof Fiona Stewart, NKI. This proved a very informative approach and indicates that plaque initiation, but not plaque growth is stimulated by radiation exposure. The second modelling approach used the strategy of fitting multiple models to the same data set (A-bomb survivors) to generate a common model. This has revealed that there is a case for concluding a non-linear dose response, at least at the higher end of the dose response curve (Cristoforo et al 2017).

2.6 Conclusions

ProCardio has provided new evidence for the evaluation of cardiovascular risk following low dose radiation exposure. We show that neither RBE nor DDREF should be excluded when evaluating risk. We show that biological mechanisms for the development of radiation-induced cardiovascular disease include changes in cell-cell signalling (including local and abscopal effects), mitochondrial dysfunction and a persistent stress responses, all of which are caused by low dose exposure. These biological effects do not involve misrepair of DNA damage or clonal expansion, and may follow a non-linear response. Indeed, modelling reveals that a non-linear development of risk with increasing dose is plausible.

2.7 Publications from the ProCardio project

Azimzadeh O, Subramanian V, Ständer S, Merl-Pham J, et al (2017a) Protome analysis of irradiated endothelial cells reveals persistent alterations in protein degradation and the RhoGDI and NO signalling pathways, Int J Radiat Biol. Jul 11:1-9. doi: 10.1080/09553002.2017.1339332.

Azimzadeh O, Azizova T, Merl-Pham J, et al (2017b) A dose dependent perturbation in cardiac energy metabolism linked to radiation-induced ischemic heart disease in Mayak nuclear workers. Oncotarget. 8:9067-9078. doi: 10.18632/oncotarget.10424.

Barjaktarovic Z, Merl-Pham J, Azimzadeh O, et al (2017) Low dose radiation differentially regulates protein acetylation and histone deacetylase expression in human coronary artery endothelial cells. Int J Radiat Biol. 93:156-164. doi: 10.1080/09553002.2017.1237059.

Baselet B., Belmans N, Coninx E. et al (2017) Functional Gene Analysis Reveals Cell Cycle Changes and Inflammation in Endothelial Cells Irradiated with a Single X-ray Dose. Front. Pharmacol 8:213 doi: 10.3389/fphar.2017.00213.

Cristoforo S., Azizova TV., Barjaktarovic Z et al. (2017) A mechanistic model for atherosclerosis and its application to the cohort of Mayak workers PLoS One Published: April 6, 2017 doi.org/10.1371/journal.pone.0175386

Haddy N, Diallo S, Chiraz E.-F. et al. (2016) Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. Circulation 133:31-38. doi.org/10.1161/CIRCULATIONAHA.115.016686

Helm A:, Arrizabalaga O., Pignalosa D. et al (2016) Ionizing radiation impacts cardiac differentiation of mouse embryonic stem cells. Stem Cells Dev. 25:178-188 doi: 10.1089/scd.2015.0260

Lowe D. & Raj K. (2014) premature aging induced by radiation exhibits pro-atherosclerotic effects mediated by epigenetic activation of CD44 expression. Aging Cell 13:900-10. doi: 10.1111/acel.12253.

Mancuso M, Pasquali E, Braga-Tanaka I. et al. (2015) Acceleration of atherogenesis in ApoE-/- mice exposed to acute or low-dose rate ionizing radiation. Oncotarget. 2015 6:31263-71. doi: 10.18632/oncotarget.5075.

Subramanian V, Seemann I, Merl-Pham J, et al (2017) Role of TGF beta and PPAR alphas signalling pathways in radiation response of locally exposed heart: Integrated global transcriptomics and proteomics analysis. J Proteome Res.16:307-318. doi: 10.1021/acs.jproteome.6b00795.

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3 ISSUES RELATED TO THE CONCEPT OF ORGAN DOSE

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3.1 Introduction

The absorbed dose in a point is defined on pure physical grounds as the statistical average of the energy imparted by ionizing radiation per unit mass:

$$D = \lim_{dm \to 0} \frac{d\bar{\varepsilon}}{dm} \qquad (1)$$

where $d\bar{\varepsilon}$ is the mean energy imparted by ionizing radiation to a point of interest in an infinitesimal volume of matter and *dm* is the mass of this infinitesimal volume. The unit of absorbed dose is the gray (Gy), and 1 Gy is equal to 1 J·kg^{-1}.

Point definitions are of no use in practical radiation protection, therefore dose quantities are generally referred to targets of finite volumes, such as organs, tissues or substructures thereof:

$$D = \frac{\bar{\varepsilon}}{m_T} \qquad (2)$$

being m_T the finite mass of the volume of interest.

However, the response of a biological system to an exposure to ionizing radiation does not depend solely on the amount of energy deposited. Other factors such as type and energy of the incoming radiation, different susceptibilities of different organs and tissue types for producing radiation-induced effects, influence of dose rate, duration (acute vs. chronic irradiation), uniformity of exposure are not taken into account in the definition of absorbed dose.

Under the assumption that long-term stochastic effects (e.g. cancer induction) of low dose-exposures (below 100 mGy for photons) can be reasonably described by the so-called Linear No-Threshold (LNT) relationship, the International Commission on Radiological Protection (ICRP) has introduced the protection quantities equivalent dose (for organs and tissues of the human body) and effective dose.

The equivalent dose in a target tissue or organ T is defined as:

$$H_T = \sum_R w_R D_{T,R} \qquad (3)$$

where $D_{T,R}$ is the absorbed dose in a target tissue or organ T due to radiation type R and w_R are the corresponding radiation weighting factors which allow for the differences of the various radiation types in causing stochastic effects. Radiation types include photons, electrons, muons, protons, charged pions, alpha particles, fission fragments, heavy ions and neutrons. Values for w_R were published in ICRP Publication 60 [ICRP, 1991] and recently updated in ICRP Publication 103 [ICRP, 2007]. The w_R's are dimensionless factors, so the unit for the equivalent dose is the same as for the absorbed dose and is equal to 1 J·kg^{-1}. In

[3] On behalf of EURADOS

order to highlight the conceptual difference from the absorbed dose, the unit for the equivalent dose is given a specific name called sievert (Sv).

The effective dose E is an indicator of the risk of a detriment to a reference individual and is obtained by summing over all relevant target organs and tissues after multiplication by appropriate tissue weighting factors w_T:

$$E = \sum_T w_T H_T + w_{rem} H_{rem} \qquad (4)$$

The w_T's allow for the variations between different tissues in radiation sensitivity to the induction of stochastic effects. As for the equivalent dose, the unit of effective dose is the sievert (Sv), and 1 Sv is equal to 1 $J \cdot kg^{-1}$.

According to ICRP Publication 60 [ICRP, 1991], the summation in equation (4) extends over the 12 target organs and tissues for which explicit values of w_T had been defined and the subscript *rem* refers to the so-called remainder tissues, i.e. those tissues for which no explicit value of w_T has been defined. The dose to the remainder tissues is computed as a mass-weighted average of the doses to nine organs and tissues. A specific rule is applied in the case that one organ belonging to the remainder receives the highest dose among all body organs and tissues.

In ICRP Publication 103 (ICRP, 2007) the calculation of the equivalent dose was modified to include a total of 14 target organs and tissues for which explicit w_T values have been defined, plus 13 additional remainder tissues. The equivalent dose to an organ or tissue is calculated separately for a Reference Male and a Reference Female Person, and the effective dose is calculated from the sex-averaged equivalent doses:

$$E = \sum_T w_T \left(\frac{H_T^M + H_T^F}{2} \right) \qquad (5)$$

Here H_T^M and H_T^F are the equivalent doses in target organ or tissue T for the Reference Male and the Reference Female respectively. The summation in (5) includes also the equivalent dose to remainder tissues, which is now computed as the arithmetic mean of the equivalent doses of the tissues specified as part of the remainder. The composition of the remainder tissues is different between the Reference Male and the Reference Female.

3.2 Limitations on the use of equivalent and effective dose

The protection quantities effective dose and equivalent dose to an organ or tissue have a number of limitations. First of all, they cannot be measured directly. For external exposures surrogate measurable quantities (operational quantities) have been introduced, like ambient dose equivalent, directional dose equivalent or personal dose equivalent [ICRU, 1993; 1998; 2011]. Appropriate conversion coefficients [ICRP, 2010] relate the protection quantities H_T and E to the radiation field characteristics like particle fluence or air kerma. For internal exposures there is no possibility to define surrogate measurable quantities, so doses must be assessed by making use of appropriate biokinetic and dosimetric models [ICRP, 1990; 1993; 1994; 1995; 2006; 2015].

Moreover, the protection quantities refer per definition to stochastic effects related to low dose/low dose rate exposures and are computed for reference individuals. As stated by ICRP, H_T and E should not be used as indicators of situations where tissue reactions (deterministic effects) are expected. Further to that, the use of quantities which have been estimated for reference individuals is not recommended in the frame of epidemiological studies or for detailed specific retrospective investigations of individual exposure and risk

[ICRP, 2007]. Organ or tissue absorbed doses, not equivalent or effective doses, are the most appropriate quantities in these cases.

3.3 The concept of organ dose and heterogeneous exposures

The concept of organ dose, i.e. the dose delivered to a target organ and tissue with finite size and mass, is implicit in all quantities considered above, and, as we have seen, it is indicated in some situations as the quantity of choice. Averaging the dose delivery process over a finite volume is a mathematically practical solution, but it may not be appropriate in the case of spatially heterogeneous dose patterns. Already Dietze and Menzel (2004) had observed that "(…) The current approach of averaging absorbed dose over tissues and organs has clear limits for being meaningful when radiation with short ranges or low penetrability are concerned, in particular for internal emitters. (…) the value of mean absorbed dose in a given volume provides generally no information on the time distribution of the interactions taking place in that volume (…) the integration over a longer time period with strong variations in dose rate does not reflect these variations". ICRP Publication 103 (2007) recognizes that a number of factors affect the extent to which the average absorbed dose in an organ is representative of the absorbed dose in all regions of that organ.

For external exposures such factors include the homogeneity of the exposure and the range of the radiation incident on the body. The dose distribution within a specified organ may be homogeneous for penetrating radiation with low ionization density (low-LET[4] radiation), but for short-ranged non-penetrating radiation (low-energy photons, charged particles and generally high-LET radiation) the absorbed dose distribution within the specified organ may be very heterogeneous, and the same is valid for widely distributed tissues, like skin or red bone marrow, exposed to non-uniform radiation fluxes [Dietze and Menzel, 2004].

In the case of internal exposures the uptake, distribution and retention of activity in a tissue is driven by the physico-chemical properties of the incorporated radionuclides or of the molecules to which the radionuclides are attached. For alpha-, beta- or Auger-emitters, the short range of the emitted particles may lead to very heterogeneous dose patterns even within small volumes. In addition to the non-uniform activity distribution within the organ/tissue of interest, also the uneven location of the radiation sensitive cells in the target should be taken into consideration: the resulting dose gradients and discontinuities are neglected when averaging the dose at organ level.

There are further evidences suggesting that the concept of organ dose might not be the most appropriate indicator in the case of heterogeneous exposures and that the tissue response after irradiation with high-LET radiations may be different from that observed in individual cells. Low-dose phenomena related to non-DNA targeted effects of ionizing radiation like bystander effects, genomic instability or adaptive response [Belchior et al., 2014; Brenner et al., 2001; Hall, 2003; Hill, 2012; Kadhim et al., 2013; Little, 2003; Seymour and Mothersill, 1999] indicate, for instance, that radiation response can be observed also in cells which have not been directly exposed to radiation. In terms of dosimetry, this raises the question whether currently identified progenitor cells are indeed the primary target cells or whether all surrounding cells should be taken into acocunt. These effects that can be at least partially ascribed to cell-to-cell communication mechanisms are not explicitly considered by the current dose quantities.

The ICRP judged the available evidence not sufficient for revising its concept based upon the LNT model assumption [ICRP, 2005]. It is reasonable to consider that such effects might not be relevant for homogeneous exposures, when all cells in a target tissue are uniformly

[4] LET = Linear Energy Transfer, generally expressed in $keV \cdot \mu m^{-1}$, is an indicator of the energy locally deposited by the radiation and is related to the ionization density in the target.

irradiated and cell-to-cell communication is not needed for spreading the information about radiation damage. On the contrary, it can play a significant role for highly heterogeneous exposures in which only a subset of cells are hit by radiation and/or the dose profile between neighbouring cells is very discontinuous.

Since spatially and temporally heterogeneous dose distributions are characteristic patterns after incorporation of alpha-, beta- and Auger-emitters, the following sections will deal specifically with the case of internal exposures.

3.4 Organ doses for incorporated radionuclides

As mentioned earlier, there are no measurable quantities that can be used to estimate dose quantities after incorporation of radionuclides, so doses must be assessed by making use of appropriate biokinetic and dosimetric models [ICRP, 2007; 2015]. Biokinetic models describe the incorporation, distribution, and retention of radionuclides in the body as well as their elimination in the excreta. Consistently with the definition of organ doses, biokinetic models are expressed in the form of compartmental models, where compartments represent whole organs, groups of organs or substructures thereof. The exchanges between compartments are described as first-order kinetic processes. The activity is assumed to be homogeneously distributed in each of the compartments. With these models the activity curves and the number of nuclear transformations in each source organ are evaluated [Giussani and Uusijärvi, 2011; Giussani, 2015]. Then dosimetric models are applied, which calculate for each nuclear transformation the fraction of emitted energy which is released in the target organs, and consequently the corresponding organ doses. The stylised geometrical phantoms originally used for the evaluation of the dose coefficients have now been replaced by high-definition phantoms (computational reference phantoms) obtained from the segmentation of medical diagnostic images of actual patients [ICRP, 2009]. In these phantoms, the size and relative position of the organs and tissues, including their overlapping, are rendered more realistically than in the previous geometrical phantoms.

This approach, which considers a uniform activity distribution in the source organs and the averaging of the dose over the whole mass of the target organs is not appropriate, as already discussed, for heterogeneous activity distributions and short-ranged emissions. It must be recognised that ICRP applies special considerations for alpha- and beta-emissions in a number of important cases, including doses to target cells in the walls of the respiratory tract airways from radionuclides in the airways [ICRP, 1994a], doses to target cells in the alimentary tract from radionuclides in the lumen [ICRP, 2006], doses to cells adjacent to inner bone surfaces (50-mm layer) and doses to red marrow from radionuclides on bone surfaces and within mineral bone [ICRP, 2016]. Anyway, even when such refined substructures are taken into account, reliable data for the characterization of the corresponding model parameters are hardly available, and generally affected by a high degree of uncertainty, and doses to these substructures are finally transformed into an average value for the organ equivalent dose by applying appropriate weighting coefficients. Again, very inhomogeneous and discontinuous dose profiles will go undetected.

3.5 Heterogeneous exposures: the role of micro- and nano-dosimetric approaches in the EURADOS Strategic Research Agenda

In 2014 the European Radiation Dosimetry group EURADOS has presented its Strategic Research Agenda (SRA) [Rühm et al., 2014; 2016]. Starting from inputs from EURADOS Working Group members, the SRA formulates five visions in dosimetry. One of the five

visions is called "Towards updated fundamental dose concepts and quantities", and four challenges have been associated to this vision: (i) To improve understanding of spatial correlations of radiation interaction events; (ii) To establish correlations between track structure and radiation damage; (iii) To improve understanding of radiation-induced effects from internal emitters; and (iv) To update operational quantities for external exposure. The issue of dose heterogeneities and the characterization of particle track structures, which are related to the energy deposition patterns on microscopic and nanoscopic scales, were identified as key issues in the frame of this vision.

Recent advances in experimental techniques (development of measurement devices for track structure properties, such as miniaturized tissue-equivalent proportional counters and solid-state microdosimeters based on silicon) and numerical simulation studies applied to micro- and nanodosimetry are briefly described in the EURADOS SRA [Bashkirov et al., 2006; Cucinotta et al. 2000; Hofmann et al., 2007; Li et al., 2001]. The case of the highly localized deposition of short-lived alpha-emitting radon progeny in the bronchial region of the lung has been extensively studied using a stochastic lung model and computational fluid dynamics techniques [Balásházy et al., 2009; Farkas and Balásházy, 2015; Farkas et al., 2011; Szöke et al., 2007; 2008; 2009; 2012; Truta-Popa et al., 2011] and is paradigmatic of the extent of information which can be provided by micro- and nanodosimetric approaches. The strong heterogeneity of aerosol deposition results in high local doses to the bronchial bifurcations of the lungs, which was found to be correlated with histological evidence [Madas 2016; Madas and Balásházy, 2011].

The EURADOS vision encourages concerted research efforts in both experimental and simulation fields. The research on experimental track structure characterization, like for instance the development of miniaturized micro- and nanodosimeters or radiobiological studies with cells exposed to single particle tracks and with microbeam irradiation of *in vitro* tissue models, provides a benchmark for the validation of track structure simulations with Monte Carlo computer codes or other alternative methods more appropriate to reproduce the biological endpoints observed in the experimental studies at the nanometric scale [Rühm et al., 2016]. In parallel, more realistic models of radionuclide deposition in the various subregions of organs and tissues should be developed to enable the description of energy deposition by incorporated high-LET radiation on a micrometer and nanometer scale.

As high-LET radiation reaches only a small number of cells depositing a high amount of energy, whilst low-LET radiation affects more cells with a smaller amount of energy imparted, alternative ways of assessing high- and low-LET exposures should be investigated. In the proposed studies and approaches the exposure of the target and the observed and/or simulated effects can be investigated in dependence on such parameters as radiation fluence, distribution of particle hits, specific energy distribution, lineal energy distribution, thus giving the opportunity to assess whether one of these quantities, or other related quantities or even some combination of them might be more appropriate to describe the radiation damage due to heterogeneous exposures. The EURADOS SRA recommends that age- and sex- dependent correlation between yields of certain biological endpoints and track structure characteristics should be systematically studied to find potential weighting functions that allow to use track structure measurements for predicting biological effects. This would be a prerequisite for new dosimetric concepts quantifying radiation effects at the level of individual cells or small compartments of tissue [Rühm et al., 2014].

A thorough uncertainty analysis is required to show that the introduction of potential new approaches and defined quantities represents an effective advantage with respect to the current definitions. The establishment of uncertainty budgets for measured micro- and nanodosimetric quantities is an important task and also a major need for benchmarking the computational methods used for numerical simulation of particle tracks.

3.6 Concluding remarks

The current system of dose quantities, although of easy practical implementation and generally accepted, has undeniable limits, in particular for heterogeneous exposures and for internal emitters of non-penetrating radiation. Not only the concept of averaging absorbed doses over organs or tissues, the concept of effective dose itself has been put into question and alternative solutions have been suggested [Brenner, 2008; 2012]. ICRP judges that experimental evidences still are not sufficient for relinquishing its current system of radiation protection based on the concepts of effective dose, equivalent dose to an organ or tissue and the underlying LNT model assumption. Micro- and nanodosimetric approaches provide valuable tools for innovative experimental and computational studies. Advance research in these fields is fostered by EURADOS and presented in its Strategic Research Agenda. Such efforts could pave the way for alternative approaches to quantify radiation effects based on radiation field properties which would take account of heterogeneous energy depositions and still be practical for radiological protection purposes.

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4 NEW DATA REGARDING THE LENS OF THE EYE (FOR RADIATION PROTECTION PURPOSES)

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4.1 Introduction

The general scheme of the external dosimetry for workers exposed to ionizing radiations is summarized in figure 1. This scheme allows estimating the protection quantities - equivalent dose H_T and effective dose E - used to check whether occupational exposures are kept below the legal limits.

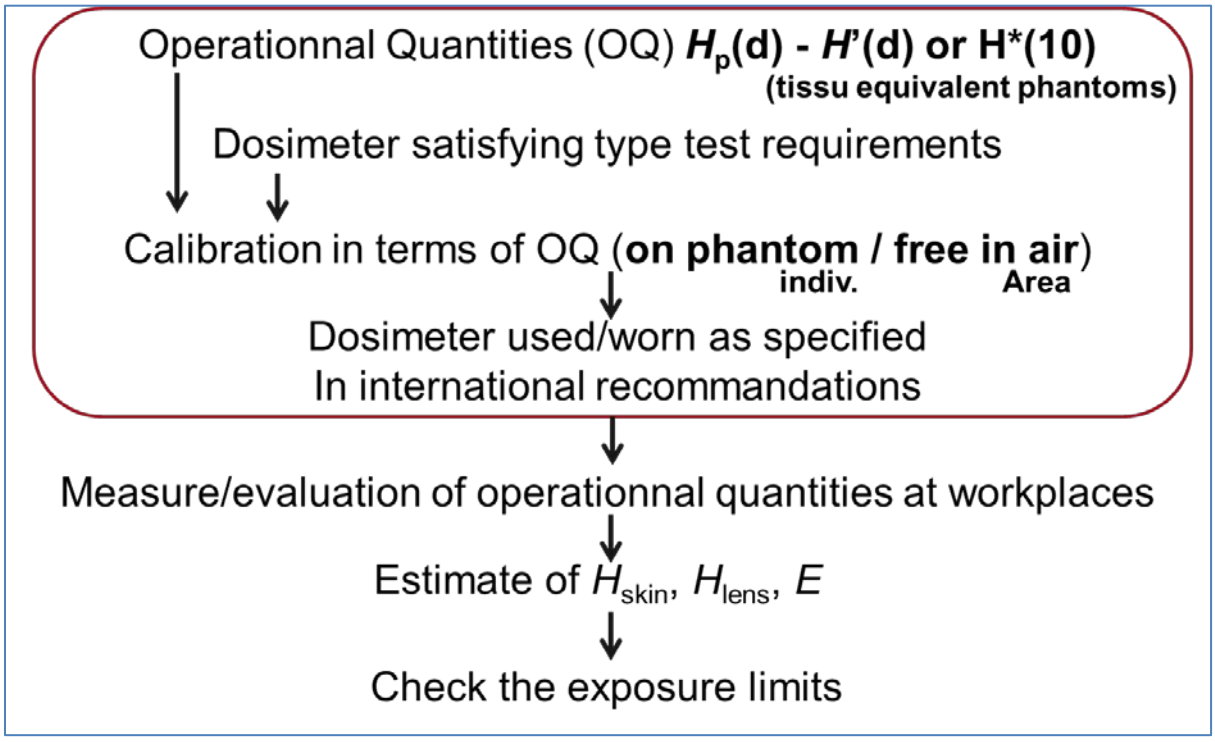

Figure 1: General schema of external dosimetry for workers monitoring

The Protection Quantities (PQ) are not measurable. They are estimated through measurements using dosimeters, calibrated in terms of Operational Quantities (OQ), and fulfilling the requirements of type test standards. In the case of eye lens dosimetry, the PQ is the equivalent dose to the lens of the eye, H_{Lens}, and the OQ for dosimeters worn by the workers is the personal dose equivalent at 3 mm depth, $H_p(3)$. Among the organs included in the list of ICRP to calculate the effective dose, as for the skin, the eye lens is an organ for which one has both OQ and PQ, the more these quantities are similar, the more the eye lens monitoring is accurate. In past decades, the eye lens exposure limit was 150 mSv per year.

It was thought that a direct monitoring of eye lens exposures was not necessary since others limits like the one for whole body monitoring - 20 mSv per year in terms of effective dose estimated through $H_p(10)$ measured with dosimeters worn on the trunk - would cover the eye lens limit. Thus, the whole body limit would have been exceeded before the eye lens “dose” could exceed its limit. The consequence was that there was no personal dosimeter for eye lens and the phantom to be used to define $H_p(3)$ and calibrate the dosimeters was not defined satisfactorily. For more detail on the eye lens dosimetry, the technical Information sheet of the French radiation protection society – SFRP - "Regulatory limits, Measurement, Dosimetry and Medical surveillance" summarizes the information [1].

Since ICRP (in 2011) proposed a drastic decrease of the exposure limit for the eye lens [2] down to 20 mSv per year, the former way of dealing with the eye lens exposure was not anymore acceptable and it has been agreed that eye lens doses must be monitored accurately. Many works were conducted to be able to check accurately the eye lens occupational exposure limit. Thus, the definition of $H_p(3)$, was refined [3,4,5,6,7], introducing an new "head phantom" – right cylinder with 20 cm diameter. A few dosimeters specially designed to measure $H_p(3)$ [8] are now commercially available (Radcard [9], UK Ratundascitech [10], Public Heath England design [11], IRSN [12], Landauer [13], Dosilab [14] …), and many workplace studies including the eye lens exposures were published.

Of course the best way to evaluate H_{lens} is to wear a dosimeter - specially design to measure $H_p(3)$ - close to the eye. On the other hand, it is often reported that wearing a dosimeter close to the eye is a constraint and the ergonomics of dosimeters are intended to obviate this difficulty. Another possibility is to use an indirect evaluation of $H_p(3)$ through the whole body dosimetry results in terms of $H_p(10)$. Thus, the workplace studies allow evaluating the foreseen values of $H_p(3)$ and $H_p(10)$ and it comes that a ratio $R = H_p(3) / H_p(10)$ may allow evaluating a posteriori $H_p(3)$ from the values of $H_p(10)$ in routine without wearing a dosimeter close to the eye.

The use of this indirect method must avoid under estimating $H_p(3)$. It is to prevent this issue that a method, taking into account the uncertainties on $H_p(10)$ and on R, associated with a criterion to choose between a direct measurement or indirect evaluation of $H_p(3)$ was proposed [15].

4.2 Summary of the indirect evaluation method

Let **$R = H_p(3) / H_p(10)$,** determined, with its associated standard uncertainty, U(R), during the work place study. Taking into account the exposure limit in terms of $H_p(3)$ proposed by the ICRP - 20 mSv a year on average over 5 years without exceeding 50 mSv for one year - as well as the expanded uncertainties U(Hp10) on the measure of $H_p(10)$ and U(R) on the value of R, one can define a maximal value of the personal dose equivalent at 10 mm depth, $H_p(10)max$, corresponding to each of these limits:

$$H_p(10)_{max} = (H_{lens,limit} / (R + U(R))) – U(Hp10) \qquad \text{Equation 1}$$

$$H_p(10)_{max20} = (20 / (R + U(R))) – U(Hp10) \qquad \text{Equation 1a}$$

$$H_p(10)_{max50} = (50 / (R + U(R))) – U(Hp10) \qquad \text{Equation 1b}$$

So, if $H_p(10)$ measured is lower than $H_p(10)_{max20}$ or $H_p(10)_{max50}$, for a given value R+U(R), it can be considered with a "confidence" depending on the coverage factor that the H_{lens} limit may not be exceeded. We will specify this point in the last part of this publication.

The graph below is obtained from the mathematical models (1a and 1b) by introducing the equations of the "trumpet" curves (2a and 2b) [16] which allow defining, with a 95 % confidence level, the eligible maximal error in routine for the measurement of $H_p(10)$. These equations take into account the smallest value of $H_p(10)$ which must be able to be measured, that is H_0 = 0,17 mSv for a monthly monitoring in dosimetry of photons [17,18].

The upper trumpet curve equations (2a, 2b), which are the most conservative ones are given here after.

$$H_p(10)_{ul} = 1.5\ H_p(10)_t\ (1 + H_0 / (2\ H_0 + H_p(10)_t)) \quad \text{if } H_p(10)_t \geq H_0 \quad \text{Equation 2a}$$

And $H_p(10)_{ul} = 2\ H_p(10)_t$ if $H_p(10)_t < H_0$ Equation 2b

Where $H_p(10)_t$ is the true value of the dose equivalent.

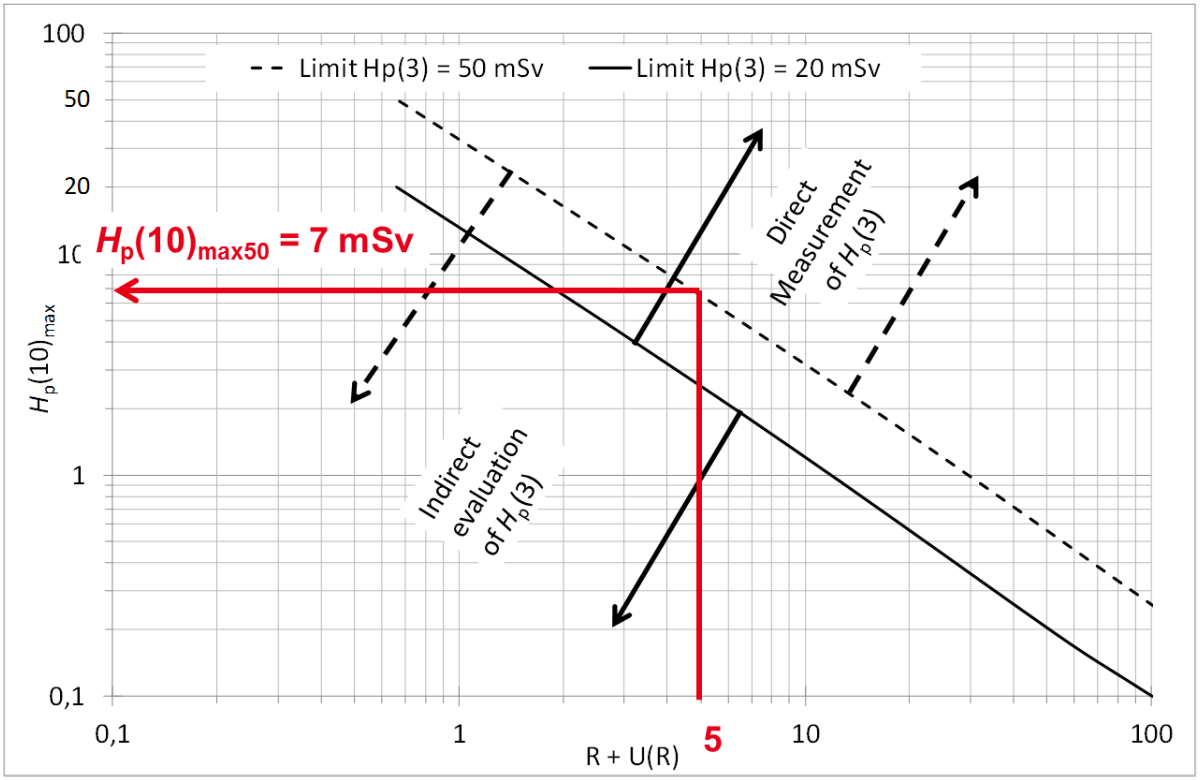

Figure 2: Visualization of the domain where the indirect evaluation and direct measurement method can be used.

In figure 2, both straight lines in diagonal show the border between the domain where the direct measurement of $H_p(3)$ is necessary and the one where an indirect evaluation of $H_p(3)$ is possible for an exposure limit in 20 mSv (solid line) and 50 mSv (dashed line). For example, if the value of R+U(R) is equal to 5, the maximum value of $H_p(10)$ beyond which, for an exposure limit of 50 mSv, a direct measure of $H_p(3)$ is necessary is 7 mSv.

4.3 Implementation of other evaluations of the measurement uncertainty on $H_p(10)$ in the proposed indirect evaluation method

Today, new trumpet curves equations and new values of H_0 are proposed within the framework of the standardization. They are inspired by criteria taken from the IEC standard dealing with the type test of the passive personal dosimeters. Two hypotheses are envisaged depending on the photon energy higher or lower than 65 keV [5](see below). In both cases the value of H_0 is fixed to 0,1 mSv.

$$0.71\left(1-\frac{2H_0/1.33}{H_0/1.33+H_p(10)_t}\right)x \leq \text{response} \leq 1.67\left(1+\frac{H_0}{4H_0+H_p(10)_t}\right) \qquad \bar{E} > 65\ keV$$

$$0.5\left(1-\frac{2H_0/1.5}{H_0/1.5+H_p(10)_t}\right)x \leq \text{response} \leq 2 \qquad \bar{E} < 65\ keV$$

These two hypotheses were introduced into the mathematical model (1a and 1b) to estimate their impact.

In figure 3, the red curves (solid and dashed lines) present the results obtained with the data taken from the standard ISO 14142-2000 (identical to figure 2). The black curves (solid and dashed lines) take into account the criteria for the photons of energies above 65 keV. The blue curves (solid and dashed lines) correspond to the criteria for the photons energy lower than 65 keV.

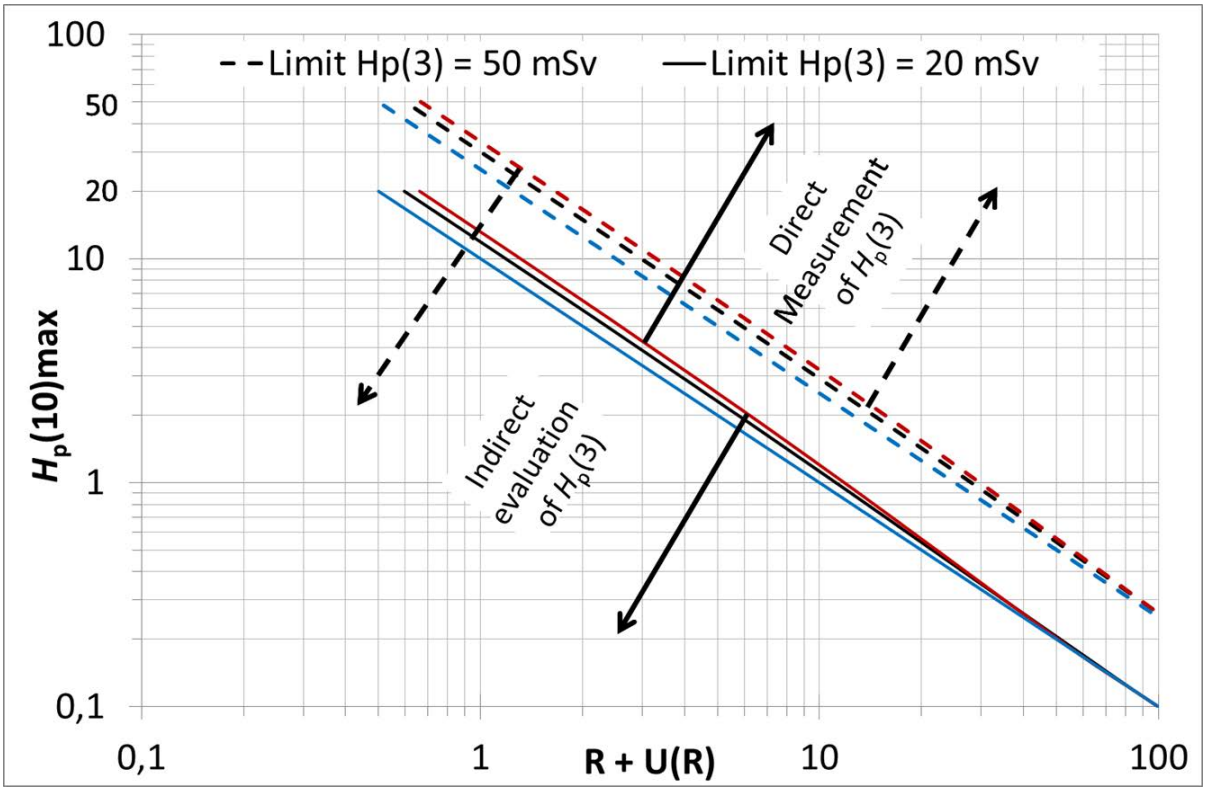

Figure 3: Comparison of the domain depending on the trumpet curves hypotheses.

So, in figure 3 and table 1, for a value of R+U(R) equal to 1, and an exposure limit of the eye lens of 20 mSv, the maximum value of $H_p(10)$ below which an indirect evaluation is possible is 13.2 mSv, 12 and 10 mSv considering the former trumpets curve equations or the new

[5] It came since the EU Scientific Seminar that this limit would be changed to 10 keV.

ones for photons of energy higher and lower than 65 keV respectively. Table 1 below presents the values of $H_p(10)_{max20}$ et $H_p(10)_{max50}$ in mSv according to the three trumpet curves equations, for values of R+U(R) between 0.8 and 10 and the limits in terms of $H_p(3)$ of 20 and 50 mSv. It can be seen that the impact of the alternate trumpet curve equations is visible but does not change the landscape between indirect and direct method and so the possibility to use one or the other.

Table 1: Detail of the values used to draw the curves of figure 3.

R+U(R)	$H_p(10)_{max20}$; Limite $H_p(3)$ = 20 mSv			$H_p(10)_{max50}$; Limite $H_p(3)$ = 50 mSv		
	ISO 14142-2000	E > 65 keV	E < 65 keV	ISO14142-2000	E > 65 keV	E < 65 keV
10	1,20	1,12	1,00	3,18	2,91	2,50
7,5	1,64	1,52	1,33	4,29	3,90	3,33
5,0	2,52	2,31	2,00	6,50	5,89	5,00
4,0	3,18	2,91	2,50	8,15	7,39	8,34
3,0	4,28	3,90	3,35	11,0	9,88	12,0
2,0	6,50	5,90	5,00	16,5	14,9	12,5
1,0	**13,2**	**12,0**	**10,0**	33,2	29,8	25,0
0,8	16,5	14,9	12,5	41,5	37,3	31,3

4.4 Probability to announce an indirect evaluation of $H_p(3)$ lower than the limit whereas a measurement of $H_p(3)$ may show that this limit is exceeded

Considering a Gaussian distribution of the estimated values of $H_p(3)$, its standard deviation, $u(H_p3)$, is calculated from the uncertainties on the measurement of $H_p(10)$ and on R using the sandwich law to calculate the combined uncertainty [19] without taking into account the possible correlations - equation 3.

$$u(\mathrm{H}p3) = \sqrt{\left(\frac{\partial \mathrm{Hp3}}{\partial \mathrm{R}}\right)^2 \mathrm{u}^2(\mathrm{R}) + \left(\frac{\partial \mathrm{Hp3}}{\partial \mathrm{Hp10}}\right)^2 \mathrm{u}^2(\mathrm{Hp10})} \qquad \text{Equation 3}$$

The probability to indicate a value of $H_p(3)$, through the indirect evaluation, lower than the limit while this limit is exceeded corresponds to the green part of the distribution of the values of $H_p(3)$ (figure 4). It can be calculated through the integral of the figure 4 where $H_p(3)_m$ and u(Hp(3)) are the evaluated value and its standard uncertainty respectively.

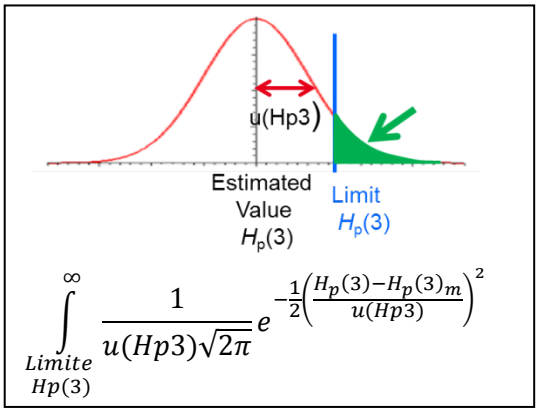

Figure 4: Evaluation of the probability "false-negative" that is to say indicated falsely a value lower than the limit while this limit is exceeded.

Table 2 below presents, as an example, the results of the calculation of this integral for an indirect evaluation in the case of a limit in terms of $H_p(3)$ of 20 mSv, a standard uncertainty on R, u(R), equal to 25 %, a one decade range for R+U(R) between 0.5 to 5 and $H_p(10)$ up to 20 mSv. This range of the ratio, R, has been chosen because it covers most of the situation known at the date of the EU scientific seminar [20]. In every case, the possibility of "false-negative" is very low. The most unfavourable case, 0.23 %, is found for a value of R+U(R) equal to 2 and a value of $H_p(10)$ equal to 13.2 mSv corresponding to a value of $H_p(3)$ equal to 9.9 mSv.

Table 2: Estimate of the "false-negative" probability

R + U(R)	10		7,5		5		3		2		1		0,5	
R	7,50		5,63		3,75		2,25		1,50		0,75		0,375	
Hp(10)	*H* p(3)	P	*H* p(3)	P	*H* p(3)	P	*H* p(3)	P	*H* p(3)	P	*H* p(3)	P	*H* p(3)	P
< 1,2	< 9,0	< 1.7E-03	< 6,75	< 1.2E-06	< 5,5	< 1E-08	< 2,7	< 1E-06	< 1,8	< 9E-09	< 0,9	< 3,3E-08	< 0,45	< 1E-12
1,20	9,0	1,7E-03	6,75	1,2E-06	4,50		2,70		1,80		0,90		0,45	
1,64			9,23	1,8E-03	6,15	1,0E-08	3,69		2,46		1,23		0,62	
2,52					9,45	1,9E-03	5,67		3,78		1,89		0,95	
3,18							7,16	1,2E-06	4,77		2,39		1,19	
4,30							9,68	2,1E-03	6,45		3,23		1,61	
5,00									7,50	9,3E-09	3,75		1,88	
6,50									9,75	2,1E-03	4,88		2,44	
8,00											6,00		3,00	
9,00											6,75		3,38	
10,0											7,50	2,1E-06	3,75	
12,0											9,00	3,5E-04	4,50	
13,2											9,90	2,3E-03	4,95	
15,0													5,63	
20,0													7,50	1,6E-06

4.5 Conclusions and answers to the remarks received during the EU scientific seminar

A remark was made during the EU scientific seminar about the difficulty to use the indirect method when the so called “double dosimetry” is used to estimate $H_p(10)$ through two dosimeters one worn above and one worn below a lead apron. This remark raises the issue of the personal protective equipment – lead apron, leaded glasses and face guards. Four cases can be met whether the apron and the eye protections are worn together or not.

To answer this remark it has to be reminded that the reading of a dosimeter must be traceable to a national reference through a calibration method described in the ISO standards; that is to say on phantom for a personal dosimeter and of course without a protective equipment between the dosimeter and the phantom. Thus, the reading of the dosimeter worn above the lead apron is not traceable to the International system of units and, strictly speaking, the ratio R must be calculated with the reading of the dosimeter worn under the lead apron. Of course the uncertainty associated to R might be quite large in such a case, and so the value of R+U(R) might be larger than expected, therefore the domain in which the indirect method can be used would be reduced. This should not be a problem because the values of $H_p(10)$ below the lead apron are small so far below the maximum value.

Table 3: Analysis of the cases where protective equipments are used or not.

Case	Lead apron	Eye lens protection	Uncertainty on the value of R, U(R)	Foreseen consequences
1	No	No	This case is included in the table to be compared to the cases where personal protective equipment is worn.	
2	Yes	No	Assuming that the value of $H_p(10)$ below the lead apron is small but above the detection threshold, U(R) might be larger than in case 1.	The domain in terms of $H_p(3)$ values in which the indirect method can be used would be smaller compared to case 1.
3	No	Yes	Assuming that the value of $H_p(3)$ behind the leaded glasses is small, U(R) might be larger than in case 1	The domain in terms of $H_p(3)$ values in which the indirect method can be used would be reduced compared to case 1. The accuracy of $H_p(3)$ would be worse than in case 1 but it is foreseen that $H_p(3)$ is very low.
4	Yes	Yes	Assuming that both values of $H_p(3)$ and $H_p(10)$ under the protected equipment are small but above the detection threshold, U(R) might be larger than in case 1	

Last but not least, if the workplace study shows that the whole body "dose" is under the detection threshold and the eye lens dose is not, of course the indirect method cannot be used. Such a case is very unlikely since no whole body dose should means no eye lens dose.

To conclude this article, compared to the situation of past decades, an accurate monitoring of eye lens "doses" is now possible thanks to:

- conversion coefficients from air kerma to $H_p(3)$ calculated in the “head phantom” and published jointly by ENEA and CEA/LNHB within the framework of the ORAMED FP7 contracts (lead by SCK-CEN) [21]. Later those coefficients were used to calculate some conversion coefficients for the calibration radiation fields [22]
- the introduction of the cylindrical phantom in the ISO standard dealing with the calibration of the personal dosimeters,
- the eye lens dosimeters commercially available,

- the implementation in national regulations of the new eye lens dose limits following the publication of the EU Directive 2013/59/Euratom.

It is also possible to choose between a direct measurement and indirect evaluation of the eye lens doses to overcome, when it is possible, the constraint of wearing a personal dosimeter close to the eye while reducing the risk to under estimate $H_p(3)$ [15].

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Information about the indirect method to evaluate $H_p(3)$ included in this paper were presented in international conferences before the EU Scientific Seminar "Emerging issues with regard to organ doses":

- Individual monitoring IM2015 / Bruges – Belgium
- EPRI 2016, Radiation Induced Cataracts: Science, Policy, and Impacts to Radiation Protection / Charlotte - North Carolina - USA

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5 EVALUATION OF RADIATION RISKS FROM MEDICAL EXPOSURES: ORGAN DOSE APPROACH VERSUS EFFECTIVE DOSE APPROACH

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Abstract

To assess radiation risk in an organ or tissue, the average absorbed dose is usually used. The effective dose received by patients during a radiological examination is also sometimes used as a risk indicator. The consensus on this issue has not yet been reached. The objective of this work is: a) comparison of the risk of stochastic effects of irradiation of patients undergoing radiographic examinations, estimated by absorbed doses in organs and sex- and age -dependent risk coefficients with the risk assessed via the effective dose, and b) discussion of the advisability of accounting for age and sex when assessing the risk for the purpose of the patient protection. Typical parameters for the selected six types of pediatric examinations were collected from 33 X-ray units operating in pediatric hospitals and 54 X-ray units operating in hospitals for adults in 2009-2014 in the city of St. Petersburg and four other regions of Russia. We calculated for both adults and children mean absorbed doses to exposed organs and tissues, and effective doses, based on available X-ray examination parameters. Lifetime radiation risk was assessed in two different ways, i.e. with account for patient age and sex using mean organ doses, and by simple multiplication of effective dose by nominal risk coefficient from ICRP Publication 103. The study results demonstrated that for most of the age groups, effective doses increase in the order Skull-Chest-Thoracic spine-Pelvis-Abdomen-Lumbar spine. In some examinations, both absorbed and effective doses were larger in children or adolescents than in adults. The radiation risk is higher in children and adolescents than in adults undergoing similar examinations. Radiation risk per examination monotonically decreases with age in adulthood. The risk for females is larger by a factor of two to four than for males for different age groups following radiography of chest or thoracic spine. The range of risks following radiography examinations lies within minimum or very low risk ranges. As follows from a comparison of the risk estimates obtained by two methods, for some examinations the simplified risk assessment based on effective dose underestimated risk in children (girls) by a factor up to 4-5 and for adolescents by a factor up to 2-3. In contrast, risk for senior patients (65+) assessed via effective dose can be overestimated by about an order of magnitude. The significant age- and sex-dependence of radiogenic health risk is an important consideration for radiologists when planning X-ray examinations. So far, no such study has been conducted with respect to nuclear medicine. While effective dose was not intended to provide a measure of risk associated with medical X-ray examinations, simple adjustments to ICRP's nominal risk coefficient to account for age and possibly also sex differences can make it a useful instrument for the justification of examinations. Similar views were preliminary expressed by ICRP Task Group 79 working on the report 'The Use of Effective Dose as a Risk-related Radiological Protection Quantity'.

5.1 Introduction

The concept of the radiation risk of stochastic health effects of irradiation and the criteria for acceptable risk are key in the current system for the radiation protection of humans from low doses of ionizing radiation (IR) since the development of the basic ICRP Publication 26 in 1977 [1] and especially ICRP Publication 60 in 1990 [2]]. As soon as dose limits have been established in [1], updated in [2] and reconfirmed in ICRP Publication 103 in 2007 [3], risk values are not used any more as radiological criteria [3, 4]. There are very few exceptions where risk values are still directly used in practical radiation protection, and these are:

- Justification of medical exposures,
- Protection against potential exposure.

This paper is limited with consideration of medical exposures.

To assess the level of radiation risk in an organ or tissue, the average absorbed dose in this organ or tissue is usually used. However, since the development in the 1970s [1] of the biophysical concept of the effective dose, this value is widely used in radiation protection, including the protection of patients.

The effective dose is defined as the value regardless of the absorbed dose from the sex and the radiosensitivity from sex and age. It is quantitatively related to the average risk of radiogenic carcinogenic and hereditary health effects, provided that the entire population is irradiated in equal doses: the nominal detriment-weighted risk is taken equal to $5.7\ 10^{-2}\ Sv^{-1}$ or $5.7\ 10^{-5}\ mSv^{-1}$ [3].

The effective dose received by patients during the examination is also sometimes used as a risk indicator. However, the age and sex composition of patients undergoing various medical examinations can significantly differ from that of the whole population. So, there are cohorts of patients with pronounced age-sex differences: for example, with the X-ray examination of children for scoliosis of the spine or women for breast cancer. For these specific cohorts, the radiation risk can be assessed incorrectly if the effective dose is used as its measure.

Estimates of the risks of stochastic effects of irradiation of sex- and/or age-matched cohorts of patients undergoing X-ray examinations, obtained with absorbed doses in organs and on the basis of an effective dose, were compared in [5-7] and generalized by the ICRP Working Group 79 in [8]. However, the consensus on the applicability of an effective dose as risk indicator for medical exposures cannot yet be considered achieved. In particular, such a judgment requires more data relating to different medical technologies and obtained using different methodologies.

The purpose of this work is:

1. Comparison of the risk of stochastic effects of irradiation of sex- and/or age-matched cohorts of patients undergoing radiographic examination assessed by absorbed doses in organs and sex- and age-dependent risk coefficients with the risk assessed on the basis of the effective dose [3];
2. An estimation of the merit of the accounting of a sex and age at an estimation of risk for the purposes of patient protection from radiation as a result of radiographic examination.

5.2 Methodology

In order to achieve the study goals, we selected representative set of six X-ray examinations covering various body parts and for each of them did the following:

1. Calculated for both adults and children mean absorbed doses to exposed organs and tissues, and effective doses, based on available X-ray examination parameters;
2. For ICRP radiation risk model [3] defined sex- and age-dependent risk coefficients for persons exposed to low doses during X-ray examinations;
3. Assessed lifetime radiation risk from the X-ray examinations under consideration in two different ways, i.e. a) with account for patient age and sex using mean organ doses and sex- and age-dependent risk coefficients [3], and b) by simple multiplication of effective dose by nominal risk coefficient;
4. Compared lifetime radiation risks assessed in two different ways by calculating their ratio.

Six types of common X-ray examinations were selected for our study, i.e. the generic skull, chest, thoracic spine, lumbar spine, abdomen and pelvis radiographic examinations. Input parameters used for the calculation of patient doses for both adults and children were the collected parameters relevant to the X-ray unit (radiation output, tube voltage, filtration, etc.) and each X-ray examination (projection, size of examination field, focus-film distance, exposure, etc.) [9, 10].

Typical parameters for the selected six types of radiography examinations were obtained from the data collected from 33 X-ray units operating in 2009-2014 in pediatric hospitals and 54 X-ray units used for adults in the city of St. Petersburg and Belgorod, Bryansk and Tyumen regions of Russia [9, 10]. Total filtration for the X-radiation was equivalent to not less than 2.5 mm Al and focus-receptor distance was 100 cm for most examinations, except for chest radiography of adults where it was 150 cm.

Mean absorbed doses to 13 organs and tissues and 'other organs' needed for the assessment of effective doses to reference patients of different ages and both sexes were calculated for the six selected X-ray examinations by means of the computer code PCXMC [11]. Doses were assessed for five ICRP age groups of reference children and adolescents (0-1, 1-2, 2-7, 7-12 and 12-17 years) and for adults (>17 years) [12] and then interpolated to 10 y age bands corresponding to data available concerning the age dependence of radiation risk.

In order to assess lifetime radiation incidence risk ${}^{inc}R_p(A, G)$ for a person of particular age A (y) and sex G based on organ doses caused by the X-ray examination under consideration P, the calculation procedure used was as follows:

$$ {}^{inc}R_P(A,G) = \sum_O D_P(A,G,O) \cdot r(A,G,O) \text{ , dimensionless,} \quad (1) $$

where: $D_P(A, G, O)$ is the mean absorbed dose in the organ or tissue O of a patient of gender G and age A due to the X-ray examination P, mGy. Organ doses in each age group are equal for males and females, since calculations were made for a single phantom, except for doses in the genitals and the female breast;

$r(A, G, O)$ is the lifetime radiation risk incidence coefficient due to exposure of the organ or tissue O in a patient of gender G and age A, mGy^{-1}.

The coefficients of lifetime radiation risk of cancer incidence for the ICRP composite population, depending on sex, are given in table A.4.18 of ICRP 103 [3], and the models of age-dependence upon exposure for nine organs and all solid cancers are in tables A.4.6 and A.4.7 of ICRP 103 [3]. The sex-age risk coefficients for eight organs are explicitly given in [13] and used in this article with a slight correction.

Age dependence of the risk coefficient for cancer of four other organs/tissues of the indicated in [3] (bone, skin, ovaries and red bone marrow), and "other tissues", in the absence of detailed data, was taken similar to that for all solid cancers [3, 13]. The risk factors for the hereditary effects were simplified to be constant from birth to the period of fertility decline without taking into account the duration of the forthcoming life [5]. The sets of sex-age coefficients of radiation risk (incidence) for men and women of eight age groups used in this work are given in Table 1 [3, 5,13].

For the conversion from the radiogenic incidence ${}^{inc}R_p(A, G)$ of organ O to detriment D, we used their ratio from Table A.4.18 [3], different for different organs and tissues, but not dependent on age and sex, except of genitals. The values of ratio $(D/I)_O$, dimensionless, used in this paper are given in the rightmost column of Table 1. Then calculate the lifetime detriment-weighted radiation risk ${}^{det}R_P(A, G)$ as follows:

$$ {}^{\det}R_P(A,G) = \sum_O D_P(A,G,O)\cdot r(A,G,O)\cdot (D/I)_O \text{, dimensionless.} \quad (2) $$

Formulas (1, 2) and risk coefficients in Table 1 were tested by calculation with the initial condition: all organs and tissues were irradiated at a dose of 1 mGy. As a result of the calculation it was obtained that the average value of lifetime risk for people of both sexes of all eight age groups ($5.7\cdot10^{-5}$) was exactly consistent with the nominal risk/detriment coefficient r_n=$5.7\cdot10^{-5}$ mSv^{-1} [3].

Another, simplified approach to assessing radiogenic risk is based on the use of an effective dose, although the latter is not intended for these purposes. The corresponding formula for calculating the radiation risk/detriment ${}^{det}R_p\ (A)$ for a person of any gender and age at the time of irradiation A (years) from performing an X-ray examination P takes into account the dependence of the effective dose on age but not gender and does not take into account the dependence of radiosensitivity on sex and age:

$$ {}^{\det}R_P(A) = E_P(A)\cdot r_n \text{, dimensionless,} \quad (3) $$

where: $E_P(A)$ is the effective dose for the X-ray examination p of a patient of age A and any gender, mSv,

r_n is the nominal lifetime radiation risk/detriment coefficient equal to $5.7\cdot10^{-5}$ mSv^{-1} for members of the public of any age or gender (0 – 85 years) [3].

Table 1a: Lifetime risk coefficients r(A, O), 10^{-4} Gy^{-1}, for incidence of radiation-induced cancer and genetic effects for males at different age at exposure A, y.

Organ or tissue	Age at exposure group, years									Detriment/ Incidence, dimensionless
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-85	**0-85**	
Oesophagus	24	21	19	18	16	14	10	3	**15**	0.85
Stomach	170	132	101	74	51	31	14	3	**68**	0.85
Colon	217	172	135	103	74	45	21	4	**91**	0.73
Liver	104	81	62	45	30	17	7	1	**41**	0.90
Lung	87	92	97	101	101	88	58	14	**76**	0.79
Bone	17	13	10	8	5	3	1	0	**7**	0.73
Skin	2473	1927	1482	1106	775	468	213	38	**1000**	0.004
Breast	–	–	–	–	–	–	–	–	**0**	–
Ovary	–	–	–	–	–	–	–	–	**0**	–
Bladder	94	79	66	55	44	31	17	4	**46**	0.38
Thyroid	60	26	10	4	1	0	0	0	**12**	0.39
Red bone marrow	119	93	71	53	37	22	10	2	**48**	1.47
Other solid cancer	388	303	233	174	122	73	33	6	**157**	0.79
Gonads (heritable)	30	30	30	30	30	15	5	–	**20**	1.27
TOTAL	3784	2970	2318	1771	1286	808	391	74	**1580**	0.31

Table 1b: Lifetime risk coefficients r(A, O), 10^{-4} Gy^{-1}, for incidence of radiation-induced cancer and genetic effects <u>for females</u> at different age at exposure A, y.

Organ or tissue	Age at exposure group, years									Detriment/ Incidence, dimensionless
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-85	**0-85**	
Oesophagus	18	17	17	17	19	20	18	7	**16**	0.85
Stomach	233	179	134	96	66	40	20	4	**91**	0.85
Colon	96	76	59	45	32	20	10	2	**40**	0.73
Liver	46	36	28	21	15	10	5	1	**19**	0.90
Lung	172	184	195	204	202	178	120	30	**153**	0.79
Bone	18	14	10	8	5	3	1	0	**7**	0.73
Skin	2537	1968	1490	1076	723	435	211	40	**1000**	0.004
Breast	790	482	290	171	96	49	21	4	**224**	0.71
Ovary	53	41	31	23	15	9	4	1	**21**	0.94
Bladder	78	67	57	49	40	31	20	5	**41**	0.38
Thyroid	268	113	45	17	5	2	0	0	**53**	0.39
Red bone marrow	91	71	54	39	26	16	8	1	**36**	1.47
Other solid cancer	332	258	195	141	95	57	28	5	**131**	0.79
Gonads (heritable)	35	35	35	35	30	–	–	–	**20**	1.27
TOTAL	4767	3540	2641	1940	1369	870	467	99	**1851**	0.36

5.3 Results and discussion

5.3.1 Organ doses and effective doses

The distribution of radiation dose amongst organs and tissues depends in a complex way on the X-ray examination, unit features, exposure parameters, patient mass and size, etc. An indication of the absorbed organ doses and effective doses to patients of various age groups undergoing six selected radiography examinations is provided by Table 2. Organ doses vary from a few micrograys in organs located beyond the direct radiation beam to a few milligrays in directly exposed organs. Effective doses are substantially (by a factor of two to fifteen) lower than the maximum organ doses.

Table 2: Highest mean absorbed dose in organs (mGy) and effective dose (mSv) associated with patient radiography.

Examination (projection)	Highest organ dose (mGy)			Highest effective dose (mSv)	
	Organ, tissue	Age group	Dose (mGy)	Age group	Dose (mSv)
Skull (AP+LAT for persons <5y, PA+LAT for persons ≥5y)	Salivary glands, oral mucosa	10-19	0.65	10-19	0.043
Chest (AP+LAT for persons <5y, PA+LAT for persons ≥5y)	Breast	10-19	0.26	10-19	0.089
Thoracic spine (AP+LAT)	Thymus	10-19	1.68	10-19	0.40
	Heart	10-19	1.15		
Lumbar spine (AP+LAT)	Stomach	20+	1.78	10-19	0.53
Abdomen (AP)	Stomach	20+	1.37	20+	0.41
Pelvis (AP)	Urinary bladder	10-19	0.75	20+	0.20

AP – Anterior-posterior projection,

LAT – Lateral projection,

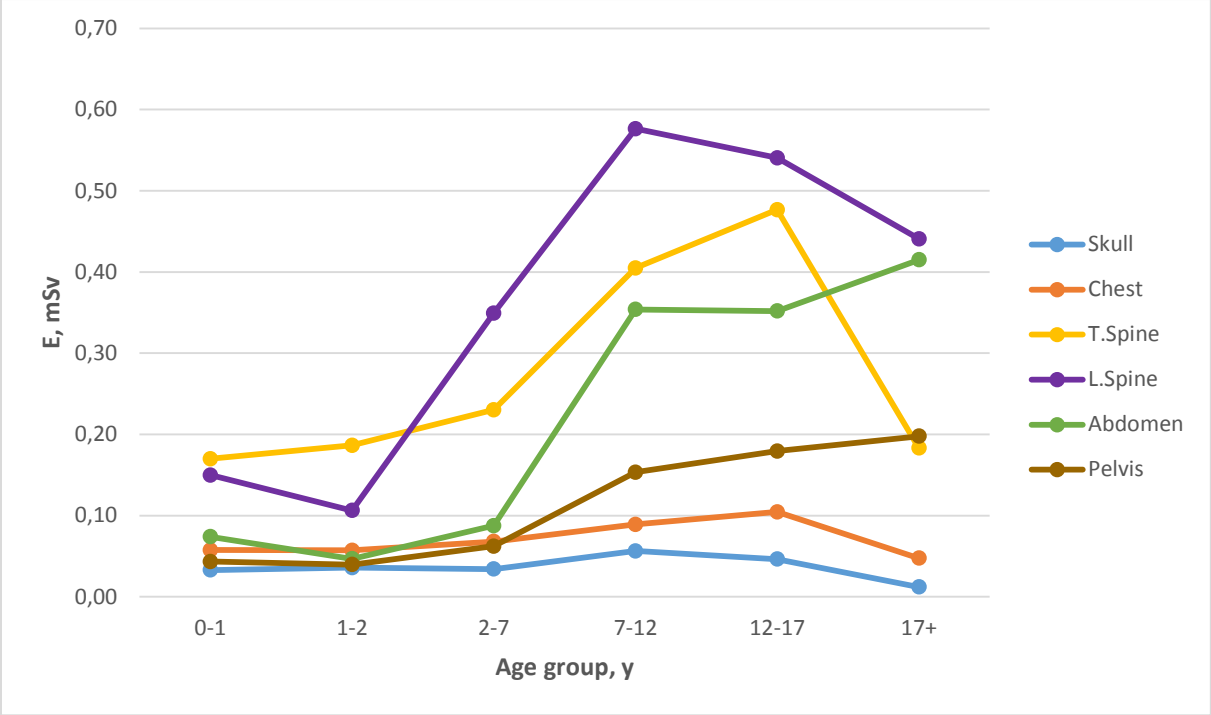
PA – Posterior-anterior projection.

Figure 1 demonstrates that for most of the age groups, effective doses increase in the order Skull-Chest-Thoracic spine- Pelvis-Abdomen-Lumbar spine because of increase in both body thickness in the examined areas, and their radiosensitivity and examination features.

According to known radiation physics patterns it was expected that organ doses and especially effective doses are lower in children with lower body mass and thickness. This is the case if X-ray unit is tuned and examination parameters are selected properly. However, in some real cases, both absorbed and effective doses are larger in children or adolescents –

see Table 2 and Fig. 1 below. That might be caused by non-optimal selection of exposure parameters, e.g., size of exposure field, etc.

Figure 1: The dependence of effective dose E, mSv per examination, on age and examination.



5.3.2 Assessment of patient radiation risks from radiography examinations

The data presented in Table 1 illustrates, in frame of ICRP risk model [3, 13], that radiation risk per unit of absorbed dose for most organs and tissues decreases with age at exposure from a maximum in infants to a minimum in seniors and the corresponding risk ratio exceeds an order of magnitude. However, the risk of radiogenic lung cancer, on the contrary, increases slightly with age to a maximum at 30-50 years and significantly decreases only after 60 years.

Table 1 also demonstrates that the largest detriment-adjusted radiation risk per unit of absorbed dose was observed for female breast, lungs, stomach, whereas in males the most radiosensitive tissues are red bone marrow, colon, lungs and stomach. In total, the radiation risk for females exposed to uniform whole body irradiation exceeds that for males by about 40%.

Based on the assessed organ doses and on the risk coefficients presented in Table 1, detriment-adjusted radiation risks per examination were calculated for patients of various age groups and both genders arising from the six selected X-ray examinations – Fig. 2.

From Fig. 2 it follows that major factors determining radiation risk per radiological examination are the dose, age and gender. More specifically, risk is basically higher if dose is larger and age smaller; risk is larger for females than for males.

Figure 2a: Age-dependent detriment-adjusted lifetime risk ${}^{det}R_P(A, M)$, 10^{-6} per examination, for males based on organ doses.

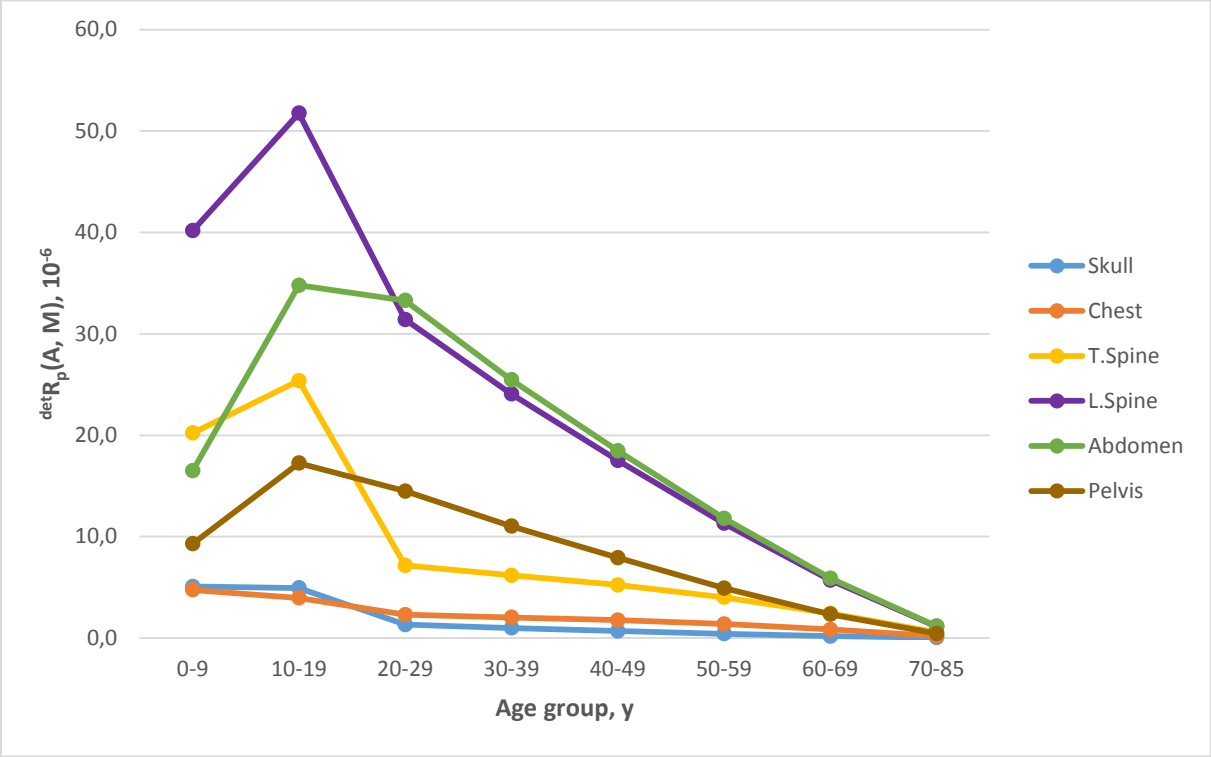
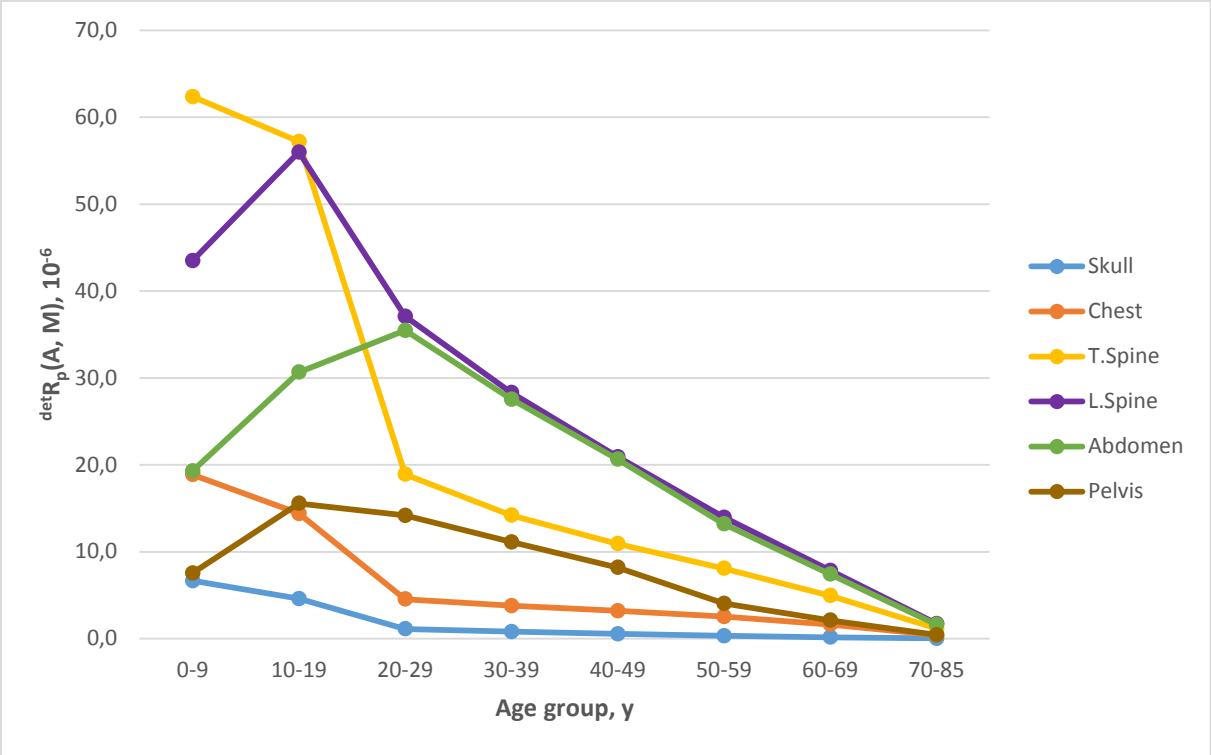


Figure 2b: Age-dependent detriment-adjusted lifetime risk ${}^{det}R_P(A, F)$, 10^{-6} per examination, for females based on organ doses.



According to our model calculation, radiation risk is higher in children and adolescents in 11 cases from 12 considered combinations (six examinations for two genders) – Fig. 2. This is caused either by larger doses (see Fig. 1) or by higher radiosensitivity of younger people (see Table 1) or both. Thus, radiation risk from chest radiography for paediatric patients exceeds that for young adults by a factor of three both because of larger dose and higher radiosensitivity. However, when body areas, where the dose strongly depends on body thickness (abdomen, lumbar spine, pelvis) are examined, adolescents are at maximum risk.

From 20 years of age, radiation risk per examination monotonically decreases with age in adulthood according to well-known epidemiological data [3, 13]. Radiation risk for senior people (70+ y) is by about an order of magnitude lower than that for all adults (20+ y) and even more so than for paediatric patients.

The substantial difference between risks for males and females per examination originates from the difference between risk coefficients (see Table 1). The ratio of these risks is quite moderate (within factor of 1.5) if head or lower part of the body (abdomen, lumbar spine, pelvis) are examined. However, when breast or/and lungs, which are more radiosensitive in females than in males, are exposed, the difference is more pronounced, i.e. risk for females is larger by a factor of two to four for different age groups following radiography of chest or thoracic spine – see Fig. 2.

The data presented in Fig. 2 illustrates that radiation risks associated with the six considered radiology examinations are generally low, i.e., in the range of $1 \cdot 10^{-6}$ to $60 \cdot 10^{-6}$ for children, adolescents and young adults. This range of risks finds its room within minimum (10^{-6} to 10^{-5}) or very low (10^{-5} to 10^{-4}) radiation risk ranges associated with medical examinations for those age groups [6, 14, 15]. The risks may be larger up to one to two orders of magnitude when more informative X-ray (e.g. computer tomography) or nuclear medicine examinations are performed [15, 16].

5.3.3 Comparison of risks assessed by means of organ doses with risks assessed from effective dose

For comparison with risk estimates as above, we also assessed risk values for the same age and gender groups for six radiography examinations by means of formula (3) based on the effective dose without account for age-sex-dependent radiosensitivity. While this risk value is proportional to the effective dose with fixed factor equal to nominal risk coefficient $r_n = 5{,}7 \cdot 10^{-5}$ mSv^{-1}, the shape of risk dependence on age is similar to Fig. 1.

We compared two risk estimates by their ratio considering that risk estimate based on organ dose corresponds better to current knowledge [3, 13]. Fig. 3 presents ratios of organ-dose-based radiation risk due to X-ray examination for various patient groups to risk based on the effective dose. Compared to risk assessment based on the effective dose as defined in [3], the more realistic risk values assessed by means of organ doses are higher by a factor 1.4 to 2.3 in boys and 1.8 to 4.8 (chest) in girls. The largest underestimation of risk value (by a factor up to almost five) when effective dose was used occurred in the case of chest radiography of girls, where both radiosensitive lungs and breast are exposed.

Figure 3a: Age-dependent ratio (dimensionless) of organ-dose-based radiation risk due to X-ray examination to risk based on effective dose for males.

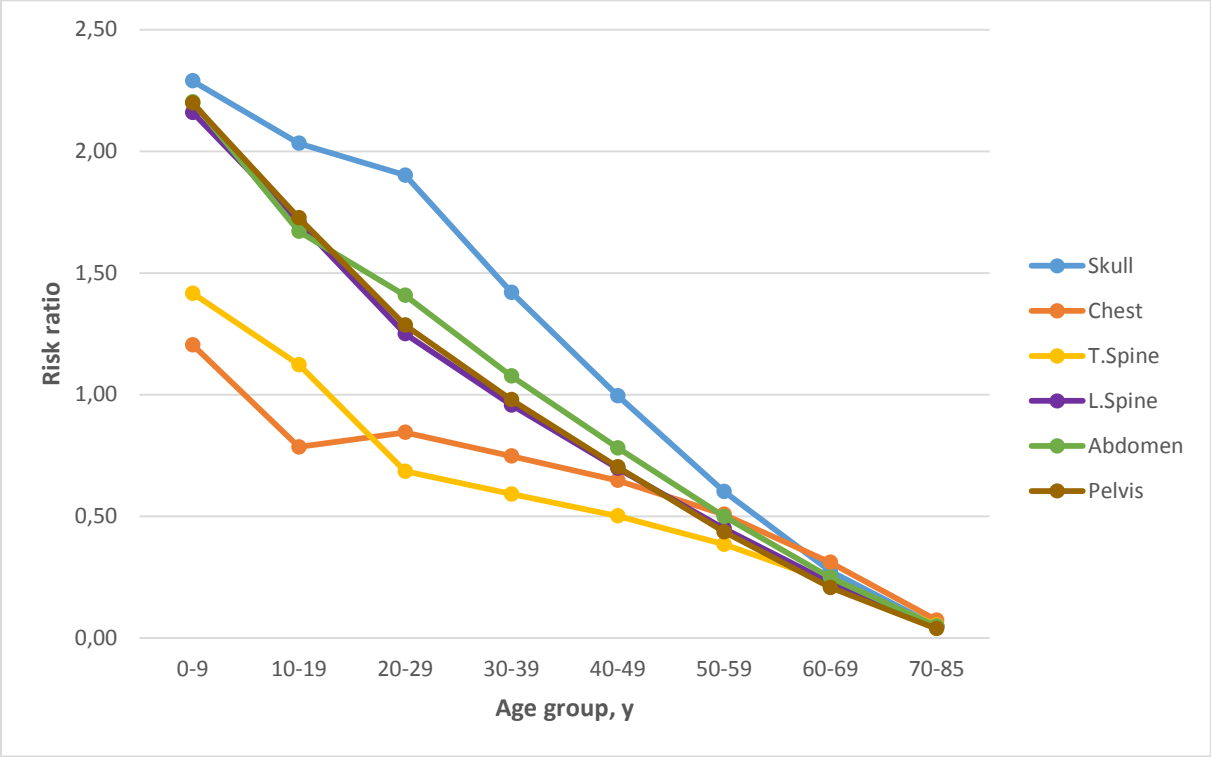
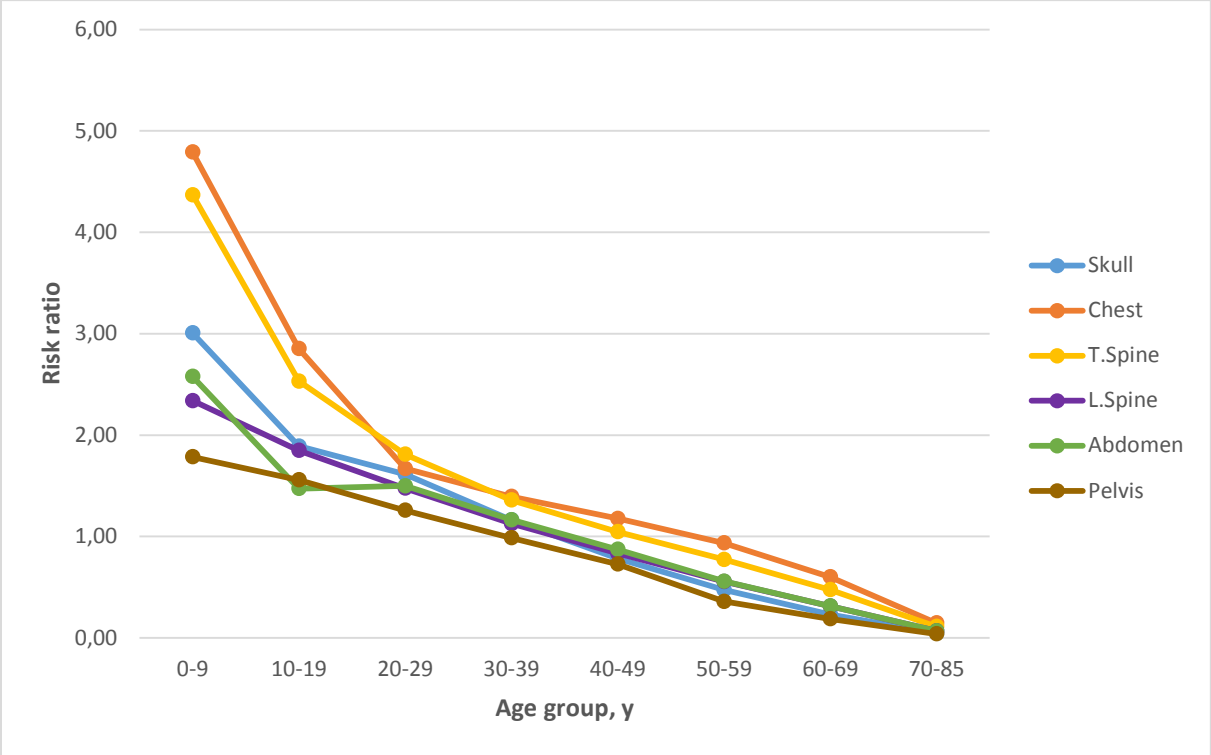


Figure 3b: Age-dependent ratio (dimensionless) of organ-dose-based radiation risk due to X-ray examination to risk based on effective dose for females.



The risk ratio is slightly smaller for adolescents, i.e., 0.8 to 2.0 in males and 1.6 to 2.9 (chest) in females. In young adults this ratio rests mainly in the range from one to two and subsequently decreases with age so that by the end of the usual labour period (60 – 69 years) is between 0.2 and 0.6 for different examinations. For a group of senior people (70+ years) this ratio lies near 0.1 and lower.

5.3.4 General discussion

A similar, more wide-scale study was conducted in the UK for the 20 types of the X-ray examinations, including radiography, fluoroscopy (with interventional examinations) and computer tomography [6, 7]. Authors assessed the lifetime risks of radiation induced-cancer for the patients of different age and gender of the ICRP Euro-American composite population, based on the typical organ doses and the corresponding risk coefficients [3], and rationed the risk values to the corresponding effective doses. The risk values assessed by means of organ doses are higher by a factor 1.5 to 3.5 for children, slightly lower for all adults and the risks for senior people are lower by a factor of 2-10, compared to the risk values assessed by the effective dose.

It is apparent that the risk ratio does not depend on the absolute dose value, but on its distribution in organs and tissues, as well as on sex and age. Dose distribution in organs and tissues is significantly different for radiography, computed tomography and nuclear medicine diagnostics with radiopharmaceuticals of different affinity. Therefore, in order to address the question of the suitability of an effective dose for risk assessment, an analysis similar to [5 - 7] should be performed for all major diagnostic technologies.

So far, no such study has been conducted with respect to nuclear medicine examinations. A strong dependence of the risk ratio obtained by two methods on the age and sex for studies related to selective irradiation of the thyroid gland with the administration of radioiodine preparations can be *a priori* expected. To a lesser extent, this effect may be due to the preferential irradiation of the lungs and other organs under examination by radiopharmaceuticals. These questions deserve detailed elaboration.

It should also be noted that the modern concept of radiation risk, based on cohort incidence data, is associated with significant uncertainty, reflecting the variability of radiosensitivity in the studied cohort of individuals. The use of the same risk coefficient for an individual patient is associated with an even greater uncertainty. Therefore, the ambition for high accuracy of the forecast of individual radiation risk is limited by the current level of knowledge.

So, our data [5, 7 and this paper] and more wide-scale UK study [6, 7] show that direct use of an effective dose for risk assessment in patients undergoing X-ray examinations can lead to a significant underestimation or overestimation of risk in different sex-age groups of patients. As expected, for some examinations the simplified risk assessment based on E underestimated risk in children by a factor up to 4-5 and for adolescents by a factor up to 2-3. In contrast, risk for senior patients (65+) can be overestimated by about an order of magnitude.

By all means, the significant sex- and age-dependence of radiogenic risk for different cancer types is an important consideration for radiologists when planning X-ray examinations. It is important to bring this information to radiologists and offer them a simple tool that will help to assess the risk in different age groups of patients via an effective dose with acceptable accuracy.

Thus, when developing Russian recommendations for radiologists for the purpose of justification of X-ray and radionuclide examinations [15], we deliberately simplified them as follows:

- For a rough radiation risk assessment, it was found reasonable to divide the patients into three age groups: children and adolescents (<18 y), adults in the working age (18–64 y) and seniors (65+ y);
- Age-dependent multipliers of the nominal risk coefficients from [3] have been applied to those age groups: 2 for children and adolescents, 1 for the adults and 0.1 for the seniors;
- Gender-dependent risk coefficient multipliers should not be applied because radiation risk for women exceeds the radiation risk for men in average only by 40 %.

On this issue, the ICRP Task Group 79 expressed itself as follows [8]: "Effective dose is in widespread use in medical practice as a measure of risk, thereby going beyond its intended purpose. While doses incurred at low levels of exposure may be measured or assessed with reasonable reliability, health effects have not been demonstrated reliably at such levels but are inferred. However, bearing in mind the uncertainties associated with risk projection to low doses or low dose rates, it may be considered reasonable to use effective dose as a rough indicator of possible risk, with the additional consideration of variation in risk with age, sex and population group".

5.4 Conclusions

The results of current and past [5, 7] assessments at IRH and more wide-scale UK study [6, 7] concerning the radiation risk for patients of different age and sex associated with numerous modern medical X-ray technologies confirmed strong dependence of risk from the examination type and parameters, age and sex of patients.

Thus, detriment-adjusted risk of radiation-induced cancer and hereditary effects in children and/or adolescents is considerably higher (by up to a factor of five) than in adults, and risk in senior patients is lower by an order of magnitude than in younger people. Risk from medical exposure of the female thorax is higher than for males.

As follows from comparison of risks assessed by two ways, for some examinations the simplified risk assessment based on effective dose underestimated risk in children by a factor up to 4-5 and for adolescents by a factor up to 2-3. In contrast, risk for senior patients (65+) can be overestimated by about an order of magnitude.

The significant age- and sex-dependence of radiogenic health risk is an important consideration for radiologists when planning X-ray examinations.

No similar study has been conducted so far with respect to nuclear medicine examinations studies. This issue deserves detailed study.

While effective dose was not intended to provide a measure of risk associated with medical X-ray examinations, simple adjustments to ICRP’s nominal risk coefficient to account for age and possibly also sex differences can make it a useful instrument for the justification of examinations.

Similar views were preliminary expressed by ICRP Task Group 79 working on the report "The Use of Effective Dose as a Risk-related Radiological Protection Quantity".

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6 SUMMARY

Prepared by Laurence Lebaron-Jacobs

on behalf of the Working Party "Research Implications on Health and Safety Standards" of the Article 31 Group of Experts[6]

6.1 Introduction

This document provides the background, summarizes the presentations and the results of the round-table discussion, and tries to emphasize the potential implications of the Scientific Seminar on "Emerging issues with regard to organ doses", held in Luxembourg on 17 May 2017. It takes into account the discussions that took place during the seminar and during the subsequent meeting of the Article 31 Group of Experts, although it is not intended to report in an exhaustive manner all the opinions that were expressed. The document has been submitted for comments to the lecturers, as far as their contributions were concerned.

6.2 The Article 31 Group of Experts and the rationale of the Scientific Seminars

The Article 31 Group of Experts is a group of independent scientific experts referred to in Article 31 of the Euratom Treaty, which assists the European Commission in the preparation of the EU Basic Safety Standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. This Group of Experts has to give priority to the protection of health, to safety and to the development of the best available operational radiation protection. To this end, the Group of Experts is committed to proactively scanning new or emerging issues in science and technology, and ongoing developments in the area of radiation protection and informing the European Commission on potential policy implications.

In this context, a Scientific Seminar is devoted every year to emerging issues in Radiation Protection – generally addressing new research findings with potential policy and/or regulatory implications. Following suggestions from the Working Party RIHSS, the Article 31 Group of Experts selects the topic of the seminar. The WP RIHSS is charged with the preparation and the follow up of the seminar. Leading scientists are invited to present the status of scientific knowledge in the selected topic. Additional experts, identified by members of the Article 31 Group from their own country, take part in the seminars and act as peer reviewers. The Commission convenes these seminars in conjunction with a meeting of the Article 31 Group of Experts, in order to allow the Group to discuss the potential implications of the presented scientific results. Based on the outcome of the Scientific Seminar, the Group of Experts referred to in Article 31 of the Euratom Treaty may recommend research, regulatory or legislative initiatives. The European Commission takes into account the conclusions of the Experts when setting up its radiation protection programme. The Experts'

6 Besides L. Lebaron-Jacobs (who was acting as rapporteur for the seminar), the following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of this overview: H. Janžekovič, F. Bochicchio, F. Hardeman, R. Huiskamp, P. Krajewski, J. Pedroso de Lima, and P. Smeesters. They were assisted by S. Mundigl from the European Commission.

conclusions are also valuable input to the process of reviewing and potentially revising European radiation protection legislation.

6.3 Key Highlights of Presentations at Scientific Seminar on "Emerging issues with regard to organ doses"

Abderrafi Benotmane – *Cognitive and cerebrovascular effects induced by low dose ionizing radiation 'CEREBRAD'*

On the basis of an analysis of previous studies showing the need to have sufficiently large cohorts to increase their statistical power, and dosimetric and biological data allowing to understand the mechanisms of the cognitive and cerebrovascular effects after an exposure to low radiation doses, the project CEREBRAD was developed and supported by the EU Euratom FP7. This work has a multidisciplinary approach: human epidemiology (WP2), animal studies (WP3) and mechanistic studies (WP4).

Late cognitive dysfunctions in individuals exposed *in utero* or during childhood were assessed thanks to specific neurocognitive tests in two cohorts: patients treated with radiotherapy (dose < 1 Gy) for a skin haemangioma and Chernobyl *in utero* exposed young adults. The results showed an age-dependent change in cognition: cognitive effects were observed below 0.1 Gy in the *in utero* exposed cohort, with a threshold of 0.12 Gy to the thyroid and 0.054 Gy to the cerebral hemispheres and to the temporal lobes in the medical cohort. Moreover, clean-up workers show a high level of mental disorders with an excess of cognitive dysfunction over 0.25 Gy.

Cerebrovascular complications (strokes) were detected later in life in childhood cancer survivors with a dose-dependent increase. Although the low dose risk was much higher for ischemic strokes, globally, these results are coherent with those from the A-bomb and Mayak cohorts.

Two months and four months after an *in utero* exposure to external gamma rays behavioural tests were carried out in rodents. Prenatally irradiated animals exhibited a reduced anxiety and an increased sociability-related behaviour. To study brain morphology of prenatally irradiated animals Magnetic Resonance Imaging was performed: the images showed a reduced cortical thickness from a dose of 0.33 Gy onwards, an increased ventricle size and a reduced fractional anisotropy (FA) values at the highest dose (1 Gy). Correlation studies between behavioural variables and MRI-based volumetric data were carried out. The results show dose-dependent modifications in activity, social behaviour, anxiety-related exploration and spatio-cognitive performance in mice exposed to 0.10 Gy. Moreover, microcephaly developed in these mice from an exposure of 0.33 Gy is strongly correlated to aberrant behavioural parameters. In case of a postnatal exposure to 0.5 and 1.0 Gy a significant behavioural deviation was identified both at two and four months after irradiation in female and male mice whatever the strain was.

As epidemiological studies indicate that humans exposed *in utero* to ionising radiation and environmental (Bisphenol-A, pesticides…) toxicants can have deleterious effects on their cognitive development, a co-exposure study was performed in mice. There was a shift in the dose-response curve, resulting in a lowering of the threshold dose: behavioural defects at a dose below 0.1 Gy were highlighted. In addition, the slope of the curve was more important for combined exposure indicating more severe cognitive effect with low radiation doses.

Neurobiological studies analysing the initial direct events induced by an exposure to ionising radiation at low dose and the potential cellular and molecular fingerprints of late disease occurrence were also carried out in animals. The results showed a massive apoptosis in the brain and an induction of p53 stress-related neurogenic targets identified 24h after an *in utero* irradiation. Moreover, cognitive dysfunctions appeared to be linked with impaired

neurogenesis and neuro-inflammation in the hippocampus after an early postnatal exposure at 0.5 and 1 Gy. Persistent effects (DNA damages, inflammation) were observed at low doses (20 and 100 mGy) several months after exposure (corresponding to years in humans). At adult age, persistent morphological modifications such as enlarged ventricles leading to cognitive impairments were identified.

Compared to the offspring exposed to maternal alcohol intake or to infectious agents (ZIKV) the neuropsychological development and the transcriptomic modifications of those prenatally exposed to ionising radiation are highly similar, including induction of p53 gene and its target genes involved in premature neuron differentiation. In other words, early stress during brain development can be translated by late cognitive outcome at adult age.

In conclusion, Cerebrad has thoroughly studied the dose-response relationship of mouse brain function and structure following prenatal irradiation, which unveiled effects at doses previously assumed to be harmless.

Michael J. Atkinson – *Radiation-induced cardiovascular disease: Is it time for a new biology?*

There are radiation-induced diseases where mutation and clonal expansion do not exist: for example radiation-induced cardiovascular diseases (CVD), cataract, and metabolic diseases. Radiation-induced CVD were considered for a long time as appearing at high doses (20 – 40 Gy) in the form of atherosclerosis, myocardial fibrosis, microvascular insufficiency and ischemia, acute and chronic pericarditis, valvular injury due to endocardial fibrosis, and arrhythmias. However, recent epidemiological and biological studies identified a potential risk of radiation-induced CVD at low doses. The ProCardio project, supported by the EU Euratom FP7, was conceived to address relevant questions in terms of protection of the cardiovascular system from low dose/dose rate radiation.

Preliminary results of a current epidemiological study in childhood cancer survivors from the UK, France and Spain shows that the Excess of Odds Risk (EOR) at 1Gy average dose to the left anterior descending artery of the heart is 1.50 (95%CI: 0.21 to 33.27) for ischemic heart diseases or heart failure.

Studies on electrophysiology, multiomics and cytokine expression profiles of exposed endothelial and vascular smooth muscle cell models to low LET (X-rays) versus high LET (Fe ions) radiation were carried out to answer to the question “Is there evidence for a RBE (CVD)?“. The results showed an estimated value of a RBE (CVD) between 4 and 10 for an exposure to HZE particles compared to photons.

The next step was to demonstrate whether there is evidence for an effect of dose rate (DREF(CVD)). ApoE-/- mice were acutely or chronically exposed to gamma rays and atherosclerotic lesions were measured for number, area and location. The results demonstrate that a dose of 300 mGy acutely applied is more damaging than chronically (1 mGy/d or 20 mGy/d). Thus, a dose rate correction factor (DREF(CVD)) is needed.

Then, ApoE-/- mice were irradiated on hindquarters only and atherosclerotic lesions were quantified to analyse if there is a systemic or local information exchange. An evidence for a dose-dependent radio-protective abscopal effect on atherosclerosis was shown. Moreover, a study on exosomes (nanometre-sized extracellular vesicles considered as intercellular communicators) indicated their functional role in the response of irradiated tumour cells exposed at high doses (3, 6 and 9 Gy) by improving the DNA repair in other irradiated cells.

Members of this project established a network model confirming that a single acute exposure to low doses induced an inflammatory reaction linked to an early mitochondrial dysfunction in the mouse (until 300 days) by production of ROS. In this model, it was shown various radiation-induced cellular processes such as epigenetic changes or damages to cytoskeletal

structures provoked a long-term metabolic adaptation in heart cells. In parallel, a label-free quantitative proteomics analysis of left ventricles extracted from Mayak workers who died from an ischemic heart disease was performed. A dose-dependent increase was demonstrated in down-regulated mitochondrial proteins in irradiated tissues. Finally, proteomic changes in Mayak workers' hearts fit the network model in a dose-dependent manner.

Some issues (RBEs for all radiation qualities and all endpoints, biomarkers of metabolism or mitochondrial function, which cells cause the damage, contribution of individual variation, or influence of epigenetics…) still remain to be elucidated. A hypothesis about a progressive stress damage leading to radiation-induced CVD was argued.

Augusto Giussani – *Issues related to the concept of organ dose*

The absorbed dose is a physical definition of dose by providing a quantitative description of the interactions between ionising radiation and exposed materials. However, this quantity is not adequate for radiation protection due to the dependence of the dose-response relation on the radiation quality (spectrum, energy deposition), the different susceptibilities of biological systems and the non-linearity of many biological processes (dose rate, non-uniformity of exposure). ICRP has taken into account these limitations by introducing the equivalent dose and the effective dose, which are not directly measurable. These quantities should not be used when deterministic effects are caused, but only at low-dose or low-dose rate levels to assess the occurrence of stochastic effects.

Effective dose is not recommended for epidemiological evaluations or detailed specific retrospective investigations of individual exposure and risk: absorbed dose should be used with the most adequate biokinetic biological effectiveness and risk factor data. At the end, organ or tissue doses are required for assessing the probability of cancer induction in exposed individuals. However, the main targets of radiation are cells and the content of cells, and particularly in case of incorporated radionuclides characterised by spatially and temporally inhomogeneous dose distributions within a tissue or an organ. Consequently, dose quantities averaged over a whole organ or tissue are not relevant to estimate biological effects of low doses. Biokinetic models are used to describe the distribution of radionuclides in the body and to calculate the dose, but reliable data are missing on the behaviour of radionuclides in substructures. Thus, voxel-phantoms or reference computational phantoms of adult male and female were created for calculation of more realistic and fine-detailed conversion coefficients with uncertainties lower than 5%. Micro- and nanodosimetry approaches were defined and are particularly valid for internal exposure to alpha- and Auger-emitters. For example, a microdosimetric model for inhaled radon progeny (New Mexico miners) was developed to better analyse the deposition and the distribution of attached and unattached particles and to improve our understanding on localised biological radiation effects.

One of the five visions identified by the European Radiation Dosimetry group EURADOS through its Strategic Research Agenda was called: "Towards updated fundamental dose concepts and quantities". This vision has allowed to define four challenges with the aim to improve the understanding of spatial correlations of radiation interaction events, to establish correlations between track structure and radiation damage, to improve our understanding of radiation-induced effects from internal emitters and to update operational quantities for external exposure. The assessment of uncertainties associated to measured nanodosimetric quantities and nanodosimetric characteristics of track structure is needed in the future.

Jean-Marc Bordy – *New data regarding the lens of the eye (for Radiation Protection purposes)*

The lens of the eye is a special case due to its inclusion into the ICRP's list of organs to calculate the effective dose E (a protection quantity), not measurable and the possibility to perform a routine individual monitoring of its equivalent dose (H_{lens}) throughout the dose equivalent ($H_p(3)$) which can be measured as an operational quantity. However, although measurements and evaluation of operational quantities at workplaces were possible thanks to dosimeters satisfying type test requirements, calibrated in terms of operational quantities and used as specified in international recommendations, it was not possible to estimate H_{lens}. Consequently, it was decided that a direct monitoring of eye lens exposures was not necessary regarding the eye lens exposure limit at 150 mSv per year and the one for whole body monitoring at 20 mSv per year in terms of effective dose estimated with a dosimeter worn on the chest through $H_p(10)$ that would cover the eye lens limit.

In 2011, the ICRP recommended to decrease the eye lens limit from 150 mSv to 20 mSv per year. The issue was to know how to define the dose equivalent $H_p(3)$ and how to measure it. Thus, it was agreed to have a work package in the ORAMED project, supported by the EU Euratom FP7, dealing with the correct measurement of the dose equivalent $H_p(3)$. Once the clarification of the definition of the quantity $H_p(3)$ has been established through the use of a cylinder (H=D=20cm) made of ICRU tissue as phantom, it was decided to use a water cylindrical phantom for calibration of dosimeters as recommended in ISO standards. Then, a few individual dosimeters have been developed and are commercially available. However, even if it was agreed that eye lens doses have to be measured, the implementation modalities of this monitoring was debated. At the end, a compromise between the constraint to wear an additional dosimeter close to the eye, and the need to accurately monitor the lens exposure could be to estimate $H_p(3)$ through $H_p(10)$ using a whole body dosimeter on the chest and to define an objective index allowing to calculate $H_p(3)$.

Depending on the confidence level and taking into account the uncertainty coming from the evaluation of the objective index through the study of the workplace, maximum values of $H_p(10)$, below which the indirect evaluation of $H_p(3)$ is justified, can be defined. It allows to minimise the risk to have an $H_p(3)$ value lower than the limits while its real value exceeds the limit.

Mikhail Balonov, Ilya Shatsky – *Evaluation of radiation risk: organ dose approach versus effective dose approach*

The concept of radiation risk is a key concept of the modern radiation protection system. Current effective dose limits have been established from the concept and the quantity of acceptable risk (ICRP-26 and ICRP-60) and confirmed through ICRP-103 recommendations. In the application of the system of radiation protection, the risk value is not directly used anymore as a radiological criterion with two exceptions: justification of medical exposures and protection against a potential exposure.

In ICRP-103 and -105 publications, it is recommended to use risk values for the tissues at risk, and for age- and sex-distributions of patients to assess risk in case of medical uses of ionizing radiation. However, the helpfulness of simple age- and sex-adjustments to the nominal risk per unit (E) is questioned. A study was performed at IRH, St. Petersburg, Russia, to assess lifetime risk of cancer incidence from six X-ray radiography examinations (skull, thorax, abdomen, lumbar spine, pelvis, and mammography) for twelve age- and sex-groups of patients. Risks were calculated and compared using organ doses with age- and sex-specific risk coefficients and effective doses with nominal risk coefficients. The results showed that the significant sex- and age-dependence of radiological risk for different types of cancer had to be considered for radiologists when planning X-ray examinations. Moreover, the simplified risk assessment based on effective dose underestimated risk in children (0-9 y) by a factor up to 4-5 and for adolescents by a factor up to 2-3, and overestimated risk for

senior patients (65+) by about an order of magnitude. Similar more wide-scale UK study (HPA, Chilton) has come to similar conclusions.

The assessment of risk can be easily corrected by an adequate age- and sex-dependent factor for children and young women, but not always for senior patients considering a cautious approach in terms of radiation protection. Then, the results showed that risk from medical exposure of the female thorax was higher than for males. Thus, the use of effective dose for practical reasons with a simple adjustment of the nominal risk per unit according age and sex is possible, but only if a high precision is not necessary (i.e. justification and information). In 2015, when Russian recommendations for radiologists in terms of justification of X-ray and radionuclide examinations were proposed, they were simplified following the results of this previous study. Similar views were expressed by ICRP Task Group 79.

Finally, as the effective dose is not intended to provide a measure of risk associated with medical X-ray examinations, a simple adjustment to ICRP's nominal risk coefficients considering age and possibly also sex differences allow to use the effective dose for the justification of medical radiological examinations.

6.4 Presentations at the Roundtable

Abderrafi Benotmane, Mike J. Atkinson, Augusto Giussani, Jean-Marc Bordy, Mikhail Balonov, Pierre Scalliet, Ted Lazo, Francesco Bochicchio (Moderator)

The round table discussion started with two short presentations.

Emerging issues with regard to organ doses – Pierre Scalliet

Dose levels in radiotherapy are close to tolerance. Organ failure is clearly possible as well as cancer induction, but it is a life-saving treatment for patients who are facing a deadly disease. It has been proven that radiotherapy prevents breast cancer recurrence, but a second primary cancer can occur. The objective is now to reduce the dose to normal tissues during radiotherapy. Proton therapy could be an interesting alternative given the treatment is more targeted and less normal tissues are exposed to ionizing radiation. A clinical validation of normal tissue dose reduction techniques, as well as studies on the physiology of cancer survivors who have been treated with radiotherapy and on second primary cancer risk is needed.

Organ dose variability with gender, age and BMI – Ted Lazo

The effective dose is not directly representative of an individual's risk because individuals have specific age and gender. As the protection of children is extremely high on the list of "values" that drive radiological protection decisions, discussions with parents in post-accident situations and patients could be useful. A current work on dose variability has been engaged at the University of Florida, the Organ Project, to model the range of variation in external-source organ dose with gender, age and BMI. An expanded library of dose conversion coefficients for individual organs was established**.** While based upon U.S. body morphometries, the phantom library is scalable and can thus be applied to any exposed population/nationality.

7 CONCLUSIONS

Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts[7]

From the presentations and discussions, the members of the Working Party identified the following important issues.

Radiation-induced effects on the brain, the cardiovascular system and the lens of the eye have been observed at low and intermediate doses in parallel to stochastic (cancer, hereditary effects) and high dose tissue effects. Studies are ongoing to elucidate the mechanisms implicated in the genesis of these effects, such as epigenetic mechanisms and the role of the mitochondria. Similar mechanisms are suspected to induce other radiation-induced chronic non-cancer effects, particularly in childhood cancer survivors, such as metabolic diseases (i.e. diabetes).

While clear radiation-induced health effects are observed at intermediate doses (100 to 500 mSv), biological effects (with an uncertain link to health outcomes) are already observed at lower doses in the order of a few tens of mSv. Yet, the dose effect relations may be totally different from those in cancer. Adequate biomarkers for long term radiation-induced health effects are still lacking.

Although many uncertainties exist, the current knowledge is nevertheless sufficient for taking into account the risk of such effects in radiotherapy, interventional radiology and cardiology, pediatric radiology (CT) and in accidental situations (evacuation and relocation levels). As these effects present a cumulative character, the introduction of occupational lifetime dose limits should be discussed for workers.

Difference of risks related to gender, age and lifestyle can be important and should be taken into account in the risk evaluation.

Risk related quantities should be further developed and harmonized, taking also into account gender and age differences, and should not be limited to cancer risk. Appropriate risks communication strategies need to be developed for these situations, avoiding oversimplification and taking into account gender, age and lifestyle.

Appropriate policy and strategy shall be developed to enable a long-term follow up of exposed persons (particularly children) in the above-mentioned situations including non-cancer effects.

Combined exposures to radiation and other environmental agents decrease significantly the dose at which brain effects are observed (under 100 mSv). Such co-exposures should be further explored, also for other organs

In radiotherapeutic exposures, doses to distant non-targeted tissues should be studied, including doses from secondary neutrons. High quality data (radiation-induced health effects data and dosimetric data) should be accessible and combined to develop methods for reduction of the doses to critical organs (heart, vessels, and brain) and to distant non-targeted tissues. Moreover, lifestyle and combined exposures would have a link with individual radiosensitivity (epigenetics) of each patient leading to the need of a personalised medicine, particularly in radiotherapy and in case of high dose diagnosis imaging. This should be part of the education and training of physicians. A better knowledge is required

[7] The following members of the Working Party on Research Implications on Health and Safety Standards of the Article 31 Group of Experts contributed to the preparation of these conclusions: H. Janžekovič, L. Lebaron-Jacobs, F. Bochicchio, F. Hardeman, R. Huiskamp, P. Krajewski, J. Pedroso de Lima, and P. Smeesters. They were assisted by S. Mundigl from the European Commission.

about a potential link between the out-of-field low doses and second primary cancer after radiotherapy: measurements as well as modelling are needed. In epidemiology, despite the existence of several cohorts of patients treated by radiotherapy, a large-scale study is needed on children exposed to radiotherapy requiring a long time follow-up and national registries in each country.

Finally, there is a need to find better indicators of dose inhomogeneities, particularly for internal emitters and to explore the potential implications of these inhomogeneities.

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