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SOMMAIRE **INHOUD**

Scientific meeting on the Belgian transposition of the EU Basic Safety Standards Directive (Brussels, 20 October 2017)

Proton Therapy - from the Need to the Solution (Brussels, 23 June 2017)

Emerging issues with regards to organ/tissue dose (Brussels, 9 December 2016)

Annales de l'Association belge de Radioprotection, Vol.42, n°3, 2017
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol. 42, nr 3, 2017

SCIENTIFIC MEETING ON THE BELGIAN TRANSPOSITION OF THE EU BASIC SAFETY STANDARDS DIRECTIVE

Brussels, 20 October 2017

HGR-CSS (FOD Volksgezondheid - SPF Santé Publique)
Eurostation II Victor Hortaplein 40
Proceedings

This section of the present issue of the Journal of the Belgian Radiation Protection Society is dedicated to the presentations made in the context of the above scientific meeting. The timing of this seminar was chosen on the basis of the fact that the transposition of the EU Basic Safety Standards Directive in national legislation being due by 6 February 2018, and draft legislation being submitted 3 months earlier, the main changes to the national legislation should have been finalised by that time. This also meant that the purpose of the seminar was not to provide input to the drafting of new national legislation, but to inform the members of our society of the main changes that would affect them, and to contribute through the discussions to a good understanding of the reasons for change and on the consequences.

Bearing in mind that the representatives of the Belgian authorities who made the presentations reported on the final stages of work, no full articles were asked for but merely extended abstracts indicating their main points. The full presentations are available on the website of the BVS-ABR (http://www.bvsabr.be/events.asp?ID=63). There is no extended summary of the overview presentation of the overall Belgian policy for the transposition (presented by Annie Vanderlinck, FANC-AFCN). On the other hand, there is a full paper on the Belgian policy with regard to radon in homes and workplaces (Boris Dehandschutter). A summary of the discussions was drafted by the chair of the scientific meeting, Augustin Janssens.

Annales de l'Association belge de Radioprotection, Vol.42, n°3, 2017
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol. 42, nr 3, 2017

Council Directive 2013/59/Euratom, an Introduction

Augustin Janssens[1]

The new BSS Directive (2013/59/Euratom), laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, was adopted by the Council on 5 December 2013. The new Directive will need to be transposed in final measures by 6.2.2018, and under the terms of Art. 33 of the Euratom Treaty Member States should transmit draft national legislation three months before, in order to allow the Commission to make recommendations and foster harmonisation.

The Directive reflects the latest recommendations of ICRP (Publication 103) as well as the parallel development of international BSS. The Directive incorporates the previous BSS (96/29/Euratom) and other legislation in the field of radiation protection. This includes Euratom Directive 97/43 on medical exposures, so that now all categories of exposure are addressed in one document. Among the main novelties in the new Directive we find:

- Indoor radon exposure in dwellings and workplaces,
- Radioactivity in building materials,
- Justification and type-approval of consumer goods,
- Graded approach to regulatory control,
- Extension of the concepts of exemption and clearance to naturally occurring radionuclides,
- New features in radiation protection of occupational, medical, non-medical imaging and public exposures,
- Emergency preparedness and response.

1 Augustin Janssens was formerly the head of the EC's radiation protection unit; no part of this presentation however should be regarded as representing the views of the European Commission, nor should it be referred to in interpreting the Directive or its implementation in national legislation; only the actual text of the Council Directive has value for this purpose. This presentation was made on the basis of an earlier presentation by Pierre Kockerols, EC JRC. Contact: janssens@pt.lu.

The purpose of the seminar is to provide a comprehensive overview of the Belgian approach to transpose the Directive and to address some of the novelties that may lead to important changes in the Belgian legislation. However, some issues had been addressed not so long ago at other scientific meetings of the Society, for instance the management of NORM industries, other, like medical exposures, would warrant a full meeting. The issue of emergency preparedness and information had also been covered about one year earlier, but the specific aspect of coordination across borders is an important novelty in the BSS and hence was incorporated in the present programme.

An important issue in the Belgian legislation is the organisation of radiation protection, in part reflecting the new definitions of RPE and RPO in the BSS. On this aspect the BVS-ABR had already offered its views. Since then, the drafting by FANC had proceeded, but it was considered appropriate to recall the earlier standpoint of our Society.

Finally, one should consider the national transposing measures from the perspective of harmonisation. The Euratom Treaty calls for uniform Basic Safety Standards, nevertheless it is stated in the recital of the Directive:

- As recognised by the Court of Justice of the European Union in its case-law, the tasks imposed on the Community by point (b) of Article 2 of the Euratom Treaty to lay down uniform safety standards to protect the health of workers and the general public does not preclude, **unless explicitly stated in the standards**, a Member State from providing for **more stringent measures of protection**.
- As this Directive provides for minimum rules, Member States should be free to adopt or maintain more stringent measures in the subject-matter covered by this Directive, **without prejudice to the free movement of goods and services** in the internal market as defined by the case-law of the Court of Justice.

The Directive has been carefully drafted so as to make it clear when the requirements are truly minimum requirements, when uniformity is expected (for instance the dose limits), when there is flexibility in the means to achieve the stated objectives, and when more strict numerical values are precluded (for instance the default general exemption and clearance levels).

A further important point is that when Member States adopt national provisions, these shall contain a reference to the Directive or shall be accompanied by such reference on the occasion of their official publication (Article 106). Member States shall determine how such reference is to be made. Indeed, in the recital it is stated that:

- In accordance with the Joint Political declaration of Member States and the Commission on explanatory documents of 28 September 2011, Member States have undertaken to accompany, in, justified cases, the notification of their transposition measures with one or more documents explaining the **relationship between** the components of a **directive** and the **corresponding parts of national transposition** instruments. With regard to this Directive, the transmission of such documents is justified.

The publication of this "table of correspondence" should facilitate a proper understanding of the different national measures, which for historical reasons are scattered across many pieces of legislation and regulatory decisions. In this way the idea of the BSS to offer a comprehensive body of requirements across all exposures situations and categories of exposure may be preserved.

Transposition of Directive 2013/59/Euratom on "Basic safety standards" in Belgium

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The Basic Safety Standards Directive represents significant progress on a European scale in protecting the health of workers and the general public.

This document consolidates five other directives[2], which are currently in force and are already enshrined in Belgian national legislation.

Belgian legislation had already anticipated that some requirements would be tightened up, especially in the fields of medical applications, management of non-sealed radioactive sources and management of nuclear emergencies, as well as in the Radon issue for the general public as a whole and in workplaces in particular. Belgium had already created a legal framework for consumer products containing small quantities of radioactive substances.

Within FANC, an initial assessment was carried out to define a number of topics requiring further attention: these included emergency planning, the new concepts of 'Radiation Protection Expert' and 'Radiation Protection Officer', the exposure of professional workers, in particular the protection of emergency response workers, the protection from "any deliberate exposure of individuals for non-medical imaging purposes"[3] and finally the

2 Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom.

3 BSS definition: "exposure for non-medical imaging purposes": any deliberate exposure of individuals for imaging purposes where the primary purpose of exposure is not to bring about health benefits for the exposed individual.

new IAEA reference RS-GS-1.7 which will be used to define exemption and clearance levels.

Belgium, and FANC in particular, is keen to be regarded as an official and serious partner on the international scene, specifically by playing an active role in meetings of the HERCA Group.

FANC has entered into bilateral relationships with France, Luxembourg and the Netherlands to promote a shared understanding of the requirements arising from the Basic Safety Standards Directive within Member States.

FANC's active involvement in radiation protection groups set up by the French Nuclear Safety Regulator (ASN) have also led to useful developments in the protection of patients, workers and the general public. Progress with transposition efforts can be classified in three categories:

1. New requirements that have already been implemented in Belgium: protection from natural sources of ionising radiation, NORM and radon, and protection for aircrews, monitoring and detection of orphan sources, dosimetry for exposed workers, diagnostic reference levels for patients, organisation of basic and ongoing training for radio-physicists, clinical audits, justification and monitoring of consumer products containing small quantities of radioactive substances, and protection of pregnant women.
2. Regulatory requirements that need to be improved in the following areas: protection from construction materials, protection during exposure in medical/legal situations, protection for individuals undergoing non-medical imaging procedures, clear division of responsibilities between practitioners and referrers involved in medical radiological procedures, protection and training for emergency workers.
3. New topics: ensuring a clear division of the responsibilities of the parties involved in the organisation of radiation protection within the different types of nuclear installations, especially the duties of the Radiation Protection Expert, the duties of the Radiation Protection Officer and, if applicable, the relationships with radio-physicists, and the implications of new standards for clearance and exemption levels in Belgium.

The complexity of the current regulatory texts is such that the FANC Law of 15 April 1994[4] needs to be amended, and a range of royal decrees need to be published such as GRR-2001[5], along with technical regulations to specify the decision-making criteria used by FANC.

The various texts will need to be published in several stages, with the first stage entailing amendments to the FANC Law of 15 April 1994 (in 2014: transfer of responsibility for the worker exposure register and in 2017: review of health physics in Belgium).

A second stage includes the publication of a royal decree implementing the review of health physics control in Belgium, which was established as a priority as a result of comments made by the IAEA Integrated Regulatory Review Service mission in 2013.

The Royal Decree of 20 July 2001, GRR-2001[4], will be amended in a third stage, although its overall structure will not change. This amendment will incorporate new requirements or topics such as protection of the general public from radiation due to construction materials, improved protection for outside workers and emergency workers, management and protection of sealed sources, general framework for non-medical imaging procedures, clearance and exemption levels, etc.

The final stage of the Basic Safety Standards Directive transposition will be the publication of both a FANC Law amendment with regard to radiophysics and a royal decree on the use of ionising radiation for medical purposes including non-medical imaging procedures using medical equipment.

4 Law of 15 April 1994 on the protection of the public and the environment against the hazards of ionising radiation and on the Belgian Federal Agency for Nuclear Control.

5 Royal Decree of 20 July 2001 laying down general regulations for the protection of the public, workers and the environment against the hazards of ionising radiation.

Annales de l'Association belge de Radioprotection, Vol.42, n°3, 2017
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol. 42, nr 3, 2017

Implementation of the "RPO" and "RPE" concepts in the Belgian regulations

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A FANC regulation project is in development at this moment. It aims at improving the organization of Health Physics in licensed facilities and/or in organizations that are involved in the transport of radioactive materials. It also modifies in depth several central provisions of the General Regulations (Royal Decree of 20 July 2001 laying down general regulations on the protection of the population, the workers and the environment against the dangers of radiation ionizing – hereafter the "GRR-2001"), in particular the status and the role of Authorized Inspection Organisations (AIOs).

The project integrates the concepts of "RPO" (Radiation Protection Officer) and "RPE" (Radiation Protection Expert) of the European Directive 2013/59 /Euratom laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation (hereafter "the Directive") and as such, transposes these concepts in Belgian law.

Article 23 ("Health Physics") of the current GRR-2001 will be renewed with, amongst others, the tasks and responsibilities assigned to various actors. A Health Physics Department (HPD) always needs to exist within the organization of every licensee or operator. In its simplest form, the licensee/operator performs the tasks belonging to the HPD himself. While leaving to licensees a large freedom to organize their HPD, the regulatory project identifies certain key functions within the HPD:

- The head of the HPD, who directly reports to the licensee/operator. He is protected against dismissal for reasons related to the execution of his function. The head of the HPD needs to be in all cases a member of the staff of the licensee/operator.
- The Radiation Protection Agent(s) ("AgRP" of "AgSB") is (are) responsible for radiation protection in the workplace. This agent

can either be a dedicated employee, performing only health physics tasks within a centralized HPD, or can be any other employee that may perform some radiation protection tasks in addition to its main occupation at its workplace. The tasks assigned to this agent include the tasks assigned to the RPO by the Directive. Except for special cases, Radiation Protection Agents need to employees of the licensee/operator.

- The Recognized Expert in Health Physics (QHPE) is in charge of more specialized (technical) high-level and punctual tasks in radioprotection and safety. The tasks assigned to this expert include the tasks in radiation protection that are assigned to the RPE by the Directive. This expert does not necessarily need to be part of the licensee/operator's staff.

By analogy with the provisions of the law on well-being at work and its implementing decrees, shared HPDs that are organized by different licensees are possible under certain conditions and with FANC's approval. If the licensee/operator employs a QHPE, this QHPE becomes the head of the HPD. If the licensee/operator has no QHPE within his staff, the head of the IDPBW/SIPPT (Service for Prevention and Protection at Work) or one of his deputies will be in charge of the management of the HPD. In all cases, the head of the HPD has to receive a training which is, at least, similar to the training of a Radiation Protection Agent, covering all radiological hazards related to the facility/activity.

The criteria and the process for the recognition of QHPEs (by the FANC) are reviewed and clarified in article 73 of GRR-2001, as a consequence of the reform of education system by the Bologna process and taking into account the relevant experience gained since 2001.

Radiation Protection Agents are not recognized by the FANC. They are identified and designated by the licensee/operator, and have to receive a minimum theoretical and practical training, as specified in a Technical Regulation of the FANC (to be published)

The so-called Authorised Inspection Organisations ("AIOs") cannot perform regulatory functions anymore in delegation of the FANC. The

regulation project considers the AIOs as organizations employing QHPEs who perform radiation protection tasks for and under the responsibility of the licensee/operator who have not such experts within their organization. The criteria and a clear process for the recognition of AIOs are formulated in the new Article 74 of the draft regulation.

As a conclusion, the FANC considers that

a) the concept of *RPO* will be transposed into the Belgian regulations by *the Health Physics Department (HPD)*, since:
   - the HPD need to be organized always within the licensee/operator's organization, the head of the HPD directly reporting to the licensee/operator;
   - the tasks assigned to the RPO by the Directive always need to be performed within the licensee/operator's organization by Radiation Protection Agent(s) of the HPD;
   - the RPO, as mentioned by the Directive, may consist of a section/department;
   - the HPD may be one single person (a Radiation Protection Agent), a section or even an entire department with several people including Radiation Protection Agents and Recognized Experts in Health Physics.

b) The concept of *RPE* will be transposed into the Belgian regulations *by the Recognized Experts in Health Physics* (QHPE), since:
   - these experts need to be recognized by the FANC;
   - these experts may be external, in which case they need to be employed by an AIO;
   - these experts are in charge of the tasks assigned to the RPE by the Directive, for and under the responsibility of the licensees/operators.

However, in addition to radiation protection, the Belgian QHPE also needs to be competent in nuclear safety, which, according to the Belgian safety authority, cannot be separated from radiation protection. The QHPE is also required to give approvals, which goes further than the advisory role assigned by the Directive.

Annales de l'Association belge de Radioprotection, Vol.42, n°3, 2017
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol. 42, nr 3, 2017

European Basic Safety Standards: Experience with the regulatory control of practices involving consumer goods

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Previously, intentionally adding radioactive substances to consumer goods was prohibited in Belgium although Directive 96/29/EURATOM [1] provided the possibility to do so under certain conditions. Based on these provisions, other Member States from the European Union have granted specific exemption from authorisation for certain consumer goods containing radioactive materials above the general exemption values. With the free circulation of goods and services in an open European market, this situation was not sustainable. With the publication of the Royal Decree of 30/09/2014 [2], Belgium transposed the articles of the 2013/59/EURATOM Directive regarding consumer goods, maintaining the general prohibition for the addition of radioactive materials to consumer goods, but at the same time creating the possibility for granting a licence for this addition under two conditions: the individual or societal benefit resulting from the practice outweighs the health detriment that it may cause (justification) and it satisfies the general exemption and clearance criteria set out in Annex VII of the Directive.

In practice, the manufacturer, importer or distributer is required to submit a licence request to the Federal Agency for Nuclear Control (FANC), the national competent authority for all issues regarding radioactivity. Within FANC, a specific transversal and multidisciplinary evaluation group will analyse the request, giving much attention to its justification process, which consists of several aspects including the radiological impact, availability of alternatives, the economic/ecological impact, the advantage and

disadvantages, risk of malicious use, possible end-of-lifecycle problems (NORM/waste), etc. And, of course, verifying the first condition before starting the evaluation process: is it a consumer good?

Since this legislation has entered into force, three requests – all lamp manufacturers - have been received of which for one a licence was granted, one is still running, and one was withdrawn by the manufacturer as - due to some technical fabrication adjustments - no radionuclides were needed anymore for proper functioning of the product.

The consumer goods were all high intensity discharge (HID) lamps either containing krypton-85 (from 10 to 8000 Bq), thorium 232/228 (from 10 to 2000 Bq) or a combination of both, which are used in industrial or medical applications, the entertainment sector, cinema, etc. Reasons for adding these radionuclides are a reliable ignition, a decrease of the electrode potential leading to better metallurgical properties, colour quality, high energy efficiency and a longer life-cycle. The radiological impact of different transport scenarios including incident[6] situations was limited [5]: for Kr-85 < 7.2 µSv/y (normal) and < 3.2E-04 mSv (incident[7]) and for Th-232/228 < 7 µSv/y (normal) and < 2.4E-03 mSv (incident[8]). HID lamps have a high energy efficiency being around 90 to 100 Lm/W which is equivalent to LED technology (e.g. 20 to 30 Lm/W for halogenic lamps). Although the LED technology is evolving at high speed, it (currently) cannot replace all HID lamps. Radioactive substances are currently needed for reliable ignition and life-cycle extension e.g. with Kr-85, 100% ignition after fabrication and life expectancy of 750 hours; without Kr-85, 4 to 8% ignition failure after fabrication and 60% fail to ignite after 200 hours. The risk of malicious use was considered to be very low and waste streams to be limited since the lamps are rather used in (semi) industrial applications.

6 Road accident (lorry driver, clean-up worker), damaged packing at cargo handling (fork lift truck driver, repackaging), fire at cargo handling bay (fire-fighter, clean-up worker).

7 Highest dose was calculated for the driver of a lorry carrying a consignment of Kr-85 lamps (with a total activity of load 1.8E07 Bq) involved in a road accident.

8 Highest dose was calculated for a worker involved clean-up operations at a wharehouse following a fire of Th-232 lamps (with a total activity of load 2E06 Bq).

Having evaluated all pro & con's, FANC authorised (currently 1 manufacturer) to produce specific types of HID lamps containing either Kr-85 (max. 8 kBq) or Th-232/228 (max. 2 kBq) for a period of five years. Additional license conditions require that all information leaflets give appropriate information on the radionuclides present and encourage end-users to bring the lamps at their end-of-life to existing recycling circuits or to return it to the manufacturer. Besides this authorisation, a FANC Decree [4] is published specifying the HID lamps which are exempted from authorisation if exclusively used in their foreseen application and gives alternative exemption values for transport and storage: maximum 40 MBq for Kr-85 and 50 kBq for Th-232/228.

During the evaluation process some issues or points of interest were identified. Two related issues are the lack of expertise on the applicants' side regarding the radiological aspect and the lack of expertise of the regulator regarding the specific consumer products. To remediate the latter issue, the Agency held a few technical hearings with the applicant for better understanding. The applicant(s) referred for most questions to a document of the Health Protection Agency [5], which is a study commissioned by the European Light Companies (ELC) and to some IAEA documents [7, 8]. Another issue was the 'poor' justification brought by the manufacturer which was initially by default "there's no alternative". Although all applicants stated that no (immediate) alternative was available, one of the manufacturers withdrew its application during the process as - due to some technical fabrication adjustments - radionuclides were no longer needed for proper functioning of the product. The other applicants revised and updated a few times their list of HID lamps during the evaluation process. In some cases - due to technical evolutions - less activity was needed, or only Kr-85 or only Th-232/228 was added (no combination anymore of both radionuclides) and in other cases, HID lamp types were meanwhile "replaced" by alternatives such as LED. It is therefore advisable to limit the authorisation or exemption of consumer goods to a sufficiently short time period, as the speed of technological developments can be high. While in this case the waste impact on the environment is rather limited [6], careful attention has to be given to this issue. Finding the right balance between economic benefits and ecological/radiological costs can be difficult in justification.

Another point of interest is to maximise harmonisation at European level. However, while guides and common practices are given by Directive 2013/59/EURATOM, each member state has its own application process and resulting outcome. With the free circulation of goods and services in the open European market, this may not be sustainable. A European application process might be a way forward, which has the additional benefit of avoiding the need for manufacturers, importers or distributers to submit a demand for authorisation and exemption in each Member state.

KEYWORDS European BSS, 2013/59/EURATOM, consumer goods, justification, authorisation and exemption, High Intensity Discharge lamps (HID lamps)

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[2] Royal Decree of 30/09/2014: Koninklijk besluit tot wijziging van het koninklijk besluit van 20 juli 2001 houdende algemeen reglement op de bescherming van de bevolking, van de werknemers en het leefmilieu tegen het gevaar van de ioniserende stralingen (ARBIS) [3] en van het koninklijk besluit van 24 maart 2009 tot regeling van de invoer, de doorvoer en de uitvoer van radioactieve stoffen voor wat betreft de vrijstelling en het gebruik van beperkte hoeveelheden van radioactieve stoffen in consumptiegoederen. Gepubliceerd in het Belgisch Staatsblad op 30/10/2014.

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Annales de l'Association belge de Radioprotection, Vol.42, n°3, 2017
Annalen van de Belgische Vereniging voor Stralingsbescherming, Vol. 42, nr 3, 2017

European Basic Safety Standards: harmonisation of the requirements concerning radon

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SUMMARY

This paper gives an overview of the requirements of the 2013/59/Euratom Directive with respect to the dispositions concerning radon in dwellings and in workplaces. For the first time in the European Basic Safety Standards, the Directive explicitly addresses radon in dwellings as a regulatory issue in the framework of an existing exposure situation, requiring a reference level with optimisation above and below. Radon in workplaces is also considered an existing exposure situation, unless an annual dose of 6 mSv cannot be avoided, in which case it enters the regulatory frame of a planned exposure situation. All aspects of the management of radon have to be described on a national (member-state) level in a National Radon Action Plan. In preparation of this transposition, several harmonisation and concertation initiatives have been taken on an international level trough international bodies like HERCA and the European Radon Association. Hence, existing Belgian regulations have to be adapted in order to comply with these new requirements.

KEYWORDS

European BSS, 2013/59/Euratom, radon, action plan, prevention, remediation

1 INTRODUCTION

Radon is the second leading cause of lung cancer after smoking worldwide. Pooled epidemiological studies in different parts of the world converge to the quantified excess relative risk of 16% per 100 Bq/m³ increase, up to concentration levels as low as 100 Bq/m³ (Darby et al., 2005; WHO, 2009). This led to a call for stricter regulatory control on the subject, allowing to better estimate and reduce the health burden of the population due to indoor radon exposure at home and at work. The European Directive (2013/59/Euratom, 2014, called hereafter the BSS) addresses radon in over 9 articles, classifying radon as an existing exposure situation. This introduces the concept of reference level (« … level of … activity concentration above which it is judged inappropriate to allow exposures to occur … even though it is not a limit that may not be exceeded. »). The value of the reference level should not exceed (unless justified by national prevailing circumstances) 300 Bq/m³. For Belgium, up to now using an action level of 400 Bq/m³ following the EC recommendations (EC, 1990), this implies a significant increase of the number of affected buildings. Additionally, the Directive explicitly asks for the protection of new buildings to be addressed in the regulations. The implementation of these changes requires a strong collaboration between the authorities on national, regional, provincial and local level. The current paper presents the proposals to rework the existing Royal Decree of 20 July 2001 developed by the working group and fine-tuned by the stake-holders, submitted to juridical and political approval (state October 2017). Therefore, the definitively published regulations (by February 2018) might still differ from the proposals described in this paper.

2 EUROPEAN HARMONISATION

Since the publication of the European Directive 2013/59/Euratom in January 2014, several international initiatives have been undertaken to discuss the implementation and to attempt to harmonise or at least to converge the regulatory approaches by the different member states. Some months after the publication of the Directive, a Workshop has been organised in September 2014 in Paris by ASN-NRPA, specifically addressing the Radon National Action Plans and focussing on dwellings (Radon National Action Plan Workshop, 2014). Exchange of experience and information between 20 participating countries led to the following principal conclusions: the national radon action plans should aim at reducing the individual as well

as the collective risk with a long-term goal of reducing the exposure of the population (public and workers) to radon and reduce the number of radon induced lung cancers. Due to the multidisciplinary character of the radon issue, a key-factor to success is a tight collaboration on a local, regional and national level between regulators, administrations, academic and technical (building) expertise centres, NGO's and professional associations. A series of good practices has been distilled from the presented experiences, such as the link to other Indoor Air Quality (IAQ) and energy programmes in buildings, the development of guidelines and standards, training and education of building professionals and the need for a well-developed communication plan and -strategy.

The second main event regarding the harmonisation/concertation between member states transposing the BSS had been the ERA Workshop in Krakow, Poland, on the design and implementation of the BSS and National Radon Plans (ERA, 2015). The main subject of discussion was the concept of reference level in the practical/juridical sense of meaning and how it can be used and explained in a regulatory approach as a tool for optimisation in contrast to a (dose) limit. Using a reference level of 300 Bq/m³ and treating it in practice as a kind of limit without much effort for optimisation below the reference level will result in a very limited impact on the exposure of the population to radon. Applying an optimisation process up to the recommended reference level of 100 Bq/m³ (WHO, 2009), called the 'target level', is feasible for new constructions and for remediation practices. The complexity of the message, the risk perception of the population, the large number of stake-holders involved and the need for efficient protection of new buildings all require a strong and clear communication plan.

Finally, the HERCA Workshop 'Radon in Workplaces' in Geneva in October 2015 focussed on the approach of the transposition of the BSS specifically for workplaces (HERCA, 2015). Additional to the main conclusion of the above-mentioned meetings, a specific problem for workplaces is the dose conversion factor (DCF). Article 35 of the BSS states that a workplace where the effective dose of 6 mSv/a is exceeded shall be managed as a planned exposure, and requirements set out for occupational exposure need to be laid down. However, there is no consensus on the dose conversion factors to be used to calculate the annual effective dose from

an annual average radon concentration in different situations. If the most recent suggestion of ICRP (ICRP Sydney meeting 2015) is used, a value of 12 nSv per WLM for both dwellings and workplaces shall be used. This DCF significantly differs from the values published previously in ICRP 65 (ICRP, 1990) and UNSCEAR 2000, figure 1. Using the latest DCF in workplaces would imply that exceeding on average a radon concentration of 400 Bq/m³ during working hours would lead to a dose above 6 mSv/a and hence treating this workplace as a planned exposure situation. The working group proposed on this subject to apply the occupational exposure requirements related to optimisation, to the radiological surveillance of workplaces (adapted to radon exposure), to information of the workers and, in some cases, to individual monitoring.

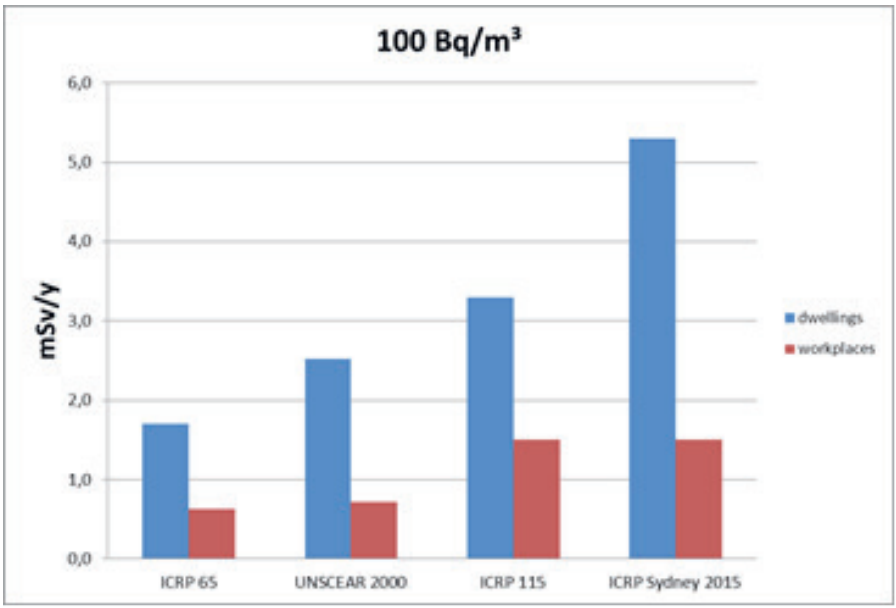

Figure 1. Annual effective doses corresponding to 100 Bq/m³ using dose conversion factors from different literature sources.

In specific working conditions where the equilibrium factor and/or the attached/unattached fraction of radon decay products can differ greatly from the supposed averages, specific assessments may be needed to accurately evaluate the annual effective dose. More in general, as exposure to radon in workplaces depends largely on specific circumstances (exposure time,

dust levels, equilibrium factors, temporal radon concentration variations, etc.), detailed guidelines to measurement and risk evaluation can improve to a great extent the protection of the workers (and in due case the visiting public).

Finally, the involvement of Labour Unions, Occupational Health and Safety services and Employers' associations in the implementation and dissemination of the regulations and the requirements is put forward as recommendation.

3 RADON IN WORKPLACES

Radon in workplaces has been already regulated in the framework of 'work activities involving natural radiation sources' in the Royal Decree of 20 July 2001 (ARBIS, 2001) in a graded approach. Specific workplaces (Art. 4 ARBIS) in defined areas (FANC Decree 2015) are subject to notification (Art. 9, ARBIS) and corrective measures if the action level of 400 Bq/m³ is exceeded. In cases where the exposure level of 800 kBq h/m³ (or the annual dose of 3mSv) continues to be exceeded (Art. 20.3, ARBIS), (part) of the regulations for practices is imposed through a process of licencing. Executive ordinances on procedures and protocols have been published and applied since 2001 (www.fanc.fgov.be). As far as radon in workplaces is concerned (Art. 54 and 103, 2013/59/Euratom), apart from conceptual wording (existing exposure replacing interventions, optimisation, reference level replacing action level), no major changes have to be applied to the existing regulations (ARBIS) and FANC decrees.

4 RADON IN DWELLINGS

In the existing Royal Decree (ARBIS, 2001), radon in dwellings is addressed in the section dealing with surveillance of the territory (Art. 70, ARBIS). This article states that the exposure of the population to radon has to be monitored in the areas defined by - and following the procedures of FANC. An intervention (that regulates the decrease of the radiation level) can be undertaken if risk analysis requires this (Art. 72bis).

The European BSS address, for the first time, radon exposure in dwellings in a Euratom Directive with binding requirements. Essentially, member states have to regulate radon in dwellings as an existing exposure situation

by applying a reference level that should not exceed 300 Bq/m³ (Art. 74, 2013/59/Euratom). Additionally, areas of concern need to be identified, and specific information about radon, measurements, prevention and mitigation provided. The overall management of radon in workplaces and in dwellings has to be specified in a national radon action plan by the member states (Art. 103 and Annex XVIII, 2013/59/Euratom).

The implementation of the above-mentioned aspects of radon in dwelling required an adaptation of ARBIS Article 21 to define the dose levels in workplaces, Article 22 to introduce the Reference level of 300 Bq/m³, Articles 70 and 72bis on the surveillance and intervention principles, and most important, the introduction of a new Article (proposed reference 72bis3) describing the National Radon Action Plan.

5 THE NATIONAL RADON ACTION PLAN

Classification of the territory in terms of radon risk

Based on the available indoor radon measurements, an estimation can be made concerning the exposure of the Belgian population to radon. Indoor radon measurements taken into account for mapping purposes and for the estimation of the indoor radon exposure are purely based on ground-floor measurements of single-family houses. Since in Belgium about 75% of the population lives in this kind of dwellings, it nevertheless gives a good and conservative estimate of the population exposure.

During the last 20 years, several national and local (provincial and municipal) measurement campaigns allowed to assess the exposure of the Belgian population (Table 1), highlighting the statistical variations (population weighted) in the different regions and for the radon prone areas (RPA).

Table 1. Average radon exposure of the Belgian population (population data for 2010). AM: arithmetic mean, MED: median, GM: geometric mean, GSD: geometric standard deviation. Values are in Bq/m³. RPA: radon prone areas. % gives the percentage of single family houses above the indicated radon concentration (in Bq/m³).

	Population	dwellings	AM	MED	GM	GSD	% >100	% >200	% >300	% >400	% >800
Belgium	10,584,534	3,742,000	57	44	46	1.7	10.0	2.1	0.9	0.6	0.2
Wallonia	3,435,879	1,325,000	84	60	75	1.7	26.0	4.5	2.6	1.6	0.4
Flanders	6,117,440	2,191,000	44	37	36	1.2	3.2	0.1	0.05	0.0	0.0
Brussels	1,031,215	226,000	44	37	36	1.2	4.0	0.1	0.1	0.0	0.0
RPA	376,568	130,000	220	127	137	1.9	43.0	33.0	17.0	13.0	4.3

These data allowed to classify the municipalities on the territory in terms of radon hazard (FANC Decree of 30 November 2015). Reclassification of the data to the new reference level of 300 Bq/m³ shows the classification of Belgian municipalities in terms of percentage of dwellings exceeding the reference level of 300 Bq/m³ (Figure 2).

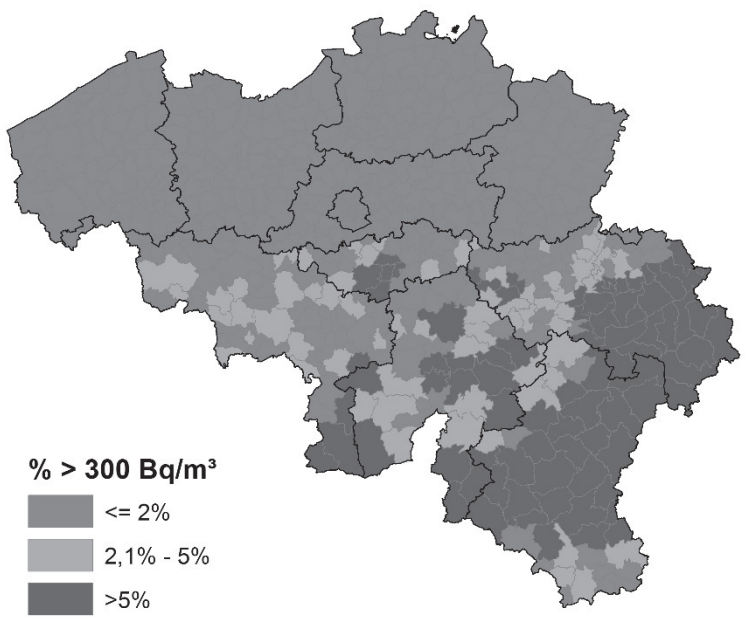

Figure 2. Classification of Belgian municipalities in terms of % of dwellings above the reference level.

Table 2 gives an estimate of the number of dwellings (single family houses) for each category of radon exposure. In the radon prone areas, about 43% of the dwellings have indoor radon concentrations above 100 Bq/m³ (table 1), corresponding to about 56,000 dwellings (table 2). In this area, we find nearly all of the very high radon concentrations (about 5,600 dwellings with concentrations above 800 Bq/m³).

Table 2. Estimate of the number of dwellings (single family houses) in the different categories of radon exposure (Bq/m³).

	dwellings	**>100**	**>200**	**>300**	**>400**	**>800**
Belgium	3,742,000	360,000	84,000	36,000	21,000	5,600
Wallonia	1,325,000	280,000	79,000	35,000	21,000	5,600
Flanders	2,191,000	700,00	some	some	0	0
Brussels	226,000	9000	5,000	some	0	0
Radon prone areas	130,000	56,000	43,000	22,000	17,000	5,500

Based on these data, it can be estimated that about 480 lung cancers per year (about 7% of the total number) can be attributed to radon exposure, using the increase of 16% lung cancer risk per 100 Bq/m³ (Darby et al., 2005).

Detailed measurement campaigns in schools and public buildings have highlighted the same regional variations in these types of buildings as in dwellings. In the case of schools, high radon concentrations often coincided with other indoor air quality (IAQ) problems such as high CO_2 concentrations. Remediation solutions in these cases always aim at a general improvement of IAQ.

Radon reference level

The present action level of 400 Bq/m³, affecting an estimated number of 21000 dwellings, will be replaced by a reference level of 300 Bq/m³, involving about 36000 dwellings (that is around 1% of the dwelling stock). The notion of reference level is different from the action level, in the sense that it requires optimisation above and below the reference level. A reference level, « … level of … activity concentration above which it is judged inappropriate to allow exposures to occur … even though it is not a limit that may not be exceeded. »

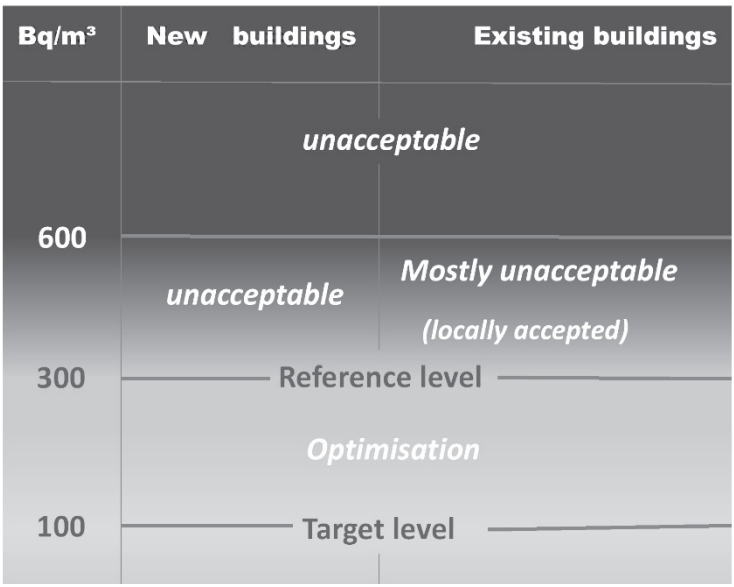

Figure 3. Meaning and proposed approach of the reference level concept

Protection of new buildings

In order to reach the goal of reducing the exposure to radon of the whole population (reducing the collective dose), protection of new buildings is indispensable. Providing airtight interface between the ground and the building, in some zones combined with a possibility to ventilate the space beneath the building slab gives the best assurance for low indoor radon concentrations once the building is occupied. Although simple in theory, assuring the airtightness of the perforations trough the slab for tubing and cables is not straightforward and requires special attention from and training of building professionals.

6 CONCLUSIONS

Transposition of the European Basic Safety Standards into Belgian regulations requires some specific updates of the existing Royal Decree (ARBIS). Specifically, introducing the reference level of 300 Bq/m³, protection of new buildings and the explicit definition of the National Radon Action Plan are the most important changes.

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Samenwerking met buurlanden in geval van een nucleaire noodsituatie

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1. Inleiding

Internationale samenwerking, en meer specifiek samenwerking met de buurlanden bij nucleaire noodsituaties wordt voorbereid en, in geval van een reële noodsituatie, uitgevoerd binnen de bredere context van de nucleaire noodplannen en het nucleaire crisisbeheer. Het nucleair en radiologisch noodplan voor het Belgische grondgebied, dat momenteel geactualiseerd wordt, is een kaderplan dat de leidende principes bepaalt met betrekking tot de voorbereiding op, het beheer van, en de verwerking van de gevolgen van nucleaire en radiologische noodsituaties die beleid en/of coördinatie op nationaal niveau vereisen.

Hoewel het toepassingsveld van het nationaal nucleair noodplan breder is, richt het zich in eerste instantie op noodsituaties met betrekking tot nucleaire installaties van Klasse I op het Belgische grondgebied, maar eveneens op aangrenzende kerncentrales in de buurlanden. Gelet op de doorgaans beperkte afstand tot de grens van deze installaties, variërend van enkele kilometers tot enkele tientallen kilometers, dringt internationale informatie-uitwisseling en/of samenwerking zich onmiddellijk op bij elke situatie die leidt tot activering van noodplannen. Binnen de organisatiestructuur overeenkomstig het nieuwe nucleair noodplan, op zich vrij complex gelet op het grote aantal betrokken actoren, worden bijgevolg duidelijke contactlijnen geplaatst tussen de federale overheden en internationale instanties zoals de Europese Unie (EU) en het Internationaal agentschap voor Atoomenergie (IAEA) enerzijds, en tussen federale en lokale overheden en onze buurlanden.

2. Internationale samenwerking

De informatie-uitwisseling en samenwerking met de internationale instanties is gebaseerd op richtlijnen van de Europese Commissie (EC) en op conventies afgesloten met het IAEA. Het betreft in eerste instantie informatie-uitwisseling omtrent noodsituaties en de evolutie ervan. Een getroffen lidstaat is ertoe gehouden noodsituaties waarbij maatregelen voor de bevolking zich opdringen of waarvan de gevolgen zich uitstrekken over de landsgrenzen heen te melden aan de internationale instanties, evenals de nodige vervolg informatie te verzekeren omtrent radiologisch/ technische aspecten en maatregelen die worden genomen. Deze informatie-uitwisseling verloopt via specifieke webapplicaties: WEBECURIE voor de EC en USIE voor het IAEA. De informatie wordt via deze kanalen door de EC en het IAEA verder verspreid naar andere lidstaten. Ook de respons van andere lidstaten ten aanzien van de noodsituatie verloopt via deze weg. België neemt verder als uitgangspunt aan dat bij een noodsituatie op het Belgische grondgebied, elk bericht dat bezorgd wordt aan de internationale instanties, ook gelijktijdig rechtstreeks aan onze buurlanden wordt gestuurd. Voormeld dispositief wordt jaarlijks meerdere malen geoefend via de zogenaamde ECURIE- en CONVEX oefeningen van respectievelijk de EC en het IAEA.

Inzake internationale samenwerking, kunnen getroffen lidstaten verder beroep doen op internationale bijstand via het Europees Civiele Bescherming mechanisme van de EC en via RANET van het IAEA. Dit impliceert dat de nodige voorbereidingen moeten getroffen worden binnen de eigen crisisorganisatie om deze bijstand te kunnen ontvangen in het kader van het concept “Host Nation Support”, concept dat nu ook in het geactualiseerde Belgische nucleair noodplan wordt ingevoegd.

3. Bilaterale samenwerking

De informatie-uitwisseling in een bredere internationale context, volstaat evenwel niet om tegemoet te komen aan de behoeften van landen die getroffen kunnen worden door de gevolgen van een nucleair ongeval dat zich voordoet in een naburig land. Zoals trouwens aanbevolen door de internationale instanties moeten hiervoor directere bilaterale afspraken gemaakt worden tussen buurlanden.

België heeft met zijn buurlanden bilaterale politieke samenwerkingsakkoorden afgesloten, algemeen voor alle types van risico's of specifiek met betrekking tot nucleaire noodplanning en crisisbeheer.
Deze politieke akkoorden, moeten worden omgezet in bilaterale operationele afspraken tussen actoren op basis van het principe van samenwerking tussen homologe instanties, of m.a.w. tussen instanties die een gelijkaardige rol/functie vervullen in de respectieve landen. Volgende domeinen van samenwerking worden daarbij beschouwd: alarmering op federaal en lokaal niveau, radiologisch-technische evaluatie, afstemming van beschermingsmaatregelen, informatieverstrekking aan de bevolking, strategisch-operationele coördinatie op lokaal niveau, bijstand, zenden van een verbindingsofficier, organisatie/deelname aan bilaterale nucleaire noodplanoefeningen.

Belangrijk element binnen deze bilaterale samenwerking is bijgevolg de identificatie van deze homologe partners, zowel in de voorbereiding op nucleaire noodsituaties als tijdens het crisisbeheer ervan.

4. Faciliteren van grensoverschrijdende samenwerking

Daarnaast wordt de voorbereiding op nucleaire noodsituaties en het nucleaire crisisbeheer ook besproken en georganiseerd binnen andere structuren zoals EU-regio's, het Benelux samenwerkingsverband en tenslotte de werkgroep HERCA-WENRA bestaande uit de nucleaire toezichthouders van Europese landen, waaronder voor België het Federaal Agentschap voor Nucleaire Controle.

EU-regio's

EU-regio's werden opgericht om binnen de Europese Unie de grensoverschrijdende samenwerking tussen instanties op lokaal/regionaal niveau te bevorderen. Indien deze samenwerking zich bijvoorbeeld in eerste instantie kan richten op het socio-economische en het algemeen belang, wordt binnen bepaalde EU-regio's ook ruime aandacht besteed aan veiligheidsaspecten, waaronder ook de voorbereiding op nucleaire noodsituaties en het crisisbeheer. De EU-regio Maas-Rijn, met betrekking tot de kerncentrale van Tihange, en de Grande Region voor wat betreft de kerncentrale van Cattenom zijn hier voorbeelden van. Deze EU-regio samenwerkingsverbanden leiden tot concrete afspraken tussen de

betrokken actoren, waarbij wel een aandachtspunt is dat deze afspraken complementair en coherent dienen te zijn met deze gemaakt in het kader van bilaterale of internationale verbanden.

Benelux-secretariaat – werkgroep crisisbeer

Ook binnen het Benelux samenwerkingsverband wordt ruime aandacht besteed aan het intensiveren van grensoverschrijdende samenwerking inzake voorbereiding en beheer van risico's, inclusief het radiologisch/ nucleaire risico. Het MOU van 1 juni 2006 inzake de samenwerking op het terrein voor het beheer van crisissen met grensoverschrijdende gevolgen vormt de basis voor deze samenwerking. Binnen de werkgroep crisisbeheer wordt jaarlijks een programma m.b.t. het nucleair risico uitgevoerd. Zo verzekert het Benenlux-secretariaat momenteel de uitwerking van een mapping van de homologe betrokken instanties binnen de Benelux landen inzake preventie, voorbereiding op en beheer van het nucleair risico.

HERCA-WENRA – werkgroep m.b.t. noodsituaties

De activiteiten van de de werkgroep m.b.t. noodsituaties binnen HERCA-WENRA zijn gericht op het ontwikkelen van tools ter bevordering van:

- Wederzijdse verstandhouding/vertrouwen in de voorzieningen inzake nucleaire noodplanning en crisisbeheer van de (buur)landen. De eerste stap inzake samenwerking is immers vertrouwd te raken met de uitgangspunten die ter zake in de verschillende landen gehanteerd worden en waar bijvoorbeeld verschillen kunnen bestaan in interventieniveaus, noodplanorganisaties of vooropgestelde beschermingsacties. In dit kader werden bijvoorbeeld "country fact sheets" opgesteld.
- De harmonisering van strategieën inzake nucleaire noodplanning en crisisbeheer tussen (buur)landen. In dit kader dient het belang van de zogenaamde "HERCA WENRA approach" benadrukt te worden.

De "HERCA WENRA approach for a better crossborder cooperation of protective actions during the early phase of a nuclear accident" werd gevalideerd in 2014 en bevat aanbevelingen aan bestuurlijke overheden met het oog op het verzekeren van een afgestemde respons tussen buurlanden in geval van een noodsituatie met grensoverschrijdende gevolgen, door het beslissen van beschermingsacties in de respectieve lanen die zowel qua type als qua omvang op mekaar aansluiten.

Samengevat bepaalt de "HERCA WENRA approach":

- In de voorbereidingsfase: bereik en bewaar een gedeeld begrip van de bestaande nationale noodvoorzieningen door het verbeteren van bilaterale of multilaterale overeenkomsten. Bedoeling is hierbij in eerste instantie vertrouwen te creëren in de noodplanvoorzieningen van (buur) landen, ondanks mogelijke verschillen met de eigen voorzieningen.
- In de vroege fase van een noodsituatie: verzeker snelle informatie-uitwisseling op basis van bilaterale of multilaterale akkoorden en door middel van verbindingsofficieren. Aanbeveling aan de eigen overheid: volg de beslissingen van het getroffen land indien de initiële respons van dit land consistent lijkt (op basis van opgebouwd vertrouwen in de voorbereidingsfase).
- In de latere fase, wanneer structurele samenwerking tot stand is gekomen, werk gemeenschappelijke situatierapporten uit ter ondersteuning van gecoördineerde beschermingsacties.

Daarnaast werden binnen de "werkgroep noodsituaties" gesimplificeerde responsschema's uitgewerkt voor ernstige noodsituaties waarbij in de vroege fase van een noodsituatie weinig informatie beschikbaar is.

Binnen de "HERCA WENRA approach" worden tenslotte ook aanbevelingen geformuleerd voor het voorbereiden van beschermingsacties rond Europese kerncentrales:

- Evacuatie zou moeten worden voorbereid rond kerncentrales in een zone van 5 km rond kerncentrales, en schuilen en "Iodine Thyroid Blocking (ITB) binnen een zone van 20 km.
- Een algemene strategie zou moeten worden bepaald om in staat te zijn evacuatie uit te breiden tot 20 km, en schuilen en ITB tot 100 km.

Het belang van de "HERCA WENRA approach" wordt in het ontwerp van (geactualiseerd) noodplan onderschreven, met name bijvoorbeeld wat betreft de voorbereidingszones voor directe beschermingsacties rond kerncentrales. Zo bepaalt het ontwerp van noodplan de noodplanningszones (waarbinnen een gedetailleerde voorbereiding moet plaatsvinden) rond kerncentrales op 10 km voor evacuatie en op 20 km voor schuilen en ITB. De afwijking inzake evacuatie t.o.v. de vooropgestelde zone van 5 km binnen HERCA WENRA, wordt verklaard door het gegeven dat in de bestaande

versie van het nationaal nucleair noodplan reeds een noodplanningszone van 10 km wordt aangehouden.

Verder voorziet het ontwerp van nationaal nucleair noodplan in het concept extensiezone, waarbinnen een strategie moet worden uitgewerkt voor de uitbreiding van beschermingsacties tot 20 km voor evacuatie, en tot 100 km voor schuilen en ITB, in overeenstemming met HERCA WENRA. Het ontwerp van plan definieert daarbij reeds een aantal basisprincipes voor de bepaling van deze strategie.

Chairman's report (Augustin Janssens)

Overview of the general discussion

This report on the discussions generated by the presentations of the different topics presented at the seminar is based both on the concluding discussion and for some of the presentations on immediate reactions, to the extent that they left sufficient time for it. No new items were introduced, and all questions and comments could somehow be related to one of the presentations, so for the sake of clarity this report has been structured along the different topics rather than in chronological order:

- General overview of the Belgian approach for the transposition of the Euratom BSS
- Experience with the regulatory control of practices involving consumer goods
- Revision of the organisation of radiation protection in Belgium, including the role of RPE and RPO
- Harmonisation of the application of the requirements on radon exposure
- Coordination between neighbouring countries in view of nuclear emergency response

General overview of the Belgian approach for the transposition of the Euratom BSS

The presentation had highlighted that the changes to the existing legislation imposed by the Euratom Directive would result in a series of additional decrees and administrative provisions. A participant regretted this fractionation and the complexity that results from it, not only for the user but also for those who are involved in teaching. The user would also probably only consider the pieces of the puzzle that would of direct concern to him, and loose the overall picture. FANC answered that indeed the initial ambition was to consolidate the legislation, in the same way as the Directive itself, but that it was soon realised that this would take too much time so that the deadline for transposition could be missed. It

was argued that the task had been easier for those (new) Member States that did not yet have extensive legislation on the subject matter before adoption of the Directive. Still, it is the longer-term objective to restructure the legislation as originally intended. Meanwhile FANC would publish a number of brochures explaining parts of the legislation and the changes therein. It was also confirmed that in accordance with the recital to the Directive Belgium would provide the European Commission with a table of correspondence between the different pieces of legislation and the requirements of the Directive. Despite the length of this table it could help users in finding their way as well. While the table is meant for use of the EC only, it could be considered to release a public version.

Experience with the regulatory control of practices involving consumer goods

While the presentation on this topic made clear that the legislation on this matter had already been adopted at a very early stage, this topic generated a lot of interest mainly because now the first practical experience with its implementation was shown. The first question was whether in addition to the thorough examination of submissions by the manufacturer or importer, FANC was pursuing an active search of products that were already on the market. It was explained that the current assessments were a first phase of the process and that further investigations would be conducted. A participant raised the example of smoke detectors and wondered whether these were actively being searched for disposal. It was confirmed that the use of radioactive substances in smoke detectors is now forbidden in Belgium, so that these are formally no longer "consumer goods", but radioactive waste. Some building owners faced the disposal of a large number of smoke detectors and the high cost of disposal by ONDRAF-NIRAS. It was suggested that this be discussed between the two authorities. The same applies to lightning rods, prohibited already a long time ago, and for which there is a plan for their recovery and disposal. Over 5000 lightning rods have already been evacuated.

While for the files that were presented the analysis concerned on the one hand the justification of the practice and on the other hand the exemption of the goods from regulatory control, there was a question on whether compliance with the exemption criteria was met also for storage and transport, and

whether exemption levels were harmonised. Another participant thought that at least with the new Directive one should hope for harmonisation of the exemption criteria, but that nevertheless the justification of practices remained a national decision. This is how it always was and continues to be with the new Directive. Participants advocated a European approach, even at world scale, rather than at national level. FANC explained that in the framework of the EC initiative on implementation of the Directive (Riskaudit Study) many delegations had raised the same issue, albeit with regard to the placing on the market of building materials rather than other consumer goods. HERCA could also play a role in agreeing between Member States on certain practices. While the Directive now requires Member States to share both the information provided by the manufacturer and the results of the analysis by the authority, Belgium would do so indeed for the case that was presented, but only when the proposed decision had been endorsed at the political level, which would probably not take very long. One should hope that other countries would benefit from the thorough analysis that had been performed.

It was further discussed whether the technical committees doing the analysis had sufficient competence to do the analysis, and whether the submissions were of good quality. It was explained that the main weakness is not with the assessment of radiological consequences but with the appraisal of the availability of alternative products. Despite the wide range of competences in the technical committees it was difficult to evaluate the information by the submitting industry, which is not inclined to highlight the advantages of competing products. It was also highlighted that the technology of illumination evolves very rapidly, in particular with the advent of LED technology, so that the technical justification is soon outdated, and one application was withdrawn because in the meantime there was no commercial benefit for it anymore.

Finally, a participant raised the case of imported children toys, that had been found to contain traces of radioactivity. The addition of radioactive substances to toys and personal ornaments is prohibited by the Directive and in Belgian law. FANC explained that it was not possible to inspect private homes, but the efforts spent to check containers at the border in search for orphan sources, notably in the port of Antwerp, were also meant

to help finding any other illicit presence of radioactive substances. This has resulted in some diamonds and other jewels to be confiscated and taken to the Mol site.

Revision of the organisation of radiation protection in Belgium, including the role of RPE and RPO

The presentations on this important subject, first by the representative of the Belgian Radiation Protection Society in relation to the advice given by BVS-ABR on an earlier draft and then by FANC on the latest draft, prompted a question on whether the role and tasks of the qualified expert on radiation protection could still be outsourced, in particular for class II and III installations. FANC confirmed that this is still possible in the new system, the presentation had not included this aspect in sake of conciseness. A participant asked why the essential training requirements in view of recognition of experts were reserved to universities only, while there was a lot of expertise elsewhere, notably in SCK-CEN. FANC replied that this is already the case for current recognitions and that a certain level of quality of education needs to be assured.

The issue on delegation and the requirement to have agents responsible for radiation protection on site for each controlled area was discussed again in the general discussion with the example of radiology and nuclear medicine departments in hospitals. FANC confirmed that the new legislation would allow maximum flexibility, and, in this case, there were different options, including having an agent per department and making use of a floating pool of agents (shared between different departments). The latter option has the advantage of carrying feedback from experience from one department to another.

It was concluded that the new organisation of radiation protection was now open only for formal consultation, notably of the Superior Health Council, but that it remained important for all the stakeholders to understand properly how this would change their job and how it would affect responsibilities and that the future practical implementation of the requirements in particular in terms of the graded approach for small installations warranted a further exchange of views within the Radiation Protection Society. FANC confirmed that the most recent version of the

text would be on its website in about a week, and the chair invited all participants to take time and look into it carefully. A participant who is also an expert in the Superior Health Council called for the experts in this field to offer help to the Council in this important file, with due regard to possible conflicts of interest.

Harmonisation of the application of the requirements with regard to radon exposure

The participants appreciated the greater effort that would be spent on reducing radon concentrations in buildings with the new reference level of 300 Bq/m^3 proposed by the Council Directive and the objective of reaching 100 Bq/m^3 on the long term, following guidance from WHO, starting with new dwellings. The fact that there is still no consensus on the conversion factor from radon concentration to dose was discussed, in particular the fact that ICRP's risk assessment is based on 50% smokers while today in Belgium only 20% of the population is smoking. One participant argued that in Flanders it would be reasonable to have right away a reference level, rather than a "target level", of 100 Bq/m^3 for new buildings

With regard to workplaces, the lower reference level implies that now some 1400 workplaces would require a measurement, and one expert wondered how these would be made aware of the need to do so. FANC informed they work according to a priority list, that in radon prone areas or municipalities workplaces would be contacted directly or through the occupational health services.

Coordination between neighbouring countries in view of nuclear emergency response

There was a strong plea to try and cooperate in the first place in view of good and coherent information to be provided in an emergency. The FANC speaker held the view that this would result less from formal agreements but from good personal links between the communicators. The formal agreements would foster in the first-place coherent decision making, which is necessary in view of credible communication.

Another participant emphasised the need for more and better communication not only on emergency measures but also on low risks. Also, communication with children is essential, emergency preparedness should start in schools. The experience in Japan shows that evacuation, whether voluntary or not,

beyond the 20-km zone is a reality, and that there are specific problems like with the evacuation of care centres. A notable decrease in life expectancy of older people was observed. Nuclear emergency preparedness needs to be embedded not only in radiation protection but also as a cornerstone in nuclear safety, and he called for a stronger role of the EU in matters of safety and emergency preparedness.

Closure

The chair thanked the speakers for their clear and comprehensive presentations, and acknowledged in particular FANC for helping with the organisation of the seminar and for their availability. He also thanked the participants for their input in the discussions and thought this was a good basis for further sharing information between the authorities and the radiation protection society. The discussions also highlighted some points that would merit further debate within BVS-ABR, but it was reminded that at this stage there is no intention to provide additional input to the authorities in relation to the forthcoming transposition of the BSS Directive.

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CONSIDERATIONS OF RADIATION PROTECTION FOR PROTON THERAPY

Innovative interpretation of a familiar concept

S. Peetermans
Vinçotte Controlatom

Introduction

Proton therapy is on the rise. The high energy proton having a finite range in matter whilst depositing most of its energy at the end of its trajectory, at the so-called Bragg peak, has raised the interest of the radiotherapy community for a more precise dose delivery and tumor control compared to traditional X-rays. The number of proton therapy facilities is rapidly increasing throughout Europe and the rest of the world. In this article, we focus on considerations of radiation protection in designing and operating a high energy proton beam for therapeutic purposes.

Interaction mechanisms of protons and neutrons

To understand the implications of proton therapy for radiation protection, we need to understand the relevant particle-matter interaction mechanisms. Protons are charged particles. Along their path through matter, they continuously lose energy through Coulomb interactions. The energy loss dE per path length dx is called the stopping power S,

$$S = -\frac{\mathrm{d}E}{\mathrm{d}x}$$

It can be described by the Bethe-Bloch equation, which for non-relativistic proton energies tends to $\propto 1/v^2$. As the proton slows down, the deposited energy in matter quickly increases, ending in a sharp *Bragg peak*.

Protons of high energies (above 10MeV) can also induce spallation when they hit a target nucleus. The process consists of several stages. At first, the *intra-nuclear cascade* takes place, where nucleons are knocked out of the nucleons, with a forward bias and very high energies, up to the incident proton energy (*i.c.* around 250 MeV). The nucleus is left in a

highly-excited state, the remaining energy is repartitioned among the residual nucleons, and de-excitation takes place by isotropically emitting nucleons of a few MeV, the *evaporating phase*. The resulting nucleus is not necessarily stable, a radioactive reaction product can be formed, a process called *activation*.

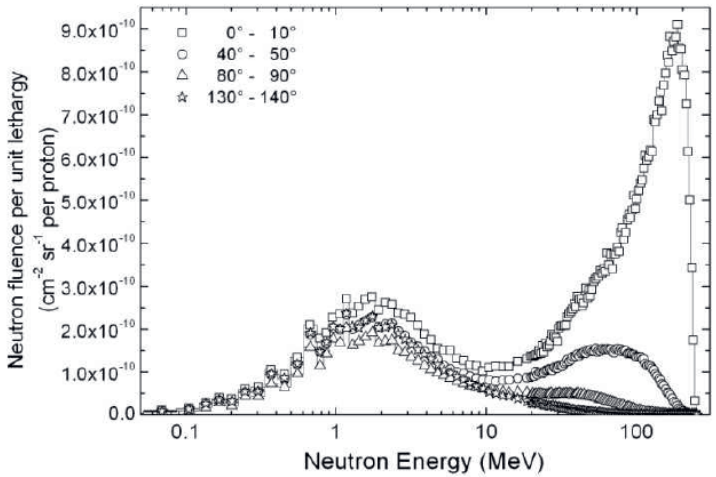

Figure 1. Unshielded neutron spectra for a 250 MeV Proton beam incident on a thick iron target [1] showing a forward biased peak up to the initial beam energy and an isotropic field of evaporation neutrons around a few MeV.

Neutrons are the dominant type of secondary radiation formed by the proton beam [2]. As they are neutral, their interaction lies with the target nuclei. They can lose energy through elastic and inelastic scattering, ending up at energies around 25meV corresponding to the thermal energy of surrounding matter at room temperature. Such *thermal* neutrons can also be captured by the nucleus, leading to a possibly radioactive daughter isotope, i.e. be a source of activation. In addition, the high-energy neutron component can, much like the proton, induce spallation reactions, which is another significant activation pathway not to overlook.

Shielding design considerations

Monte Carlo

To predict the radiation field around a high energy particle beam, with many possible interaction mechanisms and in a complex geometry, is an

intricate problem. The Monte Carlo method breaks it down to tracking single, primary particles through a modeled geometry and at each interaction step selecting a single reaction mechanism – the physics of which are well described - at random and continue following the particle(s) afterwards. After applying this for many runs of primary particles, the result approaches reality. Examples of very complete Monte Carlo simulation tools encountered in modeling proton therapy and other particle physics facilities include MCNP, FLUKA, PHITS and GEANT.

The Monte Carlo method can reach very accurate results for complex problems, but is very computationally expensive when applied to shielding problems, as a quick example shows. Suppose the dose rate needs to be decreased by 6 orders of magnitude. Already 10^6 primaries need to be generated for one to get through the shielding. Suppose we want 10% accuracy on the result, a simple Poisson estimate already implies an increase to 10^8 primaries. The situation quickly escalates if the information is required for all types of secondary particles, for all energy bins…

Analytical methods

Analytical methods on the other hand are not very time consuming. They rely on (often conservative) approximations of physics and geometry, to allow calculation. The secondary neutron field energy spectrum and intensity depends heavily on the proton beam energy *and* incidence angle. *A fortiori* the same holds for the attenuating properties of constructed shielding. Analytical shielding calculations are therefore more complex than traditional X-ray shielding, as DIN 6875-20:2014 [3] illustrates.

The neutron dose H [μSv] at 1m generated by a proton beam of energy E [MeV] and intensity I [nA.h], emitted (observed) at an angle θ[°] with respect to that proton beam is given by:

$$H = 4.5\ 10^9 \times I \times \frac{1 - e^{-3.6(E/1000)^{1.6}}}{(\theta + \frac{40}{\sqrt{(\frac{E}{1000}})})}$$

Valid for target materials of intermediate atomic mass number (e.g. concrete, Cu, Fe).

All components of the proton therapy beam line where proton losses occur, need to be taken into account as neutron source terms. These include cyclotron, quadrupoles for focusing the beam after extraction, the energy degrader and collimator follow, as well as quadrupoles for refocusing, divergence and momentum slits and lastly the patient himself. The proton current losses are generally stated by the system vendor. They are in themselves energy dependent, so an estimate has to be made by the future proton therapy facility of expected patient case mix as tumor depth control means varying the proton beam range and hence its energy.

The neutron dose decreases with distance *a[m]* as

$$\propto \left(\frac{1}{a}\right)^{1.5}$$

which decreases more slowly than inversely proportionate to the distance squared to take into account the filling of the room with scattered neutrons. It is noteworthy, that some authors prefer keeping the traditional squared decrease in the forward direction, as it is dominated by high energy neutrons from the intra-nuclear cascade.

The shielding of thickness *d* is taken into account by a decrease in neutron dose by

$$\propto 10^{-d/TVT}$$

where the tenth-value-thickness *TVT* is a function of material and neutron spectrum, taken into account by a function of proton beam energy E[MeV] and neutron emission angle θ[°]:

$$TVT = TVT_0 \times \left(1 - 0.8e^{-\frac{4E}{1000}}\right) \times f(\theta)$$

with

θ	[0°,45°[	[45°,90°[	[90°,135°[	[135°,180°]
f(θ)	1	0.73	0.49	0.38

and

Material	Mass density	TVT_0
Standard concrete	2.35 g/cm³	1.62 m
Iron	7.4 g/cm³	0.82 m

Figure 2 illustrates how the thickness of concrete, required to decrease the neutron dose by one order of magnitude, depends heavily on the proton beam energy and the emission angle of the neutron towards the point to shield.

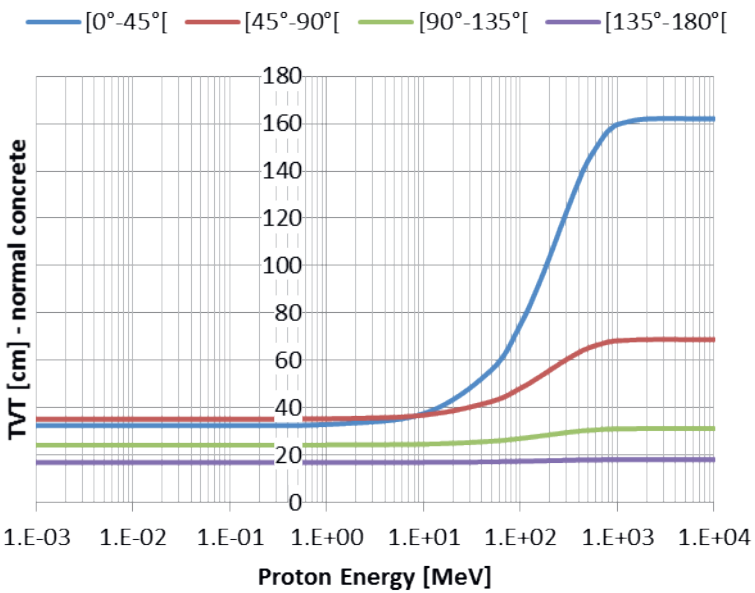

Figure 2. TVT of normal concrete as a function of the energy of a proton that is lost on a component (and a source of neutrons that are to be shielded for) for four different intervals of (proton,neutron) angle.

Activation considerations

The intense neutron fields around the proton beam line tend to activate all surrounding matter. The degree to which this poses a problem depends on the present neutron flux and the irradiated type of elements (cross-section for the formation of radioactive daughters and the half life of these daughters).

The shielding should thus not only be designed based on the immediate operational dose constraints, but also bear in mind decommissioning and the minimization of radwaste. The typical radionuclides of concern in concrete shielding are listed in table 1. If no precautionary measures are taken, the cooling time for the cyclotron vault walls to reach the clearance limit will be in the order of decennia. The time evolution of the clearance index, the weighted sum of specific activities over clearance limits for all present nuclides, will be dominated by an initial swift decay of Na-22 (formed by spallation on e.g. Si-28 present in the sand to make up the concrete) followed by a slow decay of Eu-152 (present in trace amounts only, but of concern due to the high cross-section of Eu-151 to thermal neutron capture). Co-60 is formed through thermal neutron capture on Co-59, present in e.g. steel reinforcement and possible aggregates added to the concrete.

Activation product	Mechanism	Cross section	Half life	Clearance limit
Eu-152	Thermal neutron capture	9198 barn	13.3 y	0.1 Bq/g
Co-60	Thermal neutron capture	37 barn	5.3 y	0.1 Bq/g
Na-22	Spallation	10-100 mbarn	2.6 y	0.1 Bq/g

Table 1. Activation products of concern in concrete shield walls of a proton therapy facility.

Having identified the critical radionuclides, one can think of mitigation strategies. Whereas the average concrete contains around 0.3ppm of Eu-nat, this can be reduced to <0.1ppm through careful selection of concrete components [5,6]. A wall cladding of borated poly-ethylene can further reduce the concrete wall activation. One can also limit the usage of superficial steel reinforcements and bury them deep enough in the walls not to get activated. Finally, decommissioning can also account for a certain (now limited) cooling time. Should a thin concrete layer still be predicted to get activated above the clearance limits, one can moreover physically separate them during construction (e.g. foils) from deeper lying structures for easier dismantling.

Also the air inside the bunker rooms will get activated. Spallation at O-16 an N-14 in air, tends to produce a series of lower mass number positron emitting nuclides: O-15, N-13, C-11, Be-7 and H-3. Thermal neutron

capture on Ar-40 produces Ar-41. Conservative effective engaged dose estimates vary around 400 μSv for a child, age 2-7, breathing cyclotron vault air for an entire year [7]. Possible protective measures are to increase the effective decay constant λ of produced radionuclides by having a high air renewal rate *r*:

$$\lambda_{eff} = \lambda + r$$

Furthermore, one should have lower room pressure as the secondary neutron flux and thus air activation gets higher. In other words, air should flow from the hospital in the direction of treatment room, then gantry room before finally being extracted at the cyclotron vault. Air should be extracted towards locations of minimum occupancy. Should dose constraints still not be met at the exhaust, one can resolve to installing an air buffering system, introducing an extra delay for the short lived air activation products to decay before release into the environment.

Water is also a major source of O-16 and so the same positron emitting radionuclides as in air will be produced through spallation in the water introduced inside the bunker. This includes the cooling water of the cyclotron, which should be in a closed circuit and preferentially with sump and leakage detection systems installed. Moreover HVAC can include certain water volumes within the bunker for air temperature control. Inside the cyclotron vault, where ambient neutron fluxes and activation are highest, these can e.g. be placed behind a heat exchanger, to separate them from the hospital HVAC water circuit. Inside the treatment room, neutron fluxes are generally low enough not to warrant any precautionary measures for radiators, sink,… An interesting side note, the same PET nuclides are produced at the irradiated tumor volume inside the patient offering the possibility for visualization and verification using a nearby MRI.

Conclusion

In this article a short introduction was given into some considerations of radiation protection when designing and operating a proton therapy beam line. The interaction properties of protons with matter were discussed, with emphasis on the characteristics of neutron production. These neutrons are the main source of radiation to shield for, taking into account the dependencies of initial proton beam energy and angle. Lastly, activation

by neutron spallation or thermal neutron capture is discussed as well as mitigation strategies for bunker walls, air and water.

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EFFECTS OF IONIZING RADIATION ON THE CARDIOVASCULAR SYSTEM

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Abstract

Traditionally, non-cancer diseases are not considered as health risks following exposure to low doses of ionizing radiation. Indeed, non-cancer diseases are classified as deterministic tissue reactions, which are characterized by a threshold dose. It is judged that below an absorbed dose of 100 mGy, no clinical relevant tissue damage occurs, forming the basis for the current radiation protection system concerning non-cancer effects. Recent epidemiological findings point, however, to an excess risk of non-cancer diseases following exposure to lower doses than previously thought. The evidence is the most sound for cardiovascular diseases (CVD) and cataract. Due to limited statistical power the dose-risk relationship is undetermined below 0.5 Gy, but if this relationship proves to be without a threshold it may have considerable impact on current low dose health risk estimates. In this review, we describe the CVD risk related to low doses of ionizing radiation, the clinical manifestation and pathology of radiation-induced CVD, and the importance of the endothelium models in CVD research as a way forward to complement the epidemiological data with the underlying biological and molecular mechanisms. In addition,

with our research we aim to contribute to the identification of potent countermeasures as well as a set of predictive biomarkers for radiation-induced cardiovascular disorders. As such we strive for a better life quality for ionizing radiation exposed people.

Societal concern

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the Western world. It accounts for nearly one-third of all deaths worldwide. There are multiple contributory risk factors for heart disease. Some are of a controllable nature, such as life-style and dietary factors, and metabolic disorders such as high cholesterol levels or hypertension. Others are non-controllable fixed risk factors, such as gender, age, and genetic predisposition [1], [2].

In addition, there are environmental factors affecting the risk of CVD, ionizing radiation being one such factor. And it has been known for a long time that high doses of radiation, such as those given during radiotherapy, cause damage to the heart and vasculature and thus increase the risk of CVD. The data from animal experiments have strongly supported this observation. However, for doses < 0.5 Gy, epidemiological data are suggestive rather than persuasive. Therefore, the magnitude of risk of circulatory disease in the low dose region where issues of radiation protection usually operate is not clear [3] [4] [5] [6].

Various issues such as occupational radiation exposures, future of nuclear power, manned space flights, and threat of radiological terrorism, call for a thorough understanding of low dose health risks [7]. The main concern is, however, the increasing use of ionizing radiation for diagnostic medical purposes (Figure 1) [8]. For instance, since 1993, the number of computed tomography (CT) scans has quadrupled in the US and similar trends are observed in Europe [9]. Medical radiation is the largest source of radiation exposure in Western countries, accounting for a mean effective dose of 3.0 mSv on average per capita per year from diagnostic procedures only, corresponding to a radiological risk of 30 chest X-rays [10]. Of note, in this number doses from therapeutic procedures are not taken into account. Although the health benefits of these improved diagnostic procedures are huge, concerns are raised regarding the ‘overuse’ and potential associated health risks [11].

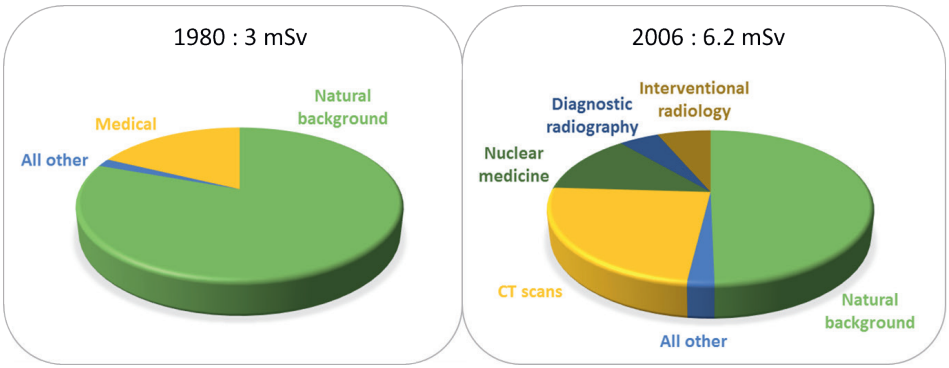

Fig 1. Average annual effective dose per person received in 1980 (left panel) and 2006 (right panel) in the United States. The large increase in the use of ionizing radiation for medical purposes, in the period 1980-2006, contributed to a total increase from 3.0 mSv in 1980 to 6.2 mSv in 2006. Similar trends are observed in other industrialized countries [1].

Clinical manifestation and pathology of radiation-induced cardiovascular diseases

The major clinical manifestations of radiation-related CVD are pericarditis, congestive heart failure and coronary artery disease. Ionizing radiation may also cause valvular disease, arrhythmias and conduction abnormalities, but a direct causal relationship is not evidenced. None of these conditions however is specific for ionizing radiation. Human observations are strongly supported by data from animal experiments [3, 6] , [12, 13].

Pericarditis. An early sign of radiation-related heart disease is acute pericarditis, which occurs already months after high dose irradiation of the heart (> 40 Gy). Acute pericarditis is an inflammatory process of the pericardium, the membrane that surrounds the heart. Since 1970, advances in radiotherapy treatments have led to significant reduction of both the dose and the volume of the heart exposed [14]. Therefore, radiation-induced pericarditis is uncommon these days.

Coronary artery disease. Obstruction of the blood flow in coronary arteries, responsible for blood supply to the heart, is referred to as coronary artery disease or ischaemic heart disease. Mild obstruction due to narrowing of the coronary arteries leads to angina (discomfort due to ischemia of the heart muscle) whereas severe blockage leads to myocardial infarction

(heart attack). Atherosclerosis is the major underlying pathogenesis causing coronary artery disease (Figure 2). It can be described as a chronic inflammatory disease of the arterial wall in which the build-up of plaques in the intima impairs normal vascular functioning [15]. Changes in the homeostatic mechanisms of the endothelium, the cell layer lining the blood vessels, contribute to the development, progression and resulting complications of atherogenesis. The development and progression of atherosclerosis is a complex process with many players [16]. Nowadays, coronary artery disease is considered as the major cardiovascular complication in patients that have received radiotherapy for thoracic malignancies [17].

Congestive heart failure. Congestive heart failure is characterized by a compromised blood pumping function of the heart, due to a reduced capacity of the heart muscles, causing under-perfusion of the body tissues. The underlying pathologies are various and include coronary artery disease, microvascular damage, hypertension, valvular heart disease, cardiomyopathies, and congenital heart disease [18].

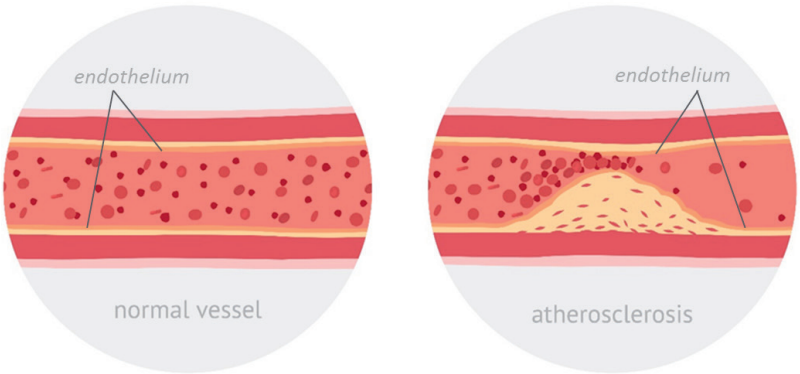

Fig 2. Cross-cut of a normal, healthy blood vessel (left) and a blood vessel with an atherosclerotique plaque hampering the blood stream (right). Damage to the endothelial is an important trigger of atherosclerosis, the underlying cause of the main CVD.

Recognition of radiation-related cardiovascular disease risk

The recognition that exposure of the heart and the vasculature to high doses of ionizing radiation can cause CVD started in the late 1960s [19]. This was mainly related to the clinical observation of cardiovascular complications in radiation-treated survivors of Hodgkin's lymphoma and other childhood cancers. Later, larger-scale epidemiological studies have found a clear association between therapeutic doses of thoracic irradiation and an increased risk of CVD in these long-term cancer survivors, confirming the earlier observations [4].

With more than 10 000 diagnoses per year in Belgium (2014, www.kankerregister.org) and around 60 % of the cases making use of radiation therapy (www.cancer.org), breast cancer patients constitute an important risk group for radiation-induced CVD. Radiotherapy regims for these patients usually include an accumulated dose of around 50 Gy in fractions of 2 Gy (www.breastcancer.org). And although modern techniques are evolving to reduce the dose to the surrounding healthy tissues, parts of the heart still receive doses of 1 to 5 Gy [20]. Several large epidemiological studies indicate increased long-term heart disease mortality and morbidity rates in breast cancer survivor treated with radiotherapy. Risks are higher for women irradiated for left-sides tumours compared with women irradiated for right-sides tumours [13], [20], [21], [22], [23]. Since radiation doses to cardiac structures are larger in radiotherapy patients with left-sided tumours than in radiotherapy patients with right-sided tumours, this implies a direct relationship between the dose to the heart and the resulting CVD risks.

Only more recently, various epidemiological findings, in particular from the Japanese atomic bomb survivors, have raised awareness of possible CVD risk following exposure to low and moderate doses of radiation. Also studies on occupational exposed cohorts have delivered informative data. More details about these cohorts follow below.

Epidemiological cohorts exposed to low dose ionizing radiation

Reviewing the epidemiological literature related to CVD and low dose ionizing radiation is complicated by the different classifications of CVD. Moreover, all CVD are often pooled in one diagnosis in epidemiological studies which hampers thorough understanding of radiation-related CVD risk. In addition, many epidemiological studies face the problem of

misclassification of the cause of death, except for stroke, for which the diagnosis tends to be reasonably good [3].

Radiation therapy patients. Over the last half century, radiation therapy (RT) has evolved to become one of the cornerstones of treatment for various types of cancers. It is estimated that more than 50 % of patients with cancer are treated with radiation therapy. Along with the development of novel chemotherapeutic agents, RT has revolutionized the prognosis of patients with various cancers. However, with more and more oncological patients having a long life-expectancy, treatment-related co-morbidity and its prevention becomes more and more an issue for cancer survivors. In this context, reports point to late secondary cardiovascular effects due to out-of-field exposure of the cardiac region during RT for breast cancer, Hodgkin lymphoma, or even the benign peptic ulcer disease in the early days workers [24]. Long-term follow-up was shown to be essential, as the cardiovascular complications usually manifest only years after completion of radiation therapy.

Hodgkin lymphoma was the earliest paradigm for the study of radiation-induced vascular disease. A first case report was published in 1924 about histological changes in the human heart after irradiation for Hodgkin lymphoma [25]. Amongst Hodgkin lymphoma patients who have received radiation, cardiovascular disease is of the most common causes of death. Studies have shown that these patients have an increased risk for coronary artery disease, valvular heart disease, congestive heart failure, pericardial disease and sudden death. The risk is particularly high in patients treated before the age of 40 years [26-29].

Also RT for breast cancer often involves some incidental exposure of the heart to ionizing radiation. The Early Breast Cancer Trialists' Collaborative Group has performed a meta-analysis on mortality data of more than 30.000 breast cancer patients 15 years after treatment. The mortality of heart disease was increased with 27 % in patients treated with surgery and subsequent radiotherapy compared to patients treated with surgery alone [22]. Evaluation of long-term mortality in breast cancer survivors may however be influenced by the varying prognosis of the different treatment regimens (surgery vs. radiotherapy). This can be circumvented by comparing women irradiated for left-sided tumours with women irradiated for right-sided tumours. Cardiac radiation doses are larger

in radiotherapy patients with left-sided tumours than in radiotherapy patients with right-sided tumours [13]. Analysis of 308 861 women with breast cancer registered in the Surveillance, Epidemiology and End-Results cancer registries database from the United States has revealed an increased heart disease mortality ratio for women irradiated for left-sided breast cancer compared to right-sided breast cancer [30]. A study related to 72 134 women diagnosed with breast cancer in Sweden and Denmark during 1976-2006 and followed-up for 30 years revealed an increased risk of ischemic heart disease, pericarditis and valvular disease in irradiated women with left-sided tumours (mean cardiac dose 6.3 Gy) compared to right-sided tumours (mean cardiac dose 2.7 Gy) [23]. In addition, major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) were analyzed in a study of 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark [20]. The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy (95% confidence interval, 2.9 to 14.5; $P < 0.001$), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast.

Due to improvement in radiation techniques (*e.g.* breathing adapted RT, CyberKnife), the risk of cardiovascular complications in relation to radiation are uncertain, but may be expected to decline. However, patients with classical risk factors like hypertension, smoking, and hyperlipidaemia may be at increased risk of radiation-related cardiovascular complications, and these risk factors should be treated aggressively [31]. Younger patients should be screened, because this patient population at risk usually has a considerable life expectancy.

Survivors of the atomic bombings of Hiroshima and Nagasaki. The most informative cohort is the Life Span Study (LSS), consisting of approximately 120,000 persons. It includes 93 000 survivors who were within 2.5 km of the hypocenters at the time of the bombings or between 3 and 10 km from the hypocenters and whose radiation doses were negligible. In addition, it includes 27 000 subjects who were in the cities

at the time of the recruitment in 1950 but not at the time of the bombings. This latter group has been excluded from most analyses since the early 1970s because of inconsistencies between their mortality rates and those for the remainder of the cohort [32]. The LSS cohort has several features that makes it uniquely important as a source of data for developing quantitative estimates of risk from exposure to ionizing radiation. The population is large, not selected because of disease or occupation, has a long follow-up period (1950–2000), and includes both sexes and all ages at exposure. In addition, doses are reasonably well characterized and cover a useful range. The LSS also has limitations, which are important to consider in using and interpreting results based on this cohort. The subjects were Japanese and exposed under wartime conditions and, in this sense, differ from various populations for which risk estimates are desired. In addition, to be included in the study, subjects had to survive the difficult initial effects of the bombings, including the acute effects of radiation exposure itself, and it is possible that this might have biased the findings [32]. Such a "healthy survival selection effect" would be however not of importance for the detrimental health outcomes of heart diseases and stroke [33]. Mortality in the LSS has been investigated since 1950s by collecting information through the national population registry and death certificates obtained throughout Japan. Cancer incidence data was available from population-based cancer registries since 1957 in Hiroshima and since 1958 in Nagasaki [34].

Preston and co-workers have evaluated non-cancer mortality from the LSS report 13 published by the Radiation Effects Research Foundation (RERF), and analyzed the data for the period 1968-1997. Based on the linear non threshold (LNT) model, excess relative risk (ERR) estimates were calculated to be 0.17 with 90% confidence intervals (CI) (0.08;0.26) for heart disease and 0.12 (90% CI 0.02;0.22) for stroke, for the period 1968-1997 [35].

Shimizu and co-workers have evaluated ERR of mortality from heart disease and stroke in the LSS cohort with a follow-up of 53 years (1950-2003) [36]. Based on a mail survey, they included information regarding sociodemographic (education, occupation type), lifestyle (smoking, alcohol intake) and health variables (obesity, diabetes mellitus) from 36 468 members of the LSS cohort. This allowed them to evaluate the effect of these confounding factors on ERR estimates. They found an ERR of 0.14 (95% CI 0.06; 0.23) for heart disease and an ERR of 0.09 (95% CI

0.01; 0.17) for stroke based on the LNT model. Whereas the LNT model fitted best the data for heart disease, the quadratic model was best to fit the data for stroke. The latter model implies relatively little risk at lower doses. Indeed calculation of ERR for stroke over restricted dose ranges revealed a ERR of 0.03 (95% CI -0.10; 0.16) for 0-1 Gy and -0.07 (95% CI -0.28; 0.16) for 0-0.5 Gy. Furthermore, they showed that the association of dose with CVD risk in the LSS cohort is unlikely to be an artefact from confounding by sociodemographic, lifestyle or disease risk factors.
The abovementioned studies have used the LSS cohort for CVD risk estimations. Takahashi and co-workers have examined the association with dose and the incidence of stroke in the Adult Health Study (AHS) cohort [37]. This cohort was established in 1958 and consists of 19 961 subjects from the LSS cohort. These survivors undergo biennial health examinations, which provide additional clinical and sub-clinical information to the death and cancer registries data. In this way, disease morbidity for a variety of conditions can be investigated. For their study, information of health examinations from the follow-up from 1980 onwards has been used, resulting in 9515 AHS participants. In this study population, risk for haemorrhagic stroke was observed to increase with dose. This was across the full range of doses for men, while in women there seems to be a threshold of about 1.3 Gy.

Occupational exposure. Studies in radiation workers are of interest since they generally involve relatively low total accumulated doses received over repeated exposures. Various studies have been performed (reviewed in [6], [5]), of which some of the most important will be discussed. The largest studied cohort consists of 275 000 nuclear industry workers from 15 countries, referred to as the 15-country study [38]. The average cumulative dose received was 20.7 mSv. An overall increasing trend, although not significant, for circulatory disease mortality was observed. The Chernobyl liquidator cohort consists of 61 017 individuals with an average cumulative dose of 0.109 Gy. An ERR/Gy of 0.41 (95% CI 0.05;0.78) was found for ischemic heart disease morbidity and 0.45 (95% CI 0.11; 0.80) for morbidity of cerebrovascular diseases, though the outcomes were not adjusted for recognized risk factors such as excessive weight, hypercholesterolemia, smoking, alcohol consumption, and others [39]. A recent publication reports a 34 % increase in stroke incidence after

a survey during 1994-2008 of a cohort of 90 957 radiologic technologists who worked with fluoroscopically guided interventional procedures [40]. In addition, mortality from stroke was also modestly elevated, although not statistically significant. No statistically significant excess risks of incidence or mortality were observed from any other cardiovascular disorders evaluated.

The Mayak cohort is of particular interest since it includes information both on mortality and morbidity, and information on confounding factors [41]. In 1948, the first nuclear energy enterprise in Russia, Mayak Plutonium Association, became operational. Since 1948 the Mayak personnel undergo regular routine medical examinations. In addition, every 3-5 years a more detailed examination is carried out in a specialized hospital. This examination system led to a unique archive of medical data, which was used to create the 'Clinic' medical-dosimetric database. Also, from a dosimetric point of view, the database is sound. Quite recently, Azizova and co-workers published a new study regarding incidence and mortality from ischaemic heart disease in an extended cohort of 22 377 Mayak workers first employed during 1948-1982 and followed up to the end of 2008 [42]. Mean total dose from external gamma rays was 0.54 ± 0.76 Gy for males and 0.44 ± 0.65 Gy for females. Risk analysis demonstrated a significant increasing trend in ischaemic heart disease incidence, but not mortality, with total dose from external gamma rays after having adjusted for non-radiation factors and dose from internal radiation (ERR/Gy = 0.1). ERR/Gy for ischaemic heart disease incidence in males was 6 times higher than in females. In addition, a significant increasing linear trend was observed in ischaemic heart disease mortality, but not incidence, with total absorbed dose from internal alpha radiation to the liver after having adjusted for non-radiation factors and doses from external gamma rays (ERR/Gy = 0.21). Mean total absorbed alpha particle dose to the liver owing to incorporated plutonium was 0.23 ± 0.77 Gy in males and 0.44 ± 2.11 Gy in females. In the same Mayak population, the incidence of and mortality from cerebrovascular disease was studied [43]. After correction for confounding factors, a significant increasing trend in cerebrovascular disease incidence was observed with increasing total external dose (ERR/Gy = 0.46 (95% CI 0.37; 0.57)). In addition, the authors show that the cerebrovascular disease incidence was significantly higher in workers with a total external dose greater than 0.1 Gy when compared to those exposed

to lower doses. Finally, having a young age during exposure was observed to be an important, aggravating modifier of radiation risk for incidence of cerebrovascular disease and stroke [44].
It must be noted that besides the classical vascular-related confounding factors, occupational studies have to deal with the "healthy worker" selection effect, similar to the "healthy survivor" selection effect in A-bomb survivors. The "healthy worker" selection effect refers to the fact workers who are healthier and have lower mortality and morbidity rates are selectively retained in the workplace, as such accumulating higher doses. One can adjust for this confounding by considering duration of employment as a confounding factor in the analysis, as done in the 15-country study [38].

Meta-analysis of epidemiological data. Taking all medium and low dose studies together, the Advisory Group on Ionizing Radiation AGIR reported in 2010 on a small but highly statistically significant excess relative risk for CVD mortality and morbidity of 0.09 ERR/Gy [3]. While heterogeneity between the studies is considerable, at least part of which is likely to be explained by confounding with unmeasured lifestyle factors in these groups, statistically significant excess risk can be detected at around 0.5 Gy. For doses < 0.5 Gy the importance of experimental studies was emphasized to provide experimental data complementary to the results of the epidemiological studies. Little and co-workers thereafter extended this meta-analysis [45]. They concluded that the estimates of population-based excess mortality risks for circulatory disease are similar to those for radiation-induced cancer. They noted that the assumption of LNT is reasonable since there is little evidence for non-linearity in the Japanese atomic bomb survivors and Mayak workers data. Nevertheless, it should be noted that Schöllnberger and co-workers advocate for the consideration and testing of other dose-response models for non-cancer effects [46, 47]. To conclude, the overall consensus of the abovementioned reports is that there is a significant elevated CVD risk for doses above 0.5 Gy [3] [48].

Epidemiology alone is not the answer. Epidemiological studies, as presented above, have limited statistical power to detect a possible excess risk of CVD following low dose exposure (0.5 Gy), due to the high background level of CVD in the population as a whole and the many potentially confounding

risk factors [3]. For example, it has been calculated that, if the excess risk is in proportion to dose, a cohort of 5 million people would be needed to quantify the excess risk of a 10 mSv dose [7]. Other factors that have an influence on epidemiological results are the distribution of the dose range, accuracy of dosimetry, the duration of follow-up after exposure and correct assignment of cause of mortality [49].

Although epidemiological studies have led to a better insight in radiation-related CVD risk, there are still many uncertainties that need to be clarified. Is there a threshold dose? Does the latency of CVD development depend on the dose? What are the sensitive targets in the heart and vasculature? Does exposure have an impact on CVD incidence or progression, or both? What is the impact of acute, fractionated or chronic exposure on risk estimates? For an accurate dose risk assessment, these questions need to be answered. Classical epidemiological studies, as described above, will not provide all the needed insight to answer these questions. A more targeted approach such as the integration of epidemiology and biology is required. For example, the assessment of subclinical endpoints by functional imaging in patients receiving radiotherapy will offer insight into the development and progression of CVD following radiation exposure [1], [49]. Also, the evaluation of cardiovascular biomarkers in radiotherapy patients may be useful. For instance, elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the blood [50, 51] have been shown to be predictive for heart failure and/or CVD mortality across a broad range of individuals [52]. Higher values of NT-proBNP were found in patients treated with radiotherapy for left-sided breast cancer compared to patients treated with other means [53].

In addition, radiobiological research is essential for understanding CVD risk specifically in the low dose region, < 0.5 Gy, for which epidemiological findings are suggestive and not persuasive. A thorough understanding of the biological and cellular mechanisms gathered through experimental studies is thus needed to complement the epidemiological findings and will be of benefit for an accurate risk estimation in the low dose region [54].

Molecular and cellular mechanisms underlying the observed radiation-induced CVD

The human and animal data indicate the important role of vascular injury and endothelial dysfunction, but also of myocardial remodeling,

degeneration and dysfunction in the pathogenesis of radiation-induced CVD [3] [55]. We will further focus on the endothelium as a critical target in radiation-induced CVD for the remainder of this review.

Endothelium is the safeguard of normal vascular functioning. The endothelium is a single layer of cells that lines the interior of the vascular system and thus has a strategic position between the blood and the surrounding tissues (Figure 2). Endothelial cells are involved in a wide range of physiological processes, such as the regulation of vascular tone, vascular permeability, blood coagulation/fibrinolysis and inflammation, which are needed to maintain proper vascular functioning [56]. Endothelial dysfunction is an important trigger of atherosclerosis, the underlying cause of the main CVD, and is considered one of the first indicators of future cardiovascular morbidity and mortality [57-60].
A dysfunctional endothelium is characterized by inflammation, DNA damage, oxidative stress, alterations of coagulation and platelet pathways, senescence and cell death, all of which being observed after radiation doses above 1 to 2 Gy as shown in may *in vitro* and *in vivo* studies [14, 61-63]. On the contrary, both protective and detrimental effects are reported for low dose exposure, suggesting that multiple mechanisms may influence radiation-induced atherosclerosis [49].

Inflammation. Endothelial expression of adhesion molecules plays an important role in recruiting inflammatory cells from the bloodstream into the vessel intima where they transform into foam cells, elements of the atherosclerotique plaque. Radiation has been shown to upregulate several of such adhesion molecules. For instance, exposure of endothelial cells to 5 Gy induced an increase in intercellular adhesion molecule 1 (ICAM-1) and E-selectin expression 6 h after irradiation [64]. Platelet endothelial cell adhesion molecule (PECAM-1), ICAM-1/2 and vascular cellular adhesion molecule 1 VCAM-1 were also observed to increase in mouse heart cells 10 weeks after local thorax irradiation with 8 Gy [65]. Interestingly, ICAM-1 and VCAM-1 remained upregulated 20 weeks after irradiation. Besides induction of adhesion molecules, cytokines such as IL-6 and IL-8, and other inflammatory molecules such as TGF-β, were shown to increase after high and moderate irradiation doses [66, 67]. In this context, the Japanese atomic bomb survivors' cohort also showed signs of a general increased

state of inflammation, with increased levels of IL-6 and C-reactive protein (CRP) [68].

DNA damage and apoptosis. Ionizing radiation is known to induce a wide range of DNA lesions, of which double strand breaks (DSB) are most severe, in a direct manner but also indirectly through the formation of reactive oxygen species (ROS) [69, 70]. Upon DNA damage, a response is initiated and the cells will activate cell cycle checkpoints which can slow down or stop cell cycle progression [71]. This gives cells the time to repair the damaged DNA or to prevent division when chromosomes are damaged or incompletely replicated. If the cells fail to repair the DNA, they can go into programmed cell death, apoptosis, or premature senescence (described below) [72]. In particular, DSB will lead to a high lethality of the affected cells.

Whereas high doses are known to induce apoptosis in endothelial cells [73], less is known about the effect of low doses. Subtle but a significant increase in DSBs were observed in HUVEC and EA.hy926 30 min after exposure to 0.05 Gy. In addition, irradiation with 0.05 Gy and 0.1 Gy induced relatively more DSB/Gy in comparison to 0.5 Gy and 2G y. Furthermore, a dose-dependent increase in apoptotic cells was observed, down to 0.5 Gy in HUVEC and 0.1 Gy in EA.hy926 cells [74]. Another study showed no increase in apoptotic endothelial cells after exposure to 0.2 Gy, but only after exposure to 5 Gy [75].

Oxidative stress, mitochondrial dysfunction and metabolic changes. Mitochondria are often regarded as the powerhouse of the cell by generating the ultimate energy transfer molecule, ATP. Mitochondrial dysfunction is part of both normal and premature ageing, but can contribute to inflammation, cell senescence, oxidative stress and apoptosis. Increasing evidence indicates that mitochondrial damage and dysfunction also occur in atherosclerosis and may contribute to the multiple pathological processes underlying the disease [76].

An increased accumulation of mitochondrial DNA damage was observed in several human fibroblast cell lines, after exposure to doses as low as 0.1 Gy [77]. Furthermore, functional impairment of mitochondria and alterations in the mitochondrial proteome were observed in isolated cardiac mitochondria from mice 4 and 40 weeks 2 Gy local heart

irradiation. Only a few alterations in the mitochondrial proteome and no effect on mitochondrial function was observed with 0.2 Gy [78], [79]. Finally, alterations in energy and lipid metabolism, and perturbations of the insulin/IGP-PI3K-Akt signalling pathway were suggested following proteomic studies on cell lines or cells isolated from mice after irradiation with doses ranging from 3 to 16 Gy [80], [81], [82].

Water radiolysis causes the formation of short-lived ROS (e.g. $^{\bullet}OH$, $HO_2^{\bullet}$, H_2O_2). However, following irradiation, cellular oxidative stress is observed after longer time periods due to an increase in the endogenous cellular production of ROS [83]. Mitochondria are believed to be the major source of these radiation-induced secondary ROS. For instance, Leach and co-workers have demonstrated that, between 1 and 10 Gy, the amount of ROS producing cells increased with the dose, which they suggested was dependent on radiation-induced propagation of mitochondrial permeability transition via a Ca^{2+}-dependent mechanism [84, 85].

It has been suggested that ROS are transferred from cell to cell by gap junctional and paracrine communication pathways in order to propagate radiation-induced biological effects at the intercellular level. This phenomenon is commonly referred to as the radiation-induced bystander effect. Multiple molecular signaling mechanisms involving oxidative stress, kinases, inflammatory molecules, and Ca^{2+} are postulated to contribute to this radiation-induced biological effects [86].

Premature senescence. The culprit of radiation-induced premature senescence is most likely severe irreparable DSB [87], but also accelerated telomere attrition has been suggested [88]. Furthermore, oxidative stress is seen as a major player in radiation-induced senescence and is involved in both radiation-induced DNA damage and accelerated telomere attrition [88-90].

In several *in vitro* studies, it has been demonstrated that ionizing radiation induces endothelial cell senescence, mainly with exposure to higher radiation doses [91-94]. An interesting study was carried out to examine the effect of chronic low dose rate irradiation (1.4, 2.4 and 4.1 mGy/h) during weeks [95, 96]. Exposure to 1.4 mGy/h did not accelerate the onset of senescence, whereas exposure to 2.4 mGy/h and 4.1 mGy/h did. Remarkably, a senescent profile was observed when the accumulated doses received by the cells reached 4 Gy. Proteomic analysis revealed a

role for radiation-induced oxidative stress and DNA damage, resulting in the induction of the p53/p21 pathway. Also, a role for the PI3K/Akt/mTOR pathway was suggested. From a related transcriptomic study, it was suggested that the observed premature senescence resulted from an early stress response with p53 signalling, cell cycle changes, DNA repair and apoptosis, observed after 1 week of exposure and an inflammation-related profile, observed after 3 weeks. In addition, a possible role of insulin-like growth factor binding protein 5 signalling, known to be involved in the regulation of cellular senescence, was suggested for the induction of premature senescence after the chronic low dose rate irradiation [97].
Oxidative stress, inflammation and cellular senescence are all consequences of the normal aging process, but are observed early in irradiated tissues, including heart, suggesting an intensification and acceleration of these molecular processes [55].

Need for experimental studies, especially in the low dose region. Since epidemiology alone can not provide conclusive data for the CVD risk < 0.5 Gy, further research is essential to elucidate the low dose effects on the cardiovascular system and the impact on CVD risk. This is, however, not straightforward due to the subtlety of low dose effects and the, most likely, little impact on clinical outcome. Besides the integration of epidemiology and biology, as mentioned above, pure radiobiological studies are needed. In contrast to cancer and hereditary effects, knowledge on the underlying biological mechanisms for other radiation-related non-cancer effects in the moderate and low dose range is very sparse and assumed to be different from high dose exposure. Therefore, research to understand the mechanisms is urgently needed (Multidisciplinary European Low Dose Initiative, http://www.melodi-online.eu/).

Conclusion

Over the last half century, RT has evolved to become one of the cornerstones of treatment for various types of cancers. It is estimated that more than 50 % of patients with cancer are treated with radiation therapy. Along with the development of novel chemotherapeutic agents, RT has revolutionized the prognosis of patients with various cancers. However, with a longer life-expectancy, treatment-related co-morbidity, like CVD, becomes an issue for cancer survivors. In addition, exposure to X-rays for medical

diagnostics are increasing dramatically at the present times. A pressing question is whether or not exposure to these very low doses can cause damage to our health. Below 0.5 Gy an increased risk cannot be evidenced by epidemiology alone, and mechanistic studies *in vitro* and *in vivo* focused on the elucidation of molecular signaling pathways are needed. In these studies attention should be paid, not only to dose, but also to dose-rate, fractionated exposures and radiation quality. In this way the current radiation protection system can be refined, making it possible to more accurately assess the cardiovascular risk in the low dose region. Finally, radiation-induced CVD, like CVD in general, is a progressive disorder, which may take years to decades to manifest. Therefore, experimental studies are warranted to fulfill the urgent need to identify non-invasive biomarkers for early detection and potential interventions – together with a healthy lifestyle – that may prevent or mitigate these adverse effects.

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

EU FP7 project Grant Agreement 295552

Coordination by Dr. M. Abderrafi Benotmane

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.

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 (131I) and radiocaesium (137Cs). Also here, prenatally irradiated subjects were followed over time, but findings are much less consistent and are subject to debate due to inconsistent dosimetry [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) are 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 attempt to illustrate the related cellular and molecular events modulated after exposure and most probably responsible for possible late cognitive and cerebrovascular diseases.

Human data

Cognitive effects of low doses

Medical irradiation during childhood

The study cohort consisted of the ANGIO cohort or hemangioma 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 to 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 standerdized 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 hemangioma. 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 FactCog (Perceive cognitive impairments) and HAD-D scores were more degraded if higher average radiation dose to the brain hemispheres than if higher radiation dose to other structures, whereas RALVT Decay recall and MOCA scores were more impacted by average radiation doses to the temporal lobes. Among all dosimetric parameters, no one had a significant correlation with the HAD-A and FactCog (perceived cognitive ability).

For 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 Perceive 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.

Chernobyl studies

Cognitive function is influenced by the radiation dose and age at exposure. The level of subjective distress caused by 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

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 hemorrhagic of the cerebrovascular diseases. When considering hemorrhagic 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 (negative) 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, this cohort the EOR/1GY was equal to 0.36 in survivors who were less than 10 years old at time of atomic bomb [19], what was 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 role 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 a role 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 consider that the very strong gradients of dose

near to borders of the radiation therapy fields, have as a consequence a very strong heterogeneity of dose within the cerebral arteries, whatever the average radiation dose.

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 postnatl IR).

Cognitive defects

Single radiaton exposure

To address persistent effects of external/internal irradiation at the embryonic or early postnatal stage, we subjected animals to a battery of behavioral 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 recapitulated in the lower activities, while irradiated animals also took longer to find a hidden platform in the Moris 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 function 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 behavior 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 behavioral paradigms (morris water maze strategies vs. spontaneous behavior), addressing different aspects of behavior. Importantly, by performing behavioral tests on both males and females, we could rule out a possible gender effect that could be attributable to the observed dose differences.

Even though slight differences in dose-responses were observed, we still can conclude that behavior 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.

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 behavior at the adult age of 2 and 4 months, preceded by irradiation at PND10.

The results obtained within CEREBRAD indicate a synergistically defective spontaneous behavior 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.

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.

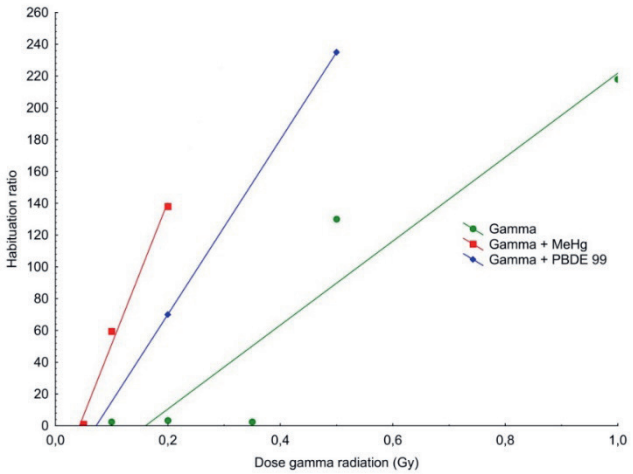

Figure 1. Habituation capability is the ratio between performance in spontaneous behaviour in a novel home environment taken from period 40-60 min and 0-20 min in 2-month-old NMRI male mice exposed on PND 10 to a single external dose of gamma-radiation (0, 0.02, 0.1, 0.35, 0.5 and 1.0) (green), a combination 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 need to focus on combining more than two agents to be more in line with our real life. Additionally, extrapolation of this reasearch to specific diets to investigate life style would emphasize other elements of our modern society that might contribute to radiation risk estimate.

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].

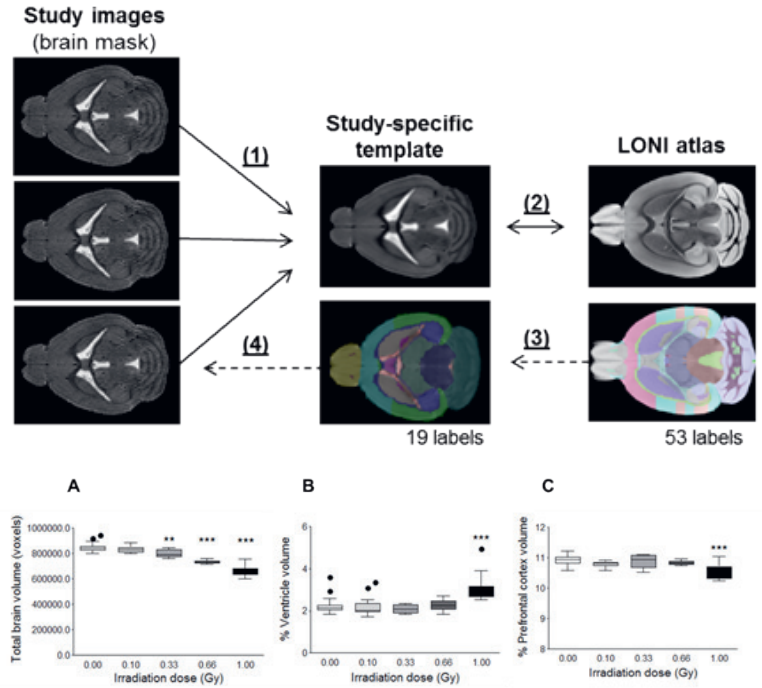

Figure 2: Brain weight changes induced by in utero exposure to radiation. (A) The total brain volume was decreased significantly from a dose of 0.33 Gy onwards. (B) When corrected for total brain volume, the volume of the ventricles was increased in the animals irradiated with the highest dose. (C) Decrease in relative frontal cortex volume in 1.00 Gy-exposed mice as compared to controls.

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 incresed 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 but also contradict 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 [31]. Furthermore, a previous study has shown that 20Gy and 40Gy brain irradiation produced an early permanent increase in BBB permeability in rats, while 10 Gy had no effect at all. 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].

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.

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 behavioral 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.

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 behavioral 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 behavioral 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 behavioral test battery and volumetric 3D T2-weighted magnetic resonance imaging (MRI). We revealed dose-dependent changes in cage activity, social behavior, 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 behavioral 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 behavioral 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 behavior.

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 behavior 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.

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 and cleanup workers as well as a hemangioma cohort treated with radiation below the age of 18 month were assessed for cognitive impairments. Although, 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 recommandations 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 need to focus on combining multiple agents/stressors (more than 2) to be more in line with our real life. Additionally, extrapolation of this research to specific diets to

investigate life style would emphasize other elements of our modern society that might contribute to radiation risk estimate.

- 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 analyzed molecular and cellular changes up to 24 weeks after irradiation. The presence of alterations at this time point strongly suggest that LD-IR might influence natural ageing and lays foundation for studies in aged mice. 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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