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RESEARCH ARTICLE

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RENEB – Running the European Network of biological dosimetry and physical retrospective dosimetry

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ABSTRACT

Purpose: A European network was initiated in 2012 by 23 partners from 16 European countries with the aim to significantly increase individualized dose reconstruction in case of large-scale radiological emergency scenarios.

Results: The network was built on three complementary pillars: (1) an operational basis with seven biological and physical dosimetric assays in ready-to-use mode, (2) a basis for education, training and quality assurance, and (3) a basis for further network development regarding new techniques and members. Techniques for individual dose estimation based on biological samples and/or inert personalized devices as mobile phones or smart phones were optimized to support rapid categorization of many potential victims according to the received dose to the blood or personal devices. Communication and cross-border collaboration were also standardized. To assure long-term sustainability of the network, cooperation with national and international emergency preparedness organizations was initiated and links to radiation protection and research platforms have been developed. A legal framework, based on a Memorandum of Understanding, was established and signed by 27 organizations by the end of 2015.

Conclusions: RENEB is a European Network of biological and physical-retrospective dosimetry, with the capacity and capability to perform large-scale rapid individualized dose estimation. Specialized to handle large numbers of samples, RENEB is able to contribute to radiological emergency preparedness and wider large-scale research projects.

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Introduction

Over the last years, the risk of a large-scale radiological event has markedly increased, not only due to possible accidents in nuclear facilities but particularly as a result of the threat of terrorist attacks against key facilities or civil targets in major cities. According to the judgement of the Central Intelligence Agency (CIA) in 2003, terrorist groups are willing to produce nuclear weapons and also are able to construct a radiological dispersal device (RDD) or an explosive RDD ('dirty bomb') (CIA 2003). The CIA assessment was that the use of such RDD could have consequences for health, environment and economy, but also could have political and social effects due to fear, injury and costly and time-consuming clean-up efforts, even if the factual damage of the RDD could be comparatively small. In 2010 the report 'Foresight into needs, possibilities and information requirements for the future' of the EU project 'MASH – Mass casualties and health care following the release of toxic chemicals or radioactive material' (Baker et al. 2010) declared it prudent to plan for the response to a mass emergency involving toxic or radioactive materials as such an eventuality may develop at a rate and reach a magnitude sufficient to impose a major crisis on society. In this context the establishment and maintenance of a European-wide coordination is emphasized with European Networks playing a key role in the development of preparedness planning to mitigate the impact of such mass emergencies. Now, in 2016, the official Communique of the Nuclear Security Summit 2016, held in Washington, testifies: 'The threat of nuclear and radiological terrorism remains one of the greatest challenges to international security, and the threat is constantly evolving' (Nuclear Security Summit 2016, Washington, Communiqué April 14, http://www.nss2016.org/).

It can be expected that malevolent attacks will occur without any advance warning and will target as many people as possible in order to cause maximum damage. Following such a scenario, the classification (or sorting) of persons according to their degree of injury (no need for immediate medical care/need for immediate medical care/medical help impossible) and exposure will be one of the initial steps for emergency management. While the triage of individuals will be done by physicians based on clinical signs and symptoms in the first instance, biodosimetry can support subsequent medical management by providing information about individually received doses to blood or to components of personal devices, such as smart phones or mobile phones.

The situation during large-scale accidents may differ from malevolent attacks, as often advanced warning of an event allows to distribute personal dosimeters and install local dosimeters for precise dose surveillance within the disaster area and close monitoring of the distribution of released radionuclides. However, even in such cases, the identification and assurance of the huge number of 'worried well' individuals, i.e. persons who are extremely distressed but have not actually received radiation doses likely to cause acute health effects, will be most important in order to prevent the healthcare infrastructure being overwhelmed and to avoid socioeconomic harm. Also in restricted accidents with an assumed smaller group of victims, the numbers of distressed persons can be enormous, as already was shown in the Goiania accident in 1987. This very severe radiological accident resulted in the death of four individuals due to overexposure and internal contamination (International Atomic Energy Agency [IAEA] 1988) (http://www-pub.iaea.org/mtcd/publications/pdf/pub815_web.pdf). Additionally, 249 persons were identified as contaminated with radioactive caesium, however, in 120 cases only the clothing was contaminated but a total of 112,800 persons felt affected and needed to be monitored for contamination. In this context, it was also shown that anticipatory stress associated with a potential exposure to ionizing radiation resulted in a level of stress similar to that from actual exposure to ionizing radiation (Collins & de Carvalho 1993). Based on the expertise from the Goiania accident, the following recommendation was given by the IAEA: '… cytogenetic dosimetry is an extremely useful technique for estimating the external whole body radiation dose and the inhomogeneity of dose of the irradiated person. It is helpful in providing useful information to the physician responsible for diagnosis and prognosis. It is suggested that national authorities review their emergency plans to ensure that laboratories capable of carrying out this work are available, either internally or by international cooperative arrangements. Intercomparison programmes should be carried out to establish a desirable level of coherence among the different laboratories' (IAEA 1988).

Biological dosimetry and EPR/OSL dosimetry was also conducted after the Chernobyl accident, e.g. for inhabitants and visitors of contaminated sites, evacuees and liquidators (Stephan & Oestreicher 1989; Silini & Gouskova 1991; Verschaeve et al. 1993; European Commission [EC] 1996; Maznik et al. 1997) and also for people living in European areas with comparably high fallout measurements due to contaminated rain (Stephan & Oestreicher 1993). Following the Fukushima Daiichi nuclear power station accident, biodosimetry was performed for restoration workers (Suto et al. 2013) and also for individuals who travelled to contaminated areas after the accident (Lee et al. 2012). However, in all these studies biodosimetry was performed by single laboratories and the number of examined persons was rather limited.

In each context, biological dosimetry (based on, e.g. cytogenetic assays) and retrospective physical dosimetry (based on EPR/OSL techniques) has been shown to be an essential tool to estimate the individually received (blood or personal device) dose without being influenced by temporal variations in blood counts or confounding factors such as chemical agents or psychogenic reactions. Based on the results of biological and personalized physical dose estimation, people needing extensive medical care due to severe irradiation can be identified and distinguished from individuals with injuries who have not received high doses of ionizing radiation (Turai et al. 2001; Voisin et al. 2001; Roy et al. 2007; Romm et al. 2011; Jaworska et al. 2015). In those disastrous situations, independently of an accidental or malevolent background, the reassurance of unsettled and anxious people is of high importance. It was shown repeatedly that psychological consequences of radiological disasters are basically connected to a perceived exposure, that in most cases clearly differ from a

calculated dose, based on measurements of the environment (Collins & de Carvalho 1993; Bromet et al. 2011; Bromet 2012). The success to reassure people to readopt a normal life will, to a great part, depend on the credibility of the authorities. To address people on a personal level by offering individualized dose estimation can clearly help to minimize psychological stress and regain trust, even if such an approach, on a large scale, will take time (over months) and probably will have to be performed based on a priority action plan. However, according to practical experiences of experts working in biodosimetry laboratories and involved in several small accidents, anxiety and fear very often do not necessarily start immediately after an assumed incident but also weeks or even months later. Thus, in the long run, biological dosimetry and personalized dosimetry will help to reduce socioeconomic harm in the affected country.

In a large-scale radiological accident or terrorist incident, the number of people that may need to be screened could easily exceed the capacity of a single or even a number of laboratories. As a consequence, biodosimetry networking has been recognized as a sensible and important emergency response strategy in several regions of the world (Turai 2000; Wilkins et al. 2008, 2011). Under the patronage of the IAEA, a regional network of six laboratories has been set up, that covers the whole of Latin America. At national levels, a similar initiative has been promoted in the USA by the US Government and networks have also been established in Japan and Canada (Mitsuaki et al. 2007; Miller et al. 2007), while in Europe, a tri-partite memorandum-of-understanding for mutual assistance between France, Germany and the United Kingdom became effective in 2004. However, this European agreement applied only for serious radiological events in these three countries and, with only one laboratory per country, the total capacity was also extremely limited. On a global level, the World Health Organization (WHO) BioDoseNet was set up (Blakely et al. 2009) and IAEA also includes biodosimetry laboratories in its Response and Assistance Network (RANET) (IAEA 2013). Currently, the best methods of biological dosimetry are based on the analysis of chromosomal damage (dicentric chromosomes, micronuclei and translocations) in peripheral blood lymphocytes and electron paramagnetic resonance in bone and tooth enamel (Lloyd et al. 2000; IAEA 2002, 2011; Blakely et al. 2005; Fattibene & Wojcik 2009; Romm et al. 2009; Willems et al. 2010; Ainsbury et al. 2011; Beinke et al. 2013; Wojcik et al. 2014). These methods have been validated in a number of small-scale radiation accidents and have been shown to be reliable tools to detect an absorbed individual blood dose of radiation with enough accuracy. During the last years, more biodosimetric methods have been identified and used, such as premature chromosome condensation (PCC), fluorescence in situ hybridization (FISH) and gamma-H2AX foci (Terzoudi & Pantelias 1997; Fattibene & Wojcik 2009; Horn et al. 2011). In addition, the electron paramagnetic resonance (EPR) and optically stimulated luminescence (OSL) on personal objects (portable electronic devices, chip cards), although not a typical biodosimetric method, has been shown to have the potential to be an excellent supplement especially if irradiation is heterogeneous (Woda et al. 2009; Trompier et al. 2010). As has been shown in the TENEB (Towards a European Network of Excellence in Biological Dosimetry) project, one or more of these methods are established in many European laboratories (Wojcik et al. 2010). However, networking for these techniques, which would consolidate the standardization and harmonization of the assays, was lacking. In 2009, all existing European laboratories with considerable experience in biological dosimetry were identified and listed with the help of the TENEB survey (www.andrzej.se/teneb/). Many of these laboratories had expressed their interest in a long-term commitment to contribute to a European biodosimetry network. These laboratories formed the nucleus for the RENEB (Realizing the European Network of Biological Dosimetry) project.

The purpose of RENEB was to use the existing knowledge and laboratory capacities, available in European countries to set up a European network of biodosimetry.

In 2012, a total of 23 organizations from 16 European countries joined forces and started to realize this project, in order to guarantee the highest efficiency in processing and scoring of biological and personalized inert samples for fast and reliable dose estimations on an individual level to support EU emergency management (Kulka et al. 2012).

Results

RENEB project partners ('starting members')

The basis for the identification of appropriate network partners was the TENEB survey (www.andrzej.se/teneb/) (Wojcik et al. 2010), listing all existing European laboratories with considerable experience in biological dosimetry. Many of these organizations had expressed their interest in a long-term commitment to contributing to a European biodosimetry network. Additional partners joined from the EU project 'MULTIBIODOSE' (http://www.multibiodose.eu) and/or were members of Working Group 10 'retrospective dosimetry' of the EURADOS association (www.eurados.org), and thus have experience in the development and application of biodosimetric tools. In total, 23 organizations from 16 European countries built the RENEB consortium at the start of the project in 2012 (Kulka et al. 2012; Voisin et al. 2012). Members comprised Civilian and Military Research Institutes, Civilian and Military Hospitals, National Health Institutes, National Research Institutes, National Radiation Protection Authorities and Universities (Table 1). Most of the partners had research experience but also practical experience in handling radiation accidents, and a number of them had specially defined missions to undertake national tasks linked to radiation protection and biological dosimetry with the status of an official national biodosimetry laboratory. Due to the direct links to many national authorities and the high number of partners who had signed the long-term commitment, it was hoped that the project would result in an operational, legally defined Biodosimetry network. Other partners, mainly from research centres and universities, brought in academic knowledge and practical experience with emerging technologies showing promise for application in biological dosimetry, and thus provide further support for the sustainability of the

Table 1. RENEB consortium partners and their contribution to the network in 2012.

Participant	Country	Assays[a]	Contact lab[b]	Commitment[c]	Involvement[d]
1 BfS	Germany	✓	✓	✓	✓
2 BIR/UULM	Germany	✓	✓	✓	✓
3 CEA	France	✓			
4 ENEA	Italy	✓			✓
5 HMGU	Germany	✓			✓
6 HPA	United Kingdom	✓	✓	✓	✓
7 ICHTJ	Poland	✓		✓	
8 INSP	Romania	✓		✓	
9 IRSN	France	✓	✓	✓	✓
10 ISS	Italy	✓	✓		✓
11 ITN	Portugal	✓	✓	✓	✓
12 LAFE	Spain	✓		✓	
13 LUMC	The Netherlands	✓[e]			✓
14 NCRRP	Bulgaria	✓		✓	
15 NCSRD	Greece	✓			
16 NRIRR	Hungary	✓		✓	
17 NRPA	Norway		✓		✓
18 STUK	Finland	✓[e]	✓	✓	✓
19 SU	Sweden	✓			✓
20 UAB	Spain	✓		✓	✓
21 UGent	Belgium	✓		✓	✓
22 UNITUS	Italy	✓		✓	✓
23 SERMAS	Spain	✓	✓	✓	✓

[a]Assays for biological or retrospective physical dosimetry; [b]National biological or physical dosimetry lab or link to national/regional lab; [c]Long-term commitment to contribute to biological dosimetry; [d]Involvement in complementary projects, associations or networks; [e]not actively involved in RENEB after 2014.

network. It should also be stressed that several partners are actively involved in quality assurance activities such as developing standards for biological and physical-retrospective dosimetry for the International Organization for Standardization (ISO) (Voisin et al. 2002; Roy et al. 2012; ISO 19238 2004; ISO 21243 2008; ISO 13304 2013; ISO 17099 2014) and this ensures high quality standards and quality management within the network. Three of the partners (BfS, IRSN, HPA) had experience in networking within the tri-partite memorandum of understanding for mutual assistance in case of a serious radiological event (but restricted to the related countries) and several of the 23 partners were involved in the biological network of the WHO, BioDoseNet (Blakely et al. 2009). Additionally, many of the laboratories were involved in education and training activities, such as intercomparisons, laboratory staff training or exchange initiatives. The RENEB consortium partners in 2012 and their contribution to the network are shown in Table 1.

Despite signing a long-term commitment within the frame of the TENEB project, some organizations decided to withdraw from this obligation, closed their laboratories (LUMC, STUK) and finalized their active involvement in networking. At the end of the project (December 2015), 21 from originally 23 partners from 14 European countries were involved in the project.

Operational network set-up

The operational set-up is based on three main pillars, (1) the operational basis, (2) the basis for education, training and quality assurance, and (3) the basis for network development. All three components are closely connected and act in a coordinated way (Kulka et al. 2015).

Operational basis

An 'Operational Network Basis' was set up with five biodosimetric tools, the dicentric assay (DCA), the FISH assay (FISH), the micronucleus assay (MN), the premature condensed chromosome assay (PCC) and the gamma-H2AX assay. In addition, the retrospective physical dosimetric tools electron paramagnetic resonance (EPR) and optically stimulated luminescence (OSL) were included. While one or more of these methods were already established and used for individual dose estimation in many European laboratories, standardization and harmonization was needed to consolidate the techniques for networking.

Intercomparisons

The specific needs and potential for improvement for both techniques and partners were principally identified by two intercomparison exercises. While the first of the exercises was restricted to the network partners, the second intercomparison was open also for potential new members and with regard to the dicentric assay and micronucleus assay also for networks outside Europe. Details and outcome of the intercomparisons are shown in independent articles, included in this special issue, for the dicentric assay (Oestreicher et al. 2016), the FISH assay (Barquinero et al. 2016), the micronucleus assay (Depuydt et al. 2016), PCC assay (Terzoudi et al. 2016), the gamma H2AX assay (Barnard et al. 2014; Moquet et al. 2016), and for physical dosimetry methods (Trompier et al. 2016b), as well as in Fattibene et al. (2014) and Bassinet et al. (2014).

Besides the identification of needs for harmonization and standardization, valuable information about shipment of samples was provided by the intercomparisons. This included information about shipment time, temperature gradient of the samples during the shipment, a possible additional dose received during the shipment and other, non-foreseeable incidents. Details about the shipment within and outside the EU are also given in the dicentric report, included in this special issue (Oestreicher et al. 2016).

Accident simulation exercise

In addition to the intercomparisons, a virtual two-part accident simulation exercise was performed over a period of 27 weeks. In contrast to the intercomparisons, this exercise was not split by assay. Instead, each participant had to evaluate the dosimetric readings derived from every tool in an attempt to gain knowledge about the possibilities and limitations of each tool and learn how the results should be interpreted. The main aims of the exercise were, however, to test the network activation procedure by allowing each partner to send an alerting e-mail about a fake radiation emergency, and to collect the responses about the availability of all the partners and their current capacity to handle samples. After responding to the alerting e-mail, the second part of this exercise comprised receipt of a panel of arranged irradiation doses for each of several potential victims. Partners had to classify these persons correctly according to criteria that included information about the individual dose estimates

Table 2. RENEB key information about the operational network performance.

Assay	Sample type	Time frame for sample collection[a]	Classification of individuals: Green/Orange/Red (<1 Gy/1–2 Gy/>2 Gy) Time from sample receipt to result[b]	RENEB capacity (analyzed persons per week)	Detection range (Gy)	Robustness[c]	Implication of individual sensitivity[d]	Stored material: Type and time range for further analysis[e]
Dic	blood	days - months	52 hours	ca. 1000	0.1–5	high	yes	fixed cells, slides: years
MN	blood	days - months	75 hours	ca. 400	0.2–5	medium	yes	slides: years
FISH	blood	days - years	120 hours	ca. 100	0.3–4	medium-high	yes	fixed cells: years
PCC	blood	hours - months	2–8 hours	ca. 50	0.1–20	high	yes	frozen lympho-cytes, fixed cells, slides: years
γH2AX	blood	days	3 hours	ca. 1800	0.2–5	low	?	fixed cells, slides: up to one year
EPR	PED[f]	hours - years	<1 hour	ca. 770	>1	high	no	glass: years
OSL	PED[g]	hours - months	<1 hour	ca. 500	>0.1	high	no	resistors: weeks

[a]Time between irradiation and sample collection; [b]Time from arrival of a sample in the laboratory until the classification of a person, without time for transport/shipment; [c]Robustness: high, little influence of disturbing factors; medium, some influence of age, smoking, other agents; low: large influence of other agents and factors; [d]Considering the individual sensitivity of a person; [e]Type of the stored material and time frame to perform further analysis; [f]PED, personal electronic device (glass touchscreen, e.g. smart phone); [g]PED, personal electronic device (resistors from circuit board, e.g. mobile or smart phone).

from different assays and allowed for discrimination between whole body and partial body exposure and the time of the irradiation. The partners were trained in handling large data sets; in addition, the repeated collection of information gave an important insight about the capacity of each lab to the state of preparedness of the network. Details and outcome of this accident simulation exercise are described in this special issue (Brzozowska et al. 2016). Key information about the operational network performance is given in Table 2, based on the findings of the accident simulation exercise (Brzozowska et al. 2016) and on a survey amongst RENEB partners (Monteiro Gil et al. 2016).

Full information about the activities of the operational basis are given in the article by Wojcik et al. (2016).

Education, training and quality assurance

In the event of an accident involving a large number of potentially irradiated people, the response kinetics of the network depend tightly on the efficiency of all labs involved in the response, not only individually but also in coordination. The best operational conditions will result from ensuring the preparedness of the network in advance of any event. Such provision includes homogenization of procedures within the individual laboratories, maintenance of qualified staff, knowledge of the laboratory capacity in crisis situations and common training through implementation of periodic exercises and intercomparisons.

Therefore, the basis for 'education, training and quality' is a significant component of RENEB, and has large influence on the performance of the whole network. This includes the 'Operational Basis' dealing with established biodosimetry assays, and the 'Basis for Network Development', providing the basic principles to include new methodologies and new partners. The applied quality standards conform with international standards including ISO 19238: Radiation Protection – Performance criteria for Service Laboratories performing Biological Dosimetry by Cytogenetics (ISO 19238, 2004), ISO 21243: Radiation protection – Performance criteria for laboratories performing cytogenetic triage for assessment of mass casualties in radiological or nuclear emergencies – General principles and application to dicentric assay (ISO 21243, 2008) and ISO 17099: Radiation Protection – Performance criteria for laboratories using the cytokinesis block micronucleus (CBMN) assay in peripheral blood lymphocytes for biological dosimetry (ISO 17099, 2014). In this regard, RENEB takes advantage of the fact that several partners are actively involved in global quality assurance and in the development of the ISO standards for biological dosimetry (Voisin et al. 2002).

Within the network, measures have been determined and actions implemented to promote a comparable high performance of the partners and quality assured integration of potential new members. The actions comprise practical training, seminars, and training cooperation with existing nuclear safety/radioprotection programmes or with European radiation protection platforms.

Training activities

Practical training events concerning quality and efficiency of the performance were carried out to correct individual shortcomings and networking problems. According to the particular needs of each partner, the training was organized by RENEB partners with appropriate expertise. In addition, training was also organized for partners who wished to widen their laboratory assay spectrum by including another assay into their own operational toolkit.

In addition to the practical training, seminars on statistics, international standards of the Organization for Standardization (ISO standards) and quality assurance and quality management (QA&QM) were given. The seminars on statistics, quality and metrology and theoretical lessons were run in parallel with applied table-top exercises. The course topics addressed basic statistical aspects related to the establishment of dose-effect calibration curves and to individual blood dose estimation, the need of a quality system for the traceability and management of particular activities, and especially practical metrology aspects. In another seminar focussing on methodology of the various techniques, a common QA&QM manual was discussed in order to identify and fix the specific QA&QM criteria for each assay.

The QA&QM programme was jointly developed by the consortium with the purpose to define the use of the

different biological and/or biophysical assays as elements of the operational basis of the RENEB network. While parts of the information from this document are contained in other international guidelines and scientific publications, e.g. IAEA Technical Reports Series on Biological Dosimetry, the RENEB document covers the full range of the assays that are included in the network. As such, the document is of primary importance for sustaining the credibility of the network partners and the readiness of the network to respond to requests from first responders, national and European authorities and Research and Development (R&D) agencies.

A long-term training programme was developed to ensure adequate organization of training for members for dose assessment in large-scale accidents and to integrate new partners in a quality assured manner. The training programme includes periodic intercomparisons that are mandatory for RENEB partners, but will be open for non-partners as well. Successful performance of the laboratory will qualify the partner to be included in dose reconstruction in real emergency situations and to participate in R&D projects.

Besides the RENEB-internal activities, training cooperation with European nuclear safety/radioprotection courses and/or European radiation protection platforms have been initiated. Informal contacts have been taken with some training structures in Europe (e.g. ENSTTI in France) and European programmes developing strong action in this field (e.g. MELODI and CONCERT-European Joint Programming). The seminar on statistics, ISO standards and QA&QM was given in cooperation with ENSTTI and a course focussing on cytogenetic assays and EPR/OSL for individualized dose estimation has been jointly developed by RENEB and EURADOS and will be open to interested scientists.

A virtual crises exercise that was complementary to the previous accident simulation exercise within the operational basis of the network was performed. The purpose of the exercise was to test the link between the national authority and the RENEB member(s), who act as national reference laboratory(s).

New member qualification

A decision table for providing information to the network on the competence level of the candidate partners and to inform these potential partners on the minimum requirement to join the network was developed and is distributed to laboratories and institutions who express an interest in becoming a network member. Additionally, a questionnaire to evaluate the technical and operational capacity of the new members has been created in order to ensure network information is current and up to date.

More considerations and findings with impact on Quality Assurance concern the impact of uncertainty on triage category (Ainsbury et al. 2016a), and lessons learned by the intercomparisons as described in the article by Trompier et al. (2016a).

All details about these activities in education, training and quality assurance are provided in the.+ article by Gregoire et al. (2016).

Network development

The established network was never designed to be a static or closed consortium, the sustainability will rather depend on openness and the ability to react in a flexible way towards new situations. This implies the awareness of new technological developments as well as dealing with the loss and gain of network members. It was a major goal of the RENEB consortium to actively identify potential new partners ('candidate partners') and promising techniques ('candidate techniques') already during the installation of the network. In this regard, a strategy was prepared to actively identify, evaluate and if appropriate integrate new partners and new techniques with potential for biodosimetry in RENEB. The recruiting strategy resulted in the application of eight new laboratories who became RENEB candidates and several new methods, including -omics technology and molecular-biological approaches, as well as some further developments of established techniques that became candidate methods. The spectrum of new techniques and the performance of new partners were evaluated, and integration steps were developed and implemented in close collaboration with Education and Training (E&T) activities.

Identification, testing and validation of new technologies

A four-point strategy was designed and applied to attract new 'candidate' techniques in biodosimetry. The strategy includes: (1) to attract people to RENEB and make them reporting new techniques, e.g. at scientific meetings, (2) to attract new techniques through the RENEB website including a 'Reporting sheet for new techniques' for a first contact, (3) direct request to RENEB members to suggest new technologies, and (4) literature search for new technologies in biodosimetry. At the beginning, a direct contact to scientists working with a promising technique was most successful. However, with the increasing awareness of the network and degree of familiarity, people used the reporting sheets to introduce particular techniques or improvements. For the evaluation and integration of potential new technologies in the network, a roadmap was elaborated. The workflow includes (1) official reporting of a suggested new method, or extensive further development of an existing technique for biodosimetry within RENEB through the reporting sheet, (2) evaluation of the suggested methods in close cooperation with the operational basis and basis for E&T and QA under consideration of fixed criteria, (3) invitation of candidate techniques to participate in intercomparisons, and (4) decision of the network about the integration based on the performance

The developed tools were applied to identify some promising techniques during the last 4 years and several candidate methods were suggested to the RENEB consortium and presented at the annual RENEB meetings. The methods included different types of the gene expression assay (qPCR, array based technology), thermoluminescence of mobile phone display glass, Raman spectroscopy and further developments of established methods as dicentric and PCC assay by combining them with centromere and telomere staining (M'kacher et al. 2014, 2015; Karachristou et al. 2015; Abend

et al. 2016). Some of these methods were included in RENEB intercomparisons and results are published in this special issue (Manning et al. 2016).

In December 2015, an additional intercomparison of new methods for biodosimetry was performed, in which the performance of established assays already included in RENEB and candidate methods was directly compared. The outcome of this exercise is published in this special issue under the title 'Validation and testing of new RENEB retrospective dosimetry techniques' (Ainsbury et al. 2016b).

Identification, evaluation and integration of new network partners

To attract candidate partners to RENEB a five-point strategy was developed: (1) to attract people to RENEB and encourage them to report their laboratory's capabilities, e.g. at scientific meetings or meetings related to emergency preparedness (e.g. from IAEA, WHO), (2) to attract new partners through the RENEB website including a 'Reporting sheet for new members', (3) suggestion of new partners by third parties, (4) to contact appropriate laboratories by national health authorities from EU countries using an information letter (developed for this occasion), and (5) to screen current publications for possible candidates. Again, the direct contact to scientists and presentations about RENEB at meetings proved to be the most effective way to attract individuals and laboratories.

In cooperation with the basis for Education, Training and Quality, formal criteria for the integration of candidate partners were elaborated. The main criteria are: (1) description of the biodosimetric methods used, (2) quality assurance and quality control procedures applied in the laboratory, (3) information about assay capacities (samples per week), (4) information about sample processing time (days to result), (5) participation and performance in intercomparisons, and (6) information about the staff levels.

At the end of 2015, eight candidate members showing a serious interest to join the RENEB network were identified and these groups have started the integration process. An overview of these candidate members is given in Table 3.

In summary, RENEB has proved to be a dynamic and open network. The campaign to scout for new partners was effective with eight laboratories showing an interest to actively participate once the network is established. All eight candidates participated in RENEB exercises (2nd laboratory intercomparison and accident simulation exercise) and presented their institutions to the RENEB consortium at one of the annual meetings.

Sustainability of the network

Integration in European and international radiation emergency and preparedness

First and foremost, RENEB was established to contribute to radiological emergency preparedness and response. Since the start in 2012, the network has been accepted as a partner by international emergency and preparedness organizations such as WHO and IAEA. Representatives of RENEB contributed to WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) (14th WHO REMPAN meeting, Würzburg, Germany, 2014) and WHO BioDoseNet Coordination meetings (Leiden, the Netherlands, 2013; Hanover, NH, 2015), as well as to meetings of IAEA addressing biological dosimetry [First research Coordination Meeting (RCM) of the IAEA-CRP on 'Strengthening of Biological Dosimetry in IAEA Member States: Improvement of current techniques and intensification of collaboration and networking among the different institutes', Vienna, Austria, 2012; IAEA/NIRS Technical Meeting 'Future of Biodosimetry in Asia: Promoting a regional Network', Chiba, Japan, 2015]. Both institutions were directly involved in the set-up of the network by acting as members of the RENEB Advisory Board. This cooperation is intended to be continued, conceivably in form of RENEB honorary members. For the international perception of the network in emergency preparedness and response, the 2nd RENEB intercomparison was of utmost importance. The joint exercise with biodosimetry partners from Latin America, North America, Asia, Africa and the involvement of laboratories from the WHO BioDoseNet and IAEA RANET strengthened the acceptance of the European network as a partner in the global Emergency and Preparedness Response. It also demonstrated that networking in biodosimetry is possible on a global level and a valuable, ready-for-service tool for emergency preparedness and response.

Integration in European radiation research initiatives

Beside the usefulness of the network for emergency response, it is obvious that the capacities of the RENEB network laboratories, the harmonization of methodologies in these laboratories and the technological advancements can serve as a resource for large research projects as well. Therefore, in order to guarantee a long-term sustainability of RENEB, joint research interests within the network partners and in particular with EU radiation research programmes were identified and the benefits of RENEB for European radiation research were outlined. At the beginning of 2016, the

Table 3. RENEB candidate members as of December 2015.

Organization	Acronym	Country	Background
Belgian Nuclear Research Centre	SCK•CEN	Belgium	Research Centre
Laboratori Nazionali di Legnano	INFN	Italy	Research Centre
Army Medical & Veterinary Research Centre	AMVRC	Italy	Army Medical and Veterinary Research Centre
Forschungszentrum Jülich	FZ Jülich	Germany	Research Centre
University of Sevilla	US	Spain	University
Dublin Institute of Technology	DIT	Ireland	Institute of Technology
Radiation Protection Centre	RPC	Lithuania	Radiation Protection Centre
French Army Biomedical Research Institute	IRBA	France	Army Biomedical Research Institute

RENEB network is well known by the radiation research community in Europe and beyond. Close links to the European Radiation Protection platforms EURADOS (http://www.eurados.org), focussing on dosimetric aspects (Rühm et al. 2014, 2016), MELODI (http://www.melodi-online.eu), focussing on low dose effects (Salomaa et al. 2013), NERIS (http://www.eu-neris.net), focussing on emergency preparedness, and ALLIANCE (http://www.er-alliance.eu), focussing on radioecological aspects, have been developed and the integration status of the RENEB network in the European Radiation Research Area has been shown to be excellent. The next steps are already initiated to integrate RENEB in CONCERT – the European Joint Programme (EJP) for the Integration of Radiation Protection Research, here, RENEB is presented as an 'analytical platform for emergency and scientific research'. Of major importance for the EJP are the Strategic Research Agendas (SRA) of the radiation research platforms, as this is the basic instrument to identify research needs and to determine priorities that should be stimulated and supported by European and national programmes. In this regard, it is encouraging that the topic 'biodosimetry' is addressed in the SRA of MELODI (http://www.melodi-online.eu/sra.html) and EURADOS (http://www.eurados.org/en/news/eurados_strategic_research_agenda). Both platforms have explicitly included the network in their SRA, as an infrastructure for retrospective dose assessment in research studies and for emergency preparedness.

RENEB SRA

As RENEB developed, an own SRA became more and more important. A draft Strategic Research Agenda for RENEB 2016+ was developed and priorities were identified regarding how to proceed after the end of the funded period of the project. The SRA addresses (1) information about the partner organizations and applied assays, (2) the different tools for dose assessment, included in the network and their specific field of application, (3) the benefit of RENEB outputs for emergency preparedness and response as well as for radiation research, with special focus on Education & Training and Quality Assurance & Management, (4) a vision at 2030 'Towards a better individual dose estimation', (5) a strategy for how to meet this vision, (6) aspects of sustainability and conclusions, and (7) priority stetting for the next steps. Development of the SRA was a major step towards supporting the long-term sustainability of the network and to facilitate the integration process of RENEB within the European radiation research community. It is intended that the SRA will always have the status of a 'draft document' and will be further developed on a regular basis.

RENEB Memorandum of Understanding

Various legal options for the formal structure of the future network have been compiled. A legally non-binding agreement in the form of a Memorandum of Understanding (MoU), signed by as many partners and candidates as possible, was identified to be the most appropriate way to start the transformation of the time-limited project into a formal structure of a sustainable network. A MoU, based on the existing tripartite network of France, Germany and the UK, was expanded and adapted to the needs of the RENEB network. The aim was provision of assistance to all EU states, including those without a national capability. In January 2016, from 30 organizations formally participating in RENEB, a total of 26 have signed the MoU, as shown in Table 4. The MoU thus forms the nucleus of a growing infrastructure, combining high quality standards in the application and

Table 4. RENEB partners with a signed Memorandum of Understanding (MoU) as of January 2016.

Acronym	OM[a]/CM[b]	Organization	Country
BfS	OM	Bundesamt für Strahlenschutz	Germany
CEA	OM	Commissariat à l'Energie Atomique et aux Energies Alternatives	France
ENEA	OM	Agenzia Nazionale per le Nuove Tecnologie, LÉnergia e lo Sviluppo Economico Sostenibile	Italy
ICHTJ	OM	Institut Chemii i Techniki Jadrowej	Poland
INSP	OM	Institutul National de Sanatate Publica	Romania
IRSN	OM	Institut de Radioprotection et de Sûreté Nucléaire	France
ISS	OM	Istituto di Superiore di Sanità	Italy
IST	OM	Campus Tecnológico e Nuclear, Instituto Superior Técnico, Universidade de Lisboa	Portugal
LAFE	OM	Fundacion para la Investigation del Hospital Universitario la Fe de la Comunidad Valenciana	Spain
NCRRP	OM	National Center for Radiobiology and Radiation Protection	Bulgaria
NCSRD	OM	National Centre for Scientific Research Demokritos	Greece
NRPA	OM	Norwegian Radiation Protection Authority	Norway
OSSKI	OM	National Public Health Centre - National Research Directorate for Radiobiology and Radiohygiene	Hungary
PHE	OM	Public Health England	United Kingdom
SERMAS	OM	Servicio Madrileño de Salud - Hospital General Universitario Gregorio Marañón	Spain
SU	OM	Stockholm University	Sweden
UAB	OM	Universitat Autonoma de Barcelona	Spain
Uni Gent	OM	Universiteit Gent	Belgium
UNITUS	OM	University of Tuscia	Italy
FZ	CM	Forschungszentrum Jülich	Germany
INFN	CM	Laboratori Nazionali di Legnaro	Italy
AMVRC	CM	Army Medical and Veterinary Research Center	Italy
SCK-CEN	CM	Belgian Nuclear Research Center	Belgium
RSC	CM	Radiation Protection Center	Lithuania
DIT	CM	Dublin Institute of Technology	Ireland
US	CM	University of Sevilla	Spain

[a]Original member; [b]former Candidate member.

validation of biomarkers and maintenance and further development of scientific and technical competence.

An important aspect of preparedness for mass casualty radiological/nuclear events at a national or international scale is the need for functional efficiency of the biodosimetry network. Besides an appropriate network structure and a legal basis, well-established communication channels and logistic procedures to handle hundreds or more samples in an efficient and timely manner had to be identified and assured to be able to provide mutual assistance between many biodosimetry laboratories.

Funding strategies

Financial issues and funding mechanisms are of utmost importance for the sustainability of the RENEB network. In the current European organizational framework, the creation of technology platforms and networks of institutions (laboratories, research centres, universities, national public bodies and in some cases companies) is encouraged by the European Commission and, in the initial phase, funded to some extend (such as RENEB) in order to develop structure and to aggregate the relevant institutions and experts. However, in the medium- and long-term, such platforms and networks must be self-sustainable, i.e. must not depend on funding from the European Commission. For a future operational and scientific platform, there are different options for funding sources. The following additional funding options have been identified by the consortium for further consideration: (1) membership fees, (2) intercomparison exercises, (3) workshops & training courses, (4) annual meetings with a registration fee, (5) partner in calls of EJP CONCERT and (6) partner in other HORIZON 2020 calls (EURATOM, SECURITY, etc.).

Dissemination activities

The awareness level of the network and broad knowledge about its activities and capability is essential for the long-term-sustainability of RENEB. Therefore, efforts were focused on dissemination activities to enhance the visibility of RENEB on national, European and global levels.

In order to promote RENEB, the consortium created a public web page (www.reneb.eu) and published three bulletins, presenting the RENEB network and progress of the work. The bulletins are available on RENEB external web page under 'Publications' chapter (http://reneb.eu/publications.html) and are distributed as paper copies, e.g. at international radiation emergency response and radiation protection meetings.

Up to now, consortium partners published 24 peer-reviewed, scientific papers with reference to the RENEB project with this special issue 'Networking in biological and EPR/OSL dosimetry: the European RENEB platform for emergency preparedness and research' highlighting the most recent successes. This is remarkable for a project that was not set up to perform research but to establish a network. RENEB has been presented at national and international meetings focussing on radiological emergency preparedness, and on research with more than 60 talks and 30 posters.

There were also numerous additional dissemination activities including the organization of seminars on statistics and QA&QM, open sessions accompanying the annual RENEB meetings in 2014 at the Hospital La Fe in Valencia, Spain, including a press conference, and in 2015 at ENEA in Rome and at the EPRBioDose meeting in Hanover, NH. A particular dissemination event 'Nuclear and Radiological Accidents – Establishing a European Network of Biodosimetry', on 26 November 2015 was held at the European Commission in Brussels and people involved in emergency preparedness and response and in radiation research were invited to learn about the capabilities of the network (http://reneb.eu/Dissemination_event_in_Brussels).

Conclusion and future prospects

The EU project 'RENEB – Realizing the European Network of Biodosimetry' has coordinated the consolidation of European laboratories that are experienced in biological and physical retrospective dose estimation with the objective of initiating a European Biodosimetry network. At the end of the project 2015, a biodosimetry network with a legal structure is established under the same acronym but slightly adapted name 'RENEB – Running the European Network of biological dosimetry and physical retrospective dosimetry'. At the beginning of 2016, 26 member organizations form the nucleus of a unique growing infrastructure, combining high quality standards in the application and validation of biomarkers and maintenance and further development of scientific and technical competence (Comments from the Advisory Board, Lisbon, December 2015: http://reneb.eu/news.htm; Lloyd et al. 2016) (Figure 1)

The major impact of RENEB is a significant improvement of citizens' reassurance through an improved emergency preparedness system, respecting the need for dose estimation on an individual level. RENEB will be activated after a radiological emergency to provide fast, professional support to first responders to deal with exposed and potentially exposed people. This activity will reduce the health consequences of a radiation emergency, in terms of both the physical and mental aspects. To address people on a personal level by offering individualized dose estimation thus will help to minimize psychological stress and to regain trust in authorities.

More specifically, the impacts of RENEB can be described as (1) Emergency preparedness and management systems contributing to socioeconomic impact and wider societal implications, (2) high quality research standards, (3) maintenance of infrastructure in the field of biological and retrospective physical dosimetry, (4) maintenance of knowledge in the field of biological and retrospective physical dosimetry, and (5) development of a model for long-term sustainability of biological dosimetry. Several of these topics can significantly contribute to EURADOS' vision for dosimetry of ionizing radiation such as 'Improved radiation risk estimation deduced from epidemiological cohorts' or 'Efficient dose assessment for radiological emergencies' (Rühm et al. 2016).

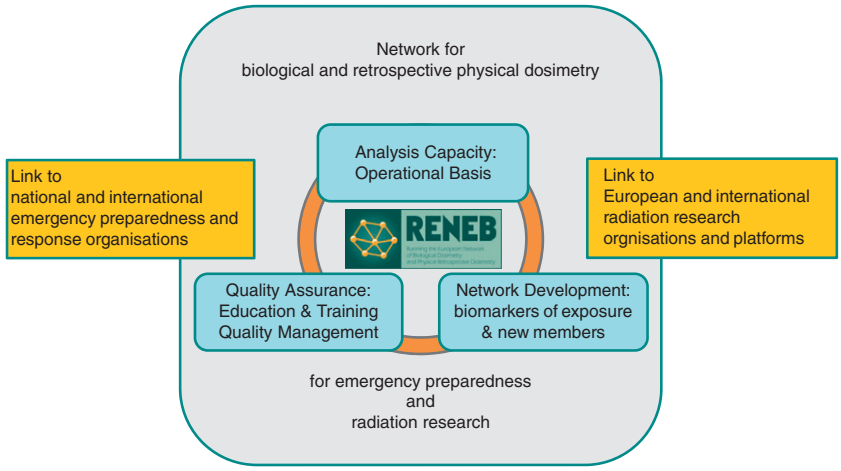

Figure 1. Activities and crosslinking of the RENEB network.

RENEB has resulted in the EU-wide preparedness for fast and reliable biological as well as EPR/OSL dose assessment following a radiological accident or terrorist attack involving a potentially large number of affected individuals (Table 2). With the help of this network implemented within/in parallel to existing emergency preparedness systems (Carr 2010, IAEA 2013, Rojas-Palma et al. 2009), it will be possible to significantly assist the emergency management by supporting medical decisions, estimating the stochastic radiation damage and also by identifying false positive exposure and thus reassuring the worried well. This especially will reduce socio-economic harm, as following an emergency, the fears and anxiety of people need to be respected and considered on an individual level.

A major requirement of cooperation in biodosimetry is the exceptionally high level of standardization and harmonization of the tools to achieve reliable and comparable dose estimates. This demands high-level education and training activities as well as accurate and attentive quality assurance and quality management. The high degree of the RENEB quality assurance and quality management will thus improve the research activities of each single laboratory involved in the training programme. It will also be available for interested laboratories outside the network and therefore have general impact on high quality research standards that include also networking aspects between laboratories, as needed for joint research approaches.

The RENEB network was established with the aim to significantly increase individual dose reconstruction capacities in case of large-scale radiological scenarios by pooling resources and servicing needs. However, the value of RENEB to support topics also outside emergency preparedness is evident. With the established strategies to guarantee consistent performance between the partner laboratories, the network has the ability and capacity to contribute to large-scale research projects with the analysis of exposure biomarkers. Moreover, RENEB – in combination with an open access database like STORE (http://storedb.org) – maintains infrastructure for online-training activities such as image-based scoring of aberrations. Additionally, in case of radiological or nuclear emergencies, it offers secure storing and processing of large quantities of data for quality assured dose estimation in radiological incidents.

RENEB ensures maintenance of competence of the actual and future network partners by providing practical training in partner laboratories and giving seminars in QA&QM, and addressing topics according to upcoming needs. While participation in the quality assurance programme of the network is mandatory for its partners, single training events are also open to researchers outside the network. This ensures for the long-term maintenance of competence in the field of biological and physical retrospective dosimetry within the network and a quality assured dissemination of knowledge to a wider community. It will also be the basis for a good integration of new skilled partners. In addition, RENEB in cooperation with EURADOS contributes to E&T activities in the European joint programming by providing training courses, e.g. in cytogenetic and EPR/OSL techniques for students and researchers, who are interested in biological dosimetry and physical retrospective dosimetry. Other training programmes are connected to European nuclear safety/radioprotection courses and/or international organizations practicing nuclear safety/radioprotection training, e.g. by inclusion of laboratories of IAEA RANET and WHO BIODOSE in intercomparisons. Developments of standards and benchmarks for quality assessment are generally openly accessible.

The long-term development of the biodosimetry network is assured by implementation of concepts to actively scout for new techniques and integrate verified methods and new members in the network. Moreover, a strong link between RENEB participants and national regulatory authorities is given by the nature of several partner institutions as governmental agencies or federal offices. Institutions like these will be able to guarantee the long-term sustainability of the project's product, the European biodosimetry network. In addition, strong links to the WHO BioDoseNet, REMPAN and IAEA RANET have been established. This strong connection of RENEB with the national and international regulatory bodies will help to consolidate the sustainability of the network.

Besides the promising results achieved so far, the network partners have to face the daily routine, often outside the field of emergency and response, and are challenged by monetary limitations of their institutions. To assure that the

key aspect of the network remains on the preparedness for a big radiological or nuclear accident, the network has to become an integral part of the radiation protection and emergency preparedness infrastructure at national and/or international levels. This therefore implies a full and binding integration of its activities into national and international operational arrangements. Several RENEB partners are employees of national radiation protection authorities, and therefore these partners are best placed to directly transfer the knowledge about the application of biological and retrospective physical dosimetry and the capabilities of the network to the national authorities. The same is the case for employees of hospitals, who are able to transfer the knowledge directly to medical centres and likely accident first responders such as ambulance staff. It will be the responsibility of all partners to actively disseminate the knowledge and promote the implementation of the network in national and whenever possible in international emergency preparedness and response systems.

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