REALISING THE EUROPEAN NETWORK OF BIOSIMETRY (RENEB)


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In Europe, a network for biological dosimetry has been created to strengthen the emergency preparedness and response capabilities in case of a large-scale nuclear accident or radiological emergency. Through the RENEB (Realising the European Network of Biosimetry) project, 23 experienced laboratories from 16 European countries will establish a sustainable network for rapid, comprehensive and standardised biodosimetry provision that would be urgently required in an emergency situation on European ground. The foundation of the network is formed by five main pillars: (1) the ad hoc operational basis, (2) a basis of future developments, (3) an effective quality-management system, (4) arrangements to guarantee long-term sustainability and (5) awareness of the existence of RENEB. RENEB will thus provide a mechanism for quick, efficient and reliable support within the European radiation emergency management. The scientific basis of RENEB will concurrently contribute to increased safety in the field of radiation protection.

INTRODUCTION

Over the last few years, the risk of a large-scale radiological event has markedly increased, not only because of possible accidents in nuclear facilities but also as a result of an enhanced threat of terrorist attacks against key facilities or civil targets in major cities. Events that highlight the need to be prepared for possible radiological accidents or attacks include the Tokaimura event in 1999, the September 11th attacks in 2001, the Madrid train bombings in 2004 and the 210Po poisoning of Alexander Litvinenko in 2006. The extent of the damage caused by the
Fukushima nuclear power plant disaster in the wake of an earthquake and a tsunami in Japan in 2011 is still beyond estimation. Furthermore, according to the judgment of national and international security authorities, it is a question of when, not if, terrorist groups will have the know-how to use radiological devices (‘dirty bomb’ or Radiation Exposure Device) to attack the public.

It can be expected that the 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 triage of patients, i.e. prioritising them according to their degree of injury and exposure, will be one of the initial steps within the emergency management. The situation during large-scale accidents may differ, as often advance warning enables precise dose surveillance within the disaster area and close monitoring of the distribution of released radionuclides. However, in such a case, 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 paramount in order to prevent the health care infrastructure from being overwhelmed and to avoid socio-economic harm.

In both contexts, biological dosimetry is an essential tool to estimate an actual absorbed dose without being influenced by temporal or individual variations in blood counts or confounding factors such as chemical agents or psychogenic reactions. Biological dosimetry will help to identify those individuals needing extensive medical care because of severe irradiation from people, perhaps with other injuries, but who have not received high doses of ionising radiation6.

In such a large-scale radiological accident or terrorist incident, the number of people who may need to be screened could thus easily exceed the capacity of a single or even a number of laboratories. As a consequence, biodosimetry networking has been recognised as a sensible and important emergency response strategy in several regions of the world2. A network of six laboratories has been set up, under the patronage of IAEA, covering the whole of Latin America. The US government is promoting a similar initiative in the USA. A global approach was started by the WHO with BioDoseNet3. At national level, networks have been established in Japan4 and Canada5, while in Europe a tripartite memorandum-of-understanding for mutual assistance has existed since 2004 between France, Germany and the UK. However, this European agreement affects only serious radiological events in these three countries and only one laboratory per country is involved, so the total capacity is still extremely limited. Now, a European Network of Biodosimetry is on the way to being realised.

REALISING THE EUROPEAN NETWORK OF BIODOSIMETRY

RENEB partners

In 2009, all the existing European laboratories with considerable experience in biological dosimetry were identified and listed with the help of the Realising the European Network of Biodosimetry (RENEB) survey6. Since then, many of these laboratories have expressed their interest in a long-term commitment to contributing to a European biodosimetry network. Now, 23 of these institutions from 16 European Union (EU) countries have formed the RENEB consortium to realise this network.

The partners are Bundesamt für Strahlenschutz (BfS, Germany), Bundeswehr Institut für Radiobiologie/Universität Ulm (BIR/Ulm, Germany), Commissariat à l’Énergie Atomique (CEA, France), Agenzia Nazionale per le Nuove Tecnologie, L’Energia e lo Sviluppo Sostenibile (ENEA, Italy), Helmholtz Centre Munich (HMGU, Germany), Health Protection Agency (HPA, UK), Instytut Chemii i Techniki Jadrowej (ICHTJ, Poland), National Institute of Public Health Romania (INSP, Romania), Institut de Radioprotection et de Sécurité Nucléaire (IRSN, France), Istituto Superiore di Sanità (ISS, Italy), Instituto Tecnológico e Nuclear (ITN, Portugal), Fundacion para la Investigacion del Hospital Universitario la Fe de la Comunidad Valenciana (LAFE, Spain), Leiden University Medical Center (LUMC, The Netherlands), National Center for Radiobiology and Radiation Protection (NCRRP, Bulgaria), National Centre for Scientific Research Demokritos (NCSR D, Greece), National Research Institute for Radiobiology and Radiohygiene (NRIRR, Hungary), Norwegian Radiation Protection Authority (NRPA, Norway), Radiation and Nuclear Safety Authority (STUK, Finland), Stockholm University (SU, Sweden), Universitat Autonoma de Barcelona (UAB, Spain), Universiteit Gent (UGent, Belgium), University of Tuscia (UNITUS, Italy) and Servicio Madrileño de Salud—Hospital General Universitario Gregorio Marañón (SERMAS, Spain).

Operational basis of RENEB

A variety of methods are available that can be used as biodosimeters or as markers of exposure7. 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 (EPR) in bone and tooth enamel. These methods have been validated in a number of small-scale radiation accidents and have shown to be reliable tools to detect an absorbed dose of radiation with sufficient precision. Indeed, the dicentric assay is regarded as the ‘gold standard’ of biodosimetry. A number of new biodosimetric methods have recently been introduced, such as premature chromosome condensation (PCC), fluorescence in situ hybridisation (FISH) and \( \gamma \)-H2AX foci. In addition, the EPR/optionally stimulated luminescence (OSL) method on personal objects (portable electronic devices, chip cards), although strictly speaking not a biodosimetric method, has been shown to have the potential to be an excellent supplementary dosimetry tool. As has been shown in a recent survey, one or more of these methods are established in many European laboratories, but what is lacking is formal networking, which would facilitate the standardisation of the assays. RENEB will provide a framework for regular inter-comparison studies and accident exercises that will guarantee rapid response and reliable dose estimates from all partner laboratories. In this regard, RENEB will run a ‘ready-to-use’ operational basis, which starts with six established biodosimetric tools, namely the dicentric assay, the FISH assay, the micronucleus assay, the PCC assay, the \( \gamma \)-H2AX assay and the EPR/OSL. All these techniques will be compared, standardised and harmonised in the participating laboratories to guarantee the highest possible reliability and accuracy.

**Basis to develop RENEB**

The established network is not 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. Thus, it is a major goal of the RENEB consortium to actively identify promising techniques and potential new partners.

In this regard, a roadmap of how to identify, validate, verify and integrate new technologies into the existing network will be developed. In parallel, a multi-stage procedure will be adopted to recognise and integrate new partners into the established network. This will involve identification, recruitment and training of candidate partners and the development of the formal criteria for their membership. The assessment of prospective laboratory capacities among consortium members and potential new network partners will further support the systematic build-up of the network. This also concerns new partners working with established and validated methods already integrated in the network. In this case, the adoption of the network standard has to be ensured. Candidate partners bringing new but already-validated techniques will be required to provide access for the existing partners.

**Quality management structure**

In the event of an accident involving a large number of potentially irradiated people, the prioritisation of resources by effective triage procedures becomes the key issue. The true value of biological dosimetry lies in the speed with which this information can be made available to the physicians, and the response time of the network depends chiefly on the efficiency of all laboratories involved in the response, not only individually but also in coordination. The best operational conditions result directly from the preparedness of the network before the event. Such provisions include harmonisation of procedures among the individual laboratories, retention of qualified staff, knowledge of the laboratory capacity in crisis situations and common training through implementation of periodic exercises. In this regard, quality management has a large influence on both the operational basis of the network, which includes proven and applied techniques, and further development of the network, which deals with new methodologies and new partners. The quality management structure thus handles operations that are directed towards project members, but also towards non-members. Within a long-term education and training programme, technical exercises according to the requirements of international standards will be performed on a regular basis. This training will be based upon the recommendations of the appropriate international (ISO) standards and will establish periodic intra- (for the qualification of individual laboratory staff) and inter-comparisons (for the qualification of the network). The programme will also include theoretical calculations and experimental design. This will provide the opportunity for members to enlarge their spectrum of methodologies by establishing validated assays on an operational basis in their laboratories. There will be efforts to connect this long-term training programme to already-existing European and global training platforms such as those supported by European Nuclear Education Network, European Network on Education and Training in Radiation Protection, European Nuclear Safety Training and Tutoring Institute and IAEA.

A quality assurance and quality management programme is also included as an essential part of Education and Training for RENEB. It is necessary.
for the network that the results will be homogeneous across all associated laboratories, irrespective of the particular organisation of the laboratory. The ISO standards 19238:2004 and 21243:2008\(^{(13, 14)}\) provide standardised guidance for all partners in order to perform the dicentric assay in a reproducible and accurate manner\(^{(16)}\). The approaches described in these standards include pre-planning, networking, reagent stockpiling, simplified sample processing, automation, medical management, radiation protection management, record-keeping and medical/legal requirements, qualification of staff and inter-comparisons. For the EPR technique and micronucleus assay respectively, ISO standards are currently being prepared and should be published within the next few years. For the assays used in RENEB for which standards are not yet available, many parts of the existing standards can easily be adapted.

Long-term sustainability

Besides the maintenance of established methods, the openness to new techniques and partners, safeguarding of high-quality standards and education and training provisions, RENEB will need a formal legal status to act as an official unit. This will be based on the development of an appropriate agenda that is valid in all countries of the partner organisations and conforms to the intrinsic ethical standards. In addition to the legal framework, financial support is needed to keep the network alive. In this context, funding options beyond the emergency preparedness system will offer an independent source to allow active operations. After the termination of the EC-funded project phase, the linkage of RENEB to the European research area and to public health organisations will facilitate the sustainability of the network. In this context, the large capacity of RENEB to collect, analyse and process samples with biomarkers for radiation exposure can contribute to the wider field of radiation protection, for example to investigate large and complex topics such as radiosensitivity, radionuclide incorporation, inhomogeneous exposure or discovery and validation of new bioindicators and methods. It can thus be useful for a large number of beneficiaries in different areas of the general community. Here, it is envisaged that the network will interact with research platforms such as Multidisciplinary European Low Dose Initiative. The funding strategy should increase stakeholder awareness that a strong and sustainable biodosimetry network provides very valuable information about the impact of new radiation technologies in medicine and industry on public health and may support the development of individualised cancer therapies as well.

Moreover, an efficient and smooth flow of action in an emergency event will be extremely valuable. In this regard, communication and logistical infrastructures will be improved. This includes the development and implementation of adequate communication strategies with different stakeholders, the general public and the media.

Awareness of RENEB—integration in international emergency preparedness systems

It is crucial for RENEB to maintain strong links and cooperation with European and international organisations, EU agencies and national bodies involved in emergency preparedness and response. A promising basis is the already-existing involvement of several RENEB partners in international activities such as the WHO BioDoseNet\(^{(3)}\) and REMPAN\(^{(17)}\) and the IAEA RANET\(^{(18)}\), as well as the contact with other relevant national and international organisations, including EU agencies and national bodies involved in decision-making for arrangements in emergency preparedness and response. Contacts to the national bodies responsible for biodosimetry arrangements will be facilitated by national representatives from the RENEB consortium countries. Furthermore, information about the development of the network will be available through presentations during the relevant radiation research and emergency preparedness meetings and state-of-the-art web pages. Here, RENEB can communicate with internal partners, as well as disseminate the activities of the network to the public. There will also be a link to radiation protection institutions, national competent authorities in emergency preparedness and response, UN organisations such as the IAEA and WHO and other international institutions, non-governmental bodies such as EURADOS and academic institutions.

In January 2012, the first RENEB meeting was held in Berlin to put the European biodosimetry network into action.

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REFERENCES


