

## RENEB – Realizing the European Network in Biological Dosimetry

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### Abstract

Creating a sustainable network in biological and retrospective dosimetry that involves a large number of experienced laboratories throughout the European Union (EU) will significantly improve the accident and emergency response capabilities in case of a large-scale radiological emergency. A well organised cooperative action involving EU laboratories will offer the only chance for a fast and trustworthy dose assessment urgently needed in an emergency situation. In this regard the European Commission supports the establishment of an European network in biological dosimetry (RENEB). The goal of RENEB is to establish a sustainable European network mainly based on biological dosimetry laboratories involving 23 organisations from 16 countries identified by the TENEBS survey, that will guarantee the highest efficiency in the processing and scoring of biological samples for fast, reliable results implemented in the EU emergency management. RENEB will also integrate recent developments in retrospective dosimetry. This goal will be achieved through 5 tasks:

- 1) To create an operational basis of the network based on coordination of the existing reliable and proven methods in biological and retrospective dosimetry.
- 2) To expand and improve the network by implementing appropriate new methods and integrating new partners.
- 3) To assure high quality standards by education and training activities. Special focus will be placed on quality assurance and management regarding the performed assays and involved laboratories.

4) To ensure a long term sustainability of the network by establishing a legal framework, linking RENEb to European and international research platforms and harmonising of transnational infrastructure.

5) To guarantee dissemination of knowledge by providing access to internal and external communication platforms and databases and close cooperation with national and global emergency preparedness systems and organisations.

## 1. Introduction

Over the last few years, the risk of a large scale radiological event has markedly increased, not only due to 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 polonium-210 poisoning of Alexander Litvinenko in 2006. The extent of the damage caused by the Fukushima nuclear power plant disaster in the wake of the earthquake and 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 (RED)] 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 the maximum damage. Following such a scenario, the triage of patients 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 allows for 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 most important in order to prevent the healthcare infrastructure 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 due to severe irradiation from people, perhaps with other injuries, but who have not received high doses of ionising radiation<sup>(1)</sup>.

In such a large-scale radiological accident or terrorist incident the number of people that may need to be screened thus could 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 world<sup>(2)</sup>. 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 WHO with BioDoseNet<sup>(3)</sup>. At national level networks have been established in Japan<sup>(4)</sup> and Canada<sup>(5)</sup> while in Europe a tri-partite memorandum-of-understanding for mutual assistance has existed since 2004 between France, Germany and the United Kingdom. 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 also extremely limited. Now a European Network of Biodosimetry is on the way to being realized.

## 2. RENEb Partners

In 2009, all existing European laboratories with considerable experience in biological dosimetry were identified and listed with the help of the TENEB survey<sup>(6)</sup>. 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 EU countries have formed the RENEb consortium to realise this network. All partner organisations are listed in table 1.

Table 1: RENEb partner organisations


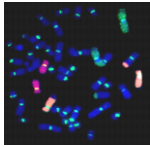
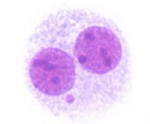
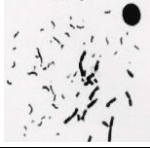
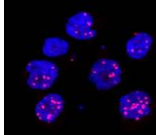

<b>Acronym</b>	<b>Participant organisation name</b>	<b>Country</b>
BfS	Bundesamt für Strahlenschutz	Germany
BIR/UULM	Bundeswehr Institut für Radiobiologie in Verbindung mit der Universität Ulm	Germany
CEA	Commissariat à l'Énergie Atomique	France
ENEA	Agenzia Nazionale per le Nuove Tecnologie, L'Energia e lo Sviluppo Economico Sostenibile	Italy
HMGU	Helmholtz Centre Munich	Germany
HPA	Health Protection Agency	UK
ICHTJ	Institut Chemii i Techniki Jadrowej	Poland
INSP	Institutul National de Sanatate Publica	Romania
IRSN	Institut de Radioprotection et de Sûreté Nucléaire	France
ISS	Instituto Superiore di Sanità	Italy
IST/ITN	Instituto Tecnológico e Nuclear, Instituto Superior Técnico, Universidade Técnica de Lisboa (IST/ITN, Portugal)	Portugal
LAFE	Fundacion para la Investigation del Hospital Universitario la Fe de la Comunidad Valenciana	Spain
LUMC	Leiden University Medical Center	The Netherlands
NCRRP	National Center for Radiobiology and Radiation Protection	Bulgaria
NCSR D	National Centre for Scientific Research "Demokritos"	Greece
NRIRR	National Research Institute for Radiobiology & Radiohygiene	Hungary
NRPA	Norwegian Radiation Protection Authority	Norway
STUK	Radiation and Nuclear Safety Authority	Finland
SU	Stockholm University	Sweden
UAB	Universitat Autònoma de Barcelona	Spain
UGent	Universiteit Gent	Belgium
UNITUS	University of Tuscia	Italy
SERMAS	Servicio Madrileño de Salud -,Hospital General Universitario Gregorio Marañón -	Spain

### 3. Structure of RENEb

#### 3.1 Operational Basis

A variety of methods are available that can be used as biodosimeters or as markers of exposure<sup>(7)</sup>. Currently, the best methods of biological dosimetry are based on the analysis of chromosomal damage (dicentric chromosomes, micronuclei and translocations) in peripheral blood lymphocytes<sup>(8,9)</sup> and electron paramagnetic resonance in bone and tooth enamel<sup>(10)</sup>. 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 dose of radiation with sufficient precision. Indeed, the dicentric assay is regarded as the “gold standard” of biodosimetry<sup>(11)</sup>. 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<sup>(7, 9, 12)</sup>. In addition, the EPR/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<sup>(9)</sup>. As has been shown in a recent survey<sup>(6)</sup>, 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 intercomparison 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 6 established biodosimetric tools, specified in table 2.

Table 2: Biodosimetric “ready to run” assays in RENEb

Assay	Acronym	Picture
Dicentric assay	Dic assay	
Fluorescence in situ hybridisation	FISH assay	
Micronucleus assay	MN assay	
Premature chromosome condensation	PCC assay	
$\gamma$ -H2AX assay	$\gamma$ -H2AX assay	
Electron paramagnetic resonance/ Optically stimulated luminescence	EPR/OSL	

All these techniques will be compared, standardized and harmonized in the participating laboratories to guarantee the highest possible reliability and accuracy.

### **3.2 *Basis for Developing the Network***

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 recognize 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 concerns also 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.

### **3.3 *Quality, Education and Training***

In the event of an accident involving a large number of potentially irradiated people, the prioritization 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 labs 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 & 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<sup>(13, 14)</sup> and will establish periodic intra- (for the qualification of individual laboratory staff) and intercomparisons (for the qualification of the network). The programme will also include theoretical calculations and experimental design as well<sup>(15)</sup>. 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 program to already existing European and global training platforms such as those supported by ENEN, ENETRAP, ENSTTI and IAEA.

A Quality Assurance & Quality Management (QA&QM) programme is also included as an essential part of Education & 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<sup>(13, 14)</sup> provide standardised guidance for all partners in order to perform the dicentric assay in a reproducible and accurate manner<sup>(16)</sup>. 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 be easily adapted.

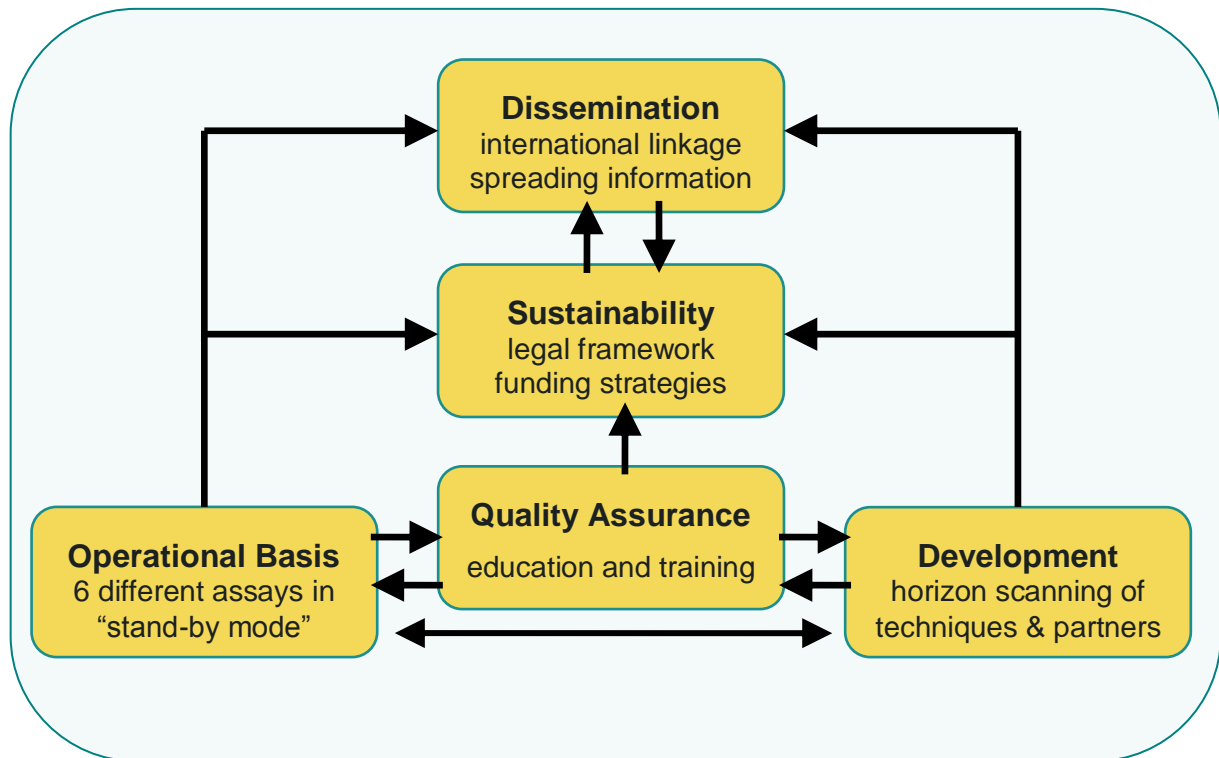


Figure 1: Structure of the RENEb project

### 3.4 Long term Sustainability of the Network

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 which is valid in all countries of the partner organisations and respects 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. A long-term funding strategy will be provided by connecting RENEb capabilities to the European research area and by establishing links to public health organisations. The network with its capability to analyse large numbers of samples can contribute to the wider field of radiation protection, for example to investigate large and complex topics like radiosensitivity, radionuclide incorporation, inhomogeneous exposure or discovery and validation of new bioindicators and methods. It can thus be useful for a large number of benefactors in different areas of the general community. Here, it is envisaged that the network will interact with research platforms such as MELODI (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 the case of an emergency event will be extremely valuable during an emergency situation. In this regard, communication and logistical infrastructures will be improved.

### 3.5 *Dissemination of RENE B - integration in international emergency preparedness systems*

It is crucial for RENE B to maintain strong links and cooperation with European and international organisations, European Union agencies and national bodies involved in emergency preparedness and response. A promising basis is the already existing involvement of several RENE B partners in international activities like the WHO BioDoseNet<sup>(3)</sup> and REMPAN<sup>(17)</sup> and the IAEA RANET<sup>(18)</sup>, as well as the contact with other relevant national and international organizations including European Union 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 RENE B 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 RENE B 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 like the IAEA and WHO and other international institutions, non-governmental bodies such as EURADOS, and academic institutions.

As shown in *figure 1*, all tasks are linked and will complete each other. Close interaction will especially be established between the network tasks “Operational Basis”, “Development” and “Quality Assurance”. The tasks “Sustainability” and “Dissemination” will be based on these functions.



*Figure 2: RENE B Kick-off meeting January 2012 in Berlin, Germany*

In January 2012 the first RENE B meeting was held in Berlin to put the European biodosimetry network into action (*figure 2*). A total of 53 participants attended the meeting, most of them members of the 23 partner organisations but also experts from IAEA, WHO and EC-organisations.



## 4. Acknowledgment

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## 5 References

1. Voisin, P., Benderitter, M., Claraz, M., Chambrette, V., Sorokine-Durm, I., Delbos, M., Durand, V., Leroy, A. and Paillole, N. The cytogenetic dosimetry of recent accidental overexposure. *Cell. Mol. Biol. (Noisy-le-Grand)*, 47, 557-564 (2001)
2. Roy, L., Roch-Lefevre, S., Vaurijoux, A., Voisin, Pa., Voisin P. Optimization Of Cytogenetic Procedures For Population Triage In Case Of Radiological Emergency. *Radiation Measurements* 42, 1143- 1146 (2007).
3. Blakely, W. F., Carr, Z., Chu, M. C., Dayal-Drager, R., Fujimoto, K., Hopmeir, M., Kulka, U., Lillis-Hearne, P., Livingston, G. K., Lloyd, D. C. et al. WHO 1st consultation on the development of a global biodosimetry laboratories network for radiation emergencies (BioDoseNet). *Radiat. Res.* 171, 127-139 (2009).
4. Mitsuaki, A. Y., Isamu, H., Hiroyuki, T., Kimio, T., Shinichi, S. S. K., Yoshiaki, K., Masao, S. S. The Chromosome Network for biodosimetry in Japan. *Radiation Measurements* 42, 1125 – 1127 (2007).
5. Miller, S. M., Ferrarotto, C. L., Vlahovich, S., Wilkins, R. C., Boreham, D. R. and Dolling, J. A. Canadian Cytogenetic Emergency Network (CEN) for biological dosimetry following radiological/ nuclear accidents. *Int. J. Radiat. Biol.* 83, 471 – 477 (2007).
6. Wojcik, A., Lloyd, D., Romm, H., Roy, L. Biological dosimetry for triage of casualties in a large-scale radiological emergency: capacity of the EU member states. *Radiat. Prot. Dosimetry* 138, 397-401 (2010).
7. Ainsbury, E. A., Bakhanova, E., Barquinero, J. F., Brai, M., Chumak, V., Correcher, V., Darroudi, F., Fattibene, P., Gruel, G., Guclu, et al. Retrospective dosimetry techniques for external radiation exposures. *Radiat. Prot. Dosimetry* 147,573-592 (2011).
8. International Atomic Energy Agency. *Cytogenetic Dosimetry: Applications in Preparedness for and Response to Radiation Emergencies. EPR-Biodosimetry 2011*, (Vienna: IAEA) (2011).
9. Fattibene, P., Wojcik, A. (Eds.). *Biodosimetric tools for a fast triage of people accidentally exposed to ionising radiation. Ann Ist Super Sanità*; 45 (2009).
10. International Atomic Energy Agency. *Use of electron paramagnetic resonance dosimetry with tooth enamel for retrospective dose assessment. Report IAEA-TECDOC-1331* (Vienna: IAEA) (2002).
11. Blakely, W. F., Salter, C. A., Prasanna, P. G. Early-response biological dosimetry - recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. *Health Phys* 89, 494-504 (2005).
12. IRPA, 2008. The 12th International IRPA Congress. [www.irpa12.org.ar](http://www.irpa12.org.ar) (2008)
13. ISO 19238 - Radiation Protection — Performance criteria for Service Laboratories performing Biological Dosimetry by Cytogenetics (2004)
14. 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. (2008)
15. Roy, L., Gregoire, E., Gruel, G., Roch-Lefevre, S., Voisin, Pa., Buset, A., Martin, C., Voisin Ph. Effect of lymphocytes culture variation on the mitotic index and on the dicentric yield following gamma radiation exposure. *Radiat. Prot. Dosimetry*, 10,1093/rpd/ncr460 (2012).
16. Voisin, P., Barquinero, F., Blakely, B., Lindholm, C., Lloyd, D., Luccioni, C., Miller, S., Palitti, F., Prasanna, P. G., Stephan, G. et al. Towards a standardization of biological dosimetry by cytogenetics. *Cell Mol. Biol. (Noisy-le-grand)*, 48, 501-4 (2002).
17. Carr, Z. WHO-REMPAN for global health security and strengthening preparedness and response to radiation emergencies. *Health Phys.* 98, 773-8 (2010).
18. International Atomic Energy Agency. *Response and Assistance Network*. (Vienna: IAEA) (2010).