"Realizing the European Network of Biodosimetry" (RENEB)

STRATEGIC RESEARCH AGENDA

November 2015

Who are we?

RENEB is a network constituted from the laboratories of 23 Institutions within 16 countries from Europe (Figure 1). For more details, see Ref [3]:

- Civilian Research Institute (1)
- Hospitals (2)
- Military (1)
- National Institutes of Health (3)
- National Research Institutes (5)
- Radiation Protection Authorities (5)
- Universities (4)

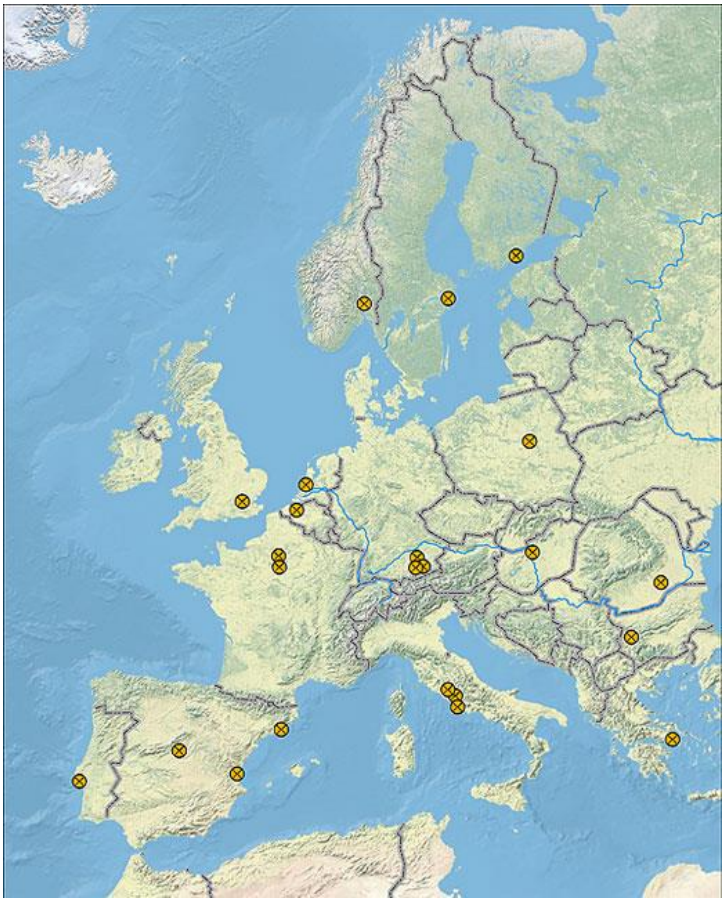

Figure 1: Current RENEB institutions, per country.

The RENEB institutions have competences in the fields of:

- preparedness and management of radiological or nuclear incidents
- biological and physical dosimetry analysis
- radiological assessment after a release of radioactivity even related to a nuclear emergency both for the individuals and the environment (water, biota, food, soils)
- public monitoring health response, technical coordination
- nuclear safety of NPP and nuclear installations
- national plan for radiological and nuclear emergencies
- triage, dose assessment

The most frequently biodosimetry assays used in RENEB project are:

- Dicentric assay (17)
- Micronuclei assay (11)
- γ-H2AX assay (12)
- FISH assay (Whole chromosome painting) (11)
- PCC assay (4)
- OSL/TL and EPR assay (3)

Other assays are used by RENEB members:

- M-FISH (4)
- Gene expression (and gene expression using RT-qPCR) (2)
- Protein expression by RT-PCR (1)
- Apoptosis, telomere length (1)

Funding sources for the different RENEB members are:

- Government (9)
- Specific national research projects (6)
- Generic national research projects (4)
- International research projects (13)
- Service Activities (3)

Which biological dosimetry for which use?

The wide use of radioactive sources and X-rays, for medical, industrial, agricultural, research and military purpose increases the risk of overexposure of workers and individuals of the general population. After a radiation accident involving one or more individuals, the first immediate questions asked are generally:

- How many people are involved?
- Who are really overexposed and who are not?
- Which of the clinical symptoms are apparent and due to irradiation?
- How to biologically quantify the overexposure to each person and what biodosimetry methods are appropriate to assess dose of each person?
- Which health effects could be imminent because of radiation exposure and later effects of overexposure could be expected?
- How to undertake medical surveillance?

Biological dosimetry is the measurement of radiation-induced biological and biophysical changes to estimate the exposure dose reflecting an equivalent of dose to the whole-body in order to assess acute and delayed health-risks. Biological dosimetry is a method used alongside physical dosimetry and clinical assessment to determine, as fast as possible and as precisely as possible, the magnitude of individual victims 'exposure to ionizing radiations and assists the medical team to define the best therapeutic strategy.

Multiparametric complementary strategies are necessary for radiation dose assessment in different accidental overexposure situations. When number of individuals potentially exposed to radiation is relatively small, and doses in such exposures is not likely to cause an immediate health risk to exposed individuals, the precision on the estimated dose remains the principal objective for assessing delayed health risks. Such assessment will require analysis of hundreds of cells per individual, which is labour intensive and will require several days for completing the analysis. In contrast, in cases of radiation accidents involving a larger number (tens to several hundreds) of individuals, potentially exposed to higher doses of radiation, a quick triage dose assessment to assess imminent and immediate health risk is more important than precision. A triage dose assessment will require a modification of the specific cytogenetic protocol, reducing the number of cells examined for radiation-induced chromosome aberrations such that a rapid dose

assessment could be accomplished within the first few days following a radiation accident to assist in the medical treatment of an exposed individual. If the number of individuals potentially exposed to radiation is relatively large, it may not be possible for any one biological dosimetry laboratory to assess radiation dose to all individuals in a timely manner, and therefore, will require help from other partnering laboratories in a local, national, or international network.

Biological dosimetry serves not only as guidance to the medical treatment decision process, but its outcome is likely to be multifarious influencing many human and health issues with possible long-term consequences. Therefore, all involved personnel including radiation-exposed individuals, physicians treating such individuals, employers, healthcare workers, lawyers as well as members of the general public must trust the outcome of biological dosimetry. All this implies that, independent of the biodosimetry method chosen to assess the dose, the method must undergo the same level of qualification, practiced with the same degree of skill, and similar results should be obtained independently of the laboratory where such a method is used. In short, there should be appropriate quality control and quality assurance processes in place, so that biological dosimetry is practiced reliably.

It is well known that exposure to ionizing radiations causes many structural and functional changes in cells. These changes could be visualized at nuclear, cytoplasmic, and membrane levels. Changes at the DNA, RNA and protein levels can also be measured and can also provide valuable information on absorbed dose. Although many dose assessment technologies have emerged during the last several decades, cytogenetic methods of dose assessment thus far remain most effective. Radiation-induced changes can be generally measured using peripheral blood samples obtained from an exposed subject immediately following exposure. Biodosimetry methods for measuring external radiation exposure have been previously reviewed, for instance in the IAEA technical guidelines[refxxxx]. Table 1 provides a summary of biodosimetry techniques that can be used under various exposure scenarios. Briefly these techniques are:

- Measurement of radiation-induced chromosome aberrations such as dicentrics and acentrics in first-division metaphase spreads obtained from lymphocyte cultures after DNA repair is complete or after second interphase leading to the visualization cytogenetic damage in the form of micronuclei are routinely used to assess radiation dose. The sensitivity and the specificity of these techniques are reasonably good, they are amenable for automation and easy to implement in a laboratory. Specifically the use of translocations for assessing (very) retrospective exposure is useful but sometimes questionable. The assess damage is executed by standard microscopy, and the assess to radiation dose is done by comparison with calibration curves.

- Direct molecular consequences of simple and double DNA strand breaks induced by exposure to ionizing radiation can be measured by specific fluorescent probes targeted to measure changes in proteins such as H2AX, MR11, BP53. Some of these techniques are amenable and automatable, demonstrate a very good sensitivity at low doses, but their principal disadvantage is the absence of stability over time.
- Premature chromosome condensation (PCC) assay performed using peripheral blood lymphocytes after fusion with Chinese Hamster Ovary cells or by a chemical induction of condensation, can assess damage by standard microscopy, and assess radiation dose by a comparison of damage with a calibration curve, which is linear. However, use of this method is confined to a few laboratories as it requires a high degree of technical skills.
- Mutation rates in certain genes can be explored individually (HPRT, HLA, Glycophorin A, etc.). However, the interpersonal variations and the lack of specificity make this approach not easily usable to evaluate a radiation exposure.
- Radiation-induced biochemical indicators have been primarily tested at individual level in the 80's, but few were revealed radiation specific and none have been worked-up to a readily deployable assay. Recent high throughout platforms have pushed forward an integrated 'omic' biology concept, simultaneously measuring fluctuations of hundreds/thousands of molecules (genes, proteins, metabolites) and giving a characteristic profile varying qualitatively or quantitatively with dose. To date, the potential is considerable, especially for evaluating low doses. Biophysical techniques of dose assessment are relatively more advanced.
- Optically stimulated luminescence (has taken progressively more significance: OSL) technology is a method making it possible to evaluate the ionizing radiation dose by measuring light emitted by irradiated objects. Body parts such as a tooth, as well as other objects routinely carried by individuals such as: ceramic prostheses, electronic components and glass of cellphones or other electronic devices, could serve as samples for making measurements. The advantage of OSL is its high specificity to radiation and its sensitivity (threshold level detection is in the mGy range with an upper level of detection limit is in the range of several mGy to several Gy); however a major disadvantage is a poor stability of the signal over time. ESR (Electron Spin Resonance) or EPR (Electronic Paramagnetic Resonance) is a spectroscopic technique that can be used to study radiation-induced radicals in biological materials such as tooth enamel or bones or fingernails, or some man-made materials. ESR has a good sensitivity in a very large dose range (1 to 1000

Gy) and a very long stability of signal over decades.

Table 1: Biomarkers explored for the purpose of biological dosimetry in a variety of possible accidental radiation exposure scenarios. Question mark (?) implies that the validity of this technique is not documented well enough for the scenario under consideration.

Techniques	Ionizing exposure scenarios			
	Recent & homogeneous Event	Recent & heterogeneous Event	Earlier Event	Large Event
Dicentric + centric rings	YES	YES	NO	YES
Micronucleus	YES	YES	NO	YES
Translocations	YES	YES	YES	NO
γ - H2AX	YES	?	NO	?
PCC- CHO	YES	YES	NO	YES
PCC- ring	YES	?	NO	?
Genes (HPRT, HLA, etc.)	YES	NO	?	?
OMICS	YES	?	NO	?
Biochemical indicators	YES	YES	NO	?
EPR, OSL, TL	YES	YES	YES	?

Finally, the wide diversity of assays available within the RENEB network laboratories have applications well beyond the confines of biological dosimetry. Indeed due to the relative scarcity of radiation accidents the biological dosimetry laboratories have typically applied their competence for other R&D programmes in the biomedical field. It follows that the required maintenance of service laboratories for emergency preparedness, including quality assurance and quality

management (QA & QM) programmes, carries over into their research activities, both alone and in collaborative work. Consequently the RENEB network constitutes an effective European resource for biological and biomedical research.

Benefits of RENEB outputs

The post-RENEB network will have significant impact on the national and international radiation emergency preparedness and response systems and also on the European radiation research area. For both emergency preparedness and research activities, quality assurance and quality management (QA&QM) are of utmost importance and demand permanent attention. In this regard the network will contribute to the deployment of scientific and technical knowledge, skills and competence, of unique infrastructures and laboratories and of Education and Training activities. The network will be pooling resources and servicing needs and requirements associated to important and relevant cross-cutting topics within the European radiation protection area, exploring synergies with the platforms MELODI, EURADOS, NERIS and ALLIANCE.

The benefits of the network for emergency preparedness and response and for research are:

- Operational basis of the network contributing to infrastructure

  A large panel of highly standardized and harmonized biological and biophysical indicators of dose provide a ready-to–use analysis platform with special focus on large scale events, such as:

  - Radiological emergency incidents with a large number of persons/casualties involved
  - Large-scale follow up studies after a radiological or nuclear emergency
  - Large-scale research initiatives such as molecular-epidemiological studies

- Maintenance of competence of the actual and future consortium

  Participation in the quality assurance programme of the network is mandatory for its partners and will be open to laboratories outside the network. This ensures for the long term a quality assurance and a high level quality standard within the network and also guarantees a good integration of new skilled partners. Furthermore performing skills, continuing methodological

developments and capacities of research laboratories will be available not only for research purpose but also for emergency preparedness. The network has implemented and promotes:

- Quality assurance programme with 2 different application foci; research and emergency
- E&T activities such as reference laboratory visits, exchange of scientists, intercomparisons
- Quality manual comprising single techniques, networking and integration of new partners
- Updating existing technologies in laboratories
- Support the development of technologies
- Young scientists grants
- Participation of the network or of network partners in R&D activities and projects

- Quality assurance of existing biomarkers and biophysical techniques and research on new biomarkers and techniques

  Evaluation of new biomarkers and techniques and critical validation of existing biomarkers was not included in the network operational basis. However it will allow a standardized integration of additional techniques by providing:

  - Validation programme for existing/ and or new biomarkers and techniques with 2 different foci, research and emergency

- Integration of the new partners and new techniques

  The network is not a static union but open to new partners and new techniques. This will result in:

  - Permanent exchange of knowledge, skills and competences
  - Dynamic, up to date network, combined with an effective quality management

- Benefit for network partner laboratories

  The participation in the network implies active participation in a standardized QA & QM programme. Additionally, being a partner in a known and recognized network will have benefits for these laboratories, such as:

  - Enhanced RTD competence
  - Contact with specific partners for joint research projects
  - Easy access to E&T activities, and quality assurance programmes

- Benefit for emergency and preparedness systems

  The national and international emergency organisations and stakeholders will get acquainted with:

  - The capacity and capability of the network for dose assessment based on biological and biophysical indicators for individual classification of persons
  - The fast activation of the network
  - The availability of a more precise individual dose estimation to a later time-point if needed
  - The contribution of the network to risk assessment and follow up studies

- Benefit for radiation research

  The network will support the European radiation research area by:

  - Deploying and making available unique scientific and technical knowledge, skills and competence on a broad and firm base
  - Contributing to the European research infrastructure as an analysis platform
  - Contributing to the European E&T programme
  - Contributing to the SRAs of the radiation protection platforms MELODI, EURADOS, NERIS ALLIANCE and the future medical platform
  - Identifying research needs in the aforementioned topical areas
  - Contributing to national and European research programmes

Vision (at 2030): towards a better individual dose estimation

The clear success of RENEB so far and the achievement of the main keypoints described in the European project are mainly due to the active participation of the 23 partners bringing together more than 60 scientists and technicians. On the operational basis of the network, the main biological and physical assays known in biological dosimetry - dicentric assay, FISH assay, micronucleus assay, PCC assay, Gamma-H2AX assay and EPR assay and OSL assay on personal objects - were harmonised and standardized within the network.
In addition, several new partners, highly qualified and well known teams, wish to become incorporated into the network showing the already good integration of RENEB in the scientific European and extra-European radiation protection field. New technological developments are proposed, such as –OMICS and combination telomeres/centromeres/dicentric assay, showing further potential for biological dose estimation in emergency situations.
RENEB is become more than an operational structure. RENEB is now a valuable hierarchical, communicational and logistical infrastructure capable of coordinating and achieving any scientific programme in the biodosimetry field. As claimed above, the individual estimate of dose is a prerequisite from medical doctors in case of overexposure suspicion, for linking levels of radiation exposure to those of damage effects and providing most appropriate treatments.
After 60 years of research, a lot of knowledge has been accumulated on ionizing radiation effects on healthy tissue and tumours. Many features were improved by the development of complementary biomarkers of dose and effects. A relatively good multiparametric approach of the dose estimation after ionizing radiation overexposure was obtained. Nevertheless important issues persist on precise questions related to the estimation of dose in specific overexposure or medical circumstances. Substantial improvement of technology and a better comprehension of the molecular and cellular mechanisms of ionizing radiation effects give the opportunity to reappraise these questions, such as described below:

- Improving the sensitivity of individual dosimetry (<0.1 Gy)

  There are today no dosimetric tools of sensitivity below 0.1 Gy. Nevertheless some requests of medical doctors, notably for correspondence with passive dosimeter estimates, need a higher sensitivity of biological indicators of dose. The quick development of so-called molecular epidemiology involving correlation between biological markers and epidemiology requires an adaptation of "old" biomarkers or already improved new biomarkers. At these dose levels, it is clear that stochastic effects are the primary concern and thus

the focus of research. It is probably not relevant for emergency triage but more relevant for risk estimation in the post-emergency phase and for reassurance of the public. New biomarkers development can be researched in the high throughput techniques and modern material including new analysis method for physical dosimetry.

- Better assessment of partial body exposure and dose inhomogeneity, also in medicine

  An overexposure to ionizing radiation is always heterogeneous, except rare whole body treatment for medical purpose, e.g. Hodgkin disease. The evaluation of exposure level and the localization of the irradiated part of body are essential to define the best follow-up. In fact, medical treatment must take into account the renewal of bone marrow by some parts of the body that were unexposed or only lightly irradiated as occurs in most radiation accidents. There exist mathematical methods for estimating the dose to the exposed partial body and to estimate the extent of the exposed part(s). However these methods are quite limited to the blood cells and knowledge is lacking on the renewal and circulation of blood lymphocytes. New tools more than adaptation of old tools could be more relevant. Knowledge of partial body exposure is necessary for proper combination of physical and biological individual dose estimate.

- High doses assessment (>5 Gy) also in medicine

  New recent radiotherapy techniques using protons and heavy ions are deeply changing the possibilities of treatment of diseases not treatable by more classical techniques. By contrast, there is a lack of information on the biological effect on these new radiotherapy modalities on the healthy tissues. It is essential to find biomarkers relied on dose simulation and tools are needed to validate the correct doses applications. Tools must be sensitive to high and fractionation doses. Additionally, these tools could be applicable to some specific overexposure accidents such as criticality accident (e.g., Tokai-mura).

- Harmonise the different existing methods and optimise existing decision tree to be used in emergency

  Single biological or physical methods often do not give sufficient information on the dose, the localization and the heterogeneity of exposure. It is necessary to harmonize the different methods for obtaining a realistic multiparametric approach using the complementary qualities and advantages of the available and future techniques in order to construct a decision tree for best medical treatment.

- Internal exposure assessment

  Accidental events or malevolent scenarios exist where people are contaminated with unknown activities of radionuclides alone, or in combination with external exposure. Existing biological dosimetry methods are mainly based on circulating blood cells and as such are more indicative of external exposure. Radionuclides in the body are generally deposited in specific locations (e.g. bone for strontium) which can sometimes lead to strong local concentrations – even if the entry concentration is low – and then local dose exposure. Some interesting possibilities are provided by analysing for radiation-induced biological changes in other less or non -mobile tissue cells (e.g. micronuclei assay on buccal cells or skin hairs) and EPR physical measurement on teeth or bone. The main issue is that the dose estimation given by classical biomarkers is better representative of the concentration of radionuclides in blood, before tissue deposition or during clearance. Such data can be inputted to existing kinetic models from incorporation to clearance of most known radionuclides which are classically used at work for radiotoxicology calculation. Additional biological tools are needed to estimate organ doses that can be included in biokinetic models to reconstruct initial activity and the biomarker approach of the RENEB network laboratories opens up possibilities in this direction.

- Chronic/ protracted exposure

  We considered for this SRA that chronic/protracted exposure is any irradiation that persists for longer than one day. This exposure situation may be applicable to radiation accidents, occupational and natural background exposures. Our present knowledge, obtained from the existing biological dosimetry methods, shows an under-estimation of the dose due to the simultaneous damage and repair. There are some mathematical modelling approaches for correcting this under-estimation but the resultant dose values often carry uncertainties due to necessary approximations. Also, there is a lack of appropriate calibration curves and methods to estimate and correct for the decline of the signal. Also, it is desirable that the method be able to differentiate between protracted and acute exposure. In other words: methods should allow one to reconstruct the exposure scenario (protracted vs acute).

- Multiple stressors (e.g. radiation qualities, chemicals)

  In many exposure scenarios, people may be exposed to both radiation and chemicals, or to a mixture of radiations of different qualities. Most working environments where radiation sources are used also contain chemical hazards

and the same possibility of multiple stressors applies to many envisaged scenarios of malevolent radiological attacks. In these different situations, information is needed about how the different stressors interact or modify the signal obtained by using a biomarker of dose or effect. In other words, either new biomarkers are needed taking into account these different stressors or new methods to deconvolute the "old" biomarkers' results from the levels of exposure of the non-radiological stressors.

- Signal stability

  Sometimes the exposure is identified and needs to be quantified years after it occurred. This is often a requirement for epidemiology purposes. It could be also for medical reasons, when a radiation aetiology is suspected for some diseases and the medical doctor searches for more concrete information. Current methods are not sufficient. The translocation is not specific to ionizing radiation and despite its persistence for longer than many other biomarkers its quantification still may be imprecise after several years. We need methods that are based on stable signals or methods to correct for the decline of signal measured long after exposure together with methods to estimate the time between exposure and detection.

- Speed of analysis

  In a large scale accident, speed of analysis and high throughput is of primary importance. It is already possible to use automated systems to give faster results for some "classic" biomarkers of dose (dicentric, micronuclei, γ-H2AX…), but without changing the characteristics of the technique or the sampling conditions. Of course, these techniques need to be optimized continuously, notably by using networking. Nevertheless other methods should be developed or improved to give faster results with high precision and high throughput.

- Inter-individual variability

  Dose-effect calibration curves are based on the average data obtained from one or several subjects. Such calibration curves do not take into account the individual variation of sensitivity of the different subjects to ionizing radiation. Depending of the biological indicators of dose or effect, the variability could be significant and increase uncertainty of results. Modification of the existing methods is required to take into account individual sensitivity to radiation, or to reduce the effect of this inter-individual variability.

- Accessibility of sampling

  For biological dosimetry purpose, many biomarkers of dose are based on blood sampling. Blood sampling can be difficult in mass casualty scenarios, due to the expected problems of organization and logistic. Adaptation of the existing methods or new techniques/new bioindicators must be developed based on samples that are easier to collect (saliva, urine...) and/or not so critical to manage.

  For physical dosimetry, the actual techniques of OSL, TL and EPR use material - glass, electronic component, teeth or bone – which needs the destruction of the sample. Such techniques must be modified with non-destructive methods or methods using items of little personal value.

To meet the vision

The following 6 points, whilst not intended to constitute a formal roadmap, highlight areas that RENEB partners consider that should be addressed to develop the strategy for the future.

1. Maintain the competence of the actual and future consortium for emergency response and research:

   According to the twin priorities of the RENEB vision namely, a consortium for emergency purposes and a powerful European platform to advance research in biodosimetry, a quality assurance programme is essential and must be developed at two levels. One being dedicated to emergencies and the second to research so that together they guarantee harmonized results for a panel of assays.
   An integral part of this quality programme must pay particular attention to the updating/upgrading of existing methods and technologies (specific seminars), and if possible contribute to the development of these technologies. For example validations, depending on the objectives, may include periodic intercomparison exercises, training courses etc.
   Finally, special focus should be directed towards young scientists and their associated grants to maintain and renew competences on each theme of interest.

2. Integration of the new partners and new techniques:

The RENEB Network in the future, whatever its legal status, should be open to the European scientific community as well as acting as the pivotal point of reference for Europe to maintain professional contact with the biodosimetry wider world. The process of integration of new members should be developed. A dynamic aspect (and procedure) is recommended in order to allow a clear status between partners with validated methods and results adapted for continuous emergency preparedness and partners more in connection with new techniques or ‘‘not yet validated techniques’’. With a mixture of these types of partners, the network is best structured to develop exchange of knowledge particularly as some partners will assume these two different roles.

Whilst formal membership of RENEB is limited to laboratories of European institutions, it is important that the network should integrate properly into the wider world scene of biodosimetry and its related research. RENEB will form the natural pivotal point of reference for Europe to maintain professional contact with the world community of biodosimetry.

3. To find synergies and partnership:

To find, build and develop the partnership, it is important to maintain and indeed seem suitable to increase the visibility of RENEB by sensitization and dissemination. Some actions as workshops, lectures in any appropriate scientific events, edition production of documents, leaflets and publications is recommended to distribute information about its activities.
Exchange of expertise and services between the different platforms (MELODI, NERIS, EURAMET, etc.) will be encouraged.
The management inside and outside the network will be developed. A consolidation inside (agreed representative) allows the possibility to have official agreements of national and international bodies and permanent representatives.

4. To listen to the stakeholders

The main idea is to develop contacts and dialogues with stakeholders associations (public, health professional, authorities) in order to understand better their positions and if possible meet their positions.

5. To reach sustainability

Sustainability will be reached if the other items outlined in these vision points are developed. It is the final objective to continue and extend the activities of the network which exists now and to establish a better common

identity based on an integrated cooperation.

6. To contribute to and be integrated in European Joint Programming (EJP)

RENEB (Realizing the European Network of Biodosimetry) was initiated as a Coordination Action (CA) project founded within the 7th EU framework EURATOM Fission Programme. The attempt was to establish a legal framework for the network and build a formal legal status to act as an official unit with the hierarchical, communicational and logistical infrastructure to establish and to maintain an operational biodosimetry network in Europe.

Based on the developments in the field of radiation research in Europe (e.g. OPERRA, CONCERT) and the memorandum of understanding for an integrative approach to European Radiation Protection Research between the four platforms MELODI, NERIS, ALLIANCE and EURADOS, it is conceivable that RENEB can contribute to and be integrated in the European Joint Programme co-fund Action (EJP) as a participant, as applicant, and on the long run, as a member:

- As a participant to contribute to the European Research Area as an infrastructure "cross-cutting" working group,
- As applicant of RENEB members answer to the calls to undertake research in the field of biodosimetry methods,
- As a member to contribute to the drafts of the calls, based on the RENEB SRA.

For this last point, to answer to research calls as a whole consortium with 21 partners may be difficult. It is suggested that appropriate members linked into a smaller group of partners may apply together with the advantage of a high quality assured cooperation established in the framework of the RENEB project.

Sustainability and Conclusion

The sustainability of an international network of institutions deploying technical and scientific skills and competence in biodosimetry is of utmost importance in the event of a radiological or nuclear accident or malevolent act involving mass scale casualties. In such a scenario a single national institution will be unable to cope in a timely manner with the need to process and analyse a high number of samples and thus will fail to respond in an effective way to the resulting emergency situation. A transitional infrastructure will therefore be required.

It must be recalled that panic and anxiety from the public and the population, as well as significant socio-economic consequences will be triggered by such an event. Some experts consider that some categories of such accidents or terrorist acts will cause "mass disruption" and will inevitably lead to social unrest. The economic and financial costs of managing such a situation are estimated to be considerable.

Thus there is a clear role for biodosimetry networking and the different assays and techniques offered by such a network, must undergo Quality Assurance and Quality Management procedures. Therefore laboratory intercomparison exercises must be regularly undertaken in order to guarantee a coherent and harmonized set of results for the same technique, in different laboratories.

Logistics aspects such as the distribution and transport arrangements for biological samples are another aspect that must be considered. Leading edge research in topics such as, inter alia, biomarkers of ionizing radiation will very likely positively impact the quality of the network results and its sustainability, through recognition, by the decision makers and stakeholders, of the ability to cope with the very demanding aspects and topics associated with emergency preparedness and response.

Financial issues and funding mechanisms are of utmost importance for the sustainability of a European network on biodosimetry. 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 a first phase, funded to some extend (such as RENEB) in order to develop its structure and to aggregate the relevant institutions and experts. However, in the medium- and long-term, such platforms and networks must be self-sustainable, not depending on funding from the European Commission. However, possible funding resources may come from European Union funded projects in different programmes (EURATOM,

SECURITY, etc.).

As a no formal approach, the following funding sources (Figure 2) can be envisaged for a future operational + scientific platform:

- Membership fees (1000 € / institution?) – baseline
- Partner in calls of EJP CONCERT
- Partner in other Horizon 2020 Calls (EURATOM, SECURITY, etc.)
- Intercomparison exercises (participation fee: ~1000-1500 € as is done by EURADOS)
- Workshops & Training Courses (fee to participate)
- Annual Meetings with a registration fee (typical value 250 €)

Note that these listed funding sources (see also Fig.2) are currently successfully used by some of the established platforms.

Figure 2: Possible funding sources for the RENEB+ platform.

It is assumed that, at the end of the EU project phase, the majority of consortium members will have signed a MoU, thus building a nucleus of the future RENEB + and guaranteeing a basic ongoing existence of the biodosimetry network. Additionally, strong links to the European Platforms and Associations have been established, e.g. by being included in the SRAs of MELODI and EURADOS. RENEB also is accepted as partner by international emergency and preparedness organisations such as WHO and IAEA. Furthermore, the RENEB network is included in EJP CONCERT with regard to infrastructure aspects (WP 6). These measures will prevent a breakup of the network after the end of 2015. Besides these consolidated arrangements, further actions are under consideration to ensure a sustainable and active network. In this regard, the establishment of further funding mechanisms and firm integration in European activity structures will be crucial for RENEB +.

Finally,

A consensus exists about the following:

- **RENEB+ will not be a Technology Platform**
- **RENEB+ will be an independent/autonomous European Network**
- **RENEB+ will be "servicing" the needs of Technology Platforms, namely:**
  - **MELODI**
  - **NERIS**
  - **EURADOS**

Priority setting for the next steps

In order to proceed towards the aimed objective the following measurements have to be taken:

- Establishment of a sustainable nucleus of the RENEB network by signing the MoU by the consortium members
- Enlargement of the current network by integrating new partners as members
- Advancement of activities for identification, validation & implementation of new techniques & assays
- Advancement of activities for the maintenance of competence of the network partners, including intercomparison activities, QA & QM programme, harmonisation activities
- Implementation of advanced Education and Training in Biological Dosimetry (at large) at utmost concern
- Setting up specialised data and image sharing systems, optimized for research and for emergency preparedness
- Implementation of basic & applied research according to the Vision 2030.
- Promotion of new synergies and partnerships, also beyond the EU
- Optimisation of infrastructures & laboratory cooperation

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The Strategic Research Agenda was discussed during the yearly RENEB meetings and more specifically during an ad-hoc seminar which was held at Versailles (France) on 26 and 27th of January, 2015.

The RENEB SRA Group (26-27 January 2015)

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Also contributing to the meeting and/or to the SRA but missing on the photo are: Pedro Vaz and Octavia Monteiro-Gil from IST, Alicja Jaworska (NRPA), Elisabeth Ainsbury (PHE), David Lloyd and Philipp Voisin, initiator and host of the meeting