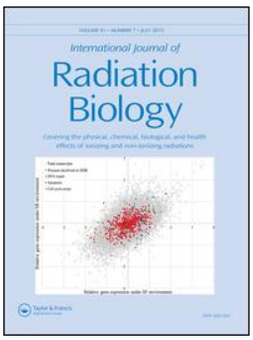

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RESEARCH ARTICLE

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The harmonization process to set up and maintain an operational biological and physical retrospective dosimetry network: QA QM applied to the RENEB network

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ABSTRACT

Purpose: The European Network of Biological and Physical Retrospective Dosimetry 'RENEB' has contributed to European radiation emergency preparedness. To give homogeneous dose estimation results, RENEB partners must harmonize their processes.

Materials and methods: A first inter-comparison focused on biological and physical dosimetry was used to detect the outliers in terms of dose estimation. Subsequently, trainings were organized to improve both tools dose estimation. A second inter-comparison was performed to validate training efficiency. Simultaneously, based on ISO standards, a QA&QM manual on all dosimetry assays was produced which states a common basis and harmonized procedures for each assay. The evaluation of the agreement of RENEB partners to follow the QA&QM manual was performed through a questionnaire. The integration of new members into the network was carried out in the same way, whatever the assays.

Results: The training courses on biological and physical dosimetry were judged to be successful because most of the RENEB members' dose estimates improved in the second inter-comparison. The QA&QM manual describes the consensus for the minimum requirements and the performance criteria for both dosimetry assays. The questionnaire revealed that the whole network capacity currently can manage between 15 and 3800 samples once.

Conclusion: The methodology used to harmonize all dosimetry practice within the network RENEB was highly successful. The network is operational to manage a mass casualty radiation accident for immediate dose assessment.

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Introduction

In a radiological emergency, dosimetry assays (dicentric chromosome, micronuclei (MN), gamma H2AX, Premature Condensed Chromosome (PCC), Electron Paramagnetic Resonance (EPR) and Optically Stimulated Luminescence (OSL) methods) are vital tools for determining the doses received by a large number of victims (IAEA 2011; Kulka et al. 2015). After the first triage by clinical symptoms they help stakeholders and medical staff to identify patients who have actually been exposed and need medical care from those who have received little or no radiation (Voisin et al. 2001; Roy et al. 2007; Jaworska et al. 2015). Biological and retrospective physical dosimetry can provide support in categorization of individuals into three groups (MULTIBIODOSE 2011); low doses (<1 Gy), moderate (1 to 2 Gy) and high doses (>2 Gy). After this categorization, biological and retrospective physical dosimetry can further contribute by estimating precisely the victims' dose. This second step is essential to adapt the treatment, especially if the irradiation is localized (Bertho & Roy 2009; Vaurijoux et al. 2009). Furthermore, accurate knowledge of the dose is also important for the long-term medical follow-up, especially in the case where no medical treatment is required immediately after exposure. This also allows people who have not been exposed to be reassured.

Dependent on the staffing levels and experience, a biological or physical dosimetry laboratory can manage fast identification and precise dose estimation between 10 and 100 patients in a period of several months. It is therefore essential that laboratories combine their efforts to handle a large number of patients.

A European network of biological and retrospective physical dosimetry 'RENEB' has been set up to develop the capacity and the capability to significantly contribute to

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European Radiation Emergency Preparedness (Kulka et al. 2015).

One important task to be performed is to ensure that in the case of major accident all network participants are able to effectively provide fast and reliable dose estimates. The network will be most efficient if all partners' laboratories have the same competence level and follow the same operational procedures.

The present manuscript describes the different steps to be followed for an operational, harmonized network.

Material and methods

Education and training

One major step to qualify a network is the results of inter-comparison. A first inter-comparison on biological and physical dosimetry allowed identification of laboratories requiring training on specific assays (Barquinero et al. 2016; Oestreicher et al. 2016; Trompier et al. 2016a). Furthermore, some laboratories required training on assay(s) that they do not master. Depending on the assay and the laboratory, the training addressed the method itself, the use of dose effect curves when relevant and provision of dose estimates. In all cases, the training was organized by the laboratory considered as the reference lab, i.e. the most highly competent lab, for the specific assay. The duration of the training was usually one week. The cost was supported by the RENEB project.

QA&QM program

In order to harmonize the procedures of biological and retrospective physical dose assessment, the basic requirements for standardization of the methods have been specified in a quality manual with common procedures for the entire Network. Each reference laboratory contributed to the specific parts of the manual dedicated to the assay(s) in which they are skilled. The QA&QM program was defined according to the appropriate ISO standards (ISO 21243 2008; ISO 13304 2013; ISO 17099 2013; ISO 19238 2013) during a seminar involving all RENEB members. The proposed common parts and technical annexes were sent to all the partners for their approval.

Questionnaire

To avoid multiple, repeated, audits to check the QA&QM program of each partner, a questionnaire has been designed. The questionnaire describes the minimum requirements of the performance of member laboratories and their technical and staff capacity for each biological and physical assay. Several items were investigated: equipment checking, capacity of the laboratory, laboratory organization, qualification of staff to perform dose estimation (low and high), sample transportation, interpretation of the results, and periodic audit on the technique, characterization and written report of the radiation source. The results defined the laboratory capacity and capability level in biological or physical dosimetry, according to the QA&QM program. The aim was to allow evaluation of the capacity of the network in case of mass casualty radiation emergency situation and identify areas for improvement.

New member qualification

New members wishing to join the network are provided with another questionnaire, to be answered before integration, to ensure their operational effectiveness for the emergency network whatever the assay. The questionnaire, designed according to the QA&QM program, checked the following items: dosimetry techniques used; laboratory infrastructure (staff members, processing capacity of samples in a sudden request, time to result); automated systems used (e.g. foci counting, metaphase finder, automatic TL/OSL reader); written procedures (sample treatment, calibration curve fitting, aberration scoring, statistical interpretation and staff qualification); certification of the laboratory/department/institute; accreditation/certification of one or several techniques according to standard ISO; written procedures when the technical process of the laboratory is not adequate for standards; organization and/or participation in inter-comparison or virtual crisis exercises (at national/international level); internal/external audits for the qualification of the procedure/laboratory for the technique(s).

To be qualified as a RENEB member, a laboratory must participate in regular inter-comparison exercises according to the criteria established during the RENEB program. For each new member or new assay, biological or physical, the criteria are: (1) to know the number of samples that can be processed following a sudden request to respond to a multi-casualty event; (2) to have written procedures for sample treatment, calibration curve fitting, aberration scoring, and staff qualification; to have established calibration curves, with details of radiation qualities and dose ranges; (3) to have the ability to perform statistical methods for dose estimation; and (4) to produce a standardized guide to perform the assays according to the QA&QM manual.

Results

Education and training

Two inter-comparisons on biological dose estimation of irradiated samples were organized within RENEB. The first inter-comparison focused on biological assays (DCA; FISH; MN and PCC) has shown that the majority of RENEB partners reached the criteria for biological dosimetry indicator scoring and dose estimation: the calculated 95% confidence interval, associated to the estimated dose, should contain the physical dose delivered to the sample (Barquinero et al. 2016; Oestreicher et al. 2016). However, deviations from the statistically approved intervals for the dicentric (DCA), translocation detection by Fluorescence in situ Hybridization (FISH), micronucleus (MN) and Premature Condensed Chromosome (PCC) (Terzoudi et al. 2016) assays were observed for a few laboratories, indicating the requirement for training for these partners. Training courses were mainly dedicated to DCA,

FISH, MN, γH2AX and PCC assays. After completion of the practical training, a second inter-comparison was performed also on irradiated samples (Barquinero et al. 2016; Oestreicher et al. 2016; Terzoudi et al. 2016). The results showed the benefits of training sessions. Many of the RENEB members obtained physical dose in the 95% confidence interval of their assessed dose.

Regarding the retrospective physical dosimetry assay, the two inter-comparisons were planned within Multibiodose project and EURADOS (Trompier et al. 2016a). A first inter-laboratory comparison was organized on retrospective physical dosimetry for the two assays (EPR and OSL) jointly with the Multibiodose project and EURADOS (Bassinet et al. 2014; Fattibene et al. 2014). This first inter-comparison showed differences of sample preparation (misidentification of resistors for OSL and variability of response of the different glass sheet for EPR) higher than differences of laboratory practice. Training focused on investigation and discussions were coordinated to resolve these difficulties. A second inter-comparison aimed to test the OSL protocols during an exercise organized within the FP7 security research project CATO leading to mimic real accident conditions. The overall results of this second inter-comparison will be published in a future paper. Regarding the EPR assay, the second inter-laboratory comparison has consisted of re-evaluating samples of the first inter-comparison but with alternative approaches. A protocol improvement is still foreseen but more investigations are needed to fully establish the EPR technique on the glass touch screen of a mobile phone (Trompier et al. 2016a).

In addition to the practical training courses seminars on statistics, ISO standards and quality assurance and quality management were given. A collective training course organized at IRSN (France) was: (1) basic statistical aspects related to the establishment of dose-effect calibration curves and to dose estimation; (2) how a quality system is needed and will help in the traceability and management of the activity performance; and (3) particularly to fulfil metrology criteria.

QA&QM program

To harmonize the practices of the different laboratories in the RENEB network, a quality manual has been produced for the various biological and physical dosimetry techniques that are currently used in the network. Based on the appropriate ISO standards (ISO 21243 2008; ISO 13304 2013; ISO 17099 2013; ISO 19238 2013), the QA&QM manual describes the minimum requirements to follow, the rules for organization and traceability. The manual and its appendices also state the performance criteria for biological and physical assays (protocols, parameter evaluation and dose estimation). The standard protocols established within the partners are listed with the aim of standardizing the working methods of the network members.

The QA&QM manual defines rules regarding: (1) role of the responder reference laboratory and the service laboratory; (2) information on the radiation sources used for dose-effect curves or for irradiation of samples for inter-comparison (Trompier et al. 2016b); (3) information on the establishment of calibration curves for the different assays; (4) performance of sample collection and sample preparation by assay; (5) conversion of the specific observed criteria of the assay into an estimate of absorbed dose; (6) report of minimum dose detection level, results and quality controls; (7) organization of inter-comparisons; (8) quality assurance and quality management of RENEB laboratories.

The assays that have components within the quality manual are currently: DCA, MN, FISH, PCC, γH2AX, EPR and OSL. Many parts of the standards can be easily adapted to the other assays proposed in RENEB (Ainsbury et al. 2016a).

It is expected that each member participating in the network should establish a QA&QM program relating to operation of each (established or new) biological and physical assay used within its laboratory. The resulting homogeneity of practices should guarantee that dose estimates produced by network members will be comparable irrespective of the laboratories' organization and the specific emergency scenario. Therefore a key strength of the QA&QM manual is to obtain the responsible authorities' trust with respect to results provided using the biological and physical dosimetry tools.

Questionnaire

The answers of the questionnaire revealed that the majority of laboratory partners have a very good level of staff qualification and are well organized to respond to a mass casualty accident. Laboratories have implemented transport, reception and stock procedures and have traceability on sampling and on former patient radiation exposure. The majority of laboratories send a quality report for dose estimation to the requestor, most likely a physician. The integration and the connection of these laboratories with the national emergency response system are also important mainly in mass casualty accidents and have been checked during an exercise.

Despite the overall good performance of the partner laboratories, some criteria in biological dosimetry have been identified, where improvements could be made. There is a deficiency of consumable stock management in some laboratories, which could be a problem in case of a mass casualty incident. This could be resolved by an agreement with the purchaser. There are only a few laboratories that adapt culture conditions depending on the number of lymphocytes of the exposed individual. A few laboratories determine and then include on their reports the minimum detectable dose level. Finally, only few laboratories have periodic audits on their technique(s).

New member qualification

A questionnaire was established to evaluate technical and operational capacities of new members wishing to integrate into the network. This questionnaire has been successfully answered and applied by Lithuania (RPC) and French military (IRBA) biological dosimetry laboratories.

The network will be open to external new biological and physical laboratories; however, the participation in the quality

assurance program of the network is mandatory for all partners. This ensures a long-term high level quality standard within the network for the long term and also guarantees a good integration of new skilled partners. Furthermore, the current skills, continuing methodological developments and capacities of research laboratories, will be available not only for research purposes but also for emergency preparedness.

Discussion

To date, a variety of markers (dicentric chromosome assay (DCA), micronuclei (MN), gamma H2AX, Premature Condensed Chromosome (PCC), Electron Paramagnetic Resonance (EPR) and Optically Stimulated Luminescence (OSL) methods) used for dose assessment in cases of an accidental radiation exposure have been identified as the most appropriate biological and physical retrospective indicators (Lloyd et al. 2000; Ainsbury et al. 2011; IAEA 2011; Beinke et al. 2013; Fattibene et al. 2014). These dosimetry techniques have been adapted to the special needs of various emergency scenarios. In this regard, networking between laboratories was identified as the best way to handle a very large number of samples in the case of a mass casualty emergency. Consequently, a network for biological and retrospective physical dosimetry was established with these six operational dosimetry assays and more than 20 laboratories, most of them highly experienced in this field. The strength of RENEB is that all members were equally involved to establish an efficient network. They were also motivated to participate in inter-comparison exercises, to be trained by skilled laboratories and finally to contribute to the harmonization of the network in terms of dose assessment.

To test the efficiency of the network, inter-comparisons have been performed for DCA, FISH (Fluorescence in situ Hybridization) for translocation detection, MN and gamma-H2AX, EPR and OSL. The results of such inter-comparisons have been analysed differently according to the network (García et al. 2013; Depuydt et al. 2013; Bassinet et al. 2014; Fattibene et al. 2014; Barnard et al. 2015; Wilkins et al. 2015; Moquet et al. 2016; Oestreicher et al. 2016). It is therefore important to fix the adapted criteria for inter-comparison analysis as it can have an impact on the conclusion of the proficiency of a laboratory. Based on ISO 13528 (ISO 13528 2005), the Z-score has been first used in Di Giorgio's publication (Di Giorgio et al. 2011). However, this is not the only parameter to take into account. The major limitation of the Z-score is that it depends on the results of all the laboratories involved in the exercise. In this field some harmonization still needs to be made to take into consideration statistical methods applied currently for inter-comparison analysis (Ainsbury et al. 2016b).

In bio-dosimetry, inter-comparison can focus on quantifying the frequency of damage (dicentric chromosome, FISH, γH2AX foci, MN) or on the dose assessment (all assays). However, when based on the dose, the calibration of the radiation facility has to be similar between the different laboratories estimating the dose, i.e. same units (Trompier et al. 2016b). If not, some discrepancies between biological dose assessments can be attributed to differences in protocols, in calibration curves rather than in calibration of radiation facilities.

As mentioned, usually networks are based on the results of periodic inter-comparisons (García et al. 2013; Bakkiam et al. 2015; Wilkins et al. 2015). The strength of this network is the opportunity to perform some training to overcome weaknesses detected after inter-comparison results but also to allow some members to be trained in new biological and retrospective physical assays. As in all networks, some highly skilled laboratories can share their practices with other laboratories. Training courses require some time to organize but are very efficient to increase the performance of a given laboratory. The overall cost is a minor factor compared to the time spent to learn without such support. It is therefore crucial when harmonizing a network to provide the possibility to organize scientists' exchanges. For this purpose, European Programs jointly with the IAEA usually provide some support for training courses.

ISO standards are already available for the DCA (ISO 21243 2008; ISO 19238 2013), the MN assay (ISO 17099 2013) and EPR (ISO 13304 2013), but such standards are not used in all laboratories and they are specific to one assay. The QA&QM manual established during this program contains information applicable to all assays as well as details of each assay specific to the RENEB network. Furthermore, as many of the assays have no formal standards, it was useful to have a common basis for a QA&QM program.

The different assays included in RENEB have very different levels of maturation. This has a clear impact on the level of both validations and harmonization, which is also heterogeneous. The level of expected requirement per assay has been widely discussed by the partners. The level of the requirements included in the manual is a consensus but is not yet fully applied in all the RENEB laboratories. The QA&QM manual might be too complex for some laboratories. Some laboratories are national standard accredited (IRSN (France), SERMAS (Spain), NCSRD (Greece)); others belong to certified institutions (BIR and BfS (Germany), PHE (England)) whereas some others have just developed internal quality systems. Therefore, to check to what extent a quality system is applied, audits should be performed. However, auditing of this type is rather intrusive and costly. Within RENEB, no such audits have been performed. Instead, the capability of a given laboratory has been evaluated based on inter-comparisons but also questionnaires. Many partners support the idea that inter-comparison results should be sufficient to prove the quality of a partner for participation in a joint emergency response.

The RENEB network was open to any new members wishing to integrate the network. When an inter-comparison was organized, they were asked to evaluate their capacity and capability. However, to date, all partners have been accepted in the network because the criteria for acceptance have not been clearly fixed. Nevertheless, a questionnaire has been prepared to gather some ideas about the integration of new partners, whatever the dosimetric assays. New members should respect the procedures developed in the QA&QM manual in order to join the network and then participate in

an inter-comparison. Such procedures should guarantee a high standard level of biological and physical dose estimation across the network.

To ensure comparable and reliable dose estimates, not only each partner laboratory but also each assay must be subjected to critical examination with special focus on consistency of results, mainly for biological dosimetry. There are a considerable number of publications with challenging or even contradictory information about the applicability and use of apparently well-established biomarkers (Greve et al. 2012). Even for relatively well-established assays such as the MN assay, the predictive potential of these assays is still in question (Djuzenova et al. 2006).

This was one rationale of the RENEB project, which involved laboratories specialized in biological and physical dosimetry. Such a program stresses the differences between laboratories and the importance of having QA procedures. In order to be used in biological and physical dosimetry, the assays need to follow prescribed validation steps. Deviations from the QA&QM manuals will only be acceptable if studies have been performed to prove that an alternative protocol gives the same results.

Biodosimetry is useful in emergency situations but also in research where some links between health effects and dose are under investigation. The aim is to better estimate the risk linked to ionizing radiation exposure. In this research field, some networks are also required to handle a large number of samples as requested by molecular epidemiology studies. Such studies cannot be performed by a single laboratory. However, to be able to produce robust data it is essential to standardize the assays among the biological laboratories.

During this program, links between laboratories were extensively tested creating a well-structured network. The funded part of the RENEB program is now over and the lack of funds may lead to a different organizational structure. There is no guarantee that all partners will have the opportunity to take part in future inter-comparisons.

Despite the close links between laboratories, in case of emergency the way the network will be activated has not been fully tested. Theoretically, when the IAEA handles an accident, the agency will contact the RANET laboratories where many complementary competences are registered. Among them, dose evaluation using biological or physical tools can contribute to the management of the accident situation. However, only four biological dosimetry laboratories are registered through IAEA RANET; the majority of the RENEB laboratories could not be activated directly by these means. In a real incident, due to the close contacts established between the RENEB partners, it is intended that the national reference laboratory of the country where an emergency situation has occurred would request directly the RENEB partners for assistance. This is also agreed between the RENEB laboratories through a Memorandum of Understanding and stated in the RENEB QA&QM manual (9.2 Use of the network for large scale exposures). However, national authorities play also a critical role in the management of such emergency situation as a link between emergency teams and dosimetry laboratories.

For this reason a virtual exercise has been conducted to test the links between a local authority and each local reference laboratory. A request for assistance was sent to the various authorities to provide an opportunity to identify/correct the emergency focal point within RENEB. The major conclusions were that all the authorities have correctly identified the national reference laboratory either performing biological or physical dose evaluation.

In conclusion, the 23 RENEB laboratories are ready to manage between 15 and 3800 samples immediately, according to the dosimetry assay (Monteiro et al. 2016) and the vast majority of them follow the quality assurance rules. This can contribute to a group of highly trained laboratories with the availability of a large panel of highly standardized and harmonized biological and physical indicators of dose. RENEB provides a ready-to-use analysis platform with a special focus on large scale events, such as radiological emergency incidents with a large number of persons/casualties, large-scale follow up studies after a radiological or nuclear emergency. A framework for maintenance of competence of the current and future consortium has also been successfully created.

Disclosure statement

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