multibiodose

Guidance for using MULTIBIODOSE tools in Emergencies

for Radiation Emergency Response Organisations in Europe

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The opinions and views contained in this document are solely those of the group of experts in biodosimetry that are members of the MULTIBIODOSE consortium and do not necessarily represent the opinions and views of the consortium members´ organisations or of the European Commission.

Contents:

1. How to use this guidance

This guidance is intended for authorities involved in radiation protection and emergency preparedness as a source of information about the possibilities and limitations of biodosimetric triage tools developed and implemented during the MULTIBIODOSE (MBD) project and about the laboratories that are prepared to use these tools.

Chapter 3 (pages 8–10) contains the information about the MBD laboratories. This chapter is supplemented with detailed contact information to the laboratories in ***Appendix I (pages 32–34).*** **The information in Chapter 3 and Appendix I is the most important information from the point of view of radiation emergency responders. It is proposed that one of these laboratories is promptly contacted if the need for biodosimetric triage should occur. If needed, this laboratory will then initiate the network.**

Chapters 5 (pages 15–20) and ***8 (conclusions, page 29)*** of this guidance contain a general overview over the capacities for biodosimetric triage of MBD laboratories and describe organisational requirements for the effective use of the biodosimetric triage tools. It is desirable that these chapters are taken into consideration when preparing radiation emergency plans and in-house plans of radiation protection and health protection authorities, as well as hospitals designated to treat potential radiation casualties. Information in Chapters 5 and 8 is supplemented with ***Appendix IV (pages 39–46)*** that contains examples of protocols for taking and transporting samples. The knowledge of requirements for the logistics connected to the sampling is crucial for performing effective biodosimetric triage in a mass casualty radiological emergency.

Chapter 4 (pages 11–14) gives an overview over the features and characteristics of the biodosimetric triage tools and ***Chapter 6 (pages 21–27)*** elaborates on the usefulness of MBD tools in different generic, emergency scenario categories. These chapters are included in the guidance in order to give a collective view of the MBD biodosimetric tools and of their usefulness. The same refers to ***Chapter 7 (page 28)*** and ***Appendix II (pages 35–36).***

The Appendices III and V give a general overview over other important biodosimetry resources.

2. Introduction

In the event of a large scale radiological emergency, the triage of individuals according to their degree of exposure forms an important initial step of the accident management. Although clinical signs and symptoms of a serious exposure may be used for radiological triage, they are not necessarily radiation specific and can lead to a false diagnosis. Biodosimetry is a method based on the analysis of radiation-induced changes in cells of the human body or in portable electronic devices and enables the unequivocal identification of exposed people who should receive medical treatment.

The MULTIBIODOSE (MBD) consortium developed and validated several biodosimetric assays and adapted and tested them as tools for biological dose assessment in a mass casualty event. The main goal was to increase both the speed of analysis and the total biodosimetric capacity of the MBD laboratories.

Special focus was put on situations when dose estimates for a large number of individuals will be required by health service professionals and radiation protection authorities in a relatively short period of time (days, weeks or a month).

Different biodosimetric assays were validated against the 'gold standard' of biological dosimetry - the dicentric assay. The assays were harmonised in such a way that in an emergency situation they can be run in parallel in many MBD laboratories. A dedicated MBD statistical software tool was developed that allows collating results obtained with the different assays.

The aim of this guidance is to give a concise overview of the developed biodosimetric tools as well as how and when they can be used in an emergency situation.

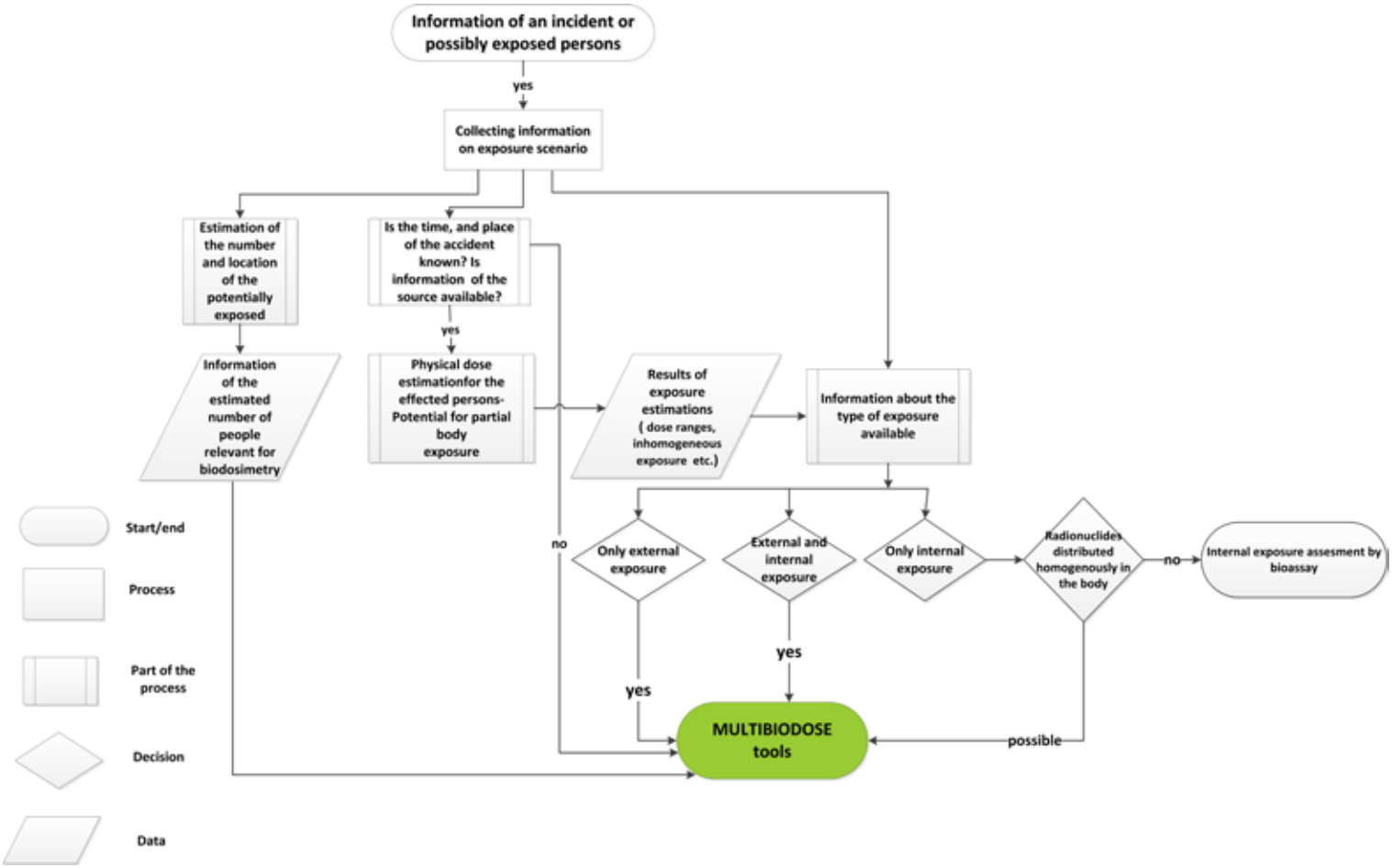


Figure 2.1. Flowchart that illustrates the need for specific information about exposure scenario in order to achieve most effective use of MBD tools in an emergency.

3. Status of MULTIBIODOSE (MBD) biodosimetry laboratories in EU countries and their connection to radiation emergency response organisations

Among MULTIBIODOSE participants are representatives from radiation protection authorities, health protection authorities, independent research institutes and universities. The full list is given at the end of this chapter.

STUK in Finland and NRPA in Norway are the authorities competent in nuclear and radiation emergency preparedness and response both at home and abroad. Thus they represent decision makers in the field of biodosimetry.

Health protection authorities like the HPA in the UK will likely be decision makers in small scale emergencies but in the case of a major emergency they will act under the authorities responsible for nuclear and radiological emergency. This is the Nuclear Decommissioning and Security Directorate in the UK

Public bodies of the National Health System like ISS wil act as technical support organizations to competent authorities responsible for nuclear and radiological emergency and for public health. In Italy these are respectively the Department of Civil Protection of the Prime Minister Office and the Ministry of Health.

The dedicated radiation protection institutes IRSN In France and BfS in Germany will be strongly involved in decision making in the field of biodosimetry but in case of large and international emergencies will act as technical support organisations for other decision makers like the Authorite de Surete Nucleaire(ASN) in France and Federal Ministry of the Environment in Germany. Other radiation research institutes in MBD consortium - the HMGU in Germany and INCT in Poland - do not have clear organisational connection to radiation emergency response decision makers and may act as support organisations on demand. The same applies also to the laboratory at Stockholm University in Sweden.

Other universities in the MBD Consortium have agreements with the national radiation protection and radiation emergency response authorities like Universitat Autònoma de Barcelona with Nuclear Safety Council in Spain (Consejo de Seguridad Nuclear C.S.N.) and Ghent University with the Federal Agency for Nuclear Control (FANC) in Belgium.

One organisation in the Consortium - BIR - is a military Institute but affiliated to the University of Ulm.
It must also be stated that some needs for biological dose estimations can occur in situation with terror and criminal acts and in such cases decision makers will probably be also forensic and military services.

As described above the MBD laboratories have different status with regard to their response in radiological events and thus differences in the availability of resources among laboratories exist. Several organisations have permanent arrangements for biodosimetry and have permanent staff working with MBD assays (STUK, HPA, BfS, IRSN, Ghent University) while others are research laboratories that are able to switch into biodosimetry for research projects like MBD, inter-comparison exercises and emergencies.

A list and description of MULTIBIODOSE partners (in alphabetical order) is given below:

Autonomous University of Barcelona (UAB), Spain - www.uab.es. UAB is a research and education entity. UAB is a pioneering and innovative research institution. It is one of the responsible laboratories for biological dosimetry in Spain.

Bundeswehr Institute of Radiobiology affiliated to the University of Ulm (BIR-UULM), Munich, Germany - www.radiation-medicine.de. BIR-UULM is a Federal Defence research institute.

It is the responsible laboratory for radiation accidents and biological dosimetry of the German Armed Forces.

European Radiation Dosimetry Group (EURADOS), Braunschweig, Germany – www.eurados.org. EURADOS is a non-profit organization which promotes research and development and European cooperation in the field of the dosimetry of ionizing radiation. It is a network of more than 50 European institutions and 250 scientists. WG10 deals with retrospective dosimetry.

Federal Office for Radiation Protection (BfS), Munich, Germany – www.bfs.de. BfS is a scientific-technical Superior Federal Authority in the portfolio of the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety. The BfS is the official laboratory charged with the performance of biological dosimetry in Germany since 1982.

Health Protection Agency (HPA), Didcot, UK – www.hpa.uk. The HPA is a UK-wide public health organisation that delivers advice and services to the UK government and others, and undertakes relevant research. It is the responsible laboratory for radiation accidents and biological dosimetry in the UK. On 1 April 2013, the functions of the HPA have been transferred to Public Health England (PHE; www.gov.uk/PHE).

Helmholtz Zentrum München (HMGU), Munich Germany - www.helmholtz-muenchen.de. HMGU is a research institution of the Federal Government and the State of Bavaria within the Helmholtz Association of German Research Centres. The Institute of Radiation Protection deals with all aspects of radiation protection and specialises in the application of EPR and OSL dosimetry in cases of radiation accidents.

Institute for Radiological Protection and Nuclear Safety (IRSN), Fontenay-aux-Roses, France – www.irsn.fr. IRSN is the French national public expert in nuclear and radiological risks. It is the institute for radiation accident dosimetry (physical and biological).

Institute of Nuclear Chemistry and Technology (INCT), Warszawa, Poland – www.ichtj.waw.pl. INCT is a state radiation research institute. INCT is the responsible laboratory for biological dosimetry in Poland.

Istituto Superiore di Sanità (ISS), Rome, Italy – www.iss.it. ISS is the leading technical and scientific public body of the Italian National Health Service. Its activities include research, control, and training in radiation protection and in emergency response for the aspects related to public health. It deals with EPR and OSL dosimetry in cases of radiation accidents.

Norwegian Radiation Protection Authority (NRPA), Østerås, Norway – www.nrpa.no. NRPA is the governmental agency dealing with every aspect of radiological emergency preparedness and response including public health in Norway.

Radiation and Nuclear Safety Authority (STUK), Helsinki, Finland – www.stuk.fi. STUK is a national authority in radiation protection and nuclear safety. It is the responsible laboratory dealing with radiation accidents and biological dosimetry in Finland.

Ghent University (UGent), Belgium - www.ugent.be. The Radiation and DNA Repair Research unit in the Faculty of Medicine and Health Sciences is the responsible biological dosimetry laboratory in Belgium.

University of Stockholm (SU), Sweden – www.su.se . The Centre for Radiation Protection Research is a research entity financially supported by the Swedish Radiation Protection Authority.

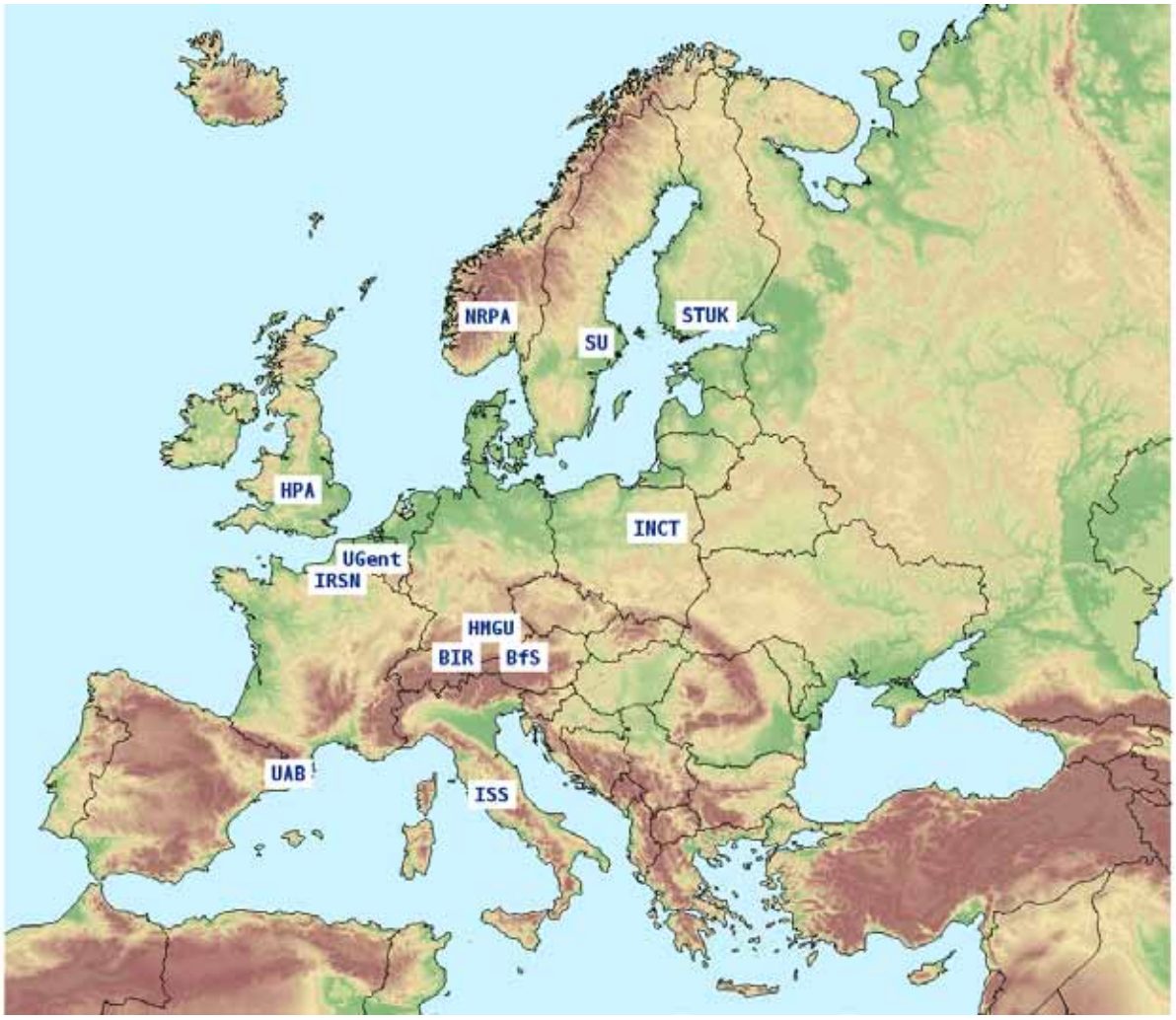


Figure 3.1. Map showing the location of the MULTIBIODOSE partner institutes.

Generally, the biodosimetry laboratories involved in the MBD consortium are small, with few researchers and technicians working with MBD assays for biodosimetry purpose. Although the MBD consortium has made significant improvements in the speed of dose assessment for several assays through automation and concerted actions, the bottleneck for the total capacity of the network remains in the human resources. It is common that the same staff members perform several techniques at the same laboratory. Additionally, for dose estimations based on the EPR and OSL measurements of portable electronic devices the bottleneck lies in the availability of instrumentation and existing facilities. During the MBD project three MBD laboratories have been validated for both EPR and OSL measurements of portable electronic devices. Another 27 laboratories were validated through the EURADOS network.

The contact details of the MBD biodosimetry laboratories can be found in Appendix 9.I.

4. Characterisation of MBD tools

Within MULTIBIODOSE the following dosimetric assays were tested and validated for their suitability as tools to triage exposed people in case of a large-scale radiological emergency:

- Manual and automated dicentric assay
- Automated micronucleus assay
- Gamma-H2AX assay
- Skin speckle assay (SSA)
- Serum protein assay (SPA)
- Electron paramagnetic resonance (EPR)
- Optically stimulated luminescence (OSL)

In the following, the tools will be briefly characterised. The tools were tested for their ability to identify a person exposed to a dose higher than 1 Gy of gamma radiation with high degree precision.

Manual and automated dicentric assay

The dicentric assay is based on assessing the frequency of dicentric chromosomes in peripheral blood lymphocytes (PBL) of the exposed person. The dicentric chromosome is specific for ionising radiation and the spontaneous frequency is very low in the healthy population. It is standardised on the international level (ISO 19238 and ISO 21243) and regarded as the gold standard of biological dosimetry. The assay requires collecting ca. 5 ml of venous blood. Subsequently, in vitro culturing of PBL for a 48 h period is necessary for visualisation of chromosomes. Dicentrics can be scored manually under the microscope or automatically/semi-automatically with the help of an image analysis system coupled to a microscope equipped with a motorised stage. The absorbed dose can be assessed up to a few months after exposure.

We have tested the dicentric assay and found that manual scoring of 50 cells per donor or automatic scoring of 150 cells per donor is sufficient to identify a person exposed to a dose higher than 1 Gy with a high degree precision. Partial body exposure covering 50% of the cells and protracted exposure (irradiation time of 16 hours) were also tested and found detectable. Moreover, we successfully tested the possibility of manual scoring of chromosome images. This approach gives the possibility of quick input from a large number of laboratories in the analysis.

Automated micronucleus assay

The micronucleus assay is based on assessing the frequency of micronuclei in peripheral blood lymphocytes (PBL) of the exposed person. Micronuclei (MN) are not specific for ionising radiation and the spontaneous frequency is much higher than that of dicentrics. However, radiation is a very potent inducer of MN, so a high frequency of MN strongly indicates radiation exposure. A large number of cells can be scored within a time shorter than that required for scoring dicentrics. The standardisation of the assay on the international level is ongoing (ISO 17099). Similarly as the dicentric assays it requires collecting ca. 5 ml of venous blood. Subsequently, in vitro culturing of PBL for a period of ca. 72 hours is necessary. MN can be scored automatically with high speed using an image analysis system coupled to a microscope equipped with a motorised stage. The absorbed dose can be assessed in a meaningful way up to one year after exposure.

We have shown that automatic scoring of 1000 cells per donor with the MN assay is sufficient to identify a person exposed to a dose higher than 1 Gy with a high degree precision. Protracted (irradiation time of 16 hours) whole body, and partial body exposures were also tested and found detectable.

Gamma-H2AX assay

The gamma-H2AX assay is based on analysing the formation of DNA repair protein clusters – called gamma-H2AX «foci» - in peripheral blood lymphocytes of an exposed person. Similar to micronuclei, the foci are not specific to but indicative of ionising radiation exposure and the spontaneous frequency is quite low. The analysis can be done manually or automatically using a microscope or automatically using a flow cytometer. The assay has high sensitivity (if used within a few hours post exposure); that it only requires a drop of blood (finger prick) and it does not require culturing of lymphocytes, as is the case of the dicentric and MN assays, and therefore provides results within a few hours. The assay has a low signal stability: the absorbed dose

(whole and partial body) can be assessed up to ca. 1–3 days after exposure.

We developed a portable system for the «on site» analysis of foci, but it did not yield reliable results. Subsequently, we successfully validated the microscope-based, manual and automated analyses of foci. This system is able to detect whole body exposure up to 1–3 days after the radiation exposure.

Skin speckle assay (SSA)

The skin speckle assay is based on the ability to detect radiation-induced speckle patterns in the skin. The assay is specific to radiation-induced skin damage and its unique advantage is the possibility to detect a dose to a small area of the skin in a totally non-invasive and very fast way. We tested the SSA assay and found at least one month must pass between radiation exposure and analysis before a radiation-induced skin speckle pattern is detectable. For this reason this assay is not suitable for a timely triage of people exposed in a large-scale radiation emergency.

Serum protein assay (SPA)

The change of concentration of selected proteins in serum following localised exposure of skin to radiation was tested in samples collected form patients treated by external beam radiotherapy as a tool for identifying partial-body exposure. Although promising results were obtained in earlier mouse experiments, the changes in protein concentration in patients showed very strong individual variability that makes the assay unsuitable for use in emergency situations, when the individual levels of proteins before radiation exposure are not known.

Electron paramagnetic resonance (EPR)

EPR is a spectroscopic technique for studying radiation-induced radicals in biological or artificial materials. Ionising radiation induces radicals in glass displays of portable electronic devices like smart phones. Consequently, these can be used as individual dosimeters, but must be removed and destroyed for measurement. The advantage of EPR is high radiation specificity, good sensitivity in the high dose region radiation (>1 Gy) and very long signal stability (several months). The method has poor sensitivity to low doses (detection threshold = 1 Gy). Analysis must be carried out in a laboratory equipped with an EPR spectrometer. The method is currently in the process of ISO standardisation.

Optically stimulated luminescence (OSL)

OSL assesses the dose of ionising radiation by measuring light emitted from irradiated objects. Electronic elements used in mobile phones have luminescent properties and can be used as individual dosimeters, but require removal and destruction of the electronic circuitry board. OSL has very high specificity and sensitivity to radiation (from several mGy to several Gy), but poor signal stability: there is a signal loss of 50% in the first 10 days after irradiation and fading correction must be applied. Analysis must be carried out in a laboratory equipped with an OSL reader.

MBD dedicated statistical software

A major challenge for the MULTIBIODOSE project was to develope a tool bringing together the results of the different biodosimetric methods to rapidly form a single judgement regarding the status of an exposed person. To this end a statistical software tool was developed that allows categorising an exposed person into one of the following dose categories: GREEN (< 1 Gy), YELLOW (1-2 Gy) and RED (> 2 Gy). The program is open to incorporate new dosimetric tools that may be developed in the future. Detailed description of the software and uncertainties of dose estimate using MBD methods is given in the Appendix II.

Table 4.1 presents the characteristics of different MBD methods. Table 4.2 illustrates the time needed to process the samples and table 4.3 illustrates the total time needed to analyse different quantities of samples by one laboratory and also by several laboratories simultaneously.
Examples of protocols for collection and shipment of samples are presented in Appendix IV.

Table 4.1. General characteristics of the assays.

Assay	Time span after exposure during which the assay can yield usable results			Exposure scenario that can be detected by each method alone			Specific for ionizing radiation	Sensitivity[1] of the assay (dose range in Gy)	Automated (A) / manual (M) analysis
	Days	Weeks	Months	Acute	Protracted	Partial body			
Dicentrics manual	√	√	√	√	√	√	√	0.1 - 5	M
Dicentrics automated	√	√	√	√	√	√	√	0.1 - 5	A
Dicentrics telescoring	√	√	√	√	√	√	√	0.1 - 5	M
Micronuclei	√	√	√	√	√	√		0.3 - 5	A
Gamma H2AX	√			√				0.2 - 5	A/M
EPR (ped)[2]	√	√	√	√	√		√	1 -> 10	A
OSL (ped)	√	√		√	√		√	0.01 - > 10	A

[1] for most low LET radiation qualities such as gamma and X-rays
[2] ped: portable electronic devices

Table 4.2. Approximated, optimal duration of sample analysis using different MBD methods. The aim of this table is not to provide precise time estimates, but rather to give a comparative overview of the characteristic of each method.

	Time per step per sample Time in hours		
	Culture of cells	Preparation of slides/samples	Analysis
Dicentrics manual	48	4	0.5
Dicentrics automated	48	4	0.2
Dicentrics telescoring[2]	48	4	0.5
Micronuclei	72	4	0.2
Gamma H2AX	0	2	0.1
EPR (ped)1	0	0.2	0.2
OSL (ped)	0	0.3	0.06

[1] ped: portable electronic devices
[2] Telescoring does not include the time required for capturing and web page uploading of metaphase images

Table 4. 3. Approximated optimal duration (in days) between the time point of sample arrival at the laboratory and the completion of dose estimation results, calculated for different numbers of samples analyzed by one or five laboratories. The aim of this table is not to provide precise time estimates, but rather to give a comparative overview of the characteristic of each method. Bear in mind that the times may change based on the momentary capacity and work load of a laboratory.

	Total time to analyse samples[1]					
	Time in days					
	1 sample 1 lab	50 samples 1 lab	100 samples		1000 samples	
			1 lab	5 labs	1 lab	5 labs
Dicentrics manual	2.5	6	9	5	65	16
Dicentrics automated	2.5	4	5	3	24	7
Dicentrics telescoring	2.5	6	9	4	65	13
Micronuclei	3.5	4	5	4	20	6
Gamma H2AX	<1	1	1	1	3	3
EPR (ped)[2]	<1	1	4	1	40	14
OSL (ped)	<1	1	4	1	40	14

[1] does not include time for shipment of samples
Calculation made for one person per lab working 8 hours per day
In case of telescoring all cultures are done by one lab
In case of automatic scoring the machine works 24h /day
[2] ped: portable electronic devices

5. Emergency preparedness; Organisational requirements for effective use of MBD tools

(Preparedness for the use of MBD tools: logistic, protocols, information to the relevant end-users)

A. General remarks

Biodosimetry laboratories within MBD are specialized laboratories with expertise in biological dosimetry, radiation biology, cytogenetics, basic radiation protection, and biophysical methods for biodosimetry. These laboratories do not form routine components of hospitals or health service laboratories. Rather, they are assosiated with radiation protection authorities or institutions working in the field of radiation research. Therefore, it is a prerequisite that the emergency response organisations, the relevant hospitals and health services that may potentially act in radiological and nuclear emergencies have a harmonised approach in their emergency plans regarding biodosimetry. Both the emergency response organisations and hospitals should have minimal standard procedures to implement biodosimetry.

Such procedures are defined by the IAEA in technical documents (EPR MEDICAL 2005 and EPR Biodosimetry 2011) and ISO standards (Practical advice can also be found in the TMT handbook -http://www.tmthandbook.org).

The Multibiodose consortium proposes that the national authorities and medical service units responsible for radiological emergency preparedness would communicate with the MBD biodosimetry laboratory, or, if one does not exist in their country, with the MBD biodosimetry laboratory in another country. This laboratory will be in charge of the biodosimetry service. In case of a radiological emergency this laboratory will either perform the required biodosimetric analysis or, if the number of samples exceeds its capacity, will coordinate sharing samples between MBD laboratories and collecting the results. This laboratory will also decide which biodosimetry assays will be the optimal ones for use in the particular emergency scenario. Further, this laboratory will be in charge of the dose estimate calculations and statistical analysis of the results using the dedicated software (described in chapter 4 and Appendix II).

The MBD consortium recommends the parallel application of as many MBD tools as possible. Each method has its specific characteristics, so the total results can give valuable information about the exposure scenario and its time point. This is illustrated in table 5.1.

Table 5.1. An example of how combined application of the MBD tools enables scenario identification. YES/NO indicates whether an assay demonstrates a significant radiation exposure.

	Dicentrics	Micronuclei	G-H2AX	EPR	OSL
Whole body exposure	YES	YES	YES	YES	YES
Partial body exposure I	YES	YES	YES	NO	NO
Partial body exposure II	NO	NO	NO	YES	YES
Eposure >24h ago	YES	YES	NO	YES	YES
Eposure >10 days ago	YES	YES	NO	YES	YES

Partial body exposure I: ped outside irridation field
Partial body exposure II: ped inside irridation field

Table 5.2. Approximate total capacity of the MBD laboratories as of February 2013, taking into consideration personnel and instrumentation resources. In principle, this guidance is written for biodosimetric triage. However, for the sake og comparison we include information about full mode dosimetry in this table.

Method	Cytogenetic assays (dicentric and micronucleus assays)		Gamma H2AX		EPR and OSL in portable electronic devices	
time period	week	month	week	month	week	month
full mode	100	380	NA	NA	690	2860
triage mode	**1080**	**4120**	**2260**	**9040**	**4190**	**17890**

NA: not applicable as the test is only used for triage mode.

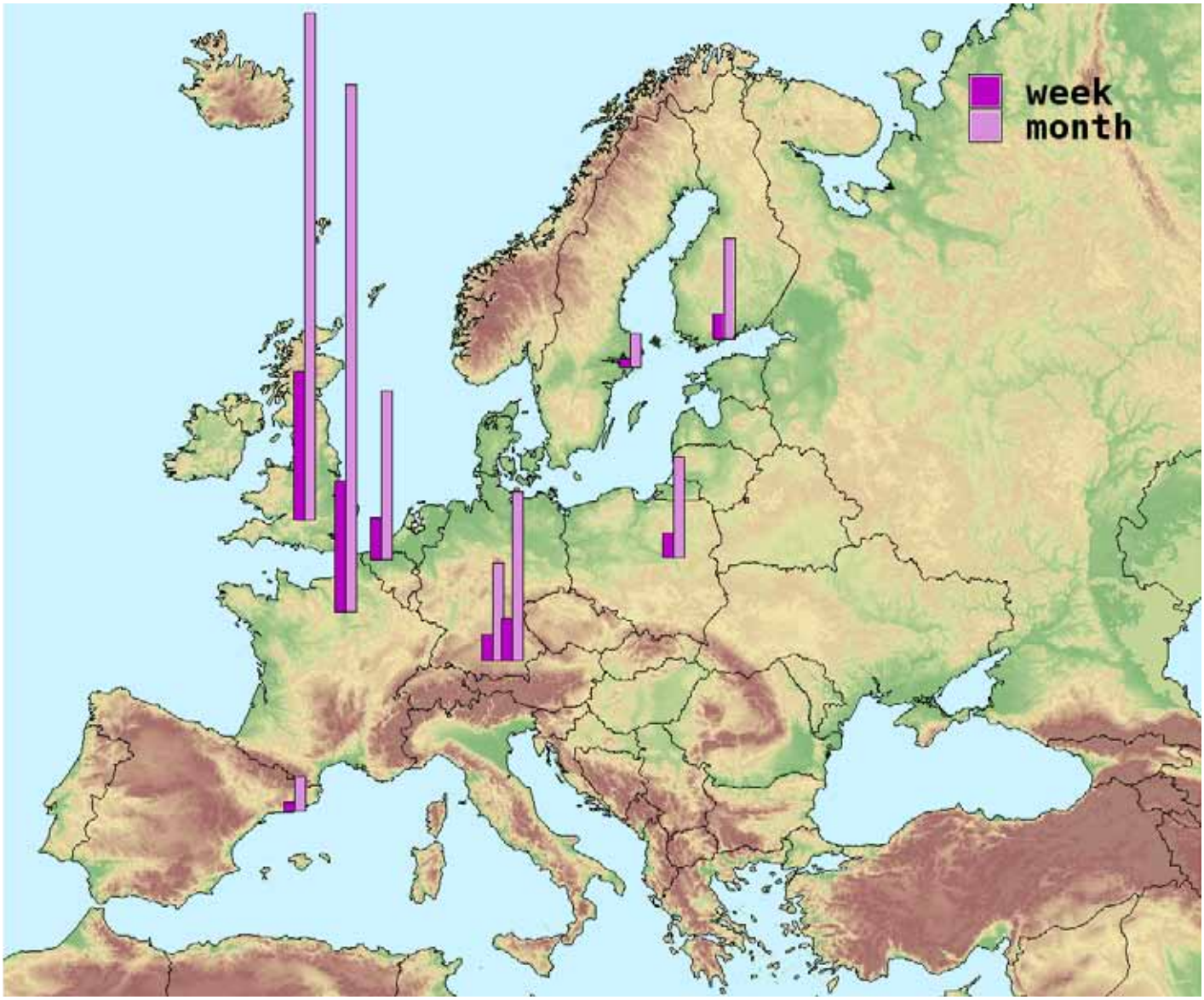


Figure 5.1. Geographical locations of MBD biodosimetry laboratories and their capacities in numbers of exposed cases triaged by dicentrics and micronuclei. The aim of the graph is to give a comparative overview. Please see table 5.2 for numerical values.

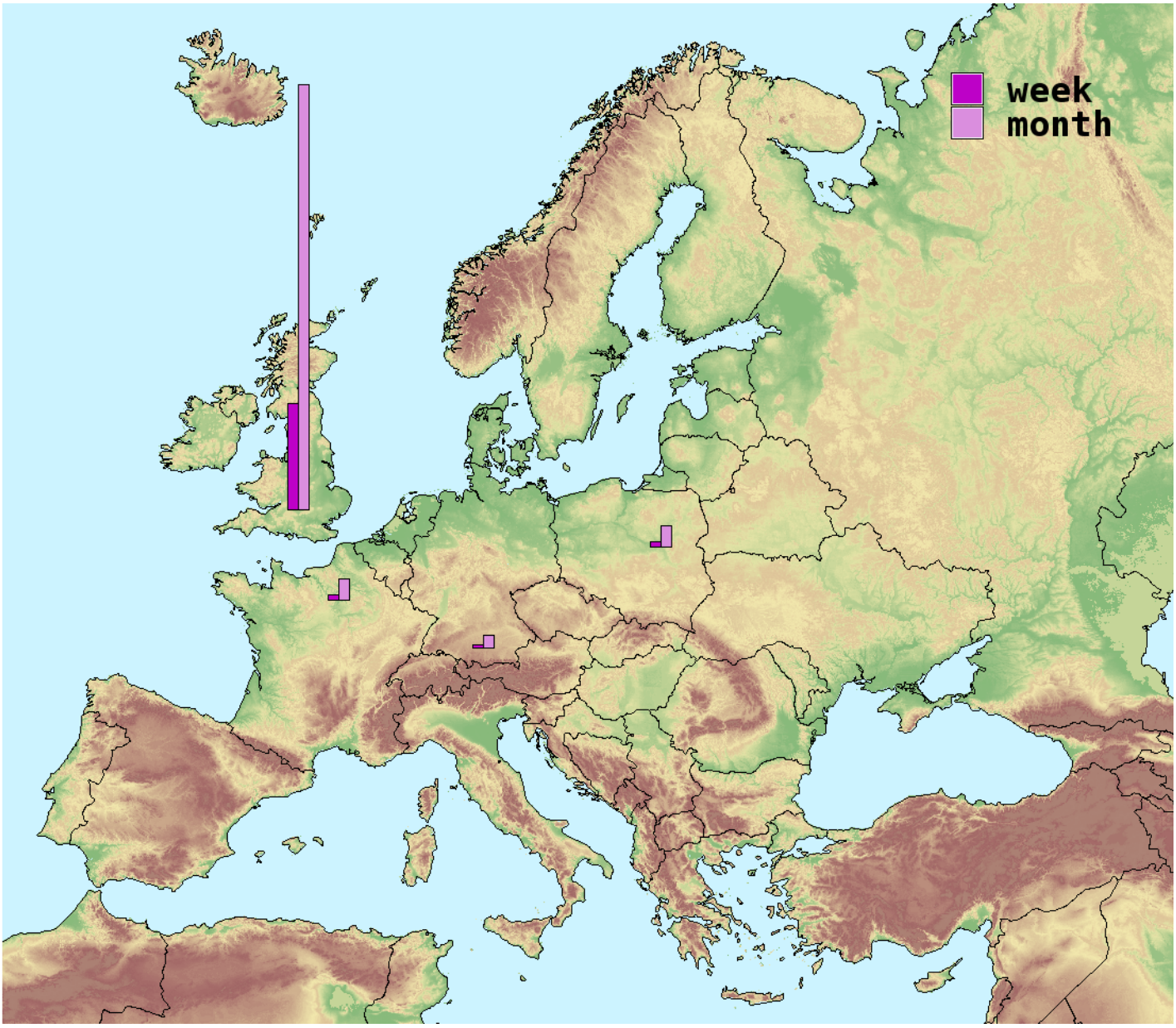


Figure 5.2. Geographical locations of MBD biodosimetry laboratories and their capacities in numbers of exposed cases triaged by gamma H2AX. The aim of the graph is to give a comparative overview. Please see table 5.2 for numerical values. The scale of bars is reduced by a factor of ~ 8 as compared to capacity to cytogenetic assay in figure 5.1.

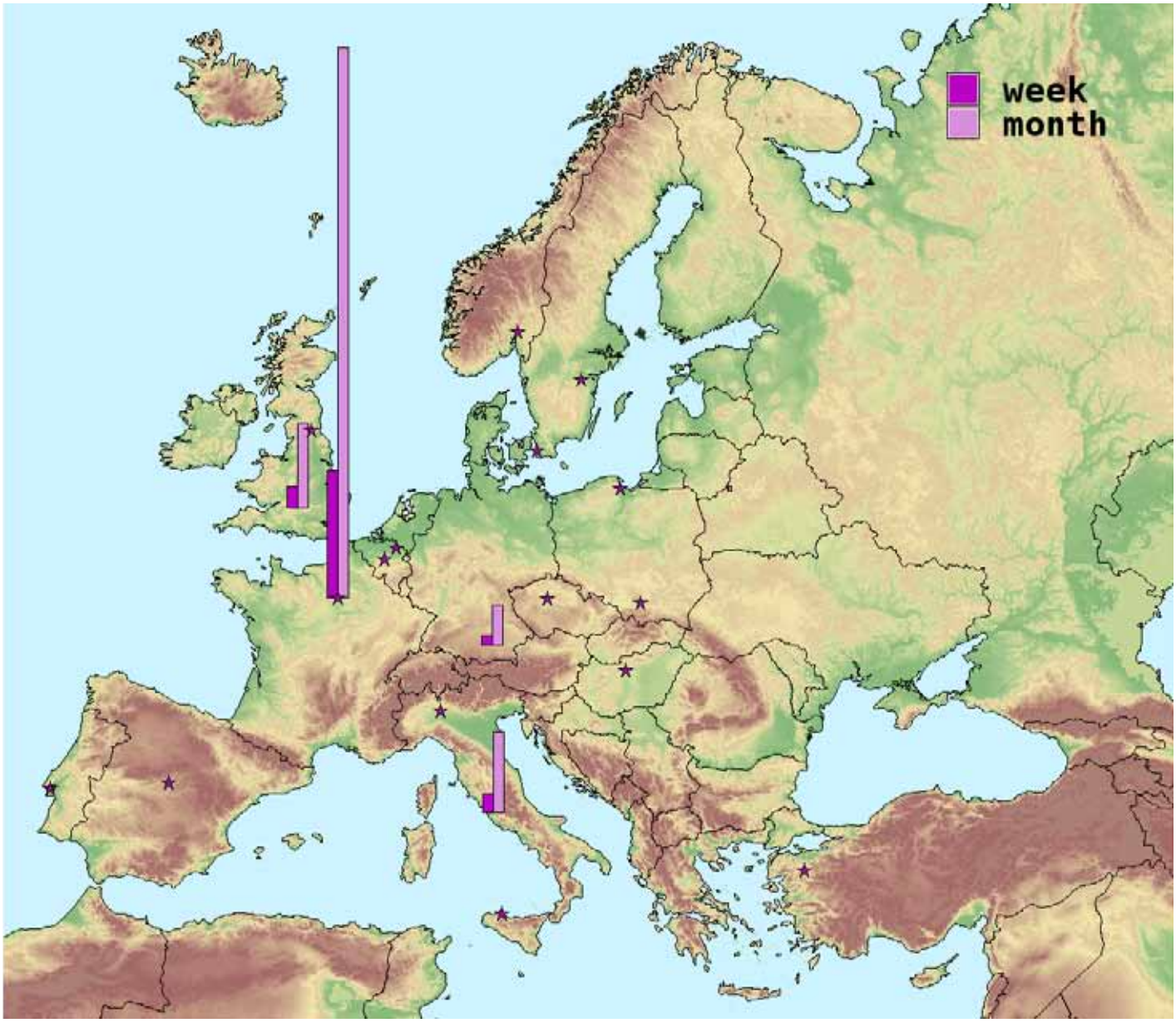


Figure 5.3. Geographical locations of MBD laboratories performing EPR and OSL in portable electronic devices, and their capacity in numbers of cases per week or month to triage exposed victims. Please see table 5.2 for numerical values. The scale of bars is reduced by a factor of ~10 as compared to capacity to cytogenetic assay in figure 5.1. Stars mark the location of laboratories associated with EURADOS that have either EPR or OSL competence and may be asked for assistance in case of a large emergency.

It must be stressed that the numbers given in the tables and shown on the maps are based on many assumptions like workload, the availability of human resources, feasibility to perform several assays at the same time, availability of consumables, etc. The numbers can easily change if resources in MBD laboratories are modified.

B. Preparedness for the use of MBD tools: logistic, protocols, information to the relevant end-users

The multi-parametric and multi-laboratory approach for the effective use of MBD biodosimetry tools requires that the responders involved in the radiological emergency are aware of the feasibilities and limitations of the assays and the availability of laboratories performing these assays.

It should also be pointed out that the costs of biodosimetric analyses are not negligible, because the assays are labour-intensive. The full manual analysis of one sample by the dicentric assay may cost from several hundred to about 1000 €. In case of a mass casualty situation samples will be analysed in the triage mode that will be cheaper but the analysis of one sample by the dicentric assay may still cost about 200 €. The same cost applies to the estimate for a micronucleus assay analysis of one sample in the triage mode.

The cost of analysis of portable electronic devices by EPR or OSL is cheaper per sample, because, except for instrumentation, there is no need for expensive reagents. The analysis requires a relatively short period of time, but is labour intensive and the portable electronic devices must be dismantled and parts of them have destroyed in the analysis. This implies costs for the individual, the health service or the insurance company.

Decision makers in public health emergency should be aware of the possibilities and methodological restrictions of the different assay as described briefly in paragraph 3 and should be aware of the information given in Chapter 6 of this guidance.

Procedures for contacting the biodosimetry laboratory, as well as for taking blood samples and the logistics connected to the transport of blood and portable electronic devices should be available in advance. Special considerations have to be taken regarding transport conditions of the blood. The protocols should include the forms for collecting the available information about the exposure, blood collection and storage, and the health status of the individual.

There are a number of available protocols and manuals that should be adjusted to the national context. Countries with well-established biodosimetry services have all these protocols in place. Examples of protocol and information material are given in Appendix IV.

6. The use of MBD tools for acute biodosimetry in an emergency response

A. General introduction and possible exposure scenarios

Nuclear and radiological emergencies can result in the need to perform dose assessment on samples from few to thousands of people (a mass casualty scenario). The affected people can include professionals working with industrial or medical radiation sources or in nuclear facilities. In many scenarios, however, also members of the public can be exposed. Some scenarios could result in a limited number of people receiving high doses that lead to the development of the acute radiation syndrome and a large number of people receiving moderate or low doses.

A scenario can also be envisaged where a large number of people are affected by the emergency with only few being really exposed. Among the unexposed will be individuals with signs and symptoms like vomiting, diarrhoea or dizziness that can be interpreted as signs of exposure. These so called worried well require biodosimetry. The need for biodosimetry will be especially high in situations with limited availability of information about the exposure scenario. This will most probably be the case in emergencies where the victims are members of the public.

Exposure scenarios can be grouped into the following categories:

1. Accidents associated with professional use of radiation in nuclear facilities (including nuclear power plants), industry, research and medicine.
2. Accidents with sources out of regulatory control (so called orphan sources).
3. Accidents resulting from malevolent use of radiation sources and radioactive material (including terrorist attacks).

The first category scenario will most likely lead to exposure of patients or professionals working with radiation. There may be only a limited number of people exposed to doses exceeding the occupational limit of 20 mSv per year in Europe or 50mSv per year in USA. An exception in this category was the Chernobyl catastrophe. The present-day doses are expected to be lower than those received in the past. Within industrial use of sealed radiation sources, the current number of events with significant exposure of the individuals is only about 10 percent of the number in the 1970's. Better radiation protection regulations and introduction of the ALARA (As Low As Reasonably Achievable) principle has led to a reduction of the number of serious (severe) accidents in industrial application of radiation sources.

Old sealed sources, orphan sources or other sealed sources used in a malevolent way, can pose a significant threat of exposure of the general public. In such a scenario, the need for biodosimetry is evident. If a high activity source is placed in a public place and not discovered promptly, the number of exposed people requiring biodosimetry may increase to very high numbers.

Exposure to open radiation sources leading to contamination may also generate the need for using biodosimetry. Biodosimetry is seldom used for assessment of exposure from internal contamination. Whole body counting and measuring radioactivity in urine, feces or fragments of human tissue generally give more accurate dose estimates. However, the prolonged deposition of radioactive material on the surface of the human body can lead to significant exposure. An example of such a case is the Goiania accident in 1987, where more than one hundred thousand people were potentially contaminated with ^{137}Cs. Among them several people developed signs of the acute radiation syndrome, mostly due to gamma irradiation from external contamination. In such cases biodosimetry can provide valuable information to support the medical treatment.

B. Categorization of the scenarios according to the mode of exposure

As mentioned in the previous chapter, exposure to radiation can be categorized as internal and external. The biodosimetric methods are not best suited for internal exposure assessment due to generally lower acute doses and to an inhomogeneity of radionuclide deposition in the body. Possible scenario leading to internal contamination of a large group of people is the disper-

sion of radioactive material as a result of an accident, a criminal act or a terror incident.

One of the most feared accident types are those occuring in nuclear power plants. There will likely be a need for biodosimetry to diagnose some of the workers and other persons that were in the proximity of the plant or installation. The number of people identified for biological dosimetry probably will not be high, and radiological biodosimetry triage will probably not be required for the members of the public. This view is based on the experience of the Fukushima Daiichi catastrophe. One should however not forget that after the Chernobyl catastrophe, there was a strong need for biodosimetry of a large number of people, both among the power plant employees and those who were ordered to mitigate the consequences of the accident (the so called liquidators).

Among other scenarios where dispersion of radioactivity and contamination of the people and the environment is likey to occur, are scenarios with the use of radiological dispersal device (RDD, dirty bomb), contamination of food and water supplies, attack on transport or installation containing radioactive material feasible to disperse etc. In all these scenarios radiological triage will be needed and biodosimetric triage may play a crucial role in the implementation. It could be assessed that biodosimetric triage will not be the method of choice because it is not suitable for internal contamination. The past events, however, show that public demand and political decisions can necessitate the use of these assays. Here, the main aim can be to reassure the public.

Accidents that are considered most suitable for mass casualty biodosimetry are, however, those resulting from the use of strong sealed radiation sources (radiation exposure device - RED) in a public place. This can occur through a deliberate criminal (terrorist) act, or a forgotten old source that was misplaced and entered the public domain. Other accident categories that necessitate the use of biodosimetry on large groups of people are attacks on nuclear installations that will result in damage to the physical protection barriers of the facility sources, or the use of the improvised nuclear devices.

C. Categorization of the scenarios according to the timescale of collecting and delivering samples for biodosimetry

Events that require biodosimetry can be grouped according to the time that elapsed between exposure and the awareness that the event occurred.

1. When the group of exposed people is well characterised and the time and place of exposure are readily known, the biodosimetric analysis can be carried out within a short time i.e. few hours to some days after the event. Scenarios of such events are detonations of dirty bombs, attacks on nuclear installations or transport, announced placing of strong radioactive sources in a public zone, etc. The number of affected people may be very large and biodosimetric tools and the networking of many laboratories, like the MBD network, will be of particular help.

   First inquires for biodosimetry will most probably come from medical doctors dealing with seriously damaged casualties with signs and symptoms of acute radiation syndrome (ARS). The doctors will have an urgent need for dose assessment in order to predict the development of ARS. There will also be a need to identify individuals who were exposed to doses below 1 Gy and may not develop ARS, but are at risk for late effects of radiation exposure. Finally, there will also be a demand for dose assessment to reassure the worried well. However, it should be noted that these categories of patients are not the primary concern of biodosimetric triage.Precise evaluation of these patient doses can wait until the triage is completed.

2. A different situation will be found when the time point and place of exposure are not readily known. Examples of such events are orphan sources misplaced in public places or homes, hidden strong radioactive sources positioned in public places or public transportation systems, crowded city centres, stadiums and similar. Such events will probably be discovered after a time delay and the uncertainty regarding the time and distance that a victim spent near the source will complicate the calculations of individual absorbed dose. Exposed individuals will probably be identified based on symptoms when they contact medical doctors. This will trigger the action of identifying the nature of the source. Subsequently health- and radiation protection authorities

will try to identify potentially affected groups of the public. Consequently, the need for biodosimetric analyses during the first few days will be low. Later, when the knowledge about the event increases and as media reports trigger public attention, the numbers of candidates for biodosimetric analyses may be expected to reach hundreds or thousands.

D. Categorisations of the scenarios according to the number of people who require biodosimetry

Following a large scale radiological event the number of requests for biodosimetric analyses can range from few to a few hundred thousand. A mass casualty event will probably be associated with destruction of infrastructures so acute biodosimetry will not be on the list of prioritised actions. By acute biodosimetry we mean dose assessment during the first week after an event.

From the perspective of biodosimetric triage, the most demanding scenario is the situation when there is a small number of highly irradiated people in a large group of potentially exposed. The highly irradiated cases will in most cases be identified based on their clinical symptoms, but it can be expected that the health service centres will be overwhelmed with false positive cases (worried well) of overexposure that will require reassurance.

Table 6.1. Exposure scenarios grouped according to demand for a prompt need of extensive biodosimetric triage.

Generic scenarios
An improvised nuclear device, explosion of a sealed radiation source or an explosion of a strong radioactive sources may generate the need for prompt biodosimetric triage and results would be desired as soon as possible.
Hidden radiation sources placed in public places as terror or criminal acts, or misplaced, forgotten old sources (called also orphan sources, or according to IAEA terminology sources out of regulatory control) could also generate thousands of candidates for biodosimetric triage. In contrast to the first group the demand for biodosimetry will be delayed as compared with the incidents described above. The samples will arrive at the biodosimetry laboratories over the following months.
Incidents in close the nuclear facilities and even accidents in nuclear power plants (as we have learned from Fukushima accident) will not generate the need for acute biodosimetric triage. The need might be in the order of hundreds. Biodosimetric follow up, however, may be desired later.
RDD (dirty bombs) will probably not generate many candidates for biodosimetric triage, except for those who were very near the point of the explosion and some worried well individuals.
Incidents with overexpose in industry, medicine and research will probably affect small number of people and small scale of biodosimetric triage will be probably followed by full mode biodosimetry.

E. Applicability of MBD tools in different scenario categories.

As mentioned in chapter 4, it is recommended to use all MBD assays, as the results may provide important information about the nature of the irradiation. However, this may not always be possible and not necessary in accidents where the exposure conditions are well characterised. This chapter attempts to show which assays will work best in scenarios described in table 6.1. The laboratory designated to perform biodosimetry will be in charge of choosing the assays or at least in giving advice. However, it is recommended that some knowledge about the assays is available in the health protection and emergency response organisations.

The example of the generic scenario type is described in the upper rows of tables 6.2 to 6.4.

The assays applicable for a particular scenario are marked with «Y». Double «YY» indicates strong applicability, «N» marks assays that are not useful.

In the action part (lower part) of the tables only the recommended assays are marked.

Table 6.2. Decision table when few individuals are involved, and the time of exposure is known.

Exposure time and time of sampling of blood or ped is known. Characteristics of the exposure conditions is provided. Few individuals. Some individuals may receive doses of 1Gy or more.							
Assay	Dicentrics manual	Dicentrics automated	Dicentrics telescoring	Micronuclei automated	Gamma H2AX	OSL ped	EPR ped
Features of the event scenario							
Few affected people and/ or PBE	YY	Y	N	Y	Y	Y	Y
Sampling time: less than 24h after exposure	YY	Y	N	Y	YY	Y	Y
Sampling time: more than 24h after exposure	YY	Y	N	Y	N	Y	Y
Sensitive individuals in the group (pregnant women, children etc.)	YY	Y	N	Y	Y	Y	Y
Choice of the suitable assays							
Choice of the assay	YY	Y		Y	Y/N	Y	Y

ped: portable electronic devices
PBE: partial body exposure

Table 6.3. Decision table for scenario with a large number of people, and when the exposure time and date are not known.

Exposure time not known and characteristics of the exposure are ill defined. Biodosimetric triage for a group of patients with suspected radiation exposure arriving at the hospital after first conventional medical triage							
Assay	Dicentrics manual	Dicentrics automated	Dicentrics telescoring	Micronuclei automated	Gamma H2AX	OSL ped	EPR ped
Features of the event scenario							
ARS symptoms among the patients (possible exposure over 1Gy)	Y	YY	Y	YY	N	N	Y
Inhomogeneous exposure (partial body)	YY	YY	Y	Y	N	N	Y
Large number of patients, more than 100	N	YY	Y	YY	N	N	Y
Sensitive individuals in the group (pregnant women, children etc)	YY	Y	Y	Y	N	Y	Y
Choice of the suitable assays							
Choice of assays when the number of exposed individuals is low	YY	Y		Y			Y
Choice of assays when the number of patients is high		YY	Y	YY			Y

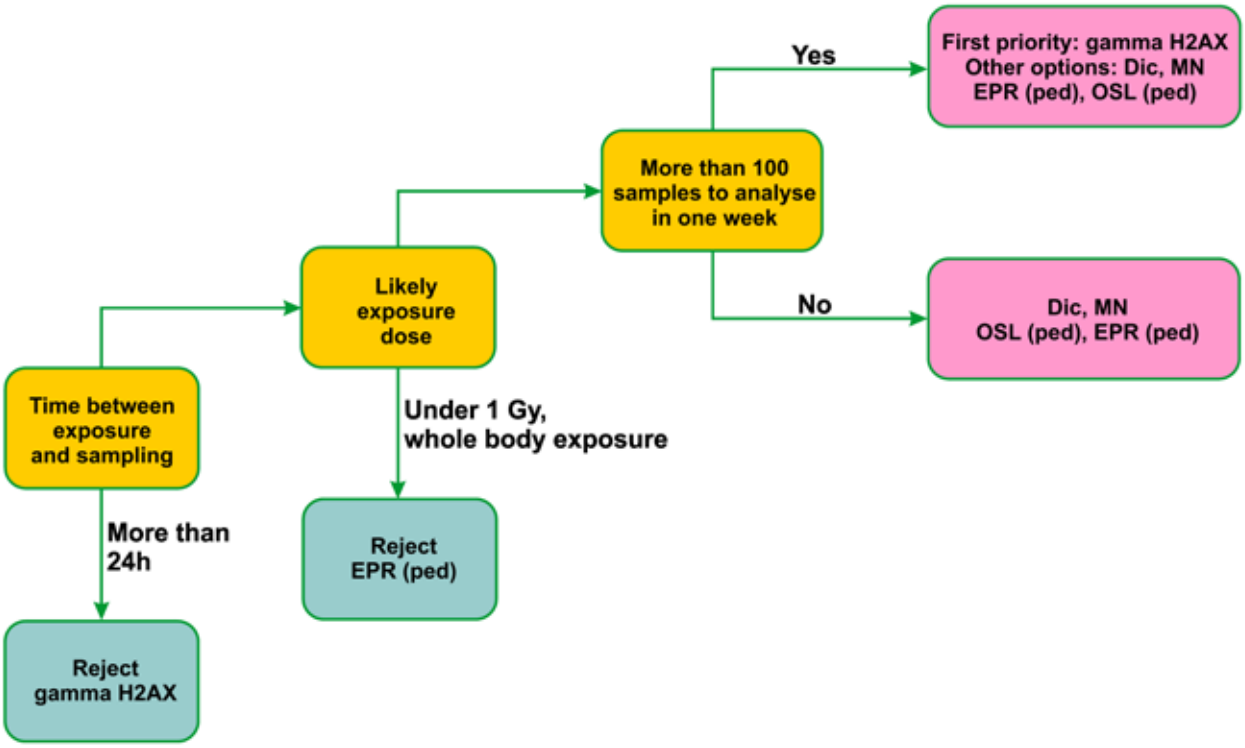
Table 6.4. Decision table when a large number of individuals appears continously in health centers some time after exposure.

Time point of exposure known (ca 24-48h or more before appearance in the health service center) and characteristics of the exposure known. Few individuals may receive doses exceeding 1Gy. Biodosimetric triage for a large group of individuals contacting local health services and radiation protection authorities, no signs and symptoms of ARS							
Assay	Dicentrics manual	Dicentrics automated	Dicentrics telescoring	Micronuclei automated	Gamma H2AX	OSL ped	EPR ped
Features of the event scenario							
Number of affected people less than 100 during the first week	Y	YY	Y	YY	N	Y	N
Large number of patients, more than 100 during the first week	Y	YY	YY	YY	N	YY	N
Sensitive individuals in the group (pregnant women, children etc)	YY	Y	Y	Y	Y	Y	Y
Choice of the suitable assays							
Choice of the assay for the majority of victims	Y	YY	YY	YY		Y	

ped: portable electronic device
ARS: acute radiation syndrome

Shown below is a decision tree that may be applied for the choice of MBD tools when some characteristics of the accident scenario are known.

Figure 6.1. Decision tree when time of exposure is known.



7. MBD tools for follow up of people involved in radiation emergency in the intermediate phase of emergency and afterwards

After the first triage of many exposed people, there will be the need for more precise dose estimation for those identified as exposed to doses higher than 1 Gy. Some of these people may be without early clinical symptoms but the medical assistance may be needed at some point in the future. Those exposed to higher doses will be under medical treatment and more detailed knowledge of exposure characteristic will be desireable.

The number of people requiring precise dose assessment most probably will not be large, and thus the full mode dicentric assay can be used for dose confirmation. OSL and EPR in personal electronic devices may give some additional information.

Demand may exist for delayed biodosimetric assessment of other groups of people. This demand will be justified by the potential risk of late, stochastic effects of radiation like cancer. Speed of performance will no longer be an issue in these cases but sensitivity will be important. Thus sensitive assays, and those that can be used at long times after exposure, will be chosen. Among MBD tools, candidates for the later follow up are the dicentric assay and EPR in portable electronic devices.

8. Conclusions

1. The Multibiodose consortium tested, adapted, and validated several biodosimetry assays for their use in triage biodosimetry in a mass casualty situation. Automation of assays and telescoring of cytogenetic images have also been validated. Application of EPR and OSL assays in portable electronic devices was developed and validated not only among MBD laboratories but also in 27 EURADOS associated laboratories, some of which are located outside the EU. The intercomparison exercises and validation of results between the laboratories has made it possible to act in a concerted way in case of a mass casualty accident. As a result of this, both the speed of performing the assays and the throughput of the laboratories is optimised.

2. The combined application of MBD tools is recommended in order to comprehensively manage complex radiation exposure scenario. The developed dedicated MBD statistical software enables the combination and comparison of results from different assays for deciding on the triage category of an individual according to the following triage categories: GREEN (< 1 Gy), YELLOW (1-2 Gy) and RED (> 2 Gy).

3. The MBD consortium proposes that:
   - In an emergency situation a MBD laboratory in the affected country (or another national laboratory designated to perform biodosimetry) will act as the «core» or «administrative» laboratory.
   - This laboratory will be in charge of the decision regarding which assays should be used and how other laboratories can be involved.
   - The laboratory will give advice to the health and radiation protection authorities about collection of samples.
   - This laboratory will collect the results from other MBD laboratories and will apply the MBD statistical software for the whole spectrum of applied MBD assays. In the end, this laboratory will provide the health and radiation protection authorities with dosimetric and radiological triage categorisation results to support medical and public health decisions.

4. For effective use of MBD tools it will be required that national radiation emergency plans, in-house plans of radiation protection and health protection authorities, and emergency plans of the hospitals designated to treat radiation casualties include a plan for performing biodosimetry. This plan should include at least updated contact details of the biodosimetry laboratory that is designated to perform biodosimetry in a country or a region. It would be also desirable that the plan contains, for example, information about: protocols for sampling of blood or portable electronic devices, details of transport requirements for the samples, information forms about the individual and his/her exposure characteristics.

9. Appendices

Appendix I
Contact list to MULTIBIODOSE laboratories

Stockholm University (SU) laboratory
Centre for Radiation Protection Research
Stockholm University
Svante Arrhenius väg 20C
106 91 STOCKHOLM
SWEDEN
Contact person: Andrzej Wojcik,
(MULTIBIODOSE Project Coordinator)
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Bundesamt fuer Strahlenschutz (BfS) laboratory
Biologische Dosimetry, SG 1.1
Bundesamt fuer Strahlenschutz
Ingolstaedter Landstr. 1
85764 OBERSCHLEISSHEIM / NEUHERBERG
GERMANY
Contact person: Horst Romm
Phone: +4930183332214
E-mail: hromm@bfs.de

Ghent University (UGent) laboratory
Ghent University
Faculty of Medicine
Department of Basic Medical Sciences
Radiation and DNA repair laboratory
De Pintelaan 185, B3 6th floor
B-9000 GENT
BELGIUM
Contact person 1: Hubert Thierens
Phone: +32 9 264 66 43/+32 9 264 65 19
Contact person 2: Anne Vral
Phone: +32 9 332 51 29
E-mail: biodosimetry@ugent.be

Public Health England (formerly the Health Protection Agency (HPA)) laboratory
Public Health England
Cytogenetics & Biomarkers Group
Centre for Radiation, Chemical and Environmental Hazards
CHILTON, DIDCOT, OXON, OX11 0RQ
UNITED KINGDOM
Phone: +441235 82510-4 or -7 (working hours)
+441980 612100 (out of hours emergency response switchboard)
E-mail: body.monitoring@phe.gov.uk

Institut de Radioprotection et de Sûreté Nucléaire (IRSN)
Biological dosimetry laboratory
Institute for Radioprotection and Nuclear Safety
Laboratory for Biological Dosimetry
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92262 FONTENAY-AUX-ROSES CEDEX
FRANCE
Contact Person 1: Eric Gregoire
Phone: +33 (0) 1 58 35 91 39
Email: eric.gregoire@irsn.fr
Contact Person 2: Sandrine Roch-Lefèvre
Phone: +33 (0) 1 58 35 86 27
Email: Sandrine.roch-lefevre@irsn.fr

EPR/OSL laboratory
Institute for Radioprotection and Nuclear Safety
Laboratory for ionizing radiation dosimetry
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FRANCE
Contact Person: François Trompier
Phone : +33 (0)158 35 7241
Email: francois.trompier@irsn.fr

Istituto Superiore di Sanitá (ISS) laboratory
Istituto Superiore di Sanitá
Department of Technology and Health
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Contact person: Paola Fattibene
Phone: +390649902248
E-mail: paola.fattibene@iss.it

Radiation and Nuclear Safety Authority (STUK) laboratory
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Contact person: Carita Lindholm
Phone: +358975988486
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Universitat Autònoma de Barcelona (UAB) laboratory
Departament de Biologia Cel•lular, de Fisiologia i d'Immunologia
Universitat Autònoma de Barcelona
Edifici C, Campus UAB
08193 CERDANYOLA DEL VALLÈS
SPAIN
Contact person: Lleonard Barrios
Phone: +34935812776
E-mail: lleonard.barrios@uab.cat

Institute of Nuclear Chemistry and Technology (INCT) laboratory
Centre for Radiobiology and Biological Dosimetry
Institute of Nuclear Chemistry and Technology
ul. Dorodna 16, 03-195 WARSAW
POLAND
Contact person: Sylwester Sommer
Phone: +48225041228
E-mail: s.sommer@ichtj.waw.pl

Helmholtz Zentrum Muenchen (HMGU) laboratory
Helmholtz Zentrum Muenchen- German Research Center for Environmental Health
Institute of Radiation Protection
Ingolstaedter Landstrasse 1
D-85764 NEUHERBERG
GERMANY
Contact person for OSL laboratory: Clemens Woda
Phone: +498931872802
E-mail: clemens.woda@helmholtz-muenchen.de
Contact person for EPR laboratory: Albrecht Wieser
Phone: +498931873069
E-mail: wieser@helmholtz-muenchen.de

Institut für Radiobiologie der Bundeswehr (BIR) laboratory
Institut für Radiobiologie der Bundeswehr
Neuherbergstr. 11
D-80937 MÜNCHEN
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Contact person 1: Christina Beinke
Phone +49 89 3168-2273 (-2251)
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E-mail: institutfuerradiobiologie@bundeswehr.org

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Head, Department 6.5: Neutron Radiation
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Tel: +49-531-592-6500 and -6501
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Appendix II, Part A:
MULTIBIODOSE software

Background
The Multibiodose software has been created to allow data from an incident to be combined from several different assays, to reach a single dosimetric triage decision.

The software is written in Java and the program links to databases created in SQLite, in which the incident data will be stored. One SQLite database is created per incident. At the end of the MULTIBIODOSE project, the current version of the software is Version 1.0, with a release date of the 30th April 2013.

The database is created and administered by the laboratory in whose country the incident occurred, or, in the event that a retrospective dosimetry laboratory is not present in that country, the laboratory who is assigned the status of 'lead laboratory' by the local authority who has taken charge of the incident. The lead laboratory takes responsibility for collection and analysis of physical/biological samples, assigning work to the other laboratories involved in the Multibiodose consortium/RENEB/BioDoseNet/etc networks. The lead laboratory also takes responsibility for maintaining the integrity of the data, i.e. for sample coding etc, and for reporting to the authority in charge.

Overview of software operation
The software is freely available online and can be downloaded from www. multibiodose.eu/software. MULTIBIODOSE_software_1.0.zip which contains the software itself: MULTIBIODOSE_1.0.jar; the manual corresponding to the current release: Multibiodose-software_manual_1.0.pdf; a test database: Test_Incident.db; the list of incident databases: Incident_List, and the lib folder which contains the libraries that are required to run the software.

The manual contains full instructions for downloading and running the software. On starting the program, the main window of the software will appear, which contains two options: Firstly, to look at and amend (add or delete) the data from an existing incident, or, secondly, to create a new database associated with a new incident (Figure 1).

If a new incident is selected, then the user will be asked a series of questions about the type of scenario, as detailed in (Figure 2, below). The answers to these questions determine the weighting schedule for the assays – i.e. which assays are relied upon in order to calculate the final triage category. Weights are generated automatically by the software and are assigned based on the recommendations in the main text of this Guidance.

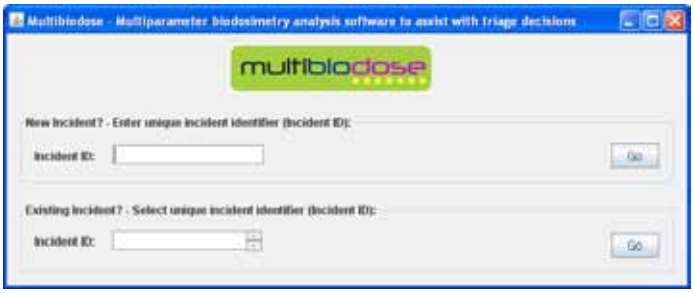

Figure 1. The main graphic user interface of the Multibiodose software.

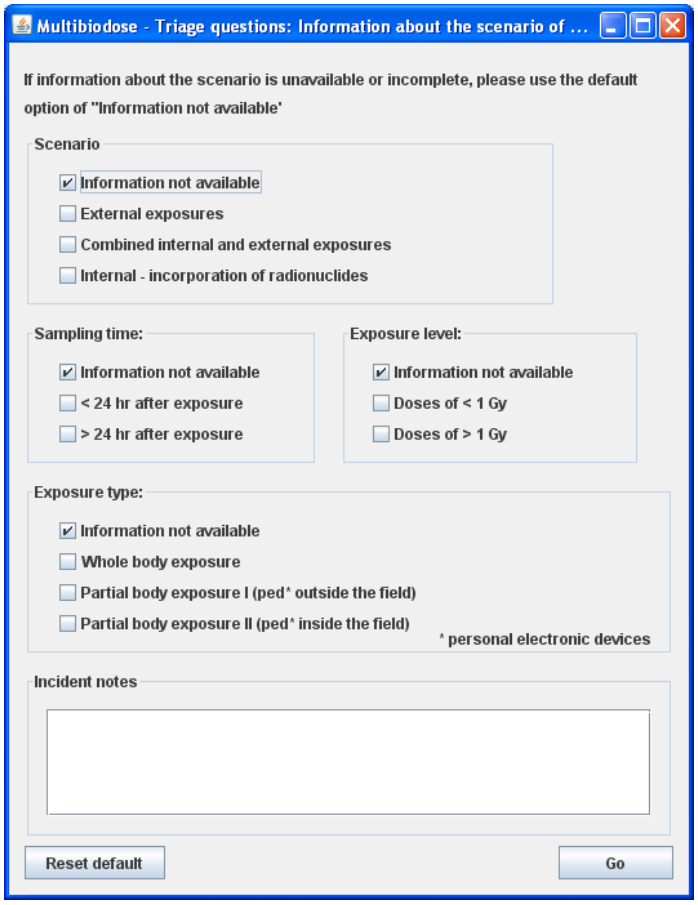

Figure 2. Dosimetric triage questions to be answered for a new incident.

If a new incident is selected, the user is presented with a screen with an empty table, into which the data for the scenario can be entered, as illustrated in Figure 3.

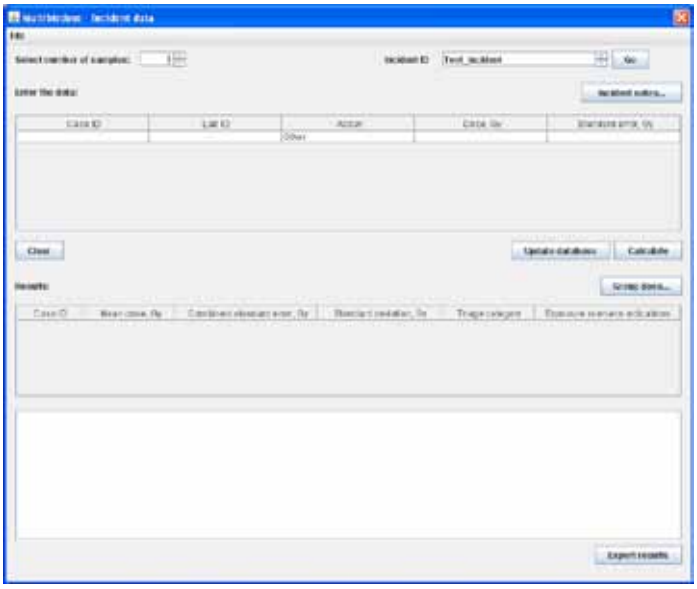

Figure 3. The data entry graphic user interface for a new incident (Test_Incident).

Once the incident has been created, next time the software is restarted, the newly detailed incident should appear on the drop down list of existing incidents.

If an existing incident is selected, then another screen will appear, containing all the current data for that incident, as in Figure 4.

The user can then add lines to the database, by increasing the number of samples in spinner box on the top, and then entering the data into the appropriate columns.

When changes are made to the table, for instance when adding new results, the 'Update database' button should be pressed to ensure the new results are saved. Failure to do this may result in loss of the additional data.

Data can be copied and pasted to/from the table from the table by right clicking when the mouse is over the table.
The table can be cleared by pressing the 'Clear' button.

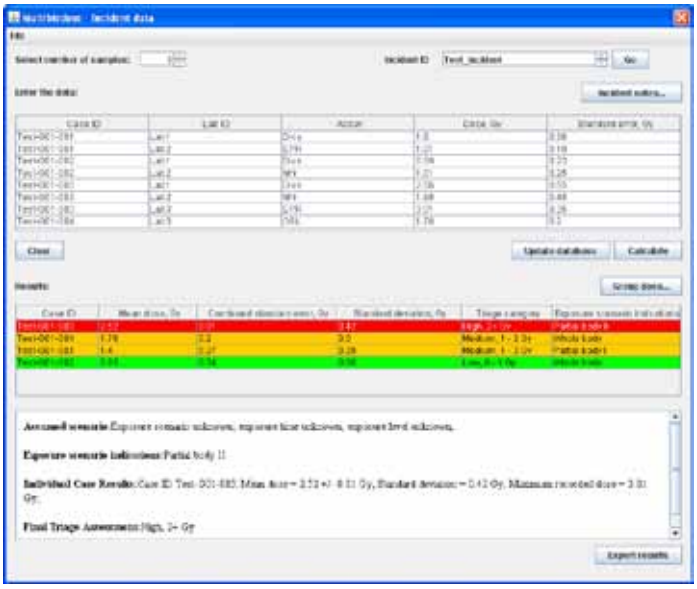

Figure 4. The graphic user interface with details of the current data for Test_Incident, after the 'Calculate' button has been pressed.

Once the most up to date data has been added to the database, pressing the 'Calculate' button gives the user the results, as illustrated in Figure 3.

The triage categorisation results are based on the weighted results for each case, and the choice is from the categories detailed in the main text:

- GREEN: Low, < 1 Gy;
- YELLOW: Medium, 1 – 2 Gy;
- RED: High, 2+ Gy.

The results based on the combined ('group') data can be viewed by pressing the 'Group dose' button.

The data and results can be exported to a Microsoft Excel ® file by pressing the 'Export results' button.
For more information about the software please visit www.multibiodose.eu/software or contact the software administrator at MULTIBIODOSE-software@gmx.com.

Appendix II, Part B: Notes on factors contributing to uncertainty for the MULTIBIODOSE assays

During the MULTIBIODOSE project, a lot of work was carried out to attempt to improve the uncertainty analysis techniques and reduce the uncertainty in the dose estimates provided by the different techniques. Nevertheless, retrospective dosimetry is still a developing field and as such each of the assays discussed in this guidance have a number of sources of uncertainty which it has not been possible to fully quantify or which, in a number of circumstances, might lead to greater uncertainty than expected.

In order to provide a full picture of the current status of each of the techniques, we have used an approach which involves qualitative assessment of the effect of different experimental factors on the relative magnitude of the uncertainty in the dose estimate provided by each assay. The table below provide a summary of our combined expert judgement about some of the associated experimental variables. The first table gives the factors which have been judged to give a potentially large contribution to relative uncertainty. The second table lists factors which should not have a large effect on the uncertainty in the dose, but which should be considered for instance in case of changes of circumstances or changes (further developments) in uncertainty analysis methods.

It should be noted that the judgements on the qualitative effect below give a snapshot of the situation at the end of the MULTIBIODOSE project – these should be reviewed periodically in line with scientific and technical advances in the field.

1) Experimental variables which could contribute a relatively large amount to the uncertainty in dose estimates:

Factor	Applicable to	Qualitative magnitude of effect on uncertainty in dose estimate
Circumstances of exposure, including type of radiation, dose, dose rate	EPR, OSL	Large
Partial body/inhomogeneous exposures	Dicentrics, MN, Foci	Depends on the proportion of the body exposed and the gradient of exposure, but overall effect could be large for all assays: extra care should be taken if partial body exposure is suspected/identified
Delayed blood sampling	Dicentrics, MN, Foci	Large for all assays if delay is substantial
Recent previous radiation exposure, e.g. medical	Dicentrics, MN, Foci	Depends on how recent exposure was, but potentially large for all assays if e.g. a very recent radiotherapy dose
Additional internal incorporation of radionuclides	Dicentrics, MN, Foci	Potentially large effect – as yet unquantified for most types of radionuclides
Drift in calibration curve	Foci	Small if curves are regularly updated and/or the recommendations for reference samples are followed; otherwise potentially large
Sampling time	Foci, EPR, OSL	Small if time is known and an appropriate calibration curve exists and is used; otherwise potentially large
Shipping effect	EPR, OSL	Large for some measurement protocols, but it has little relevance if an appropriate protocol of shipping has been set and provided to all operators.
Inter-laboratory variation (operators' training and experimental settings)	EPR, OSL	Judged to be small if appropriate training is given/skills are maintained and own labs' calibration curves are used
Storing effect (temperature and light)	EPR, OSL	Large, but it has little relevance if an appropriate protocol of sample storing has been set and provided to all the operators
Counting statistics	OSL (in resistor)	Small to large, depending on dose and equipment and number and size of resistors available on the electronic board
Fading correction	OSL (in resistor)	Large, also depending on the knowledge of the time of exposure
Shielding of circuit board by the other parts of the mobile phone	OSL (in resistor)	Small to large, depending on radiation quality

2) Sources of uncertainty that are judged to contribute a relatively small amount to overall uncertainty:

Factor	Applicable to	Qualitative magnitude of effect on uncertainty in dose estimate
Circumstances of exposure, including type of radiation, dose, dose rate	Dicentrics, MN, Foci	Judged to be small if appropriate calibration curves are used
Fractionated or protracted doses	Dicentrics, MN, Foci	Small if identified and accounted for, e.g. through application of G function in dicentric assay; Potential large effect if unidentified
Shipping effect including sample temperature and delay	Dicentrics, MN, Foci	Effect small for dicentric and micronucleus assays; magnitude of effect potential large for foci assay
Counting statistics	Dicentrics, MN, Foci	Small if minimum number of cells identified for each assay as part of the project is adhered to
Uncertainties in calibration curve	Dicentrics, MN, Foci	Small or non-existent at time of curve creation
Inter-scorer or inter-laboratory variation	Dicentrics, MN, Foci	Judged to be small if appropriate training is given/skills are maintained and own labs' calibration curves are used
Individual variation in background rate	MN, Foci	Small for MN if inter-individual uncertainty is incorporated in se on dose
Distribution of resistors on the electronic board	OSL (in resistor)	Small
Composition of glass	EPR (in Gorilla glass)	Small
Fading correction	EPR (in Gorilla glass)	Small
Uncertainties in calibration curve	EPR (in Gorilla glass)	Small

Appendix III

International networks and resources within biodosimetry

Global

IAEA Response and Assistance network RANET mechanism

A network supporting the practical implementation of the IAEA Assistance Convention (1986), consists of teams from member countries suitably qualified to respond rapidly to nuclear or radiological emergencies. One of RANET's capabilities is Dose Assessment (DA). DA capabilities include, among others, cytogenetic based biodosimetry, Electron Paramagnetic Resonance (EPR) and Optically Stimulated Luminescence (OSL). Member countries can register National Assistance Capabilities (NAC) as Field Assistance Teams (FAT) or External Based Support (EBS). As of March 2013 two countries (Argentina and Slovenia) have registered for FAT in cytogenetic based dosimetry while nine countries have declared EBS (Argentina, Canada, Finland, France, Hungary, Japan, Russian Federation, Turkey, and United Kingdom).

WHO International Health Regulations (IHR) mechanism

Revision of IHR from 2005 extends to include also radiation and nuclear emergencies. IHR is now implemented in the national legislation of 195 countries globally. IHR recognises biodosimetry as one of the important capabilities in the member countries and can assist/facilitate providing support in biodosimetry even in those countries that are not covered by the IAEA Assistance Convention.

WHO BioDoseNet

WHO BioDoseNet was established in 2008 and is a global network of over 60 biodosimetry laboratories whose role is to support management and decision-making in cases of large radiation emergency events where the capability of an individual laboratory is likely to be overwhelmed. In preparedness for such events the BioDoseNet focuses on harmonization of methodology, quality assurance, knowledge-sharing, and intercomparision exercises. Thus BioDoseNet serves a support function in the field of biodosimetry for Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) of WHO.

European

The European tripartite network of BfS, HPA and IRSN

The tripartite network of BfS, HPA and IRSN was established in 2004 and is a European biological dosimetry network of the Federal Office for Radiation Protection (BfS, Germany), the Health Protection Agency (HPA, now Public Health England, United Kingdom) and the Institut de Radioprotection et de Sûreté Nucléaire (IRSN, France). In form of a «Memorandum of Understanding» the cooporation between the three biodosimetry units is described and the financial aspects are regulated. The purpose of this biological dosimetry network is to provide mutual assistance in case of a radiological emergency to achieve fast reliable dose estimates with a high throughput of samples.

Nordic arrangements

In Nordic countries there is presently only one laboratory in Finland at STUK that serves with biological dosimetry capabilities for Nordic countries based on informal agreements. These agreements, although informal, are based on the traditionally strong collaboration between Nordic countries in the field both of radiological and nuclear emergency and public health (warranted by Nordic Radiation Emergency Assistance Agreement from 1963 and Nordic Public Health Preparedness Agreement from 2002).

There were however several collaboration projects on biological dosimetry in Nordic countries. Nordic laboratories participate also in the EU biodosimetry research projects (TENEB, this project, and RENEB). The competence in biodosimetry exists and capabilities may be built up in some other Nordic countries if needed.

The European Radiation Dosimetry Group EURADOS

EURADOS is a network of more than 50 European institutions (Voting Members) and 250 scientists (Associate Members) working in all fields of dosimetry. One of the working areas of EURADOS is retrospective dosimetry. That includes biological dosimetry as well as techniques like Electron Paramagnetic

Resonance (EPR) and Optically Stimulated Luminescence. EURADOS's aims are technical development of the techniques, harmonisation of the approaches across Europe through organisation of scientific meetings, inter-comparison exercises and training.

The EU Commission had funded recently several projects that aim to strengthen the biodosimetry capabilities in Europe:

1. TENEB (Towards a European Network of Excellence in Biological Dosimetry) Coordination support action project of the 7th framework EURATOM Programme for Nuclear Research in 2009 with the aim to assess the capacities of EU biodosimetry laboratories. 2009.
2. Multi-disciplinary biodosimetric tools to manage high scale radiological casualties MULTIBIODOSE (this project) 2010 - 2013.
3. BOOSTER BiO-dOSimetric Tools for triagE to Responders. 2010 - 2013. EU 7th framework Capability project under theme SECURITY aiming to develop new technologies for dose assessment.
4. Realizing the European Network of Biodosimetry (RENEB) 2012 - 2015. A project that aims to establish a sustainable European Network in Biodosimetry.

Other regional initiatives

In the past decade several biological dosimetry networks have been established in other regions of the word, including the Asian network, Canadian/US network and South American Network. All these networks organise training activities and inter-comparisons in order to harmonize approaches, increase quality and capacity of performance in case of mass casualty incidents through sharing efforts.

Appendix IV.

Examples for detailed protocols for taking and transporting the samples

In mass casualty radiation emergency it will be important that some information about the transportation and sampling for biodosimetry is available in advance. It would be desirable that this information is always updated.
Some examples for such protocols provided by Multibiodose partners in the end of 2012 are given in this Appendix.

Centre for Radiation, Chemical and Environmental Hazards

BLOOD SAMPLES FOR CHROMOSOME ANALYSIS

The lymphocyte fraction of the blood sample will be cultured for 48 hours before analysis and it is therefore important that the cells are free from microbial contamination. We can supply sterile lithium heparin vacutainers, or one from your own stock will be suitable. Do not use tubes that contain beads or gels. Do not use EDTA tubes. Sodium heparin tubes are OK but lithium heparin is better.

The following precautions will help to ensure that the cultures are satisfactory:-

- Sample size: ideally 10 ml from each person. Some brands of tubes are designed to hold 7 or 9ml. These are OK.
- Gently invert the tube several times to dissolve and mix the blood and heparin

If the sample is to be sent within the UK:-

1. The Royal Mail and other couriers require that the specimen should be packed in accordance with **U.N. Regulation 650** (see 'packaging' below). If you do not have such packaging we can mail it to you, but this of course will require at least 24 hours.
2. **First** class letter post is usually adequate. If delays are possible, e.g. before Christmas, then a commercial courier service may be more reliable. Telephone confirmation of despatch would be appreciated.
3. Unless otherwise arranged, the blood sample should arrive on or before Wednesday in any week, as this allows two clear days for culturing and avoids work over the weekend. There is no postal or courier delivery to our institute at weekends.

If the sample is being sent from outside the UK:-

Please try to ensure that the package is not X-rayed at airport security checks. If this could happen then include a piece of monitoring film, such as dental film, with the specimen.

We would prefer it if you used an international courier firm that will transport the sample rapidly and directly to us. If however we have to collect the specimen from London Heathrow airport then we need to know in advance by telephone, FAX or e-mail the following information:-

1. The flight number and estimated time of arrival.
2. The package's Air Waybill Number.

Packaging:-

The Royal Mail / other couriers and the International Air Transport Association (IATA) requires that blood samples should be packed to conform with **United Nation's Regulation 650** for transporting diagnostic specimens. In brief, the specimen tube(s) must be placed with sufficient absorbent

material into a rigid, crush-proof and watertight secondary container. If specimen tubes or secondary containers have screw caps these must be reinforced with adhesive tape. The secondary container should then be placed in rigid outer packaging, e.g. a sturdy cardboard box, with suitable labelling. Shipping of blood samples, not known to contain pathogens, for diagnostic purposes are characterised as “UN 3373. BIOLOGICAL SUBSTANCE, CATEGORY B” The labelling should therefore include this phrase together with a white diamond label with black letters “UN 3373”. In addition the package should be marked with the sender’s name, address and telephone number; the receiver’s name, address and telephone number; and the telephone number of a responsible person, knowledgeable about the shipment. Some international courier firms do supply special packaging that conforms with the regulation.

WHO guidance on regulations for the transport of infectious substances can be found at:
http://www.who.int/csr/resources/publications/biosafety/WHO_HSE_EPR_2008_10/en/index.html

It is not necessary for blood specimens for chromosomal analysis to be packed with ice or cooling packs.

The package itself and the 'Nature and Quantity of Goods' box of the Air Waybill should show the following wording: "Diagnostic specimen packed in compliance with IATA packing instruction 650." Also please mark the package and paperwork with “Do not X-ray”.

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Health Protection Agency
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United Kingdom

Information sheet:
Blood sampling for chromosome analysis

Reasons for a chromosome analysis

- in case no dosimeter was worn during an irradiation or irradiation in question
- in case there are discrepancies concerning the analysis of the physical radiation monitoring
- in case of an assumed overexposure

Prearrangement for the blood sampling

- Contact by phone:
  phone.: +49 30 18 333 -2210 / -2213/ -2214/ -2216
  fax: +49 30 18 333 -2205
  e-mail: HRomm@bfs.de, UOestreicher @bfs.de, Ukulka@bfs.de.

- Address:

  Bundesamt für Strahlenschutz
  Fachbereich Strahlenschutz und Gesundheit
  AG-SG 1.1 Biologische Strahleneffekte, biologische Dosimetrie
  Labor für Biologische Dosimetrie
  phone: +49 30 18 333 - 2216
  Ingolstädter Landstraße 1
  85764 Oberschleissheim / Neuherberg
  Germany

- An adequate „blood sampling system“ and user guidelines will be sent to you by our laboratory.

Blood sampling

- blood sampling only with the sent blood sampling system
- blood samples should be taken and shipped on a Monday or Tuesday if possible
- keep the blood samples at room temperature

Shipment of blood samples

- use the packaging system that was sent to you
- use an express service for the shipment
- caution: no cooling during the shipment

Data of blood sample for chromosomal analyses

Blood sample taken by :..... Date of taken blood sample :.....

Telephone-No.:.....

.....

Exposed Person (Name) :..... Date of birth:.....

Data about exposure :

1.Occupation in contest with overexposure :

2. Whole body exposure O Part body exposure O

Dose value :..... Part of body :.....

3. Type of radiation :

x - ray	O	kV
γ	O	
α	O	
n	O	keV

4. Date of overexposure :.....

.....

Precedent exposure through medical treatment :

Radiation therapy	O	Date, Part of Body.....
x - ray diagnoses	O	Date, Part of Body.....
Nuclear medicine	O	Date, Part of Body.....

Illness 4 weeks before taking the blood sample:.....

Intake of medication : O Name of medicament :.....

Smoker: no: O yes: O number of / day: .....

.....

Results of chromosomal analyses to be sent to :

Name : .....

Adress : .....

.....

Telephone-No : .....

Vertrag
über Nutzleistungen
zwischen
der Bundesrepublik Deutschland,
vertreten durch den
Präsidenten des Bundesamtes für Strahlenschutz (BfS)
- Auftragnehmer -
und
- Auftraggeber -

1.Nutzleistung des BfS
Das BfS erbringt unter dem Geschäftszeichen
[ ] ←bei Schriftverkehr bitte stets angeben
folgende Nutzleistung:

2. Vergütung der Nutzleistung
Die Vergütung der Nutzleistung bemisst sich nach der Dienstanweisung über die Erhebung von Entgelten für privatrechtliche Nutzleistungen des BfS (DA-Nutzleistungen).

☐ Die Vergütung wird nach dem Aufwand abgerechnet. Sie beträgt voraussichtlich
€.
☐ Die Vergütung wird nach Festpreis abgerechnet. Sie beträgt €.

3. Unverbindlicher Leistungstermin
Die Nutzleistung wird voraussichtlich bis zum fertiggestellt sein.
(auf 4.1 AG-BfS wird verwiesen)

4. Mitwirkungspflicht des Auftraggebers
Der Auftraggeber stellt dem BfS nach Vorgabe die zur Erbringung der Nutzleistung erforderlichen Unterlagen, Stoffe, Proben u.ä. kostenfrei zur Verfügung und übernimmt auf seine Kosten auch die Entsorgung.

5. Allgemeine Geschäftsbedingungen des BfS (AGB-BfS)
Die Nutzleistungen werden zu den nachstehenden „Allgemeinen Geschäftsbedingungen des Bundesamtes für Strahlenschutz" ausgeführt, die Grundlage dieses Vertrages sind.

6. Nebenabreden
Nebenabreden sind nicht getroffen worden. Änderungen und/oder Ergänzungen des Vertrages bedürfen der Schriftform.

7. Mit dem Abschluss des Vertrages wird die Berechtigung des BfS anerkannt, das Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit und andere Ressorts der Bundesregierung zu informieren.

Ort, Datum	Ort, Datum
Unterschrift Auftraggeber	*Unterschrift BfS* *I.A.*

BLOOD SAMPLES FOR GAMMA-H2AX FOCI ANALYSIS

The gamma-H2AX foci assay is a technique for assessing exposure to ionising radiation. The advantage of this technique is that a dose estimate can be given within 5 hours from the receipt of a blood sample. However, the rapid loss of gamma-H2AX means a blood sample needs to be taken within 1 -2 days after a radiation exposure, with the minimum detectable dose increasing from a few mGy for a sample taken within 1 hour after the exposure to ~0.5 Gy for a lag time of 2 days between exposure and sampling.

The following precautions are needed to ensure that blood samples are suitable for foci analysis:-

- Blood collection tube should contain lithium heparin as the anti-coagulant. Sodium heparin tubes are OK but lithium heparin is better[1]. We can supply sterile lithium heparin vacutainers, or one from your own stock will be suitable.
- A sample size of at least 2 ml from each person is required. Some brands of tubes are designed to hold 4, 7 or 10 ml and these are OK[2].
- The blood must be kept cold using cooling packs or wet ice (0 – 4 °C) to prevent any loss of gamma-H2AX signal. Do not allow the blood tube to be in direct contact with the ice / cool pack.
- The sample should reach us as quickly as possible, within 24 hours of being taken. This could be achieved by using a commercial express courier service or samples being delivered by a member of the company's staff, for example.
- If the first sample was taken only a few hours after exposure, a second sample should be taken at 24 h in the case of a non-uniform exposure, to allow lymphocytes to mix completely. An additional sample would also be required approximately one week after exposure, to establish the individual base level for this marker and thus further reduce the uncertainty of the dose estimate.

Packaging:

The Royal Mail / other couriers and the International Air Transport Association (IATA) requires that blood samples should be packed to conform with **United Nation's Regulation 650** for transporting diagnostic specimens. In brief, the specimen tube(s) must be placed with sufficient absorbent material into a rigid, crush-proof and watertight secondary container. If specimen tubes or secondary containers have screw

[1] EDTA blood collection tubes can be used, but the blood would then be unsuitable to use for the chromosome aberration analysis.
[2] Finger-prick samples of at least 0.09 ml (in heparin or EDTA) would also be acceptable if no phlebotomist is available. A bigger volume (at least 6 ml) would enable additional chromosome aberration analysis from the same sample.

caps these must be reinforced with adhesive tape. The secondary container should then be placed in rigid outer packaging, e.g. a sturdy cardboard box, with suitable labelling. Shipping of blood samples, not known to contain pathogens, for diagnostic purposes are characterised as "UN 3373. BIOLOGICAL SUBSTANCE, CATEGORY B" The labelling should therefore include this phrase together with a white diamond label with black letters "UN 3373". In addition the package should be marked with the sender's name, address and telephone number; the receiver's name, address and telephone number; and the telephone number of a responsible person, knowledgeable about the shipment. Some international courier firms do supply special packaging that conforms with the regulation. This packaging can also be supplied by the Cytogenetics and Biomarkers Group when an analysis is requested.

WHO guidance on regulations for the transport of infectious substances can be found at: http://www.who.int/csr/resources/publications/biosafety/WHO_HSE_EPR_2008_10/en/index.html

The package itself and the 'Nature and Quantity of Goods' box of the Air Waybill should show the following wording: "Diagnostic specimen packed in compliance with IATA packing instruction 650." Also please mark the package and paperwork with "Do not X-ray".

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PRACTICAL INDICATIONS FOR COLLECTION AND TRANSPORT OF MOBILE PHONES AND PORTABLE ELECTRONIC DEVICES (peds)

Any kind of mobile phone and ped can be used for OSL, whereas only some types of smartphones are suitable for EPR. Herein, ped means mobile phone, note books, external memory storage devices, memory keys, audio/video media players, camcorders or digital cameras.

People who are donating their portable devices, especially the mobile phones, should be clearly informed that we are not going to use their private information therein contained. For this reason it would be appropriate to let them keep sim cards and batteries.

1. Collection/selection and identification of samples

The devices can be collected on site or at the first aid department. Sim cards and batteries can be removed because they were not needed. All samples,, should be coded or identified to insure connection and traceability between estimated doses and ped owner identity.
Collected ped should be stored in the dark (boxes, bags,..).

2. Transportation and storage of samples

Collected ped should be transported in opaque boxes or bags.

Appendix V

Available important reference materials on biodosimetry

1. International Atomic Energy Agency. Cytogenetic analysis for radiation dose assessment. A manual. IAEA Technical Report Series 405 (2001).

2. International Atomic Energy Agency.Cytogenetic Dosimetry: applications in Preparedness for and Response to Radiation Emergency.EPR-Boiodosimetry.(2011)

3. International Organisation for Standardisation. 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. International Standard ISO 21243. (Geneva: ISO) (2008).

4. International Organisation for Standardisation. Radiation protection - Performance criteria for service laboratories performing biological dosimetry by cytogenetics. International Standard ISO 19238. (Geneva: ISO) (2004).

5. International Atomic Energy Agency. Generic procedures for medical response during a nuclear or radiological emergency EPR Medical (2005)

6. International Atomic Energy Agency IAEA Response and Assistance Network. EPR-RANET (2010)

7. Rojas-Palma C, Liland A, Jerstad AN, Etherington G, Pérez MR, Rahola T, Smith K, editors. TMT handbook: Triage, monitoring and treatment of people exposed to ionising radiation following a malevolent act. Oesteras: Norwegian Radiation Protection Authority, 2009. http://www.tmthandbook.org/tmtdoc/

8. WHO BioDoseNet http://www.biodosenet.org/

9. REMM Radiation Emergency Medical Management: Guidance on diagnosis & treatment for health care providers. WashingtonDC. Department of Health and Human Services; office of the Assistant Secretary for Preparedness and Response, 2012. http://www.remm.nlm.gov/

10. Fliedner TM, Friescke I, Beyrer K (eds).Medical management of radiation accidents- Manual on the acute radiation syndrome. British Institute of Radiology. London, 2001

Appendix VI

Definitions and acronyms

In order to avoid confusion, we provide definitions of some terms used in the guidance. Short descriptions of the MBD tools are given in chapter 4.

- **Acute exposure**: exposure during a short period time, usually minutes to few hours.
- **ARS**: Acute Radiation Syndrome.
- **Biodosimetric triage**: sorting of people according to the absorbed dose as assessed by biological dosimetry.
- **Biological dosimetry**: assessment of absorbed dose based on the level of biological damage inflicted by radiation. In MBD we also include EPR and OSL as biological dosimeters because we use the methods to assess the dose absorbed by personal electronic devices carried on the body.
- **EPR**: electron paramagnetic resonance.
- **Full mode biological dosimetry**: slow analysis of a sample with the intention to estimate the dose with high precision.
- **Large radiological emergency**: an accident scenario with more than 1000 exposed or potentially exposed people.
- **Partial body exposure**: exposure of a part of the body. Per unit dose, partial body exposure is associated with a lower level of health effects as compared to whole body.
- **MBD**: multibiodose.
- **OSL**: optically stimulated luminescence.
- **PBE**: partial body exposure
- **PBL**: peripheral blood lymphocytes.
- **PED**: personal electronic devices.
- **Protracted exposure**: exposure during a period of time longer than a few hours.
- **RDD**: radiological dispersion device.
- **RED**: radiological exposure device.
- **Triage mode biological dosimetry**: quick analysis of a sample with the intention to discriminate between dose categories: LOW, MEDIUM, HIGH.
- **Triage mode of biodosimetry**: fast assessment of dose by biological dosimetry with the aim to categorise people into groups of low, moderate and high exposure.
- **Worried well**: people who wrongly suspect that they were exposed to radiation. They may show such symptoms of ARS such as vomiting, dizziness and diarrhoea.

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multibiodose

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