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INSTITUT DE RADIOPROTECTION ET DE SÛRETÉ NUCLÉAIRE

OVERVIEW OF ICRU REPORT 94:
METHODS FOR INITIAL-PHASE ASSESSMENT OF INDIVIDUAL DOSES FOLLOWING ACUTE EXPOSURE TO IONIZING RADIATION

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MEMBRE DE ETSON

Genesis of ICRU report 94

- ICRU report 68 on retrospective dosimetry covers only prolonged and past exposure at low dose, not the emergency situation (*Retrospective Assessment of Exposures to Ionizing Radiation, 2002)*
- Proposal from EURADOS to write a new report dedicated to the application of retrospective dosimetry for acute and high exposure and emergency phase
- First joint EURADOS-ICRU report

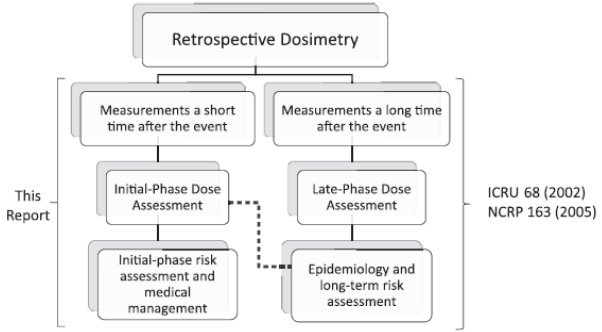


Figure 1.1 Retrospective dosimetry may be divided into dose assessment a short time after the event, or a long time after the event. The latter is primarily for epidemiology and is the subject of ICRU Report 68 (ICRU, 2002) and NCRP Report 163 (NCRP, 2009). The current Report deals with measurements a short time after the event for purposes of emergency health care. The primary consideration in this regard is the need for initial-phase dose assessment to identify those in need of medical intervention due to deterministic, tissue effects (initial-phase risk assessment). The assessed doses may also later become part of epidemiologic and long-term risk assessment (dashed line).

Aims of ICRU report 94

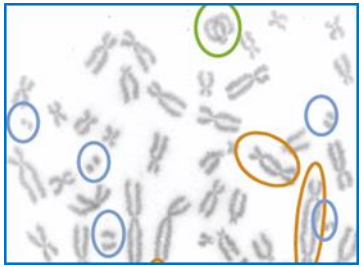
- Focus on the most topical problems at the present time: assessment of individual doses received by the members of public and early responders following acute exposures due to malevolent use of ionizing radiation sources.

- Review of methods of retrospective dosimetry (biological dosimetry, EPR, TL/OSL, neutron activation, field radiation mapping, in vivo monitoring or bioassay): characteristics, limits, complementarity

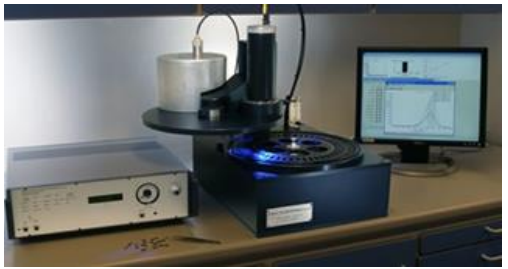
- Review of past application cases and lessons learnt

- Recommandations for on their use for various radiation exposure conditions and dose assessment needs.

Contents of ICRU report 94



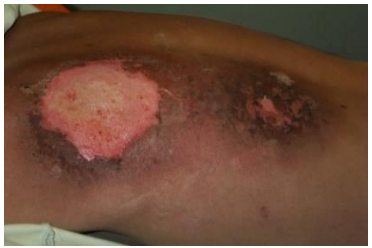
1. Introduction
2. Dose quantities
3. Biodosimetry
4. EPR dosimetry
5. Luminescence dosimetry
6. Other individual-person radiation measurements
7. External Dose Assessment Methods Based on Radiation Field Mapping
8. Summary
9. Conclusions



Aims of dosimetry in the frame of radiological accidents management

The primary purposes of the initial-phase dose assessment are:

- to identify individuals in potential danger from short-term, deterministic (tissue) effects.
- To help the medical in assessing a diagnostic, a prognostic and the medical strategies

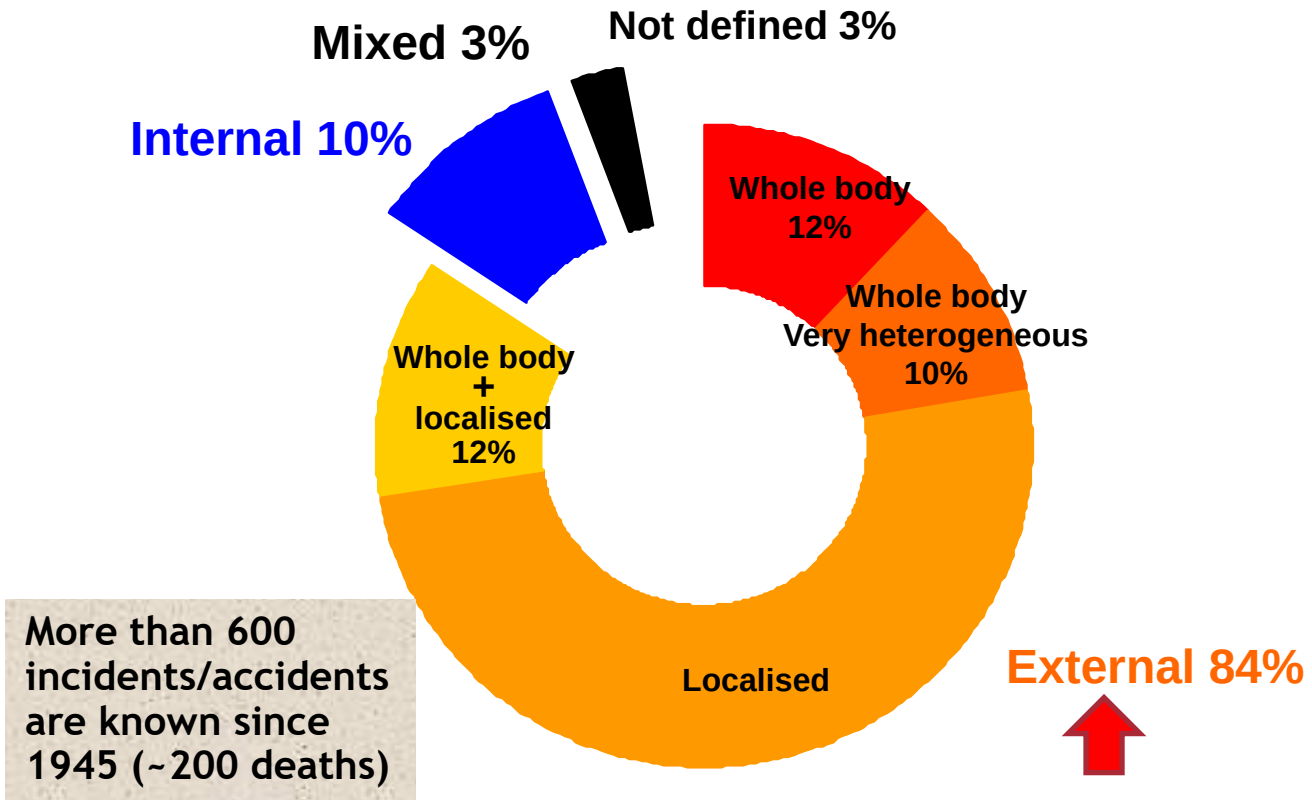


Medical management of the victims

- Dose is a marker of damages to tissues and organs which helps the physicians:
  - ✓to evaluate the radio-induced damages
  - ✓to define the therapeutic strategy

How? Assessment of the whole body dose and the dose distribution in the body (or doses to organs)

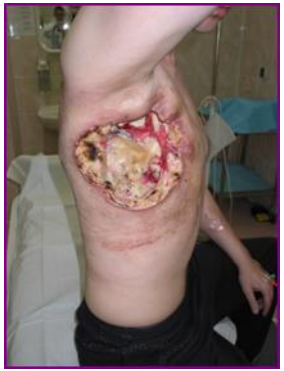
Radiological accidents: types of accidents



Radiological accidents: different scenarii of exposure

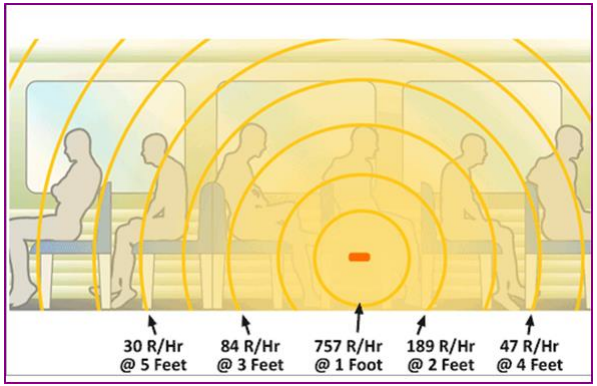
Limited number of victims:

- Orphan sources, industrial facilities, medical application (radiotherapy, brachytherapy, radiology, etc.), nuclear sites.
- Victims are identified
- Irradiation are often **localized**



Possibly large number of victims:

- Nuclear accidents, radiological malevolence,
- Large number of persons possibly involved, actual victims hardly identifiable
- Need to sort out population to identify persons actually involved and to determine severity of injuries



Radiological accidents: different scenarii of exposure

Table 1.1 Typical Scenarios Requiring Emergency Dosimetry, With a Qualitative Assessment of the Number of Individuals Who Might Need Dose Assessment in Each Case.

Emergency event	Scale of dose assessment needs after the event
Accidental	
Nuclear power plant (NPP) accident	Small to large[3]
Medical overexposure	Usually small
Occupational accident	Usually small
Transportation accidents	Usually small
Intentional	
Improvised nuclear device (IND)	Large
Radiologic dispersal device (RDD)	Expected to be large
Radiation exposure device (RED)	Small to large

Dose quantities on interest

Absorbed dose vs RBE-weighted absorbed dose ?

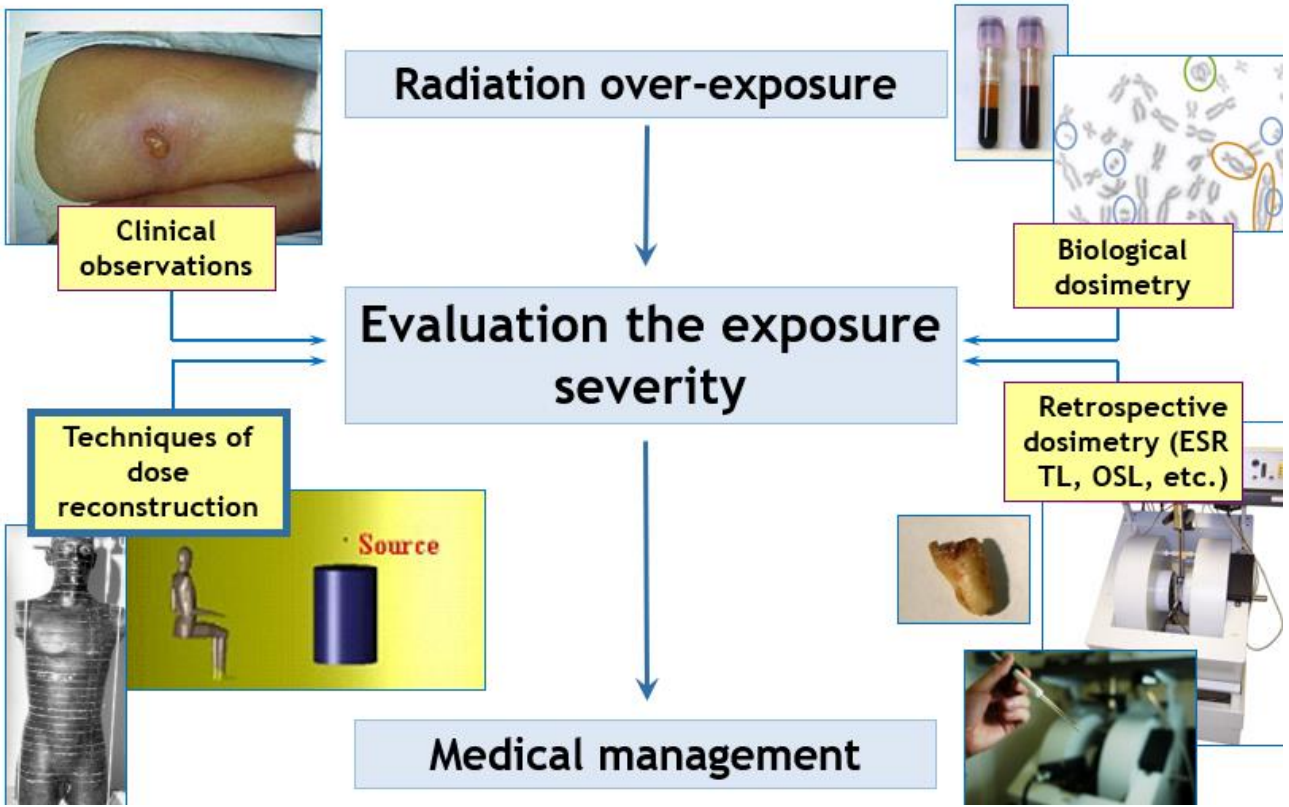
And specifically for neutron irradiation (criticality accident): kerma in tissue, dose to the element 57, surface dose , Dp(10)

Techniques described

Table 1.2 Primary Dosimetry Topics Described in This Report.

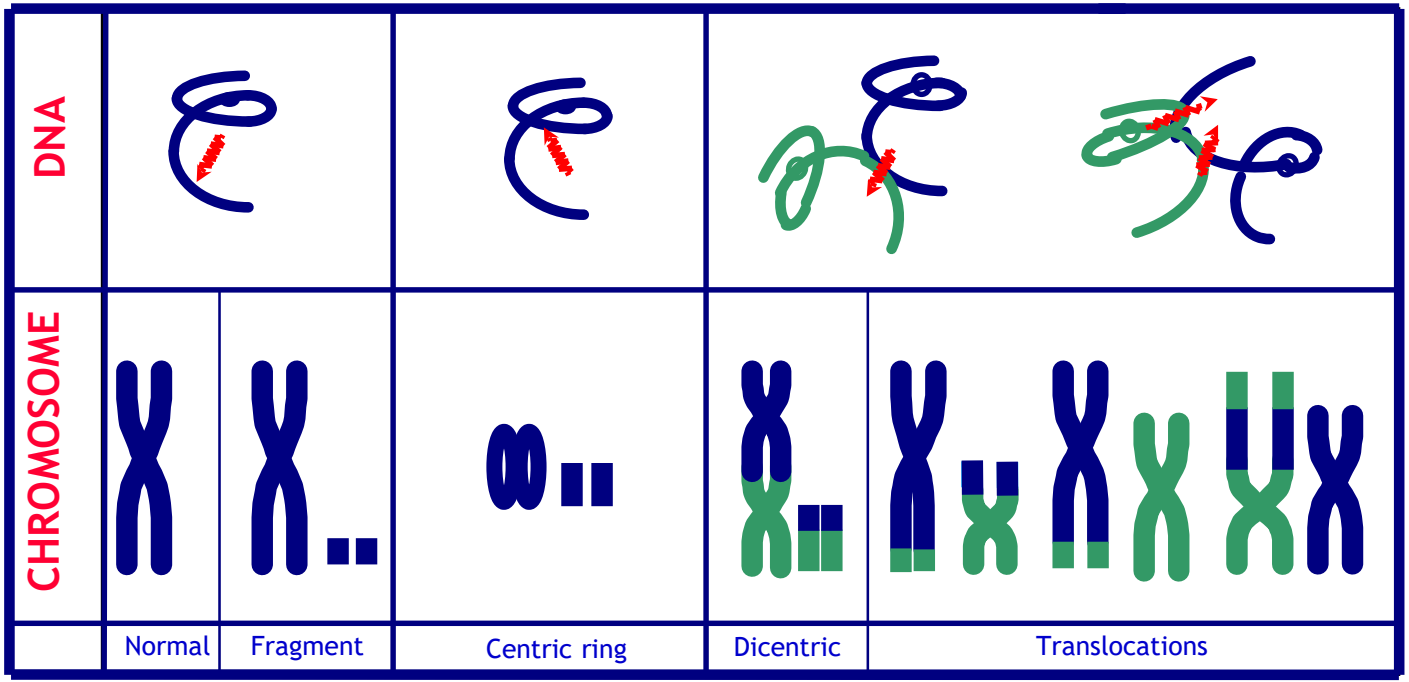
Techniques	Primary target materials
Biodosimetry	
Dicentric chromosome assay (DCA)	Whole blood or lymphocytes
Translocation analysis by fluorescence *in-situ* hybridization (FISH)	Whole blood or lymphocytes
Cytokinesis block micronucleus (CBMN) assay	Whole blood or lymphocytes
Premature chromosome condensation (PCC)	Whole blood or lymphocytes
γ-H2AX	Whole blood or lymphocytes
RNA expression	Whole blood or lymphocytes
Protein-based assays	Urine, blood plasma, blood serum, whole blood, lymphocytes
Metabolomics	Urine, blood serum, blood plasma
Physical dosimetry	
Electron paramagnetic resonance (EPR)	Teeth, bone, nails, glass from personal items, sugars, fabrics, other personal belongings
Thermoluminescence (TL)	Components of portable electronic devices, glass from personal items, dust on personal items
Optically stimulated luminescence (OSL)	Components of portable electronic devices, clothing, other personal belongings
Other	
Bioassays (*ex vivo* and *in vivo*)	Excreta, thyroid, chest, whole body
Neutron activation	Biological tissue, objects worn by the individual
Mapping and time-and-motion studies	Dose and dose rate measurements

Toolbox of dosimetric appraoch



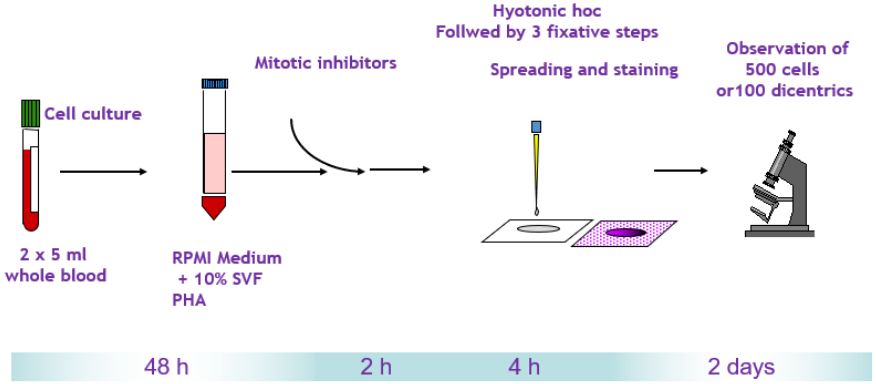
Biological dosimetry

Study of the misrepairs of the DNA



Depending of the number of damages and their topology, cell could produce different kind of misrepairs

Biological dosimetry



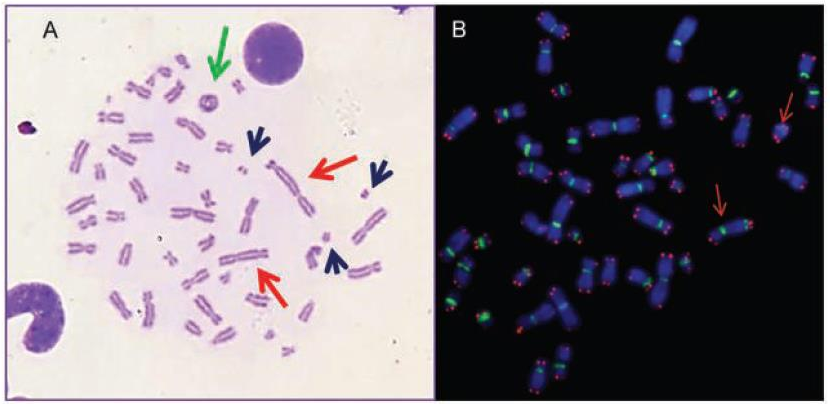


Figure 3.1 Human lymphocyte metaphase cells with a dicentric and an acentric fragment (arrows): (A) Stained with Giemsa; (B) stained with telomere and centromere PNA probes.
Source. A: courtesy of A. Testa; B: courtesy of P. Hande.
Note. PNA = peptide nucleic acid.

Biological dosimetry: calibration

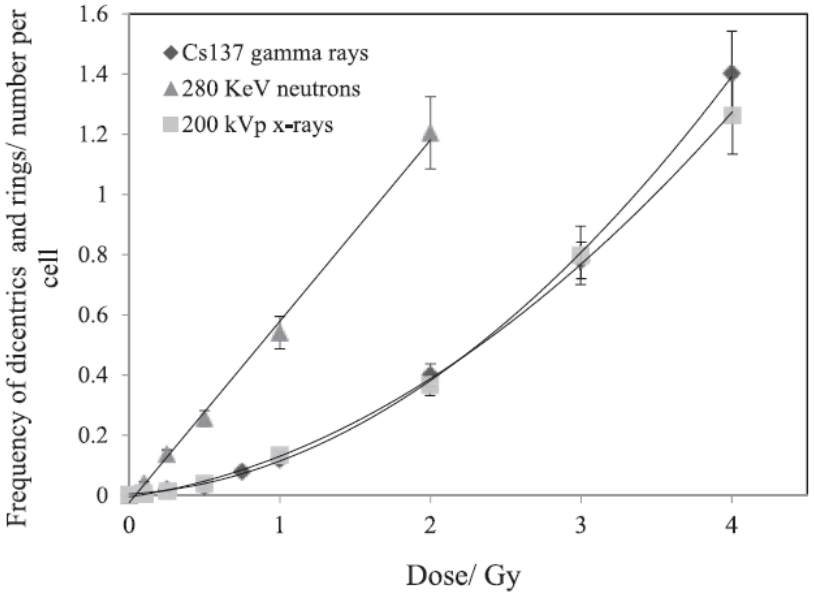


Figure 3.2 Calibration curves for dicentric chromosome assay for different qualities of radiation.
Source. Courtesy of R. Wilkins.

Biological dosimetry: stability

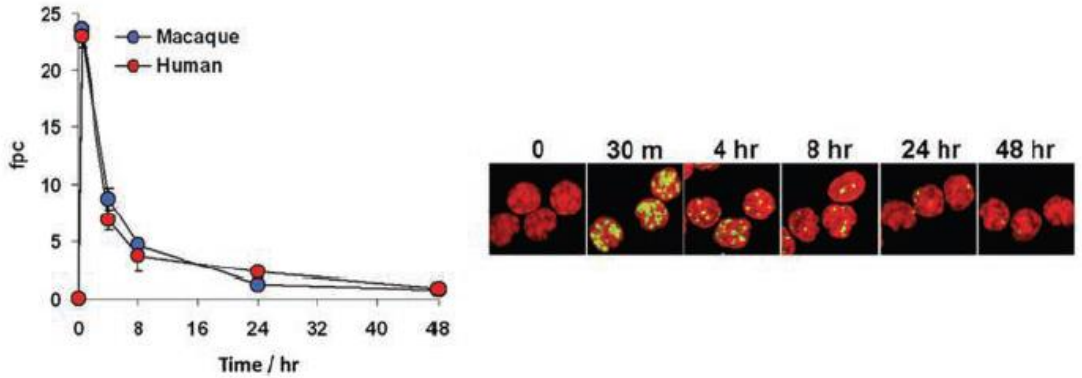


Figure 3.10 Incidence of γ-H2AX foci in macaque and human lymphocytes at various times after exposure to 2 Gy. Data are presented as averages ± standard deviations (n = 3). The right panel shows representative images of white cell preparations used for the foci per cell (fpc) determinations shown in the left panel (green, γ-H2AX; red, DNA stained with propidium iodide; Redon *et al.*, 2010).

Biological dosimetry: summary

Table 8.1 Comparison of Biodosimetry Techniques.

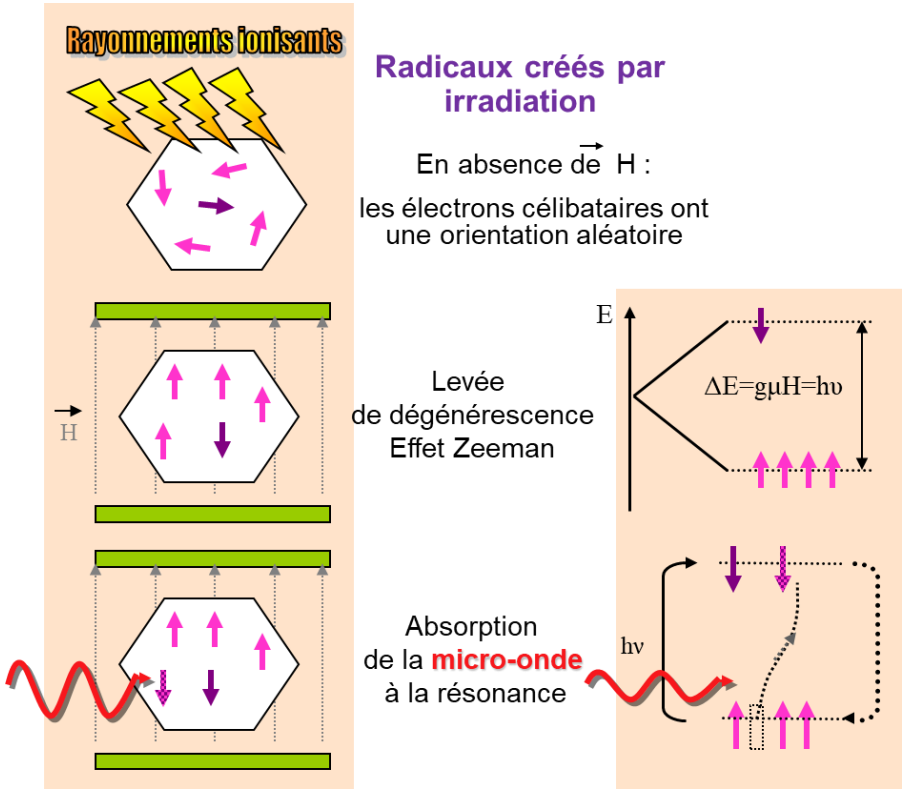
Assay	Materials	Recommended period of use since exposure (days, weeks, years)	Partial-body exposure identification	Time (h) from sample receipt to dose estimate	Specificity	Dose range (Gy) (MDD—upper limit)	Automated analysis	Standardization (ISO standard)
Dicentrics (full) Dicentrics (triage)	Whole blood, lymphocytes	Days to months Days to months	Yes No	55 52	IR IR	0.1-5 0.5-5	Yes Yes	ISO 19238 (2014a); ISO 21243 (2008)
PCC fragments PCC rings	Whole blood, lymphocytes	Days Days to months	Yes No	2 40	IR IR	0.2-20 1 > 20	Under development Under development	— —
Micronuclei	Whole blood, lymphocytes	Days to months	No	75	IR BGS	0.2-4	Yes	ISO 17099 (2014b)
Translocations (FISH)	Whole blood, lymphocytes	Days to years	No	120	IR BGS	0.25-4	Under development	ISO 20046 (2019c)
γ-H2AX	Whole blood, lymphocytes	Hours	Yes	3	IR BGS	0.5-10	Yes	—
Gene expression	Whole blood, lymphocytes	Hours to days	yes	4	IR BGS	0.5-10	Under development	—
Small metabolites	Urine, blood serum, blood plasma	Hours to days	Yes	3	IR BGS	1-10	Under development	—
Proteomics	Whole blood, lymphocytes, urine, blood serum, blood plasma	Hours to days	Yes	3	IR BGS	0.5-10	Under development	—

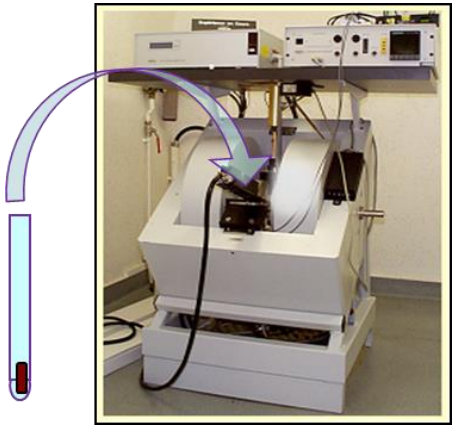
Note. MDD = minimum detectable dose; ISO = International Organization for Standardization; IR = ionizing radiation; PCC = premature chromosome condensation; BGS = non–radiation-induced background signal (due to confounding factors such as smoking, age, or other chemical exposures); FISH = fluorescence *in-situ* hybridization.

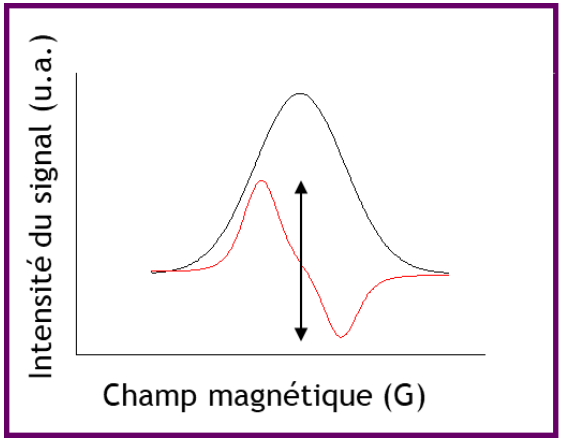
Biological dosimetry: facts and summary

- Dicentric assay knows as the « gold standard method », PCC used for very high dose (> 5 Gy)
- Should not be used alone
- Provide dose in the circulating blood approximate to whole body dose
- Statistics on aberration distribution in cells can tell about dose heterogeneity
- Delay (cell culture) and stability
- Issues with calibration
- Application to large scale?

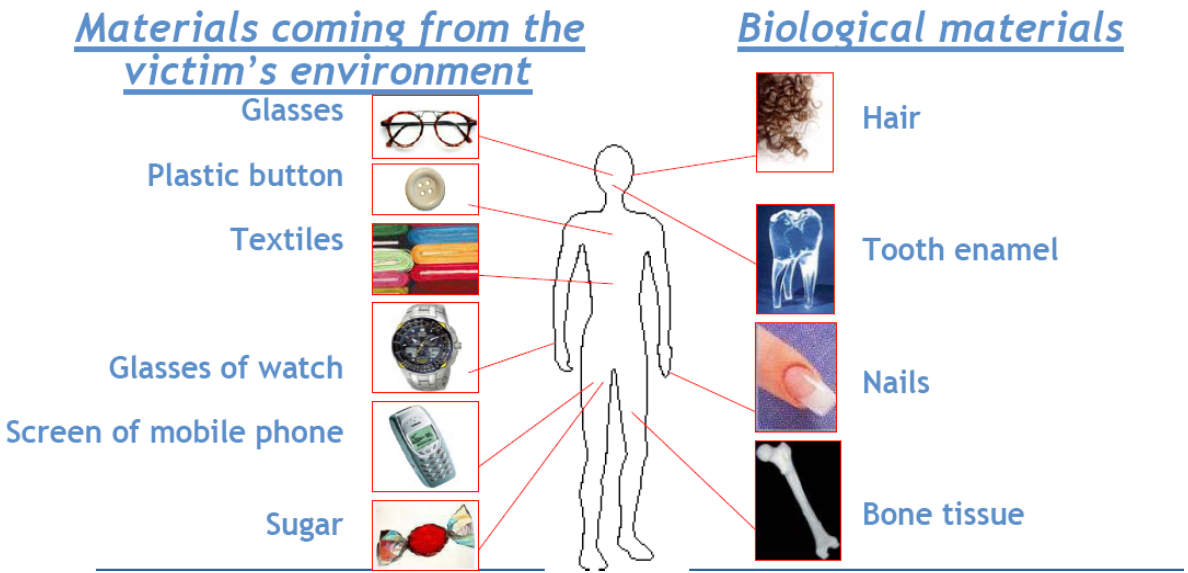
EPR dosimetry: principles

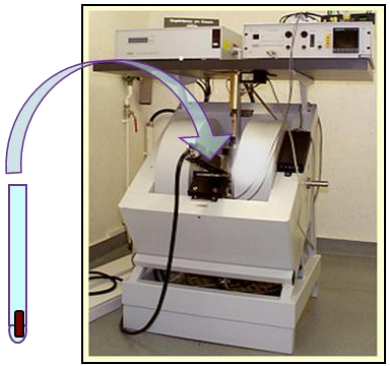


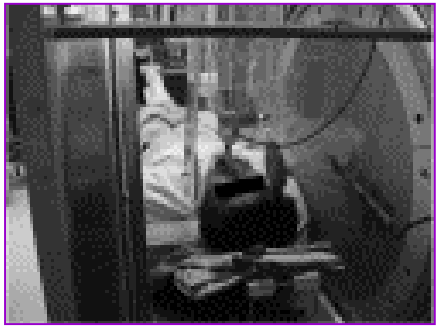


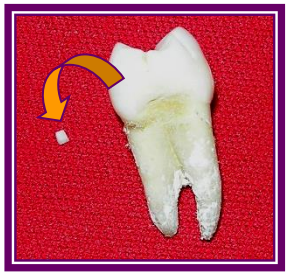


EPR dosimetry: overview

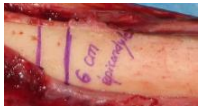




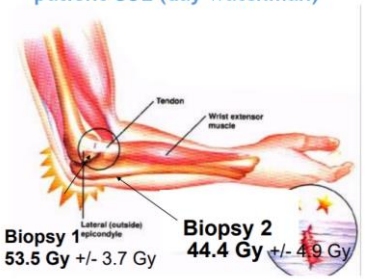




EPR dosimetry: overview



Dose assessment with ESR - patient COL (day watchman)



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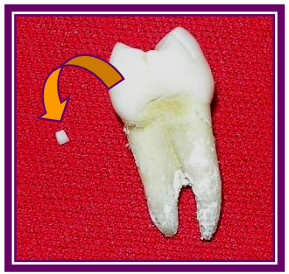
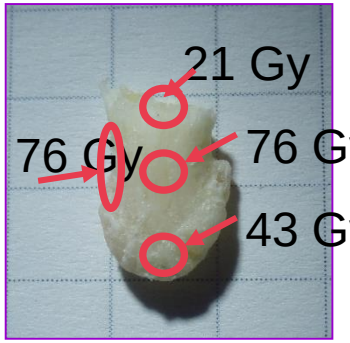
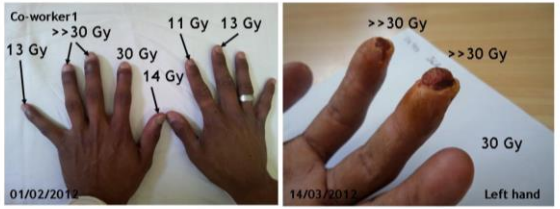


First application case of mini-biopsies of enamel in 2011 (Bulgarian accident) mesured by Q-band EPR



Application: Accident in Peru (February 2012)



Prediction of clinical signs evolution

Application: Accident in Peru (February 2012)

EPR dose estimation used to manage victims (transfer to France)

Prediction of clinical signs evolution

EPR dosimetry: summary

- Versatile techniques: numerous applications, many materials, complementary to others techniques
- Most used materials: bone (very pertinent in case of localized irradiation)
- New developments: in vivo, mini-biopsy (Q-band EPR)
- Possibly high capacity for large scale (cf. minibiopsy of enamel or glass from smartphones): (no delay, 5 min/meas.)

TL/OSL dosimetry: principles

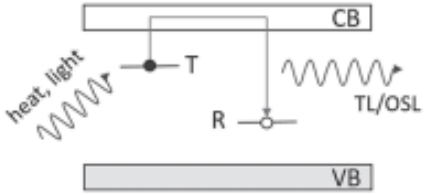


Figure 5.1 Energy level diagram in a (crystalline) insulator to illustrate the TL/OSL phenomenon. T stands for (electron) trap and R for (hole) recombination center. Both form metastable states in the forbidden zone between the VB and the CB. The black filled circle illustrates the trapped electron and the open circle the trapped hole. Note that the recombination pathway could also go in the other direction, with holes being released from the hole trap into the valence band and recombining at the electron trap. Which process actually takes place depends on the material and the defects involved. In this sense, the assignment of T and R to the electron and hole trap is arbitrary.
Note. TL = thermoluminescence; OSL = optically stimulated luminescence; VB = valence band; CB = conduction band.

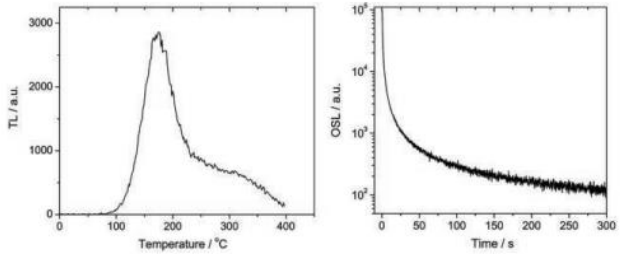


Figure 5.2 Left panel: TL glow curve of a set of surface-mount resistors from the circuit board of a mobile phone after irradiation (and preheating). Right panel: OSL decay curve of a chip encapsulation of a debit card after irradiation.
Source. Courtesy of C. Woda.
Note. TL = thermoluminescence; OSL = optically stimulated luminescence.

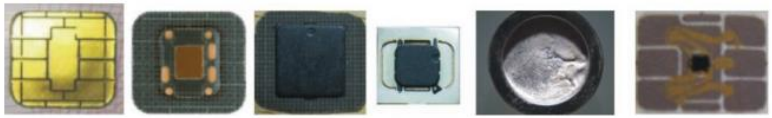


Figure 5.3 Examples of chip card technologies. From top left to bottom right: Typical front side of a contact-based chip card module found on credit and debit cards; reverse side of the same module revealing a UV-cured translucent encapsulation; the reverse side of the same type of module but with molded encapsulation; contactless module with molding, potentially found in electronic documents; extracted filler material of a contact-based molded encapsulation; flip-chips.
Source. Adapted from Woda *et al.* (2012).

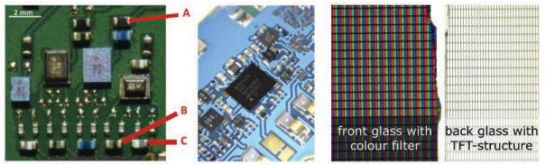


Figure 5.5 From left to right: Resistors (A) and inductors (B + C) located on the circuit board of a mobile phone. Integrated circuit on a similar circuit board. Front and back glass of a liquid crystal display.
Source. Taken, respectively, from Bassinet *et al.* (2017), Discher and Woda (2013), and Mrozik *et al.* (2017a).

TL/OSL dosimetry: summary

- Lots of developpments over the last 10 years but no application up to now, relative large communauty of researchers
- More sensitive than EPR, but larger signal unstability and destructive measurements, light effect for OSL
- Possibility of international network (see large scale accident), but bottleneck with sampling
- Interresting developpments with remote measurments with optical fiber overcoming the problem of sampling
- Promising appraoches (cf. silicate in dust)

Summary of physical dosimetry

Table 8.2 Comparison of Physical Dosimetry Techniques.

Assay	Materials	Recommended period of use since exposure (days, weeks, years)	Identify partial body exposure?	Time (h) from sample receipt to first dose estimate	Specificity[a]	Dose range (Gy) (MDD—upper limit[b])
TL or OSL: surface-mounted components	Resistors, inductors (usually alumina substrates)	Days to weeks[c]	No	1 to 2	γ, x, β	<0.1 to ~10
TL or OSL: ICs	Epoxy encapsulation	Days to weeks[c]	No	1 to 2	γ, x, β	0.04/0.25 to ~10 for TL; <0.01 to ~10 for OSL
TL or PTTL, phone glass	Protective glass or display glass (different glass formulations)	Days to weeks[c]	No	~1 to 4	γ, x, UV, β, BGS	0.3 to ~10 for TL; <10 to ~20 for PTTL
OSL, other electronic components	Chip cards	Days to weeks[c]	No	1 to 2	γ, x, BGS	<0.01 to ~10
OSL, clothing	Fabrics, shoes (e.g., polymers such as cotton, PVC, polyester)	Days to weeks[c]	No	~1	γ, x, β, BGS	<0.1/1.0 to ~10
TL or OSL: other	Plastic cards (OSL), money (OSL), dust (TL)	Days to weeks[c]	No	~1	γ, x, β, BGS	~0.1 to ~ 10
OSL, dental materials	Tooth enamel, repair ceramics	Days (for teeth) Days to weeks (for ceramics)[c]	No	~1	γ, x, UV, β, BGS	<1 to several (teeth); <0.01/~0.2 to ~10 (ceramics)
EPR, teeth[d]	Enamel (hydroxyapatite)	Days to years	Possible	~1	γ, x, UV, β, BGS	0.01 to ~10
EPR, bone	Hydroxyapatite	Days to years	Possible	Several	γ, x, BGS	1 to ~10
EPR, nails	Finger or toes (keratin)	Days[c]	Possible	2 to 4	γ, x, UV, β, BGS	~0.1 to ~10
EPR, phone glass	Protective glass or display glass (different glass formulations)	Days to years	No	~1	γ, x, UV, β, BGS	1.0/2.0 to few Gy
EPR, other	Plastic components of clothing, eyeglasses, watches	Days to years	No	~1	γ, x, UV, β, BGS	1 to few Gy

Note. MDD = minimum detectable dose; TL = thermoluminescence; OSL = optically stimulated luminescence; ICs = integrated circuits; PTTL = phototransferred thermoluminescence; BGS = non–radiation-induced background signal; PVC = polyvinyl chloride; EPR = electron paramagnetic resonance; ISO = International Organization for Standardization.

[a] Known sensitivities [to gamma rays (γ), x-rays (x), beta particles (β), and ultra-violet (UV) photons] reported in the literature; not meant to be exclusive.

[b] Approximate upper dose limit for linearity in dose response, or maximum dose to which samples have been tested in the published literature; MDD varies from sample to sample, within the range indicated (e.g., 0.1/5.0 Gy).

[c] Limited by fading of the TL or OSL signal after exposure. MDD increases with fading time.

[d] ISO standard ISO 13304 (2013).

Summary of all techniques

Table 8.4 Degree of Maturity of the Dosimetry Methods Discussed in This Report.

Maturity level	Dosimetry technique	Technique	Not yet applied	Infrequently applied	Frequently applied
Established	Biodosimetry	DCA[1,3-5]			√
		CBMN[6]			√
		FISH[7]		√	
	EPR	X-band; tooth enamel		√	
Under Development	Biodosimetry	Gene expression	√		
		γ-H2AX	√		
		PCC[8]		√	
	EPR	X-band; bone[9-21]			√
		Q-band; bone[10-25]		√	
		Q-band; tooth enamel[10]		√	
		X-band; sugar[26-28]		√	
		X-band; polymers[29,30]		√	
		X-band; glass[28]		√	
	TL/OSL	OSL; surface-mounted resistors	√		
Experimental	Biodosimetry	Small metabolites	√		
		Proteomics	√		
	EPR	Q-band; nails[31]		√	
		X-band; nails[31]		√	
		X-band; cotton[13]		√	
	TL/OSL	TL/OSL glass	√		
		TL/OSL ICs; chip cards	√		
		OSL; teeth, dental ceramics, dust, bills, clothing	√		

Lessons learnt for small scale accident

Lessons learned are as follows:

- Localized irradiation is often associated with a whole-body irradiation.
- The absence of an individual dosimeter is common for workers.
- There is a lack of accuracy regarding the circumstances of accidents.
- Retrospective techniques, if used sufficiently early, can provide key information for medical management.
- The assessment of the heterogeneity of the doses and the values of the local doses requires a multitechnique approach.
- Using a multitechnique approach can allow estimates of the contributions of local and whole-body irradiation.
- Fingernail dosimetry provided data consistent with clinical signs.

9.1.3 Overall Conclusions

In this section, the intention was to illustrate with detailed examples how the retrospective dosimetry techniques together with dose reconstruction techniques (experimental or numerical) can be used in complementary ways to provide accurate and pertinent information to medical teams for the medical management of casualties. If used sufficiently early, medical management can be improved by deploying therapy, sometimes even before the appearance of clinical signs.

Large scale accident: applications?

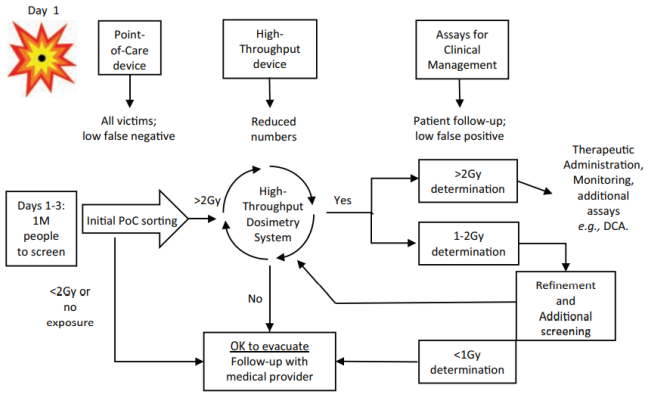


Figure 9.1 A conceptual scheme for triage following a mass casualty radiological event, consisting of an initial rapid triage/sorting at a so-called "Point-of-Care" (PoC) facility, followed by more detailed dose assessment at a "High-Throughput" (HT) facility.
Source. Redrawn from Sullivan *et al.* (2013).

Table 9.1 Radiation Dose Triage Levels for Symptoms and Medical Care Suggested by the Multibiodose Project in the European Union (Jaworska *et al.*, 2014).

Category	Triage dose	Symptoms and care
Low	<1 Gy	Unlikely to develop symptoms of acute radiation syndrome (ARS); no immediate care required
Medium	1 to 2 Gy	May experience mild or delayed ARS symptoms; follow-up care may be necessary
High	>2 Gy	Moderate-to-urgent care may be required

Note. For deterministic tissue effects, the critical quantity to be measured is the absorbed dose and a red, yellow, green decision gate is used to categorize victims into those not likely to develop symptoms, those who experience mild symptoms and may require follow-up care, and those who have a moderate-to-urgent need for medical care. For triage purposes, 2 Gy is the critical dose.

The importance of network is underlined

New developpments needed to adress the problem of meas. capacity

Recommendations

Taken as a group, the available emergency dosimetry methods, and those still under development, along with the results of laboratory-based intercomparisons conducted to date, lead to estimates of the actual absorbed dose with an uncertainty level of ~±20 %. Improvements to this number may accrue with further research. Uncertainties under actual field conditions should be expected to be larger.

10.2 Recommendations

The review and analysis outlined in this Report lead to several recommendations for deployment of existing dosimetry methods and for avenues of future research:

10.2.1 Biodosimetry

- In order for biodosimetry to be used in an emergency, it is important to have a network of cytogenetic laboratories available and organized.
- Within these networks, intercomparisons are essential for harmonization of methodology and validation of the capabilities and capacities of the laboratories. Intercomparisons can also be useful as an opportunity to test emerging assays.
- The DCA is recommended as the preferred biodosimetry tool for large-scale events. The QuickScan scoring method decreases scoring time while maintaining adequate dose estimates for triage dosimetry. For suspected higher doses (>5 Gy), however, premature chromosome condensation (PCC) is recommended.
- When it is not feasible to perform the DCA and the suspected dose is below 5 Gy, the CBMN assay is a recommended second choice.
- Advances in automation should be pursued as a method for expanding the capacity of the networks and improving throughput, which will provide more-timely dose estimates in large-scale events.
- The use of telomere and centromere probes in conjunction with the DCA or PCC assay can improve the efficiency of chromosome damage detection and can also enhance automation; however, it increases the cost of the assay and complexity.
- The use of multiple assays can be advantageous, for example, in scenarios when the timing of the event is uncertain, using both the DCA and γ-H2AX can provide additional information about the exposure conditions.
- Translocation analysis by FISH is not optimal for large-scale events due to cost and confounding factors.
- Continued research is required to develop emerging assays with Point-of-Care platforms that can provide rapid dose assessments in the field. Emerging assays also have the potential to address complex exposures

10.2.2 Physical Dosimetry

Among the physical dosimetry techniques, EPR dosimetry has been the most well used following acute radiological accidents. Of the various potential EPR dosimetry target materials, the most accurate results are from tooth enamel, allowing measurement of individual radiation doses as low as 100 mGy. It has been successfully validated in various interlaboratory comparisons and it has been applied in cases where hundreds of individuals were monitored as a part of the epidemiological studies. This method is suggested whenever possible and feasible. For this purpose, the following are recommended:

- Commercially available EPR spectrometers working in X-band can be used for these measurements. The procedure of the dose measurements is described in detail in multiple consensus documents [International Atomic Energy Agency (IAEA), 2002b; International Commission on Radiation Units and Measurements (ICRU), 2002; International Organization for Standardization (ISO), 2013]. Using calibration curves and with an accuracy level usually used for epidemiology, the dose measurements for 10 samples can be done during 1 d; 100 samples will require a week.

Invasive sampling has limited EPR's application on teeth and only teeth collected postmortem or extracted for medical reason have been analyzed. Therefore, research into other, less-invasive techniques, is required. Particularly:

- Electron paramagnetic resonance analysis in tooth enamel mini-biopsy samples using the Q-band may be a possible area for emergency dosimetry. This technique has been used in only a few laboratories and has not yet been compared with X-band measurements. From the methodological point of view, Q-band EPR on tooth enamel can be considered as a simplified version of established protocol for X-band. No chemical treatments or signal fitting procedures are required.
- Tooth enamel Q-band biopsy can be obtained relatively quickly and is considered to be harmless to the individuals. The doses can be measured as low as about 200 mGy. It does not require a particular sample preparation and commercially available Q-band EPR spectrometers can be used. About 100 sample measurements can be performed in less than 10 h in triage mode.
- Depending on the circumstances and the expected dose level, one could also consider *in-vivo* tooth enamel

10.2.4 General Recommendations for All Methods

In addition to continued research on the individual dosimetry methods, as noted above, continued field exercises and laboratory intercomparisons are recommended for all methods. Such exercises are essential to maintain capability, demonstrate technical competency, and identify weaknesses in the procedures adopted by individual laboratories. Facilities must be kept in a state of readiness and a high level of effectiveness. Field and laboratory intercomparisons are essential to achieve this.

Also essential is the establishment of laboratory networks, across nations and across geographical regions. Currently, existing networks of dosimetry laboratories are entirely informal and are funded through adjunct or extraneous sources. No funded networks exist, nor are the individual laboratories within the networks funded specifically for the purpose of maintaining a state of readiness for deployment in a future large-scale event. As a result, existing networks are informal only and lack permanence. As a result, their long-term stability is tenuous and their future is uncertain. In some regions of the world, no networks exist currently.

We also recommend that, where possible and appropriate, standards are adopted for application of each dosimetry technique. Several of the biodosimetry methods are covered by such standards (ISO standards) but others are not. Of the physical dosimetry methods only EPR (of teeth) is covered by an ISO standard. Standards will help participating laboratories establish quality assurance goals and will assist in the acceptance of results from those laboratories that adopt these standards. Thus, as research develops and protocols become accepted and established, development of ISO standards for all methods is recommended.

Conclusions

- Provide a review of existing methods and new developpments
- Provide an comprehensive overview of use and applications (for authorities and decisioners)
- Provide recommandations both for researchers, authorities and funding agency: roadmap
- This report has helped to maturate the strategies of use and research, especially for large scale