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# Disaster Medicine and Public Health Preparedness



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### Activities of ISO Working Group 18: Biological and Physical Retrospective Dosimetry

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Abstract:	<p>Biological and physical retrospective dosimetry for ionizing radiation exposure is a rapidly growing field and several methods for performing biological and physical retrospective dosimetry have been developed to provide absorbed dose estimates for individuals after occupational, accidental, intentional, and incidental exposures to ionizing radiation. In large-scale radiological/nuclear incidents, multiple retrospective dosimetry laboratories from several countries may be involved in providing timely dose estimates for effective medical management of several thousands of exposed individuals. In such scenarios, the harmonization of methods among participating laboratories is crucial for consistency in data analysis, dose estimation and medical decision-making. In this regard, ISO documents ensure that these practices are standardized globally across the laboratories by providing quality assurance and quality control documentation that guide laboratories in maintaining high-quality performance for consistency. With the intent of bringing standardization and harmonization of biological and physical retrospective dosimetry methodologies across national and international laboratories, the ISO working group 18 (WG18) was established under ISO/TC85/SC2 (Technical Committee 85, Subcommittee 2-Radiation Protection) in 1999. This manuscript summarizes some of past, current and future activities of WG18 on biological and physical retrospective dosimetry.</p>

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# Activities of ISO Working Group 18: Biological and Physical Retrospective Dosimetry

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## Abstract

Biological and physical retrospective dosimetry for ionizing radiation exposure is a rapidly growing field and several methods for performing biological and physical retrospective dosimetry have been developed to provide absorbed dose estimates for individuals after occupational, accidental, intentional, and incidental exposures to ionizing radiation. In large-scale radiological/nuclear incidents, multiple retrospective dosimetry laboratories from several countries may be involved in providing timely dose estimates for effective medical management of several thousands of exposed individuals. In such scenarios, the harmonization of methods among participating laboratories is crucial for consistency in data analysis, dose estimation and medical decision-making. In this regard, ISO documents ensure that these practices are standardized globally across the laboratories by providing quality assurance and quality control documentation that guide laboratories in maintaining high-quality performance for consistency. With the intent of bringing standardization and harmonization of biological and physical retrospective dosimetry methodologies across national and international laboratories, the ISO working group 18 (WG18) was established under ISO/TC85/SC2 (Technical Committee 85, Subcommittee 2- Radiation Protection) in 1999. This manuscript summarizes some of past, current and future activities of WG18 on biological and physical retrospective dosimetry.

## Introduction

### *Importance of standards in life sciences and industries*

The International Organization for Standardization (ISO) facilitates the harmonization of operating procedures such as laboratory protocols, to ensure that results are comparable and reproducible across different laboratories when the same methods are used. This harmonization of procedures is crucial for maintaining uniformity, reliability, consistency, and quality in industrial, medical, and educational operations. By providing guidelines and procedures, ISO standards not only help the quality control (QC) and quality assurance (QA) assessments but also improve the productivity of the organizations and industries by identifying and minimising inefficiencies through implementation of corrective action plans. ISO documents are available for the management of industries, environment, health and safety, and food safety, among others, and these documents are developed and established by the scientific wisdom of subject matter experts working as a group. There are almost 300 technical committees that are currently involved in developing and establishing ISO standards for different disciplines.

The standards established by ISO have been in routine use in the industrial world for several decades and have found their way into the biological sciences where standards are crucial for reliability of procedures, quality assurance, data comparison and data validation. Radiation biological and physical retrospective dosimetry is an actively emerging field of science where several tools have been and continue to be developed for estimating the absorbed radiation dose in potentially exposed humans. ISO standards are needed for each of the biological and physical retrospective dosimetry assays to establish consensus methodologies for dose estimation either by individual or national/international dosimetry network laboratories, specifically for use in the aftermath of mass-casualty radiological or nuclear incidents/accidents. In such a scenario, ISO standards for harmonizing the protocols among the laboratories are imperative to get consistent and reliable results for fair data comparison and validation of dose estimates<sup>1</sup>. Additionally, these ISO standards may be useful for accreditation of newly developed retrospective dosimetry laboratories. Realizing the importance of ISO standards for these laboratories, a

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2  
3 technical committee (ISO/TC85/SC2) working group (WG18) was established in 1999 to develop standards  
4 for some of the established biological dosimetry tools. This was later expanded to include retrospective  
5 physical dosimetry through the establishment of a sub working group focused on electron paramagnetic  
6 resonance (EPR). This manuscript summarises some of the past, current and future activities of the WG18  
7 on biological and physical retrospective dosimetry standards.  
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9

### 10 *Background on biological and physical retrospective dosimetry*

11 Biological and physical retrospective dosimetry is the measurement of absorbed radiation dose based on  
12 the response of biological indicators such as DNA, RNA, proteins, lipids as well as a variety of metabolic  
13 byproducts or physical measurements in biological material such as EPR in teeth or bones. Retrospective  
14 dosimetry can be used to estimate the absorbed radiation dose when individuals without personal  
15 dosimeters are exposed to unknown doses of ionizing radiation. It can also be used to confirm the  
16 radiation dose on a personal dosimeter in the case of radiation/nuclear workers and to gain information,  
17 in some instances, about the nature and level of exposures. Biological dosimetry was developed in the  
18 mid-20<sup>th</sup> century as it became evident that chromosomal aberrations increased in a dose-responsive  
19 manner after exposure to ionizing radiation and could be used as an indicator of dose to the exposed  
20 individual. The use of biological dosimetry after the “Recuplex” criticality accident in Hanford, USA <sup>2</sup> and  
21 after a radiation accident in 1969 involving industrial radiographers in the UK <sup>3</sup> is an early example of its  
22 application. Throughout the second half of the 20<sup>th</sup> century, biological dosimetry was used for diverse  
23 nuclear accidents and incidents, which allowed for not only the dose assessment, but also the  
24 improvements of the existing techniques <sup>4-9</sup>.  
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29 In the case of large-scale radiological/nuclear incidents/accidents, several hundreds and thousands of  
30 people could be exposed to substantial doses of ionizing radiation. The LD50/60 (the lethal dose that will  
31 kill 50% of the exposed individuals in 60 days) value ranges from 3.5 Gy - 4 Gy without supportive care  
32 and more than 7 Gy with supportive care. Therefore, timely assessment of absorbed radiation dose will  
33 be useful for saving human lives <sup>10</sup>. Figure 1 summarizes the methods that can be used, alone or in  
34 combination, to perform radiation dose estimates in these scenarios.  
35  
36

## 37 **Overview of ISO and WG18**

### 38 *Life cycle of developing ISO standards*

39 The ISO standards in most cases contain tested and validated procedures or protocols for the best  
40 practices in any business, industrial and educational/research organizations. There are two basic steps for  
41 the development of standards: (I) consensus among the subject matter experts about the added value an  
42 ISO standard would bring in a specific area and (II) acceptance of a standard at the national level.  
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44

45 Once there is consensus among experts in the field that a new standard would be of value, a proposal is  
46 then submitted to the relevant ISO technical committee composed of representatives from various  
47 countries and stakeholder groups. Bringing an ISO standard to life is a well-defined process, with each  
48 stage acting as a crucial checkpoint towards publication. While the timeframe might vary (18, 24, or 36  
49 months), the core stages remain essential for every standard, ensuring thoroughness, consensus, and  
50 global relevance. The life cycle of an ISO standard is depicted in Figure 2.  
51  
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53 The rigorous review process is the foundation of ISO standards' credibility and trust. By incorporating  
54 diverse perspectives and expertise, the standards reflect the global needs of the field they serve.  
55 Subsequent sections of this manuscript will delve into the specific applications of ISO standards in  
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3 retrospective dosimetry, which is a specialty under the working group ISO/TC 85/SC 2/WG18: biological  
4 and physical retrospective dosimetry.  
5

6 *History of identifying the need for standardized biological and physical retrospective dosimetry*  
7 *techniques*  
8

9 In the 1990s, there were several accidental exposures to ionizing radiation that had no accompanying  
10 physical dosimetry and, at that time, only a few biological dosimetry laboratories were available for  
11 conducting the analysis. Although biological dosimetry was available, there were issues with the  
12 acceptance of the results, particularly if they were not as expected. One solution to address the lack of  
13 confidence in the results was to establish an international intercomparison program. The first of these  
14 was conducted in 1995 with two laboratories, the Nuclear Safety and Protection Institute (IPSN, now  
15 Institut de Radioprotection et de Sûreté Nucléaire, IRSN, France) and what was then known as the  
16 National Radiological Protection Board (NRPB, now UK Health Security Agency, UKHSA). A second  
17 intercomparison was held in 2002 with 15 laboratories and included exposure to both neutrons and  
18 gamma rays<sup>11</sup>. Even though the estimations from 11 of the 15 participants fell within the  $\pm 30\%$  of the  
19 physical reference dose, the results indicated some discrepancies in the rate of dicentric chromosomes  
20 enumerated among participants. As fixed cells were transported to each laboratory, one explanation was that the  
21 quality of metaphases was affected by the transportation of the samples. Additionally, slide-making  
22 procedures may have varied between laboratories. The differences in dicentric scoring among participants  
23 could be also due to the type of radiation used and inexperience at scoring highly-damaged cells. With  
24 high-LET radiations, some metaphases may have contained numerous chromosomal aberrations such as  
25 multicentric chromosomes and centric rings that can make the scoring difficult. Another issue with the  
26 dose estimates could have been the dose-response curve used. Few of the participant laboratories had a  
27 neutron dose response curve while others used their gamma or X-ray dose-response curves. However,  
28 smaller variations were observed in the dose estimations as compared to the frequency of aberrations  
29 highlighting that experimental conditions such as slide making and scoring can be laboratory dependent.  
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35 A second solution to address the lack of confidence was to establish a process for laboratory accreditation  
36 by an independent international body<sup>12</sup>. At that time, there were only two applicable standards for  
37 laboratories:  
38

- 39 • 9001:1987 – Quality systems — Model for quality assurance in design/development, production,  
40 installation and servicing (now 9001:2015 Quality management systems — Requirements)<sup>13</sup>
- 41 • ISO/IEC Guide 25:1990 General requirements for the competence of calibration and testing  
42 laboratories (now 17025:2017)<sup>14</sup>  
43  
44

45 It was clear that there was a need to create standards specific to biological dosimetry techniques. In 1999  
46 the ISO working group 18 “Biological Dosimetry” was formed under Technical Committee 85 (Nuclear  
47 energy, nuclear technologies, and radiation protection) / Subcommittee 2 (Radiological Protection). The  
48 WG consisted of 13 specialists from 11 countries who met for the first time at IRSN and started drafting  
49 the first standard on the dicentric assay.  
50

51 Since its conception, the WG has expanded to include physical retrospective dosimetry and in 2021  
52 changed its name to “Biological and physical retrospective dosimetry” reflecting the addition of standards  
53 on EPR. The committee has now developed a suite of standards including guidance on conducting the  
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3 dicentric assay, the cytokinesis-block micronucleus assay, translocation analysis using FISH and EPR  
4 (Figure 3). A list of these standards can be found in table 1.  
5

6 A typical standard for a specific assay will contain detailed technical information on various procedural  
7 steps starting from sample collection followed by assay procedure, data generation, data analysis, dose  
8 estimation and report generation. A detailed description of statistical analysis for dose estimation will also  
9 be included in the standard. It will also contain details on quality assurance and quality control procedures  
10 specific to the assay. Often examples of useful documents are included in the Annexes (e.g. instructions  
11 for requestors, questionnaires, reporting templates).  
12  
13

#### 14 *ISO standards for biological and physical retrospective dosimetry on biological samples*

15 Ionizing radiation (IR) induces a wide spectrum of lesions on chromosomal DNA. DNA double-strand  
16 breaks are critical lesions which, when mis-rejoined, can result in microscopically detectable structural  
17 chromosome alterations. For this reason, various cytogenetic methods for detecting the structural  
18 chromosome aberrations have been developed and routinely used for radiation cytogenetic biological  
19 dosimetry. Methods for retrospective analysis using physical dosimetry have also been developed. Table 2  
20 lists the biological and physical retrospective dosimetry assays that have ISO standards or are under  
21 consideration for standardization. A brief account of these assays is provided below with the associated  
22 standards listed in table 1:  
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#### 25 Dicentric chromosome assay (DCA) <sup>15,16</sup>

26 The DCA is a cytogenetic assay which is considered the gold standard of biological dosimetry and is the  
27 most used method <sup>1,4</sup>. This assay is performed either on whole peripheral blood cells or on isolated  
28 lymphocytes cultures and involves the scoring of dicentric chromosomes that are formed after the mis-  
29 rejoining of two broken chromosomes with intact centromeres and can be easily visualized in metaphase  
30 cells (Figure 4A). Identification of dicentric chromosomes can also be optimized by the addition of Peptide  
31 Nucleic Acid (PNA) probe specific for centromeres of all the human chromosomes. Dicentric-bearing  
32 lymphocytes are unstable when passing through mitosis, therefore they disappear with time <sup>17,18</sup>. Their  
33 persistence in the human body is estimated to be between 6 and 12 months after exposure <sup>19</sup> and  
34 therefore DCA is most suitable for acute recent exposures. Since *in vitro* culturing of lymphocytes for 48  
35 h is required for chromosome preparation, the turn-around time for DCA-based dose estimation is usually  
36 72-96 h. The DCA has been used in many instances of dose reconstruction for both small and large  
37 numbers of exposed individuals <sup>4-9</sup>.  
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43 In the case of a radiological emergency, triage methods shorten the analysis time and provide timely  
44 information to the medical team to assist in the care of potentially exposed victims. In cytogenetics based  
45 biological dosimetry, triage analysis includes manually scoring either 50 metaphases or 30 dicentrics  
46 (whichever is reached first) allowing dose estimates within of  $\pm 1$  Gy of the absorbed dose <sup>4</sup>. This margin  
47 of uncertainty is sufficient to guide the medical teams in the initial treatment. Another triage option is to  
48 conduct semi-automatic analysis of 500 to 1000 metaphases, which could potentially shorten the analysis  
49 time <sup>5</sup>.  
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#### 52 Translocation analysis <sup>20</sup>

53 Similar to the DCA, translocation analysis is performed on mitotic lymphocytes, however, the  
54 translocations, which involve the exchange of parts of the chromosomes between two or more  
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3 chromosomes, are detected by fluorescence *in situ* hybridization (FISH) using probes for a specific set of  
4 chromosomes or the whole complement (Figure 4B). Symmetrical translocations, in which each resultant  
5 chromosome has one centromere, are considered stable aberrations that can pass through mitosis (unlike  
6 dicentric chromosomes) and are more easily transmitted to progeny cells. This allows them to persist in  
7 the body for many years (much longer than dicentric chromosomes) and hence are useful for  
8 retrospective biological dosimetry several years after radiation exposure. These translocations, however,  
9 increase with age and other lifestyle factors and should be corrected for when calculating dose estimates  
10 <sup>21</sup>. Some notable examples of cases where FISH-based biological dosimetry was employed include the  
11 follow-up of victims from the Hiroshima-Nagasaki bombings <sup>22</sup>; children living close to the Chernobyl  
12 nuclear accident site <sup>23,24</sup>; victims of the Goiânia accident <sup>25,26</sup>; victims of the Tallin incident <sup>27,28</sup> and the  
13 workers from the Mayak nuclear weapon manufacturing site in the Techa river region (Russia), which was  
14 contaminated mainly by radioactive strontium in the 1950s <sup>29</sup>.

#### 19 Cytokinesis-block micronucleus (CBMN) assay <sup>30</sup>

20 In the lymphocyte cytokinesis-block micronucleus assay, micronuclei resulting from mal-segregation of  
21 whole chromosomes or chromosome fragments that are excluded from the main nuclei are scored *ex vivo*  
22 in cytokinesis-blocked binucleate cells (Figure 4C) <sup>4</sup>. Unlike dicentric chromosomes which are specific for  
23 radiation exposure, micronuclei can be induced by a variety of genotoxic agents including ionising  
24 radiation. The CBMN assay, has been applied to several accidental scenarios for retrospective dose  
25 reconstruction <sup>7,31-33</sup>.

#### 28 Premature chromosome condensation (PCC) assay

29 This assay involves the use of protein kinase inhibitors (calyculin A and okadaic acid), to prematurely  
30 condense the chromosomes in the G2 phase of the cell cycle prior to reaching mitosis. This allows the  
31 visualization of chromosomes in heavily damaged cells that are permanently arrested in the G2-phase and  
32 are unable to progress to mitosis (Figure 4D) <sup>34</sup>. Alternatively, G0-PCC can be induced where the irradiated  
33 cells (usually G0-human lymphocytes) are fused with mitotic cells of Chinese Hamster Ovary using  
34 Polyethylene Glycol (PEG) as fusogen (Figure 4E) <sup>35</sup>. G0-PCC is advantageous because it can be performed  
35 directly after blood collection without the need for lymphocyte culturing as in the case of G2-PCC. One of  
36 the great advantages of the PCC assay is its capability to detect higher doses of exposure, thus being  
37 complementary to the DCA. In addition, its shorter culture time allows for a rapid dose estimation (few  
38 hours). It was notably used for victims of the Tokai-Mura criticality accident, where two individuals were  
39 exposed to doses higher than 6 Gy <sup>36,37</sup> and in the Taiyuan radionuclide manufacturing accident of 2008  
40 where it was concluded that 5 employees exposed to gamma irradiation received doses ranging from 2 to  
41 12 Gy <sup>38</sup>. This method is being proposed for the next standard to be drafted in WG18.

#### 46 Electron paramagnetic resonance (EPR) dosimetry <sup>39,40</sup>

47 Electron Paramagnetic Resonance (EPR) dosimetry can be defined as a method of radiation dose  
48 determination based on the measurements of concentration of radiation induced radicals in matter with  
49 EPR spectroscopy. EPR dosimetry is used to measure radiation doses in solid tissues of humans or animal  
50 (teeth *in vitro* and *in vivo*, bone *in vitro*, finger- and toenails *in vitro* and *in vivo*) but also personal items  
51 such as cell phone screens, watch glasses, clothes etc. (not addressed in the framework of WG18). This  
52 method has the advantage of being non-destructive to the material being measured so that repeated  
53 measurements on the same sample can be made. The other attractive features of the EPR dosimetry  
54 include linear dose dependence for most materials and tissues, the possibility to do dose measurements  
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3 immediately after irradiation, based on a physical process that is not affected by biological processes such  
4 as stress or simultaneous insults/damage that are likely to occur with irradiation such as wounds and  
5 burns. The timeframe for measurements can be made at any interval immediately after irradiation up to  
6 at least 2 weeks (fingernails), indefinitely (teeth)<sup>41</sup> or a range of times for other EPR dosimetry materials.  
7 Furthermore, the EPR signal is unaffected by dose rate and can be used for dose measurements after  
8 partial body exposures.  
9

10  
11 ISO 13304-1:2020 provides a general guidance on sample collection, their preparation for the dose  
12 measurements, EPR measurements in the samples under investigation, calibration of the EPR radiation  
13 response in the radiation dose units and some other useful information related to the application of this  
14 technique. This standard covers *in vitro* and *in vivo* EPR dose measurements in biological tissues (mostly  
15 teeth and nails) of the person, personal items and objects located in the immediate environment to the  
16 human. It usually employs X-band frequency (8-12 GHz), but higher and lower frequencies are also being  
17 considered. Specifically, this International Standard proposes a methodological frame and  
18 recommendations to set up, validate, and apply protocols from sample collection to dose reporting.  
19 However, this standard does not provide any specificity to the type of the sample (e.g. teeth, nails, and  
20 other applicable materials) used for the dose measurements. ICRU reports 68 and 94 give an analysis of  
21 the most commonly available methods of retrospective dosimetry, including EPR<sup>42,43</sup>. These two reports  
22 provide extensive lists of the references on the methodology and applications of EPR dosimetry.  
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26 Standard ISO 13304-2:2020 provides specific guidelines to perform the *ex vivo* measurements of human  
27 tooth enamel samples by X-band EPR for dose assessment (Figure 4F). This technique is the most  
28 developed EPR dosimetry method, which has been applied to reconstruct radiation doses received by  
29 Hiroshima and Nagasaki A-bombardment survivors, population and emergency personnel affected by  
30 Chernobyl accident, Southern Ural population in Russia residing in the areas contaminated by Russian  
31 nuclear weapon plant Mayak and in many other radio-epidemiological studies<sup>42,44</sup>. ISO 13304-2:2020  
32 expands and standardizes the measurement and dose reconstruction procedures and the evaluation of  
33 performance. This document is compliant with ISO 13304-1 “Radiological protection - Minimum criteria  
34 for electron paramagnetic resonance (EPR) spectroscopy for retrospective dosimetry of ionizing radiation  
35 – Part 1: General principles” with particular consideration given to the specific needs of X-band EPR  
36 dosimetry using human tooth enamel.  
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40 In the context of radiological accidents, this method has been mostly used on biopsies of bone tissues  
41 providing very pertinent information when irradiation is localized to a small volume of the body and in a  
42 less extent to biopsies of tooth enamel<sup>43</sup>. *Ex vivo* tooth enamel dosimetry (on whole tooth) has been  
43 largely used in support of epidemiological studies of ancient and/or prolonged exposure<sup>42</sup>.  
44  
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#### 46 *Factors involved in radiation dose assessment*

47 There are many aspects of radiation dose assessment by biological or physical retrospective dosimetry  
48 that are addressed within the standards:  
49

- 50 a) Radiation exposure parameters can vary from one exposure scenario to the next: level of dose,  
51 radiation quality, dose rate including single or fractionated doses and whether a person is entirely  
52 or partially exposed. Each of these factors will affect the dose estimates made and these are  
53 addressed in the standards. The amount of radiation one is exposed to can determine the number  
54 of cells required to be analysed for the cytogenetic assays. Different qualities of radiation affect  
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3 the shape of the dose response curves and advice is provided on the range and number of doses  
4 required when creating a dose response curve for high- and low-LET radiation. The dose rate also  
5 affects the shape of the dose response and advice is provided on how to apply an acute dose-  
6 response curve to non-acute exposures. Finally, it is of great importance to understand whether  
7 an individual has been exposed to a whole- or partial body- exposure as the medical intervention  
8 will differ in these two cases. The standards describe methods to determine whether an exposure  
9 is partial body.  
10

- 11  
12 b) There are continuous improvements to the assays that must reach a certain level of maturity and  
13 uptake before being incorporated into the standards. These are assessed each time a standard  
14 comes up for review. One example is the development of software tools for performing the data  
15 and statistical analysis for cytogenetic assays. Although specific software is not mentioned, they  
16 are mentioned as an acceptable tool. Automation is another improvement that is becoming  
17 widely used but has not yet been described in detail in a standard.  
18  
19 c) The type of dose assessment methodology to be employed may depend on the exposure scenario.  
20 For early response situations, the DCA, CBMN or EPR standards might be followed, whereas for a  
21 retrospective analysis, at longer times post-exposure, translocation analysis or EPR would be  
22 applicable (Table 2). Depending on the number of casualties requiring analysis, one might  
23 consider employing triage scoring that has been described in ISO 21243 <sup>45</sup> that outlines scoring  
24 methodology for rapid throughput and activation of networks for sample sharing to establish  
25 surge capacity when a laboratory's capacity has been exceeded. This standard could be applied  
26 to any of the other standards.  
27  
28 d) ISO 21243 also includes guidance on preparedness of a laboratory network prior to an event  
29 including organization, harmonization of protocols, quality assurance and control, training and  
30 intercomparison exercises to demonstrate capacities and capabilities of network laboratories to  
31 maintain performance criteria and continuous exchange of scientific and technical information.  
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### 34 *Use and impact of standards / achievements*

#### 35 Networks

36 In the case of large-scale accidents, the number of victims can easily exceed the capacity of single  
37 laboratories or organisations. Networking between experienced laboratories has been identified as a  
38 useful and important strategy in emergency management to overcome this bottleneck by sharing the  
39 workload and providing mutual assistance between laboratories. Besides increasing capacity, networking  
40 allows the broadening of the spectrum of methods and the choice of the most suitable approach for a  
41 particular scenario. In recent years, several laboratories around the world have joined forces and set up  
42 regional and/or global networks either on a formal or informal basis <sup>46</sup>. Global networks have been  
43 established by the World Health Organization (WHO) (BioDoseNet) <sup>47,48</sup>, the Radiation Emergency Medical  
44 Preparedness Assistance Network (REMPAN), and the International Atomic Energy Agency (IAEA)  
45 Response and Assistance Network (RANET).  
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50 On the regional level the key networks are the European Network for biological and retrospective physical  
51 dosimetry (RENEB), the European Radiation Dosimetry Group (EURADOS), the Latin American Biological  
52 Dosimetry Network (LBDNet), the North American Network and the Asian Radiation Dosimetry Group  
53 (ARADOS). The RENEB network of biological and physical retrospective dosimetry laboratories has been  
54 operating in Europe since 2017. The network currently includes 16 voting members and 43 associate  
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3 members from Europe and Asia <sup>49</sup>. The North American network is an informal network established first  
4 in Canada in 2002 and has now expanded to include several US laboratories <sup>50,51</sup>. LBDNet was founded in  
5 2007 and originally comprised 7 countries <sup>52</sup>. ARADOS <sup>53</sup> was established in October 2015 by researchers  
6 from China, South Korea and Japan. It consists of a host institute (China, Korea, or Japan, alternately) and  
7 four working groups (WGs) on Internal Dosimetry, External Dosimetry, Biological Dosimetry and  
8 Computational Dosimetry. In addition, India has also established a national biological dosimetry network  
9 involving 7 laboratories <sup>54</sup>.

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12 An essential requirement to achieve comparable results between the laboratory in a network is the  
13 harmonization of protocols and standardization of procedures. ISO 21243 <sup>45</sup> provides excellent guidance  
14 on the aspects of establishing a network while the ISO standards on individual techniques provide  
15 invaluable guidance for harmonizing procedures across laboratories <sup>55</sup>.

### 16 17 18 19 Inter-laboratory comparisons

20 The organisation of exercises and interlaboratory comparisons (ILC) are important tools to guarantee high  
21 quality results and to improve and optimize a network's performance. Coordination of infrastructure,  
22 logistical aspects, data management and communication are essential for managing large-scale accidents  
23 in biological and physical retrospective dosimetry to increase the throughput and to validate the workflow  
24 in a sustainable and operational network. Training and education programs and activities help to improve  
25 the ability of network members to provide reliable dose estimates. Furthermore, differences in the  
26 experimental setup or the radiation source used by the organizing institutions can help to identify  
27 potential issues and to improve and optimize the performance of the network <sup>49</sup>. International ILCs have  
28 been mainly run through RENE <sup>56-59</sup>, EURADOS<sup>55,60</sup>, LBDNet<sup>52</sup>, ARADOS<sup>53</sup> or Canada <sup>61</sup>. Typically, dose  
29 reconstruction is performed using several methods: manual and automatic dicentric chromosome  
30 analysis, manual and automatic micronucleus assay, translocation analysis, histone  $\gamma$ H2AX foci assay, PCC  
31 fusion, gene expression analysis and EPR. These ILCs are highly dependent on the use of protocols based  
32 on ISO standards developed in the frame of WG18, IAEA technical publications <sup>4</sup> and scientific  
33 publications. The focus of the RENE exercises was variable and included tele-scoring exercises, triage and  
34 full mode scoring for biological dosimetry methods, irradiation with different sources, homogeneous and  
35 heterogeneous irradiations, a field exercise, and comparisons between different assays <sup>55</sup>. There have also  
36 been several ILCs where performance of the EPR dosimetry in tooth enamel at different laboratories was  
37 compared. The most comprehensive one was carried out in 2010 <sup>62</sup>. Based on the results obtained by each  
38 participant, critical dose and detection limit were calculated by the organizers. The most recent  
39 comprehensive RENE ILC was conducted in 2022<sup>63</sup> in which the performance quality was compared  
40 between the established cytogenetic assays, molecular biological assays ( $\gamma$ H2AX foci, gene expression)  
41 and physical dosimetry-based assays (EPR, optically or thermally stimulated luminescence). The results  
42 of all ILCs have contributed to harmonization of SOPs and statistical methods for uncertainty assessment  
43 within the RENE network and EURADOS that have also fed back into revision of ISO standards for  
44 biological dosimetry.

## 50 51 **Future Perspectives**

### 52 *New Standards under consideration*

53 Premature Chromosome Condensation (PCC) is under consideration for the next biological dosimetry  
54 standard. It has been adopted widely by the biological dosimetry community and has advantages over  
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3 other cytogenetic techniques as described above. A standard dedicated to automation of different aspects  
4 of the biological dosimetry methods is also under consideration. This could potentially include both  
5 sample processing and scoring of aberrations.  
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### 7 *Emerging assays for future consideration*

8 There are several assays that are emerging as biological dosimeters but have not yet reached the maturity  
9 for standardization, for example the  $\gamma$ H2AX foci assay. The histone H2AX, a variant of histone H2A, which  
10 is a part of the histone octamer on which DNA is wound and is one of the first proteins that responds to  
11 DNA damage after radiation exposure through phosphorylation at serine 139 to the  $\gamma$ H2AX form<sup>64</sup>.  
12 Fluorescent conjugated antibodies are commercially available for easy visualization of the  $\gamma$ H2AX foci that  
13 form at the sites of DNA double strand breaks in a radiation dose-dependent manner. Although the  
14 histone  $\gamma$ H2AX assay is considered a novel biological dosimetric method, with sensitivity in the low dose  
15 range (in the order of tens of mSv) and applicability up at least 10 Gy<sup>65</sup>, many technical and methodological  
16 problems must still be solved, most notably the fast appearance (optimal peak time is 30 minutes to an  
17 hour after exposure) and disappearance of histone foci over time with only about 20% of the initial  
18 number of foci remain after 24 hours<sup>66</sup>. This means that dose estimation is limited to a short time after  
19 the event necessitating the immediate shipment of samples, preferably on ice, to the biological dosimetry  
20 laboratories for analysis. Nevertheless,  $\gamma$ H2AX assay can still be effectively used as a biological dosimeter  
21 if appropriate *in vitro* calibration curves are constructed for different post-exposure times to account for  
22 the disappearance of  $\gamma$ H2AX foci.  
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28 Another emerging technique is measuring changes in gene expression that can be measured in blood and  
29 lymphocytes post-exposure to ionizing radiation, showing promise for biological dosimetry and prediction  
30 of clinical outcomes<sup>67-69</sup>. Typically, a panel of genes encoding proteins related to the DNA damage  
31 response (e.g. DDB2, CDKN1A, GADD45A), apoptosis (e.g. FDXR, BAX, BBC3), and the development of the  
32 inflammatory reaction (e.g. GDF15, TNFSF4) is examined, showing significant and repeatable expression  
33 changes in peripheral blood cells<sup>70-72</sup>. The research and literature data confirm that the level of transcripts  
34 of various genes in the blood shows a clear dependence on the absorbed radiation dose at specified time  
35 points after exposure in the range of at least 0.2 Gy to 4 Gy. The method of analyzing gene expression  
36 changes is a fast and low-cost method that can be used in the case of a large-scale radiation exposure  
37 scenario.  
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### 41 *Automation of the DCA and CBMN assay*

42 One of the main disadvantages of DCA is that manual scoring of dicentric chromosomes is laborious and  
43 time-consuming, limiting the sample throughput of a single laboratory that would quickly become  
44 overwhelmed in the event of a mass casualty incident. Automation of DCA has been developed over the  
45 last 20 years<sup>5,73,74</sup> and has been successfully tested in the framework of the MULTIBIDOSE EU FP7 project  
46<sup>75,76</sup>. To date, several automatic DCA analysis systems have been developed and are in development<sup>77-81</sup>.  
47 The use of artificial intelligence (AI) also offers new opportunities to increase capacity in biological  
48 dosimetry and to support current and future research in biological dosimetry<sup>73,82</sup>. Automation and semi-  
49 automation of the DCA and the CBMN assay has been briefly mentioned in both ISO 19238 and ISO 17099  
50<sup>15,30</sup>, however, due to the rapid development of automation algorithms and use of AI-based tools for  
51 automation, these aspects need to be carefully considered by ISO WG18 before incorporating them in the  
52 future standards.  
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3 Analysis of MN in CBMN is not as technically demanding as the DCA which makes it more amenable to  
4 automation, drastically reducing the scoring time. Automatic and semi-automatic MN analysis has been  
5 used in many laboratories around the world in the recent years<sup>83-86</sup>. Several of these automated CBMN  
6 methods are becoming mature enough to be considered for ISO standardisation. As this method is also  
7 widely used outside of the biological dosimetry community, a standard on automation would be of use in  
8 the analysis of cytotoxic and genotoxic effects of environmental mutagens, carcinogens and clastogens.  
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11 Regardless of the automation tool or application, these systems must be validated against the  
12 standardized techniques prior to the incorporation into an ISO standard.  
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#### 14 *Electron Paramagnetic Resonance (EPR) Dosimetry standardization for large-scale event.*

15 *In vivo* EPR of teeth and finger/toenails offers the advantage of performing onsite measurements of  
16 individuals after a small or large-scale radiation event. While its feasibility for triage for such events has  
17 been demonstrated, more development/refinement is needed for its acceptance as a standardized  
18 technique<sup>87-89</sup>. In addition, *ex vivo* Q-band EPR on tooth enamel mini-biopsies has already been used for  
19 an actual radiological accident<sup>90</sup>. As the measurement takes less than 5 minutes after the biopsy is  
20 obtained and there are minimal requirements for sample preparation, this method has the potential to  
21 be implemented on a large scale, though no organized efforts are in place at this time<sup>91</sup>. Furthermore, AI  
22 could help this retrospective EPR dosimetric techniques by automating data analysis, improving  
23 calibration accuracy, and facilitating standardization. Indeed, AI algorithms can be trained to  
24 automatically identify and quantify EPR signals as well as AI-driven calibration models can improve the  
25 accuracy and precision of EPR measurements by accounting for various factors such as sample variability,  
26 significantly reducing analysis time<sup>92</sup>. Coordinated efforts could allow for more rapid standardization of  
27 technique also in case of adoption of AI tools.  
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### 32 **Limitations of standards**

33 Although standardization of biological and physical dosimetry methods is an essential step in harmonizing  
34 laboratories and ensuring robust dose estimates, standards can also have some limitations and downfalls.  
35 As the working group is comprised of international experts from different laboratories, there can be  
36 difficulties in reaching international consensus on the best procedures when drafting the standards. These  
37 differences are usually resolved through thoughtful discussions and compromise, often keeping detailed  
38 instructions for crucial points and allowing flexibility where possible so as not to be excessively restrictive.  
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41 The ISO standards should be the set of best practises, the foundation for technical and organisational  
42 usage of the described method but should also be easily applied. While retrospective dosimetry ISO  
43 standards for biological material are often used as a reference because of their scientific credibility, only  
44 a few laboratories around the world are accredited against these standards. Therefore, it is also important  
45 to ensure that the requirements of the procedures are not so prescriptive that they become too difficult  
46 to meet, making accreditation against the standard a challenge. Furthermore, maintenance of  
47 experienced personnel and a well-equipped laboratory, as required to comply with the standard, can be  
48 resource-intensive.  
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### 51 **Conclusions**

52 The ISO WG18: “Biological and Physical Retrospective Dosimetry” has been an active working group since  
53 1999. This WG, comprises members from many countries, has developed and revised six standards related  
54 to biological and physical retrospective dosimetry, five focused on methodology and one on operational  
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3 processes for large-scale events. These standards have been of great value to the establishment of  
4 networks for harmonizing methods across the network laboratories. Future developments in this area will  
5 focus on the revision of current standards and on the development of new and emerging techniques as  
6 they become sufficiently developed and validated for standardization.  
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## 10 Acknowledgements/Disclaimer

11 Mention of any brand name products does not imply endorsement. The opinions, conclusions, and  
12 recommendations herein expressed are those of the authors and do not necessarily reflect the official  
13 policy or position of the Uniformed Services University or the United States Department of Defense. This  
14 work was prepared by a civilian employee of the US Government as part of the individual's official duties  
15 and therefore is in the public domain and does not possess copyright protection.  
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## 21 Figure captions

22  
23 Figure 1. Representation of different physical, biophysical, biological and clinical dosimetry methods for  
24 radiation dose assessment.  
25

26 Figure 2. Depiction of the stages of an ISO document from proposal through to publication  
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28 Figure 3. Overview of activities of ISO WG18.  
29

30 Figure 4. Representative images illustrating damage detection by some of the commonly used biological  
31 dosimetry assays. A) Metaphase spread from the dicentric chromosome assay showing a dicentric (blue  
32 arrow) and two acentric fragments (red arrows), B) A symmetrical translocation (white arrows) detected  
33 by FISH using a cocktail of fluorescently labeled chromosome specific DNA probes C) A binucleated cell  
34 with one micronuclei detected by the Cytokinesis-block Micronucleus Assay, D) A G2-phase cell after  
35 chemically induced PCC assay showing a dicentric (blue arrow), two rings (red arrows) and three acentric  
36 fragments (yellow arrows) E) PCC chromosome (red arrow) along with metaphase CHO chromosomes  
37 (blue arrow) from the PCC cell fusion assay and F) Two EPR spectra of dental enamel (irradiated and non-  
38 irradiated) and included the g-values.  
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**Radiation Dose Assessment by Physical, Biological Retrospective Dosimetry and Clinical Indicators**

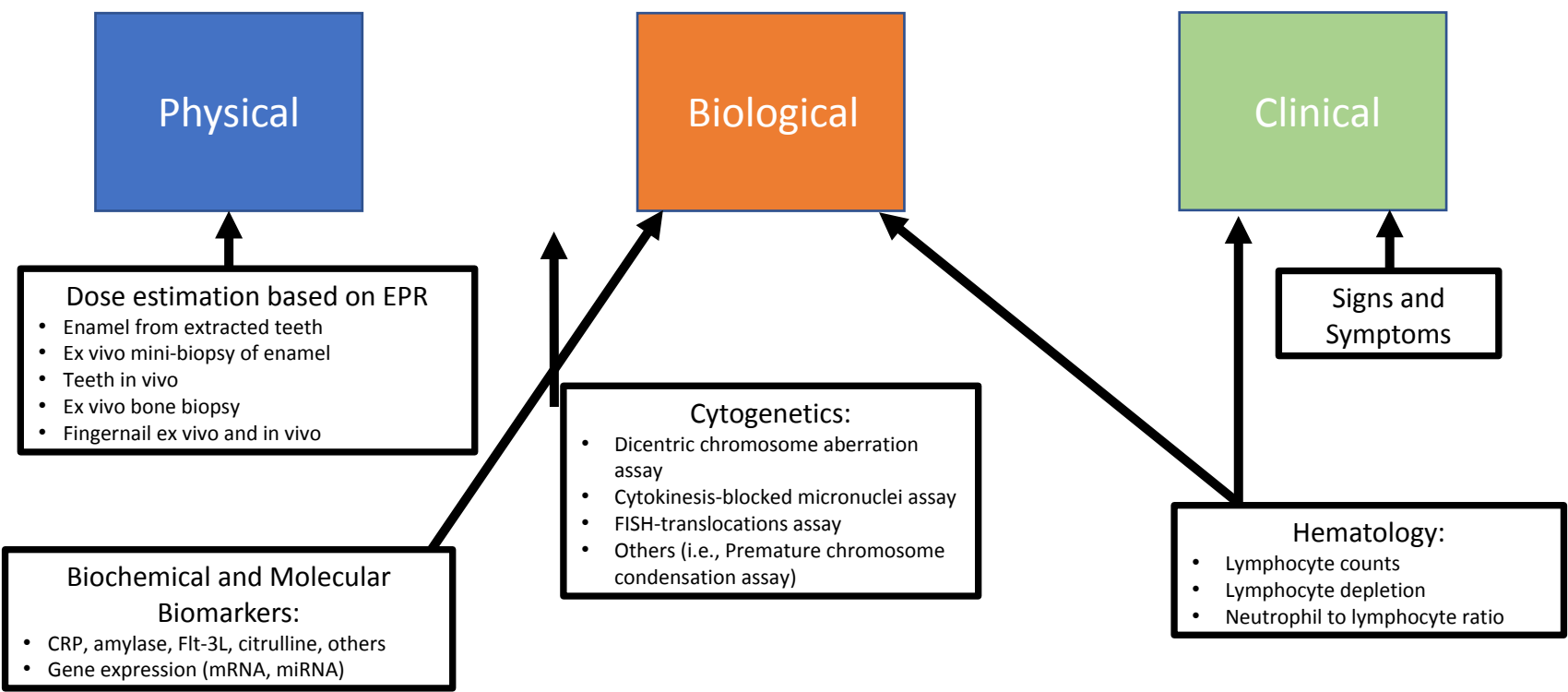
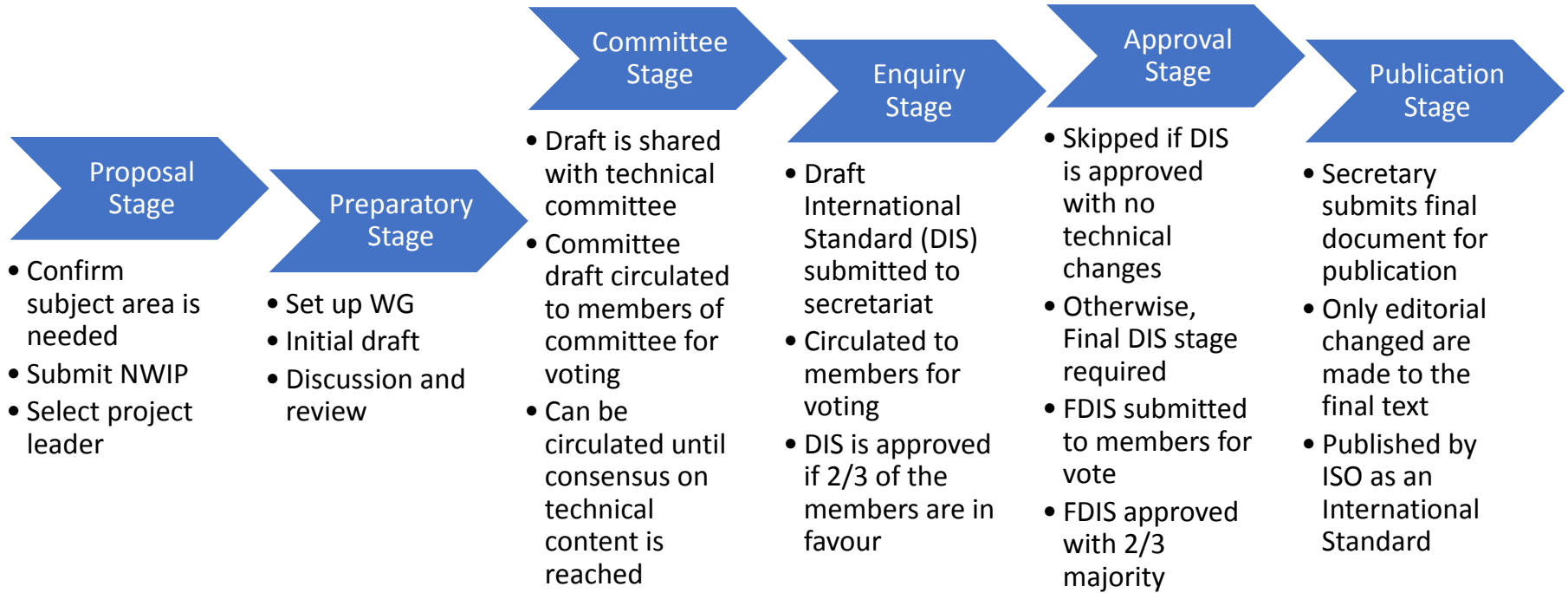
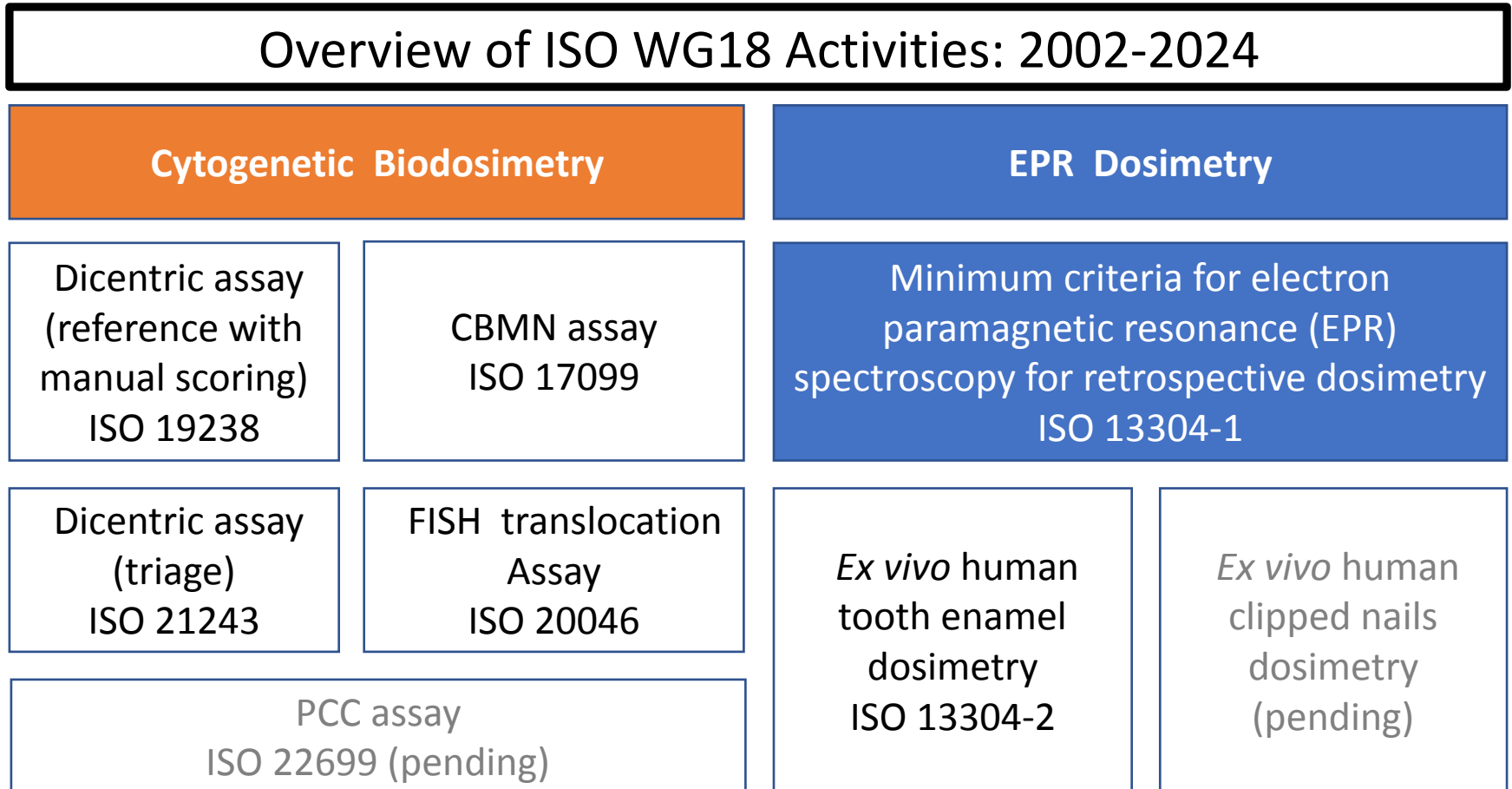


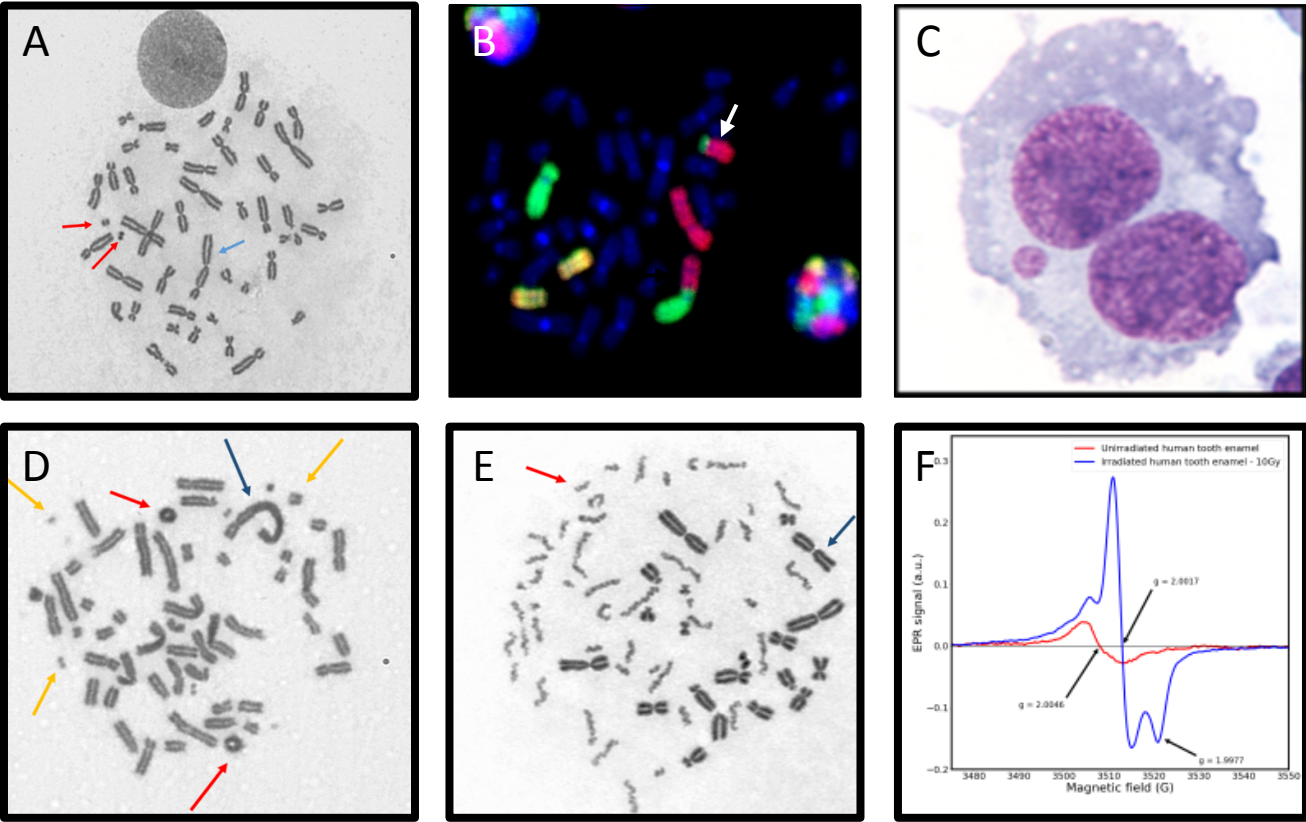
Fig. 2. Stages of an ISO document



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**Table 1. List of standards published by WG18**

ISO #	Standard title	Date first published	Date of latest revision
19238	Radiation protection -Performance criteria for service laboratories performing biological dosimetry by cytogenetics	2004	2023
21243	Radiation Protection- Performance criteria for laboratories performing initial cytogenetic dose assessment of mass casualties in radiological or nuclear emergencies — General principles and application to dicentric assay	2008	2022
17099	Radiological protection - Performance criteria for laboratories using the cytokinesis block micronucleus (CBMN) assay in peripheral blood lymphocytes for biological dosimetry	2014	2024
20046	Radiological protection — Performance criteria for laboratories using Fluorescence In Situ Hybridization (FISH) translocation assay for assessment of exposure to ionizing radiation	2019	2019
13304-1	Radiological protection — Minimum criteria for electron paramagnetic resonance (EPR) spectroscopy for retrospective dosimetry of ionizing radiation — Part 1: General principles	2013	2020
13304-2	Radiological protection — Minimum criteria for electron paramagnetic resonance (EPR) spectroscopy for retrospective dosimetry of ionizing radiation — Part 2: Ex vivo human tooth enamel dosimetry	2020	2020

**Table 2. Comparison of assays used for dose assessment**

Assays	Endpoints	Radiation scenarios			Acute photon dose range, Gy	Dose applications		ISO standard
		Acute	Protracted	Prior <sup>a</sup>		Partial-body	Triage	
Dicentric Chromosome Assay (DCA)	Dicentrics (and rings)	Yes	Yes	Not ideal	0.1 to 6	Yes	Yes	Yes
Cytokinesis-blocked micronucleus (CBMN)	Micronuclei in binucleated cells, nucleoplasmic bridges	Yes	Yes	Not ideal	0.3 to 5	No	Yes	Yes
Fluorescence in situ hybridization (FISH)	Dicentrics (and rings), translocations	Yes	Yes	Yes	0.25 to 5	No	No	Yes
Premature chromosome condensation (PCC)	Excess fragments, Rings, dicentrics, and length ratio	Yes	Yes	Not ideal	~0.2 to 30 (depending on endpoint)	Yes	Yes	Pending
Electron Paramagnetic Resonance (EPR)	EPR Signal from nail clippings, intact nails (in vivo). Tooth (in vivo), or tooth enamel biopsies, tooth enamel extracted teeth	Yes	Yes	Yes	0.05 (tooth enamel, extracted teeth) >0.4 (enamel biopsies) > 2 (nail clippings , nails in vivo, teeth in vivo)	Yes	Yes	Yes (for ex vivo tooth)

\*Table modified from IAEA cytogenetic manual (IAEA 2011)<sup>4</sup>

<sup>a</sup> Prior: An assessment of dose when blood sampling is performed greater than 3 months after radiation exposure.

<sup>#</sup> With or without the use of centromeric and/or whole-chromosome specific hybridization probes.

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