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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

Radioprotection — Critères de performance pour les laboratoires pratiquant l'estimation dosimétrique préliminaire par cytogénétique en cas d'accident radiologique ou nucléaire affectant un grand nombre de personnes — Principes généraux et application au test dicentrique

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 85, *Nuclear energy*, Subcommittee SC 2, *Radiological protection*.

This second edition cancels and replaces the first edition (ISO 21243:2008), which has been technically revised.

The main changes are as follows:

— Annex D (Estimates of dose and 95 % confidence limits for selected observations of numbers of dicentrics and cells) has been removed;

— in 8.1, General: the number of cells to be scored has been moved to Annex B;

— in 8.2, Whole body exposure: addition of a description of when not to assume an acute exposure by looking at the variance/mean and a phrase stating that for low LET radiation doses below ~0.3Gy, linearity can be assumed (as with high LET).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The potential for nuclear and radiological emergencies involving mass casualties from accidental or malicious acts recommends generic procedures for initial dose assessment to help the development of medical response capabilities. A mass-casualty incident is defined here as an event that exceeds the local medical resources. Biological dosimetry, based on cytogenetic analysis using the dicentric assay, typically applied for accidental dose assessment, has been defined in ISO 19238. Initial assessment refers to an expedited version of the dicentric assay that evaluates chromosome damage in a small number of cells and would be used in an emergency situation where rapid analysis is needed. This results in an estimated dose with high uncertainty but allows for exposure categorization. This document focuses on the use of the dicentric assay for initial cytogenetic analysis in the case of mass-casualty incidents. Many of the concepts discussed here can be applied to other biological dosimetry methods. The initial dose evaluation/categorization performed according to this document can be complemented by a more detailed analysis to reduce uncertainties according to ISO 19238 recommendations.

After a large-scale radiation emergency or malevolent act involving radioactive materials, physicians are primarily concerned with preserving life and evaluating medical signs and symptoms for early treatment decisions. It is expected that patients have already been assessed clinically and triaged on the basis of any prodromal signs and symptoms of overexposure plus available information concerning their involvement in the incident. In this early-response phase of a radiological or nuclear emergency, the purpose of cytogenetic assessment is to quickly estimate the absorbed radiation dose for each referred patient to supplement such early clinical assessment.

The role of this cytogenetic assessment is to confirm whether displayed symptoms can be attributed to radiation exposure or due to an unrelated cause. It is expected that the cytogenetic report be sufficiently informative to provide guidance to medical staff as they proceed with clinical management of the patients. This management can potentially include expedited identification of: (1) concerned, but not radiation-exposed public, through provision of advice and reassurance; (2) low/moderately irradiated patients, who do not need out-patient observation or clinical intervention; and (3) highly irradiated patients requiring active treatment for potentially life-threatening injury through optimized use of limited medical resources.

Several clinical triage systems have been developed in which irradiated patients are allocated to dose ranges (or acute-radiation-sickness response categories) based on the severity of prodromal symptoms that correspond with mild to very severe injuries. Enough experience in using clinical triage schemes (e.g. from Chernobyl) has been gained to show that the early sorting of persons into these dose or response category cohorts was adequate for the emergency planning of the patients' management. However, as time progresses clinicians are looking for more accurate estimations of doses both in the low-dose range, where irradiated persons require counselling on risks of late stochastic effects, and also for higher doses, for anticipating the shorter-term sequelae of severe tissue reactions.

It should be noted that the initial clinical triage interprets the symptoms in terms of the early phase response to partial or whole-body exposure. Protracted and fractionated exposures need higher doses in order to produce the same severity of responses.

It is expected that the cytogenetic methods achieve an initial estimate of dose or response category that is quantitatively more precise than the clinically derived categories, and take into account any evidence that the exposure might not have been received acutely or to the whole body. It is expected that the need for precision be set against the competing requirement for expedited results and it is necessary that this judgement be made at the time of the event. This will depend on the anticipated number of patients, the surge capacity of the laboratory and the rate at which the blood samples are received by the laboratory.

Expert cytogenetic biological dosimetry laboratories typically function to support national radiation protection programmes and emergency response schemes. Several of these national cytogenetic biological dosimetry laboratories have independently and successfully performed initial dose assessment in actual and simulated mass-casualty incidents. Their approaches included pre-planning, reagent stockpiling, simplified sample processing, automation, as well as modifying some of the ISO 19238 scoring criteria. Several of these national cytogenetic biological dosimetry laboratories have established networks of supplementary, satellite cytogenetic laboratories, both nationally as well as internationally. Building upon their experience, this document is intended to define criteria for performing quality-assured initial assessment of radiation dose using cytogenetic methods.

The primary purpose of this document is to provide a guideline to all biological dosimetry laboratories for performing the dicentric assay for initial dose assessment using documented and validated procedures. Secondly, it can facilitate the involvement of cytogenetic biological dosimetry networks to increase analysis capacity while ensuring dose estimates provided by the network laboratories are valid. Finally, it is expected that laboratories that are newly commissioned to carry out the initial cytogenetic analysis conform to this document in order to ensure reproducible and accurate dose assessments.

This document is written outlining the procedures for the dicentric assay specific to initial biological dosimetry assessments for potential overexposures involving mass radiological/nuclear casualties. These procedures can also be applied to other biological dosimetry methods such as the cytokinesis blocked micronucleus (CBMN) assay as described in ISO 17099. If appropriate, semi-/automation procedures can be included in the process as long as they have been well validated and described by the laboratory applying them. The criteria for selecting the level of scoring usually depends on the application of the results (e.g. medical management, radiation-protection management, record keeping and medical/legal requirements). For example, selected cases can have more cells analysed to produce a more accurate evaluation of high partial-body exposure; secondly, doses can be estimated for persons exposed to doses below the threshold for acute tissue reactions, by using the ISO 19238 criteria. These latter data also assist in counselling for the risk of late stochastic disease.

Part of the information presented in this document can be found in other international guidelines and scientific publications, primarily in ISO 19238 and the 2011 of International Atomic Energy Agency's EPR-Biodosimetry publication[1]. However, this document details and standardizes the quality assurance and quality control of performance criteria for cytogenetic assessment of individual exposures in radiological or nuclear mass casualty events. This document is generally compliant with ISO/IEC 17025[2], with particular consideration given to the specific needs of initial biodosimetry. The expression of uncertainties in dose estimations given in this document conforms with the ISO Guide 98[3] and ISO 5725 (all parts)[4].

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

1 Scope

The purpose of this document is to give an overview of the minimum requirements for performing the dicentric assay with quality control measures using mitogen stimulated peripheral blood lymphocytes for initial assessment of individuals involved in a mass casualty scenario. The dicentric assay is the use of chromosome damage to quickly estimate approximate radiation doses received by individuals in order to supplement the early clinical categorization of casualties.

This document focuses on the organizational and operational aspects of applying the dicentric assay in an initial assessment mode. The technical aspects of the dicentric assay can be found in ISO 19238.

This document is applicable either to an experienced biological dosimetry laboratory working alone or to a network of collaborating laboratories (as defined in Clause 7).

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements for this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 19238, *Radiological protection — Performance criteria for service laboratories performing biological dosimetry by cytogenetics*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 19238 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
absorbed dose
D
differential quotient of ε with respect to *m*, where ε is the mean energy imparted by ionizing radiation to matter of mass *m*:

$$D = \frac{d\bar{\varepsilon}}{dm}$$

Note 1 to entry: The gray is a special name for joule per kilogram and is to be used as the coherent SI unit for absorbed dose.

[SOURCE: ISO/IEC 80000-10, 10.81.1]

3.2
associate laboratory
laboratory that has previously been validated through *proficiency testing* (3.13) and is prepared to be contacted for assistance when the capacity of the lead laboratory is exceeded

3.3
biological dosimetry
assessment of the absorbed dose of ionizing radiation using indicators found in biological material, particularly peripheral blood

3.4
calibration curve
graphical or mathematical description of the dose-effect relationship derived by the *in vitro* (3.10) irradiation of blood samples to known physically delivered doses, and the uncertainties associated with these

Note 1 to entry: The curve is used to determine, by interpolation, the absorbed dose to a potentially exposed individual.

3.5
chromosome aberration
change in the normal structure of a chromosome involving both chromatids of a single chromosome at the same locus as observed in metaphase

3.6
cytogenetics
study of the structure of chromosomes

3.7
deterministic effect
biological (health) effect of radiation for which a threshold level of dose exists above which the severity of the effect is greater for a higher dose

[SOURCE: IAEA. IAEA Safety Glossary: 2018 edition. Vienna: IAEA, 2019]

3.8
fractionated exposure
exposure to ionizing radiation that has been divided into smaller exposures separated in time

3.9
inhomogeneous exposure
exposure that is not received uniformly over the whole body or is received only by part of the body

3.10
in vitro
technique performed in a controlled environment outside of a living organism

3.11
lead laboratory
designated laboratory primarily responsible to lead the coordination of the biodosimetric response in an emergency

Note 1 to entry: Previously referred to as a reference laboratory.

3.12
network
group of lead and associate cytogenetic laboratories trained and prepared to jointly respond to a large-scale radiological or nuclear emergency requiring *biological dosimetry* (3.3)

3.13
proficiency test
evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

3.14
prodromal
early signs and symptoms indicative of the imminent development of the full manifestation of a disease or illness, in this case related to radiation exposure

EXAMPLE Diarrhea, nausea, vomiting.

3.15
protracted
dose received over a long period of time

3.16
ring
aberrant circular chromosome resulting from the joining of two breaks within one chromosome

Note 1 to entry: Rings can be centric or acentric.

3.17
stochastic effect
radiation induced health effect, the probability of occurrence of which is greater for a higher radiation dose and which severity, if it occurs, is independent of dose

Note 1 to entry: Stochastic effects may be somatic effects or hereditary effects, and generally occur without a threshold level of dose. Examples include solid cancers and haematologic cancers (leukaemia and lymphoma).

[SOURCE: IAEA. IAEA Safety Glossary: 2018 edition. Vienna: IAEA, 2019. 278]

4 Responsibility of the laboratory

4.1 Awareness of this document

It is necessary that local, state, and federal governments' health care providers and facilities be aware of the existence of the cytogenetic biological dosimetry programme for individual dose assessment in radiological or nuclear mass casualty events as established in this document. This is critical for the laboratory to be able to receive blood samples promptly and thereby provide an initial biological dosimetry response within the time frame that is clinically useful in order to mitigate the acute health effects. Qualified laboratories and health care facilities should ensure their organizations, roles and responsibilities are well defined within radiation emergency concepts of operations at local and national levels.

4.2 Biological dosimetry request and confidentiality

Biological dosimetry investigations made by lead or associate laboratories shall be undertaken in accordance with the national regulations regarding confidentiality. This normally includes the maintenance of confidentiality of the patient's identity and medical data.

This requirement extends to

a) all written, electronic or verbal communications between the laboratory(ies) and the person or organization requesting the analysis and receiving the report,

b) protection of confidential information held within the organization where the laboratory is located, and

c) electronic record management.

Users with different access restrictions should have different privileges within the system as appropriate. The laboratory head assigns rights and access restrictions to the rest of the laboratory.

4.3 Pre-planning

Qualified laboratories shall be organized and operate in such a way that, upon receiving a request from the state/health care facility/hospital for biological dosimetry response, they can quickly and efficiently provide initial individual dose estimates. The laboratory's organization shall be clearly predefined and documented.

Each laboratory shall be responsible for

a) maintaining documentation, which includes the following:

   1) an instruction sheet to be sent to the local, regional, national health-care facilities describing blood drawing requirements and shipping procedures (see ISO 19238:2014, Annex A);

   2) a questionnaire that shall elicit patient consent (if required) and information on whole or partial body exposure, source and quality of the radiation, circumstances of the exposure, exposure location (country, city, company, etc.), date and time of exposure, previous occupational or medical exposures to radiation, intake of pharmaceuticals, infection, smoking habits, and significant exposures to any other DNA damaging agents (such as organic solvents or heavy metals) (see ISO 19238:2014, Annex B) or any other relevant information regarding the suspected or confirmed exposure;

b) maintaining a stockpile of its own reagents or having immediate access to reagents and supplies from a local, state or national stockpile or commercial entity for receiving blood samples, culturing lymphocytes, preparing metaphase spreads and analysing samples for cytogenetic biological dosimetry; these include general laboratory supplies as well as reagents and supplies specific to cytogenetic protocols;

c) maintaining the anonymity of samples. To avoid the identification of the patient while guaranteeing the traceability of the analysis, the blood samples should be coded upon arrival in the laboratory. The coding is performed in an unambiguous way according to a standard procedure. The same code shall be used for all the stages of the analysis. The code is assigned by a designated person. The decoding, interpretation of results and compiling of the report shall also be performed by a designated person. If it is required to share a sample, the same code shall be used by all associate laboratories and for communication between them.

d) considering to join a network for assistance in case of a large scale emergency situation[6].

4.4 Responsibility during service

Qualified laboratories shall be responsible for

a) providing the following to local, regional, national health-care facilities:

   1) guidance on the appropriateness of the biological dosimetry assay,

   2) information on the laboratory's capabilities in order to select an appropriate cohort of individuals whose treatment can benefit from cytogenetic biological dosimetry,

   3) information to help determine the medical consequences for individuals exposed to radiation;

b) maintaining established communication links with the local/state/federal health care facilities;

c) requesting or recommending activation of a biological dosimetry network when necessary;

d) specifying and documenting the responsibilities, roles and interrelations of all personnel whose laboratory functions affect the quality of initial biological dosimetry response;

e) receiving appropriate samples, preparing and analysing samples, providing initial dose assessment or exposure categorization, and archiving samples or slides;

f) tracking, prioritizing (based upon rapid screening or input from requestors), determining the appropriate tests and reprioritizing as the tests progress or as additional information is received;

g) reporting results in a timely manner according to the needs of the incident (e.g. faster reporting of results related to samples from individuals indicating a requirement for urgent clinical intervention);

h) retaining the responsibility for safety and quality assurance (see Clause 9).

5 Biological dosimetry process in radiological or nuclear mass-casualty incidents

See Annex A for an example of a flow diagram indicating the interactions between requestors and biological dosimetry laboratories for different numbers of samples.

6 Emergency response of the lead laboratory

The head of the laboratory shall have an emergency response plan in place, so that all members of the staff know their role.

By default or without additional information, the dicentric assay is the method-of-choice for radiation dose estimation. Other methods can be used where appropriate, based on available information about the accident. The decision to use another method should be documented and made based on a discussion between the head of the laboratory and other qualified emergency response management personnel.

Where possible, blood samples from the most seriously irradiated persons based on clinical symptoms or physical dosimetry (when such information is available) are prioritized for processing and analysis. In the absence of such information, the laboratory processes the blood samples in the order of their arrival.

The biological dose estimate(s) is(are) obtained from appropriate, robust calibration curve previously established by the individual network members. An exposure categorization is determined from the appropriate predefined procedures.

Organization of the workflow should be such that the results of biological dosimetry analyses are available as soon as possible.

According to the country and the emergency, blood samples should either

— arrive directly at the laboratory where all the processing for cytogenetic analysis occurs; or alternatively,

— be initially processed in a specialized associate laboratory in, for example, a hospital or research institute that is already linked through the network to the lead laboratory.

7 Design of a laboratory network

7.1 Overview

A cytogenetic biological dosimetry laboratory network is comprised of a lead laboratory and associate laboratories that serve as network partners to assist with the response.

In the case of an emergency incident, the lead laboratory (the laboratory that takes primary responsibility for the response) shall be a selected, qualified and validated laboratory, preferably from the country where the radiological emergency occurred. When the biological dosimetry capacity of