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Radiation protection — Performance criteria for laboratories performing cytogenetic triage for assessment of mass casualties in radiological or nuclear emergencies — General principles and application to dicentric assay

Radioprotection — Critères de performance pour les laboratoires pratiquant le tri par cytogénétique en cas d'accident radiologique ou nucléaire affectant un grand nombre de personnes — Principes généraux et application aux dicentriques

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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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.

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The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 21243 was prepared by Technical Committee ISO/TC 85, *Nuclear energy*, Subcommittee SC 2, *Radiation protection*.

Introduction

The potential for nuclear and radiological emergencies involving mass casualties from accidental or malicious acts or terrorism requires generic procedures for emergency dose assessment to help the development of medical response capabilities. A mass-casualties 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. Cytogenetic triage is the use of chromosome damage to evaluate and assess approximately and rapidly radiation doses received by individuals in order to supplement the clinical categorization of casualties. This International Standard focuses on the use of the dicentric assay for rapid cytogenetic triage involving mass-casualty incidents.

After a large-scale radiation emergency or malevolent act with involvement of 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 emergency, the initial purpose of cytogenetic triage is to rapidly estimate the dose for each referred patient to supplement this early clinical assessment.

The role of a secondary triage by cytogenetics is to confirm whether displayed symptoms can really be attributed to radiation rather than being a false positive response to some other cause. It is expected that the cytogenetic report be sufficiently informative to provide guidance to medical staff as they proceed to clinical management of the patients. This management can range from rapid identification of concerned but not radiation-exposed public (worried well), giving patients advice and reassurance before sending home lightly irradiated patients who do not need out-patient observation (i.e. dose below 0,5 Gy) or clinical intervention (i.e. dose below 1,0 Gy), through to active treatment of potentially life-threatening injury and optimized use of limited medical resources.

Several clinical triage systems have been developed where, based on severity of prodromal reactions, irradiated patients are allocated to one of 4 dose ranges (1 Gy to 2 Gy, 2 Gy to 4 Gy, 4 Gy to 6 Gy and $>$ 6 Gy) or acute-radiation-sickness (ARS) response categories (RC-01, RC-02, RC-03, RC-04) representing mild to very severe injuries. Enough experience with 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 initial 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 response to acute, more-or-less whole-body exposure. Protracted and fractionated exposures, of course, require higher doses in order to produce the same severity of responses.

It is expected that the cytogenetic triage achieve a rapid estimate of dose or response categories, quantitatively more precise than the four clinically derived categories, and also take account of any evidence that the exposure might not have been received acutely or involved the whole body. It is expected that the need for precision be set against the competing requirement for rapid results and it is necessary that this judgement be made at the time, depending on the anticipated number of patients, the surge capacity of the laboratory and the rate at which the blood samples are received at the laboratory.

Expert cytogenetic biodosimetry laboratories typically function to support national radiation-protection programmes and emergency-response schemes. Several of these reference cytogenetic biodosimetry laboratories have independently and successfully performed rapid 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. Recently, several of these national reference cytogenetic biodosimetry laboratories have also established networks of

supplementary, satellite cytogenetic laboratories, both nationally as well as internationally. Building upon their experience, this International Standard is intended to define criteria for performing quality-assured cytogenetic triage.

The primary purpose of this International Standard is to provide a guideline to all laboratories in order to perform the dicentric-bioassay - cytogenetic triage for dose assessment using documented and validated procedures. Secondly, it can facilitate the application of cytogenetic biodosimetry networks to permit comparison of results obtained in different laboratories. Finally, it is expected that laboratories newly commissioned to carry out the cytogenetic triage conform to this International Standard in order to perform the triage reproducibly and accurately.

This International Standard is written in the form of procedures to adopt for dicentric-bioassay - cytogenetic triage biological dosimetry for overexposures involving mass radiological casualties. The criteria required for such measurements usually depend on the application of the results: medical management when appropriate, radiation-protection management, record keeping and medical/legal requirements. For example, selected cases can be analysed to produce a more accurate evaluation of high partial-body exposure; secondly, doses can be estimated for persons exposed below the threshold for deterministic effects, by using the ISO 19238 criteria. These latter data also assist in counselling for the risk of late stochastic disease.

Part of the information in this International Standard is contained in other international guidelines and scientific publications, primarily in ISO 19238 and the International Atomic Energy Agency's Technical Report No.405, on Biological Dosimetry [4]. However, this International Standard details and standardizes the quality assurance and quality control of performance criteria for cytogenetic assessment of individual exposures in radiological or nuclear mass casualties. This International Standard is generally compliant with ISO/IEC 17025, with particular consideration given to the specific needs of rapid, emergency biological dosimetry. The expression of uncertainties in dose estimations given in this International Standard complies with the ISO Guide 98 and ISO 5725 (all parts).

Radiation protection — Performance criteria for laboratories performing cytogenetic triage for assessment of mass casualties in radiological or nuclear emergencies — General principles and application to dicentric assay

1 Scope

The purpose of this International Standard is to give an overview of the minimum requirements of process and quality-control components of the cytogenetic response for triage of mass casualties. Cytogenetic triage is the use of chromosome damage to evaluate approximately and rapidly radiation doses received by individuals in order to supplement the early clinical categorization of casualties. This International Standard concentrates on organizational aspects of applying the dicentric assay for operation in a triage mode. The technical aspects of the dicentric assay can be found in ISO 19238. This International Standard is applicable either to an experienced biological dosimetry laboratory working alone or to a network of collaborating laboratories (as defined in Clause 9).

2 Normative references

The following referenced documents are indispensable for the application of 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, *Radiation protection — Performance criteria for service laboratories performing biological dosimetry by cytogenetics*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
acute radiation syndrome or sickness
ARS
acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes)

3.2
associate laboratory
laboratory that has previously been validated and is prepared to be contacted for assistance when the capacity of the reference laboratory is exceeded

3.3
bias
statistical sampling or testing error caused by systematically favouring some outcomes over others

3.4
biological dosimetry
assessment of the absorbed dose of ionizing radiation using indicators found in biological material

3.5
confidence limits
CL
statistical range about an estimated quantity within which the value of the quantity is expected to occur, with a specified probability

3.6
chromosome
structure that carries genetic information

NOTE Normally, 46 such structures are contained in the human cell nucleus. During nuclear division, they condense to form characteristically shaped bodies.

3.7
cytogenetics
study of the structure of chromosomes

3.8
deterministic effect
effect from radiation that is absent below a certain threshold dose but its severity increases with the absorbed dose in human tissues due to ionizing radiation

EXAMPLES Cataract, radiation burn in the form of erythema or more serious local consequences, or acute radiation sickness/syndrome.

3.9
dicentric chromosome

chromosome aberrant in having two centromeres derived from the joining of parts from two broken chromosomes

NOTE A dicentric chromosome is generally accompanied by an acentric fragment.

3.10
dicentric assay
assay which measures radiation damage based on the frequency of dicentric or dicentric plus ring chromosomes found in metaphase cells

3.11
fractionated exposure
exposure to ionizing radiation that has been divided into small exposures separated in time

3.12
inhomogeneous exposure
exposure that is not received uniformly over the whole body or is received only by part of the body

3.13
inter-comparison
comparison between several laboratories on the accuracy and precision of their methods and dose estimates

3.14
intra-comparison
comparison within a laboratory on the accuracy and precision of their dose estimates (using different methods)

3.15
in vitro
technique performed in a controlled environment outside of a living organism

3.16
medical responders
professionals responding to an emergency situation who are dealing with providing medical care to the casualties

3.17
metaphase
stage of mitosis when the nuclear membrane is dissolved and the chromosomes are condensed to their minimum lengths and aligned for division

3.18
minimum detection level
MDL
smallest measurable amount (e.g. activity-concentration or dose) that can be detected with a probability of non-detection (type II error) while accepting a probability of erroneously deciding that a positive (non-zero) quantity is present in an appropriate background sample (type I error)

3.19
network
group of reference and associate cytogenetic laboratories trained and prepared to jointly respond to a large-scale radionuclear emergency requiring biological dosimetry

3.20
network laboratory
laboratory included in the network, both reference and associate

3.21
partial body exposure
exposure to ionizing radiation of a certain part of the body as opposed to the whole-body exposure

3.22
precision
dispersion of measurements with respect to a measure of location or central tendency

3.23
prodromal
⟨early signs and symptoms⟩ indicative of the imminent development of a disease or illness

EXAMPLES Erythema, nausea, vomiting.

3.24
protracted
⟨dose⟩ received over a long period of time

3.25
quality assurance
planned and systematic actions necessary to provide adequate confidence that a process, measurement or service satisfies given requirements for quality specified in a license

3.26
quality control
part of quality assurance intended to verify that systems and components conform with predetermined requirements

3.27
reference laboratory
laboratory primarily responsible for activating the network, communicating with emergency organizations and delivering the dose estimation results in an emergency situation

3.28
sequelae
condition resulting from prior injury or attack

3.29
stochastic effect
effect from exposure to radiation that has no threshold dose and is characterized by increasing probability of occurrence with increase of the dose

EXAMPLE Cancer.

3.30
triage
rapid process of sorting people depending on their need for immediate medical treatment (as is usually done in emergencies)

3.31
whole-body exposure
exposure to ionizing radiation of most of the body, involving the major part of hematopoetic tissues

4 Abbreviated terms

ARS Acute radiation sickness

MDL Minimum detection level

CL Confidence limits

5 Pre-planning

5.1 Awareness of the standard

It is necessary that local, state, and federal governments' health care providers and facilities be aware of the existence of the cytogenetic biodosimetry programme for individual dose assessment in radiological or nuclear mass casualties as established in this International Standard. This is critical for the laboratory to be able to receive blood samples promptly and thereby provide a rapid biodosimetry response within the time frame that is clinically useful in order to mitigate the acute health effects. Qualified laboratories and health care facilities should know their organization, roles and responsibilities, and the concept of operations in an emergency.

5.2 Roles and responsibilities of health care facilities

The health care facilities at the local, state, and/or the federal levels are responsible for the following:

a) evaluating the medical consequences for individuals exposed to radiation;

b) requesting qualified biodosimetry laboratories to provide individual dose assessments;

c) selecting the cohort of individuals who require biological dosimetry for immediate treatment, in consultation with qualified biological dosimetry laboratories;

d) obtaining informed consent from cases before requesting biological dosimetry assessment;

e) sampling blood for cytogenetic biodosimetry as soon as practical after exposure in specified blood-sampling tubes for cytogenetic biodosimetry; the health care facilities may request sampling kits from their respective national stockpiles or from a qualified cytogenetic laboratory, or use their own, if appropriate;

f) making arrangements to courier samples to the cytogenetic laboratory facility for dose assessment.

See Annex B for an example of an initial contact information form.

5.3 Roles and responsibilities of the biodosimetry laboratories

Each laboratory shall be organized and operate in such a way that upon receiving a request from the state/health care facility/hospital for biodosimetry response, they can rapidly and efficiently provide individual dose assessments. The laboratory's organization shall be clearly predefined and documented.

Qualified laboratories shall provide guidance to local, state and/or federal health-care facilities on

— the appropriateness of the biodosimetry assay,

— the laboratory's capabilities in order to select an appropriate cohort of individuals whose treatment can benefit from the cytogenetic biodosimetry.

Each laboratory shall be responsible for the following:

a) 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 biodosimetry; these include general laboratory supplies as well as reagents and supplies specific to cytogenetic protocols;

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

c) specifying and documenting the responsibilities, roles and interrelations of all personnel whose laboratory functions affect the quality of emergency biodosimetry response;

d) receiving appropriate samples, preparing and analysing samples, estimating dose, reporting and archiving samples or slides;

e) tracking, prioritizing (based upon rapid screening or input from physicians), determining the appropriate tests and reprioritizing as the tests progress, and reporting results;

f) knowing its maximal capability for samples processing (time versus number);

g) maintaining its own quality control and quality-assurance programme;

h) participating, as appropriate, in relevant educational, training and exercise programmes;

i) participating in periodic inter-comparison studies;

j) maintaining a safety plan; the laboratory head shall define written safety procedures for protection against viral, microbial, chemical and optical hazards.

6 Communication and information

6.1 Biological dosimetry request and confidentiality

Biological dosimetry investigations made by reference and/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, medical data and social status.

This requirement extends to

a) written, electronic or verbal communications between the laboratory and the person/organisation requesting the analysis and receiving the report,

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

c) electronic record management.