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Radiation protection — Performance criteria for radiobioassay

Radioprotection — Critères de performance pour l'analyse radiotoxicologique

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

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 28218 was prepared by Technical Committee ISO/TC 85, *Nuclear energy, nuclear technologies, and radiological protection*, Subcommittee SC 2, *Radiological protection*.

This first edition of ISO 28218 cancels and replaces ISO 12790-1:2001, which has been technically revised.

Introduction

In the course of employment, individuals might work with radioactive materials that, under certain circumstances, could be taken into the body. Radiation protection programmes for these individuals can include means for *in vivo* or *in vitro* measurements of radioactive material that has entered the body. The performance criteria required for such measurements usually depend upon the purpose for the radiobioassay measurement, which can include determining the internal human burden of radioactive material, estimating doses and dose commitments, radiation protection management, medical management when appropriate, and providing the necessary data for legal and record-keeping requirements.

Analytical methods for radiobioassay are not currently standardized, but are available in the literature. Guidance on the evaluation of data from the monitoring of workers occupationally exposed to the risk of internal contamination by radioactive substances is provided in ISO 27048 as well as other publications of national and international regulations and guides, the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurement (NCRP), the International Atomic Energy Agency (IAEA) and the International Commission on Radiological Units and Measurements (ICRU). Recommendations of the ICRP, NCRP, IAEA and ICRU, as well as experience with the practical application of these recommendations to the conduct of radiobioassay services and the interpretation and use of radiobioassay results in radiation protection programmes, have been considered in the development of this International Standard.

In addition to superseding ISO 12790-1:2001, this International Standard complements the requirements of ISO 20553. This International Standard develops, expands and applies the principles defined in the aforementioned standards for radiobioassay laboratories. It also provides a consensus on the statistical definitions and formulations of the quantitative performance criteria of decision threshold, detection limit, relative bias and repeatability. These concepts follow the requirements of ISO 11929. In particular, the concept of minimum detectable amount (MDA) used in ISO 12790-1:2001 has been abandoned in favour of detection limit ($y^{\#}$).

Clauses 5 to 8 primarily provide guidance for radiobioassay service laboratories, whereas Clause 9 relates to testing laboratories and provides criteria for performance testing. The information in these clauses provides beneficial insight for service laboratories, for users of the laboratory's services, and for testing laboratories, and it provides a possible basis for an inter-laboratory quality assurance plan.

In this International Standard, the following verbal forms apply:

— “shall” is used to denote a requirement;

— “should” is used to denote a recommendation;

— “may” is used to denote permission (neither a requirement nor a recommendation).

To conform with this International Standard, all radiobioassay needs to be performed in accordance with its requirements, but not necessarily with its recommendations; however, justification needs to be documented for deviations from recommendations.

Radiation protection — Performance criteria for radiobioassay

1 Scope

This International Standard provides criteria for quality assurance and control, and evaluation of performance of radiobioassay service laboratories.

Criteria and guidance for *in vivo* radiobioassay and *in vitro* radiobioassay are given in separate clauses.

The following are within the scope of this International Standard:

— the accuracy of

  — *in vivo* measurements of activity and quantities of selected important radionuclides in test phantoms, and

  — *in vitro* measurements of activity and quantities of selected important radionuclides in test samples;

— minimal requirements for detection limit;

— minimum testing levels and testing ranges;

— requirements for reporting radiobioassay results by service laboratories;

— quality assurance in service laboratories;

— quality control in service laboratories;

— protocol for reporting test evaluations by service laboratories to the testing laboratory;

— default procedures when the service laboratory customer does not specify the performance criteria;

— applications of $y^{\#}$ for different methods (see Annexes A and B).

The following are not within the scope of this International Standard:

— detailed radiochemical methods for separating radionuclides from biological samples;

— detailed procedures for *in vivo* and *in vitro* radioactivity measurements;

— biokinetic data and mathematical models for converting radiobioassay results into dose (dose assessment);

— procedures for the preparation and distribution of test samples and phantoms by the testing laboratories.

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/IEC Guide 99, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

ISO 5725-1, *Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions*

ISO 5725-2, *Accuracy (trueness and precision) of measurement methods and results — Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method*

ISO 5725-3, *Accuracy (trueness and precision) of measurement methods and results — Part 3: Intermediate measures of the precision of a standard measurement method*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99, ISO 5725-1, ISO 5725-2, ISO 5725-3 and the following apply.

3.1
accuracy
characteristic of an analysis or determination that ensures that both the bias and repeatability of the resulting quantity remain within specified limits

3.2
activity
number of spontaneous nuclear disintegrations per unit time

3.3
aliquot
⟨*in vitro* radiobioassay⟩ representative portion of a whole

3.4
appropriate blank
uncontaminated sample, unexposed person or phantom that is ideally identical in physiochemically and radiologically significant ways with the sample, person or phantom to be analysed

3.5
background
ambient signal response recorded by measurement instruments that is independent of radioactivity contributed by the radionuclides concerned

3.6
bias
systematic error of the indication of a measuring instrument

3.7
freedom from bias
ability of a measuring instrument to give indications free from systematic error

3.8
blind testing
testing of capabilities when the service laboratory is not aware that they are being tested for conformance

3.9
certified reference material
CRM
reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of the metrological traceability

3.10
concentration
activity or mass per unit volume or per unit mass

3.11
confidence interval
interval about an estimate of a stated quantity, within which the expected value of the quantity is expected to lie (with a specified probability)

3.12
decision threshold
fixed value of the measurand by which, when exceeded by the result of an actual measurement of a measurand quantifying a physical effect, it is decided that the physical effect is present

NOTE The decision threshold is the critical value of a statistical test for the decision between the hypothesis that the physical effect is not present and the alternative hypothesis that it is present. When the critical value is exceeded by the result of an actual measurement, this is taken to indicate that the hypothesis should be rejected. The statistical test is designed in such a way that the probability of wrongly rejecting the hypothesis (error of the first kind) is at most equal to a given value, α.

3.13
detection limit
smallest true value of the measurand that is detectable by the measuring method

NOTE The detection limit is the smallest true value of the measurand that is associated with the statistical test and hypothesis in accordance with the **decision threshold** (3.12) by the following characteristics: if in reality the true value is equal or exceeds the detection limit, the probability of wrongly not rejecting the hypothesis (error of the second kind) is at most equal to a given value, β.

3.14
***in vitro* radiobioassay**
measurements to determine the presence of, or to estimate the amount of, radioactive material in the excreta or in other biological materials removed from the body

3.15
***in vivo* radiobioassay**
measurements of radioactive material in the human body utilizing instrumentation that detects radiation emitted from the radioactive material in the body

3.16
measurand
particular quantity subject to measurement

3.17
monitoring
measurements made for the purpose of assessment or control of exposure to radioactive material and the interpretation of the results

3.18
minimum testing level
MTL
amount of radioactive material that the service laboratory is intended to be able to measure for participation in the performance testing programme, assuming the samples are free of interference from other radionuclides, unless specifically addressed

NOTE The MTLs are not intended to be interpreted as the appropriate detection limit required for a specific internal dosimetry programme, but rather as an acceptable minimum testing level for radiobioassay service laboratories based on good measurement practice.

3.19
phantom
surrogate person, or part of a person, used for calibration of *in vivo* measurement systems

NOTE A phantom is constructed to allow placement of radionuclides in a geometry approximating internal depositions. A phantom could be used as an **appropriate blank** (3.4).

3.20
quality assurance
planned and systematic actions necessary to provide adequate confidence that an analysis, measurement or monitoring programme will perform satisfactorily in service

3.21
quality control
actions that control the attributes of the analytical process, standards, reagents, measurement equipment, components, system or facility in accordance with predetermined quality requirements

3.22
radiobioassay
measurement of amount or concentration of radionuclide material in the body, or in biological material excreted or removed from the body (measurand), and analysed for purposes of estimating the quantity of radioactive material in the body

3.23
reagent blank
contribution of the reagents to the measurement process determined by carrying the reagents through all the operations that are used for the sample

3.24
relative bias
quotient of the bias divided by the expected value

3.25
relative standard deviation
σ_r
quotient of the estimated standard deviation of a series of determinations, y_1, y_2, ...yx_i, y_n, of a quantity divided by the arithmetic mean value, $\bar{y}$, of y_i, i.e.

$$\sigma_r = \frac{\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}{\bar{y}}$$

or, for a single measurement, the quotient of the estimate of the standard deviation divided by the value of the single measurement (synonymous with the relative standard deviation, multiplied by 100 when expressed as percent)

3.26
repeatability
closeness of the agreement between the results of successive measurements of the same measurand carried out under the same conditions of measurement

3.27
reproducibility
closeness of the agreement between the results of measurements of the same measurand carried out under changed conditions of measurement

3.28
service laboratory
laboratory performing *in vivo* or *in vitro* radiobioassay measurements

3.29
standard deviation
s
quantity characterizing the dispersion of the results for a series of n measurements of the same measurand, given by the equation

$$s = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \bar{y})^2}{(n-1)}}$$

where

y_i is the result of the ith measurement;

$\bar{y}$ is the arithmetic mean of the n results considered

3.30
systematic error
mean that would result from an infinite number of measurements of the same measurand carried out under repeatability conditions minus a true value of the measurand

3.31
testing laboratory
laboratory responsible for evaluating the performance of service laboratories in meeting the performance specifications of ISO 28218

3.32
traceability
property of the result of a measurement or the value of a standard, whereby it can be related to stated references through an unbroken chain of comparisons all having stated uncertainties

NOTE 1 Stated references are usually national or International Standards.

NOTE 2 The unbroken chain of comparisons is called a traceability chain.

3.33
transfer reference standard
TRS
material that contains radionuclide components of interest in chemical and physical forms similar to radiobioassay specimens and that is used to quantify the amount of activity present in a person or sample measured

NOTE The radionuclides used for the preparation of the TRS are, when possible, related to CRMs. The preparation procedures are verified and documented.

3.34
unbiased
in a state wherein a measurement of a random variable has zero bias

NOTE In other words, the measured value of the quantity is equal to the expected value of the quantity being determined.

3.35
uncertainty of measurement
parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurement

3.36
validation
act of defining the method capability and determining whether it can be properly applied as intended, or a test to determine whether the overall implemented analysis fulfils specified requirements

3.37
verification
act of confirming, substantiating or assuring that an action, condition or goal has been implemented, completed or accomplished in accordance with the specified requirements or a test, in order to prove that a particular step of the analysis fulfils specified requirements

4 Symbols

A_{ai} actual quantity in the test phantom or *in vitro* sample for the ith measurement

A_i value of the ith measurement in a category being tested

B_r relative bias

B_{ri} relative bias statistic for the ith measurement

n number of measurements of the same measurand

s standard deviation

s_B standard deviation of a total blank count

s_{Br} standard deviation of the relative bias applied for performance testing

t counting time interval used in the procedure (seconds)

m number of the input quantities

X_i input quantity ($i = 1,..., m$)

x_i estimate of the input quantity X_i

$u(x_i)$ standard uncertainty of the input quantity X_i associated with the estimate x_i

$h_1(x_1)$ standard uncertainty $u(x_1)$ as a function of the estimate x_1

$u_{rel}(w)$ relative standard uncertainty of a quantity W associated with the estimate w

G model function

Y	random variable as an estimator of the measurand; also used as the symbol for the non-negative measurand itself, which quantifies the physical effect of interest
$\tilde{y}$	true value of the measurand; if the physical effect of interest is not present, then $\tilde{y} = 0$, otherwise, $\tilde{y} > 0$
y	determined value of the estimator Y, estimate of the measurand, primary measurement result of the measurand
y_j	values y from different measurements ($j = 0,1, 2,...$)
$u(y)$	standard uncertainty of the measurand associated with the primary measurement result y
$\tilde{u}(\tilde{y})$	standard uncertainty of the estimator Y as a function of the true value $\tilde{y}$ of the measurand
$\hat{y}$	best estimate of the measurand
$u(\hat{y})$	standard uncertainty of the measurand associated with the best estimate $\hat{y}$
y^*	decision threshold of the measurand
$y^\#$	detection limit of the measurand
$\tilde{y}_i$	approximations of the detection limit $y^\#$
$y^\triangleleft$	lower confidence limit of the measurand
$y^\triangleright$	upper confidence limit of the measurand
α	probability of the error of the first kind
β	probability of the error of the second kind
$1-\gamma$	probability for the confidence interval of the measurand
k_p	quantile of the standardized normal distribution for the probability p (e.g. $p = 1-\alpha$, $1-\beta$, or $1-\gamma/2$)
k_q	quantile of the standardized normal distribution for the probability q
$\Phi(t)$	distribution function of the standardized normal distribution; $\Phi(k_p) = p$ applies.

5 Performance measures

5.1 Decision threshold (y^*) and detection limit ($y^\#$)

5.1.1 Preamble

The value of the detection limit indicates the ability of the service laboratory to detect a radionuclide in a sample or person. The decision threshold provides a way of distinguishing the difference between the count rate from the measurand under analysis and the count rate from the appropriate blank. For *in vivo* measurements, the sample matrix (i.e. the person) of the measurand is a variable, therefore the detection limit is person dependent. For consistency, the detection limit calculated for a given sample represented by a uniform source distribution, either in a person or in a phantom, shall therefore be used to characterize the detection capability of the service laboratory. The service laboratory shall determine and document typical values of the detection limit for documented measurement conditions for each measurand for which a service is provided.

5.1.2 General procedure for the determination of the characteristic limits

5.1.2.1 Introduction

5.1.2.1.1 Preamble

The general procedures for the calculation of the characteristic limits are given in ISO 11929. The main features are summarized here to facilitate the presentation of the examples given in Annexes A and B. Further details are provided in ISO 11929. A short presentation of the meaning of the symbols taken from ISO 11929, and the logical connection between them, is given below.

A non-negative measurand shall be assigned to the physical effect to be investigated in any given measurement task. This measurand quantifies the effect and assumes the true value $\tilde{y} = 0$ if the effect is not present in a particular case. A random variable Y, an estimator, shall be assigned to the measurand. In the following discussion, the symbol Y is used for the measurand itself. A value y of the estimator Y, determined from measurements, is an estimate of the measurand. This value shall be calculated as the primary measurement result, together with the primary standard uncertainty $u(y)$ associated with y. These two values form the primary complete measurement result for the measurand and are obtained in accordance with ISO/IEC Guide 98-1 by evaluation of the measurement data and other information by means of a model (of the evaluation), which mathematically connects all the quantities involved. In general, the fact that the measurand is non-negative is not explicitly taken into account in the evaluation. Therefore, y may be negative, especially when the measurand approaches a true value $\tilde{y} = 0$. The best estimate $\tilde{y}$ of the measurand is calculated in 5.1.2.5 from the primary measurement result y and its standard uncertainty $u(y)$. In deriving the value of $\tilde{y}$, the knowledge that the measurand is non-negative is taken into account. The standard uncertainty $u(\tilde{y})$ associated with $\tilde{y}$ is smaller than $u(y)$.

5.1.2.1.2 General model

In general, the non-negative measurand Y is a function of several input quantities X_i in the following form:

$$Y = G\left(X_1, \ldots\ldots, X_m\right) \tag{1}$$

5.1.2.1.3 Calculation of the primary measurement result y and the associated standard uncertainty

Equation (1) is the model of the evaluation. Substituting given estimates x_i of the input quantities x in the model function G of Equation (1) yields the primary measurement result y of the measurand as

$$y = G\left(x_1, \ldots\ldots, x_m\right) \tag{2}$$

The standard uncertainty $u(y)$ of the measurand associated with the primary measurement result y follows, if the input quantities X_i are independently measured and standard uncertainties $u(x_i)$ associated with the estimates x_i are given, from the following relation:

$$u^2\left(y\right) = \sum_{i=1}^{m}\left(\frac{\partial G}{\partial X_i}\right)^2 u^2\left(x_i\right) \tag{3}$$

5.1.2.1.4 Calculation of the standard uncertainty $\tilde{u}^2(\tilde{y})$

If $u(x_1)$ is known as a function $h_1(x_1)$, y is replaced by $\tilde{y}$ and Equation (2) is solved for x_1. This results in x_1 as a function of $\tilde{y}$ and $x_2, \ldots x_m$. The function replaces x_1 in Equation (3) and in $h_1(x_1)$ yielding $\tilde{u}^2(\tilde{y})$.

If $u(x_1)$ is known as a function $h_1(x_1)$, it is often sufficient to use the following approximation, especially if the primary measurement result of the measurand is not much larger than the associated uncertainty $u(y)$:

$$\tilde{u}^2\left(\tilde{y}\right) = u^2\left(y_1\right) \tag{4}$$

If only $\tilde{u}(0) = u(y_0)$ (measurement of background or blank) and $y_1 > 0$ (measurement currently carried out) are known, then the following linear interpolation often suffices:

$$\tilde{u}^2(\tilde{y}) = \tilde{u}^2(0) \cdot \left(1 - \frac{\tilde{y}}{y_1}\right) + u^2(y_1) \cdot \frac{\tilde{y}}{y_1} \tag{5}$$

5.1.2.2 Calculation of the decision threshold y^*

The decision threshold is calculated as

$$y^* = k_{1-\alpha}\tilde{u}(0) \tag{6}$$

An effect of the measurand Y is recognized as present if $y > y^*$. If not, the calculation of the confidence limits and of the best estimate $\hat{y}$ of the measurand with the associated standard uncertainty $u(\hat{y})$ are omitted.

With the approximation $\tilde{u}(\tilde{y}) = u(y)$, the relation $y^* = k_{1-\alpha}u(y)$ applies.

5.1.2.3 Calculation of the detection limit $y^\#$

The detection limit $y^\#$ is the smallest solution of Equation (7):

$$y^\# = y^* + k_{1-\beta}\tilde{u}\left(y^\#\right) \tag{7}$$

Equation (7) is an implicit equation. The detection limit can be calculated by solving it or, more simply, by iteration. The approximation $\tilde{y}_i$ for $y^\#$ is repeatedly substituted in the right-hand side of Equation (7) to produce with the starting approximation $\tilde{y}_{i+1}$. As starting approximation, $\tilde{y}_0 = 2y^\#$ can be chosen.

The detection limit does not exist if $y^\# < y^*$.

If the approximation in Equation (4) is used, Equation (7) simplifies to Equation (8):

$$y^\# = \left(k_{1-\alpha} + k_{1-\beta}\right) \cdot u(y) \tag{8}$$

If the linear interpolation in accordance with Equation (5) is used, Equation (7) becomes Equation (9):

$$y^\# = a + \sqrt{a^2 + \left(k_{1-\beta}^2 - k_{1-\alpha}^2\right) \cdot \tilde{u}^2(0)}\,; \quad a = \left[k_{1-\alpha} \cdot \tilde{u}(0)\right] + \frac{1}{2} \cdot \frac{k_{1-\beta}^2}{y_1}\left[u^2\left(y_1\right) - \tilde{u}^2(0)\right] \tag{9}$$

If $\alpha = \beta$, then

$$y^\# = 2 \cdot a \tag{10}$$

5.1.2.4 Calculation of the confidence limits

The limits of a confidence interval are provided for a physical effect, recognized as present in accordance with 5.1.2.2, in such a way that the confidence interval contains the true value of the measurand with the specified probability $1-\gamma$. The confidence limits take into account that the measurand is non-negative.

The confidence limits are calculated as follows:

$$y^{\triangleleft} = y - k_p u(y) \text{ with } p = \omega \cdot (1 - \gamma/2) \tag{11}$$