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Molecular biomarker analysis — Terms and definitions

Analyse moléculaire de biomarqueurs — Termes et définitions

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Foreword

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The committee responsible for this document is ISO/TC 34, *Food products*, Subcommittee SC 16, *Horizontal methods for molecular biomarker analysis*.

Molecular biomarker analysis — Terms and definitions

1 Scope

This International Standard gives the definition of terms used in the International Standards published in the frame of ISO/TC 34/SC 16.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 13495, *Foodstuffs — Principles of selection and criteria of validation for varietal identification methods using specific nucleic acid*

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

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 13495, ISO/IEC Guide 99 and the following apply.

3.1
absolute error
result of a measurement minus a true value of the measurand

3.2
accordance
similarity of consistent results from a qualitative method (i.e. both positive or both negative) from identical samples analyzed in the same laboratory in repeatability conditions

3.3
accuracy
accuracy of measurement
measurement accuracy
closeness of agreement between a measured quantity value and a true quantity value of a measurand

Note 1 to entry: The concept "measurement accuracy" is not a quantity and is not given a numerical quantity value. A measurement is said to be more accurate when it offers a smaller measurement error.

Note 2 to entry: The term "measurement accuracy" should not be used for measurement trueness and the term measurement precision should not be used for "measurement accuracy", which, however, is related to both these concepts.

Note 3 to entry: "Measurement accuracy" is sometimes understood as closeness of agreement between measured quantity values that are being attributed to the measurand.

[SOURCE: ISO/IEC Guide 99:2007, 2.13]

3.4
allele
one of several alternate forms of a gene which occur at the same locus on homologous chromosomes and which become separated during meiosis and can be recombined following fusion of gametes

3.5
allele competition
competitive phenomenon that results in the preferential amplification of one allelic sequence over another in a heterozygous or mixed sample during the application of nucleic acid amplification technologies such as PCR

[SOURCE: ISO 13495:2013, 3.6.1, modified]

3.6
allele frequency
frequency at which an allele appears on a specific locus in a population

[SOURCE: ISO 13495:2013, 3.6.2, modified]

3.7
amplicon
DNA sequence produced by a DNA-amplification technology, such as the PCR technique

[SOURCE: ISO 13495:2013, 3.3.1, modified]

3.8
analyte
component of a system to be analyzed

Note 1 to entry: AOI is Analyte of Interest.

3.9
annealing
pairing of complementary single strands of nucleic acids to form a double-stranded molecule

3.10
antibody
protein (immunoglobulin) produced and secreted by B lymphocytes in response to a molecule recognised as foreign (antigen) and which is capable of binding to that specific antigen

Note 1 to entry: Immunoglobulin is the common synonym for antibody.

3.11
antibody selectivity
ability of an antibody to specifically bind to an antigenic determinant (epitope) but not to other similar structures on that or other antigens

3.12
antigen
substance that is recognized as foreign by the immune system and elicits an immune response through stimulating antibody production

3.13
applicability
analytes, matrices, and concentrations for which an analytical approach may be used satisfactorily

3.14
applicability range
range of quantification
range of linearity
dynamic range
upper and lower limits of quantification as expressed by a set of reference materials (or dilutions) with a suitable level of precision and accuracy

3.15
background
intrinsic level of signal resulting from the instruments, reagents and consumables used in the reaction

3.16
baseline
level of detection or the point at which a reaction reaches fluorescence or signal intensity above the background level

3.17
bias
measurement bias
estimate of a systematic measurement error

[SOURCE: ISO/IEC Guide 99:2007, 2.18]

3.18
biotechnology-derived trait
see *genetically engineered organism* (3.73)

3.19
blocking reagent
compound used to saturate the residual unspecific binding sites

3.20
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties, and in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

Note 1 to entry: A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty.

Note 2 to entry: Calibration should not be confused with adjustment of a measuring system, often mistakenly called “self-calibration”, nor with verification of calibration.

[SOURCE: ISO/IEC Guide 99:2007, 2.39, modified]

3.21
certified reference material
CRM
reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceability, using valid procedures

EXAMPLE Human serum with assigned quantity value for the concentration of cholesterol and associated measurement uncertainty stated in an accompanying certificate, used as a calibrator or measurement trueness control material.

Note 1 to entry: Documentation is given in the form of a “certificate” (see ISO/IEC Guide 30).

Note 2 to entry: Procedures for the production and certification of certified reference materials are given, e.g. in ISO Guide 34 and ISO Guide 35.

Note 3 to entry: In this definition, “uncertainty” covers both “measurement uncertainty” and “uncertainty associated with the value of the nominal property”, such as for identity and sequence. “Traceability” covers both “metrological traceability of a value” and “traceability of a nominal property value”.

Note 4 to entry: ISO/REMCO has an analogous definition (Accred. Qual. Assur.:2006) but uses the modifiers “metrological” and “metrologically” to refer to both quantity and nominal property.

[SOURCE: ISO/IEC Guide 99:2007, 5:14, modified]

3.22
clone
population of cells, generated by asexual reproduction, that are genetically identical and direct descendants of a parent cell, derived from a single cell

3.23
collaborative trial
see *interlaboratory study* (3.84)

3.24
complementary sequence
complementarity is a property shared between two nucleic acid sequences, such that when they are aligned antiparallel to each other, the nucleotide bases at each position will be complementary

3.25
concordance
similarity or agreement of results (i.e. both positive or both negative) from identical samples that are analysed in two different laboratories in terms of qualitative analysis

3.26
construct-specific detection method
targets a specific combination of inserted DNA sequences (such as genes, promoters, terminators or other genetic elements of interest) unique to biotechnology-derived organisms

3.27
conventional quantity value
conventional value of a quantity
conventional value
attributed by agreement to a quantity for a given purpose

EXAMPLE 1 Standard acceleration of free fall (formerly called "standard acceleration due to gravity"), g_n = 9,806 65 m·s^{-2}.

EXAMPLE 2 Conventional quantity value of the Josephson constant, $K_{J\text{-}90}$ = 483 597,9 GHz V^{-1}.

EXAMPLE 3 Conventional quantity value of a given mass standard, m = 100,003 47 g.

Note 1 to entry: The term "conventional true quantity" is sometimes used for the concept but its use is discouraged.

Note 2 to entry: Sometimes, a conventional quantity value is an estimate of a true quantity value.

Note 3 to entry: A conventional quantity value is generally accepted as being associated with a suitably small measurement uncertainty, which might be effectively considered to be zero.

[SOURCE: ISO/IEC Guide 99:2007, 2.12, modified]

3.28
copy number
number of molecules (copies) of a DNA sequence

3.29
critical value
value of the net concentration or amount, the exceeding of which leads, for a given error probability, α, to the decision that the concentration or amount of the analyte in the analysed material is larger than that in the blank material:

$$\Pr\left(\hat{L} > L_C \middle| L = 0\right) \leq \alpha$$

where

$\hat{L}$ is the estimated value;

L is the expectation or true value;

L_C is the critical value.

Note 1 to entry: The definition of critical value is important for defining the Limit of Detection (LOD). The critical value L_C is estimated by $L_C = t_{1-\alpha\nu}s_o$, where $t_{1-\alpha\nu}$ is Student's-t, based on ν degrees of freedom for a one-sided confidence interval of $1-\alpha$ and s_o is the sample standard deviation.

If L is normally distributed with known variance, i.e. $\nu = \infty$ with the default α of 0,05, $L_C = 1{,}645s_o$. A result falling below the L_C triggering the decision "not detected" should not be construed as demonstrating analyte absence.

3.30
cross-reactivity
degree to which binding occurs between an antibody and antigenic determinants which are not the analyte of primary interest

3.31
cultivar
group of cultivated plants which may be clearly defined by morphological, physical, cytological, chemical or other characteristics and which, after sexual or asexual reproduction, keeps its distinct character

Note 1 to entry: The concept of "cultivar" is essentially different from the concept of the botanical variety "varietas", in that "cultivar" is an infraspecific division resulting from controlled selection, even if empirical; "varietas" is an infraspecific division resulting from natural selection. The terms "cultivar" and "variety" (in the sense of cultivated variety) are equivalent. In translations or adaptations of botanical nomenclature for particular uses, the terms "cultivar" or "variety" (or their equivalents in other languages) may be used in text.

3.32
cycle threshold
C_t
in real-time quantitative PCR, the cycle at which the fluorescence from the reaction crosses a specified threshold level at which the signal can be distinguished from background levels

3.33
denaturation
process of partial or total alteration of the native structure of a macromolecule resulting from the loss of tertiary and/or secondary structure that is a consequence of the disruption of stabilizing weak bonds

EXAMPLE Denaturation can occur when proteins and nucleic acids are subjected to elevated temperature, extremes of pH, non-physiological concentrations of salt, organic solvents, urea or other chemical agents.

3.34
denaturation of protein
physical and/or chemical treatment which destroys or modifies the structural, functional, enzymatic, or antigenic properties of the protein of interest

3.35
denatured DNA
DNA that has been converted from double-stranded to a single-stranded form by a denaturation process such as heating

3.36
deoxyribonuclease/ribonuclease
DNase/RNase
enzyme that catalyses the hydrolytic cleavage of deoxyribonucleic acid/ribonucleic acid that may produce a single nucleotide residue by cleavage at the end of the chain or a polynucleotide by cleavage at a position within the chain

3.37
deoxyribonuclease/ribonuclease inhibitor
substance that either fully or partially blocks deoxyribonuclease/ribonuclease activity

3.38
deoxyribonucleic acid
DNA
polymer of deoxyribonucleotides occurring in double strand (dsDNA) or single strand (ssDNA) form that is the carrier of genetic information, encoded in the sequence of bases (nitrogen containing ring compounds that are either purines or pyrimidines), and is present in chromosomes and chromosomal material of cell organelles as well as in plasmids and in viruses

3.39
deoxyribonucleotide triphosphate
dNTP
generic term referring to a deoxyribonucleotide that includes: deoxyadenosine nucleotide triphosphate (dATP), deoxycytidine nucleotide triphosphate (dCTP), deoxyguanosine nucleotide triphosphate (dGTP), deoxythymidine nucleotide triphosphate (dTTP) and deoxyuridine nucleotide triphosphate (dUTP)

3.40
detection assay
procedure or method that is used to identify the presence of traits, microorganisms, pests or other analytes in a biological sample

3.41
detection limit
limit of detection
measured quantity value, obtained by a given measurement procedure, for which the probability of falsely claiming the absence of a component in a material is β, given a probability α of falsely claiming its presence

Note 1 to entry: IUPAC recommends default values for α and β equal to 0,05.

Note 2 to entry: The abbreviation LOD is sometimes used.

Note 3 to entry: The term “sensitivity” is discouraged for this concept.

[SOURCE: ISO/IEC Guide 99:2007, 4.18, modified]

3.42
detection of PCR product
act of noting or discovering the existence of a PCR product by visualizing a fluorescent band (i.e. ethidium bromide staining) on an agarose gel or with fluorescent probes in real-time PCR applications or other approaches

3.43
dip stick test
see *lateral flow membrane assay* (3.90)

3.44
DNA extraction
sample treatment for the liberation and separation of DNA from other cellular components

3.45
DNA polymerase
enzyme that synthesizes DNA by catalysing the addition of deoxyribonucleotide residues to the free 3’-hydroxyl end of a DNA molecular chain, starting from a mixture of the appropriate triphosphorylated bases

3.46
DNA probe
short sequence of DNA labelled isotopically or chemically that is used for the detection of a complementary nucleotide sequence

3.47
DNA purification
see *nucleic acid purification* (3.125)

3.48
DNA sequencer
gene sequencer
genetic analyser
apparatus used for determining the arrangement of the nucleotide bases (adenine, guanine, cytosine, and thymine) in a molecule of DNA

3.49
DNA target
see *target sequence* (3.203)

3.50
electrophoresis
technique used for separating, identifying, and purifying molecules (e.g. plasmid DNA, DNA fragments resulting from digestion, RNA, protein, and PCR products) based upon the differential movement of charged particles through a matrix when subjected to an electric field

[SOURCE: ISO 13495:2013, 3.4.1, modified]

3.51
endogenous DNA sequence
defined reference DNA sequence native to a corresponding taxon

Note 1 to entry: The endogenous DNA sequence can be used to determine the quantity of genome equivalents of the target taxon if the sequence is present in a constant copy number and does not show allelic variation among cultivars of the target taxon.

3.52
end-point PCR
method where the amplicons are detected at the end of the PCR reaction, typically by gel electrophoresis and the amplified product is visualized with a fluorescent dye

3.53
environment control
control used to demonstrate that no contamination from the environment was introduced to test samples

3.54
enzyme linked immunosorbent assay
ELISA
in vitro assay used for qualitative, semi-quantitative, or quantitative purposes that combines enzyme-linked antibodies and a substrate to form a coloured or a fluorescence emitting reaction product

Note 1 to entry: Because of the presence of an antibody-linked enzyme, a colourless substrate can rapidly be converted into a coloured product or a non-fluorescent substrate into an intensely fluorescent product.

3.55
error
error of measurement
measurement error
measured quantity value minus a reference quantity value

Note 1 to entry: The concept of "measurement error" can be used both

a) when there is a single reference quantity value to refer to, which occurs if a calibration is made by means of a measurement standard with a measured quantity value having a negligible measurement uncertainty or if a conventional quantity value is given, in which case the measurement error is known, and

b) if a measurand is supposed to be represented by a unique true quantity value or a set of true quantity values of negligible range, in which case the measurement error is not known.

Note 2 to entry: Measurement error should not be confused with production error or mistake.

[SOURCE: ISO/IEC Guide 99:2007, 2.16]

3.56
event
transgene construct and its unique site of insertion into a genome

3.57
event-specific method
detection method that targets DNA sequences at the integration site unique to a specific transformation event

3.58
exonuclease
enzyme that hydrolyses (cleaves) terminal phosphodiester bonds of a nucleic acid

3.59
expanded measurement uncertainty
expanded uncertainty
product of a combined standard measurement uncertainty and a factor larger than the number one

Note 1 to entry: The factor depends upon the type of probability distribution of the output quantity in a measurement model and on the selected coverage probability.

Note 2 to entry: The term factor in this definition refers to a coverage factor.

Note 3 to entry: Expanded measurement uncertainty is termed “overall uncertainty” in Recommendation INC-1 (1980), paragraph 5 (see ISO/IEC Guide 98-3) and simply “uncertainty” in IEC documents.

3.60
external amplification control
spiked amplification control
DNA added to an aliquot of the extracted nucleic acid in a defined amount or copy number serving as a control for amplification in nucleic acid-based reactions

3.61
extraction blank control
reagent blank
negative control reaction generated by performing all required steps in an extraction procedure except for the addition of the test portion

EXAMPLE By substitution of water for the test portion.

Note 1 to entry: This control is used to demonstrate the absence of contamination during extraction.

3.62
false negative
error of failing to reject a null hypothesis when it is in fact not true

3.63
false negative rate
probability that a known positive test sample has been classified as negative by the method

Note 1 to entry: The false negative rate is the number of misclassified known positives divided by the total number of positive test samples.

