BS EN ISO 20046:2021

BSI Standards Publication

Radiological protection — Performance criteria for laboratories using Fluorescence In Situ Hybridization (FISH) translocation assay for assessment of exposure to ionizing radiation

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National foreword

This British Standard is the UK implementation of EN ISO 20046:2021. It is identical to ISO 20046:2019. It supersedes BS ISO 20046:2019, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee NCE/2, Radiation protection and measurement.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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Date	Text affected
28 February 2021	This corrigendum renumbers BS ISO 20046:2019 as BS EN ISO 20046:2021

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EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 20046

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English Version

Radiological protection - Performance criteria for laboratories using Fluorescence In Situ Hybridization (FISH) translocation assay for assessment of exposure to ionizing radiation (ISO 20046:2019)

Radioprotection - Critères de performance pour les laboratoires utilisant l'analyse des translocations visualisées par hybridation in situ fluorescente (FISH) pour évaluer l'exposition aux rayonnements ionisants (ISO 20046:2019)

Strahlenschutz - Leistungskriterien für Laboratorien, die den Fluoreszenz-in-situ-Hybridisierungs-(FISH)-Translokationstest zur Bewertung der Exposition gegenüber ionisierender Strahlung verwenden (ISO 20046:2019)

This European Standard was approved by CEN on 18 January 2021.

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European foreword

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This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by August 2021, and conflicting national standards shall be withdrawn at the latest by August 2021.

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Foreword

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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).

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

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Introduction

The purpose of this document is to define the use of fluorescent in situ hybridization (FISH) for chromosome translocation analysis on human peripheral blood lymphocytes for biological dosimetry of exposure to ionizing radiation. Biological dosimetry, based on the study of chromosomal aberrations, mainly the dicentric assay, has become a routine component of accidental dose assessment. Dicentric aberrations, however, disappear with time after exposure, making this assay useful only in the short term after exposure. Translocations, however, are more stable, allowing dose estimates to be made long times after exposure or after protracted exposures.

This document provides a guideline for performing the translocation assay by FISH for dose assessment using documented and validated procedures. The minimum requirements for testing translocation yield in peripheral blood lymphocytes, by precisely defining the technical aspects of staining chromosomes (number of chromosomes and types of painting), selecting types of aberrations and cells, scoring aberrations, converting aberration yield to dose, statistical considerations, problems related to heterogeneous, chronic or delayed exposures and extrapolation to full genome are described. Dose assessment using the FISH assay has relevance in medical management, radiation-protection management, record keeping, and medical/legal requirements.

A part of the information in this document is contained in other international guidelines and scientific publications, primarily in the International Atomic Energy Agency's (IAEA) technical reports series on biological dosimetry. However, this document expands and standardizes the quality assurance and quality control and the evaluation of performance.

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Radiological protection — Performance criteria for laboratories using Fluorescence In Situ Hybridization (FISH) translocation assay for assessment of exposure to ionizing radiation

1 Scope

The purpose of this document is to provide criteria for quality assurance (QA), quality control (QC) and evaluation of the performance of biological dosimetry by cytogenetic service laboratories.

This document addresses:

a) the responsibilities of both the customer and the laboratory;

b) the confidentiality of personal information, for the customer and the laboratory;

c) the laboratory safety requirements;

d) sample processing; culturing, staining and scoring, including the criteria for scoring for translocation analysis by FISH;

e) the calibration sources and calibration dose ranges useful for establishing the reference dose-response curves that contribute to the dose estimation from chromosome aberration frequency and the detection limit;

f) the scoring procedure for translocations stained by FISH used for evaluation of exposure;

g) the criteria for converting a measured aberration frequency into an estimate of absorbed dose (also appears as "dose");

h) the reporting of results;

i) the QA and QC;

j) Annexes A to F containing sample instructions for the customer, sample questionnaire, sample datasheet for recording aberrations, sample of report and fitting of the low dose-response curve by the method of maximum likelihood and calculating the uncertainty of dose estimate.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

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

ISO and IEC maintain terminological 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/

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3.1
absorbed dose
D
quantity of ionizing radiation energy imparted per unit mass of a specified material

3.2
acentric
terminal or interstitial chromosome fragment of varying size lacking a centromere, referred to as an excess acentric fragment when it is formed independently of a dicentric or centric ring chromosome aberration

3.3
anticoagulant
drug which prevents blood from clotting

3.4
background frequency/level
spontaneous frequency (or number) of chromosome aberrations recorded in a general population

3.5
buffy coat
layer of an anticoagulated blood sample after centrifugation that contains most of the white blood cells

3.6
calibration curve
graphical or mathematical description of the dose effect relation derived by the in vitro irradiation of blood samples to known absorbed doses

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

3.7
centromere
specialized constricted region of a chromosome that appears during mitosis and joins together the chromatid pair

3.8
chromatid
either of the two strands of a duplicated chromosome that are joined by a single centromere and separate during cell division to become individual chromosomes

3.9
chromosome
structure comprised of discrete packages of DNA and proteins that carries genetic information, which condense to form characteristically shaped bodies during nuclear division

3.10
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

3.11
colcemid
alkaloid compound that inhibits spindle formation during cell division

Note 1 to entry: It is used to collect a large number of metaphase cells by preventing them from progressing to anaphase.

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3.12
complex aberration
aberration involving three or more breaks in two or more chromosomes and is characteristically induced after exposure to densely ionizing radiation or high doses of sparsely ionizing radiation

3.13
confidence interval
range within which the true value of a statistical quantity lies with a specified probability

3.14
covariance
measure of the correlation of the variance between two (or more) dependent sets of data or parameters

3.15
decision threshold
value of the estimator of the measurand, which when exceeded by the result of the actual measurement using a given measurement procedure of a measurand quantifying a physical effect, one decides that the physical effect is present

Note 1 to entry: The decision threshold is defined such that in cases where the measurement result, y, exceeds the decision threshold, y^*, the probability that the true value of the measurand is zero is less or equal to a chosen probability, α.

Note 2 to entry: If the result, y, is below the decision threshold, y^*, the result cannot be attributed to the physical effect; nevertheless it cannot be concluded that it is absent.

3.16
detection limit
smallest true value of the measurand which ensures a specified probability of being detectable by the measurement procedure

Note 1 to entry: With the *decision threshold* (3.15), the detection limit is the smallest true value of the measurand for which the probability of wrongly deciding that the true value of the measurand is zero is equal to a specified value, β, when, in fact, the true value of the measurand is not zero

3.17
dicentric
aberrant chromosome bearing two centromeres derived from the joining of parts from two broken chromosomes, generally accompanied by an acentric fragment

3.18
fluorescence in situ hybridization
FISH
technique that uses specific sequences of DNA as probes to particular parts of the genome, allowing the chromosomal regions to be highlighted or "painted" in different colours by attachment of various fluorochromes

3.19
fluorochrome
molecules that are fluorescent when appropriately excited

Note 1 to entry: They are used for FISH cytogenetics to highlight specific chromosomal regions.

3.20
genome equivalent
number of translocations that would be observed with all chromosomes painted, calculated from the number of translocations detected with a limited number of painted chromosomes

3.21
insertion
chromosome rearrangement in which a piece of one chromosome has been inserted within another chromosome

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3.22
interphase
period of a cell cycle between the mitotic divisions

3.23
linear energy transfer
LET
radiation energy lost per unit length of path through a biological material

3.24
metaphase
stage of mitosis when the nuclear membrane is dissolved, the chromosomes condensed to their minimum lengths and aligned for division

3.25
protocol for aberration identification and nomenclature terminology
PAINT
terminology used in FISH analysis for describing chromosomal aberrations

3.26
precision
concept employed to describe dispersion of measurements with respect to a measure of location or central tendency

3.27
proficiency test
evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons

3.28
quality assurance
QA
planned and systematic actions necessary to provide adequate confidence that a process, measurement or service satisfies given requirements for quality

3.29
quality control
QC
part of quality assurance intended to verify that systems and components conform with predetermined requirements

3.30
radiation-induced translocation
among the observed translocations, the ones that can be attributed to a radiation exposure i.e. not translocations induced by other sources (e.g. age, lifestyle factors)

3.31
ring
aberrant circular chromosome resulting from the joining of two breaks within one chromosome

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

3.32
service laboratory
laboratory performing biological dosimetry measurements

3.33
stable aberration
aberration which is not lethal to the cell and can be passed on to daughter cells (e.g. simple translocation)

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3.34
stable cell
cell without unstable aberrations, that may be entirely undamaged or contain stable type aberrations only, and are likely to survive division

3.35
translocation
stable chromosome aberration in which parts of two or more chromosomes are exchanged

3.36
unstable aberration
aberration which is lethal to the cell (e.g. dicentrics/centric rings/acentric fragments)

4 Translocation assay by FISH

4.1 General

The frequency of chromosomal aberrations seen at metaphase in cultured human peripheral blood lymphocytes is used for absorbed dose estimation after suspected exposure to ionizing radiation. This document focuses on retrospective evaluation of exposures which occurred in the past or protracted exposures where the dicentric assay (see ISO 19238) and the cytokinesis block micronucleus assay (see ISO 17099) are not applicable due to the decrease in this type of damage over time. The aberrations to be used are translocations and insertions in stable cells. For the application of this document, the service laboratory shall choose which type of aberrations to score for the purpose of assessing absorbed dose estimates and shall be consistent throughout.

It has been well established that the background translocation frequency in individuals varies with age due to various confounding factors (i.e. nutritional status, genotoxic exposures, lifestyle factors, malsegregation of sex chromosomes). This is an important consideration to take into account for absorbed dose estimations using translocation analysis.

Hereafter, chromosome aberrations are referred to as translocations but may include insertions if determined by the service laboratory.

4.2 Culturing and fixation

Similarly to ISO 19238, lymphocytes are cultured by a method that maximizes first-division metaphases. This requires whole blood, or lymphocytes separated from the other blood components, to be incubated in a culture medium containing a mitogen that stimulates lymphocyte cycling into mitosis. For translocation analysis, cell cycle control is recommended. A mitotic blocking agent, colcemid, is added to arrest and collect dividing lymphocytes in metaphase. The duration of the cell culture and the timing of the addition of the arresting agent are optimized to ensure an adequate mitotic index.

Metaphases are recovered from the cultures, using a hypotonic salt solution and fixing in a mixture of methanol and acetic acid. Fixed cells are dropped on microscope slides and stained. The exact protocol for cell culture, harvesting metaphases, and staining employed by a service laboratory shall be formally documented (See Clause 9).

4.3 Types of staining

Whole chromosome FISH staining shall be conducted and can involve one colour painting for all selected chromosome pairs or two or three different colours, one for each pair of chromosomes selected. Painting of three of the larger chromosomes covers about 20 % to 24 % of the total human DNA content, however there are many choices of the number of fluorochromes and which chromosomes could be selected for painting. It is recommended that chromosomes selected cover a large amount of DNA.

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Some examples are described below:

a) one colour painting of three chromosome pairs [e.g. chromosome pairs 1, 4 and 8 all painted with FITC (green)];

b) three colour painting of three chromosome pairs [e.g. chromosome pair 1 painted with Texas Red (red), chromosome pair 2 painted with FITC (green) and chromosome pair 4 painted with FITC and Texas Red (yellow)].

It is possible to increase the number of painted chromosome pairs to analyse a higher proportion of the genome, but the staining of a few chromosome pairs is an efficient method in most cases.

All chromosomes should be counterstained with a fluorescent DNA dye such as DAPI (4',6-diamidino-2-phenylindole). The use of a pan-centromeric probe may also be added but is not necessary for translocation analysis, when the centromeres can be clearly identified.

4.4 Scoring

Microscope slides containing stained cells are methodically scanned to identify suitable metaphase cells. The frequency of translocations observed in an appropriate number of scored metaphase cells is converted to an estimate of radiation dose by reference to calibration data.

There are many types of chromosomal aberrations visible with whole chromosome FISH including stable and unstable, which should all be recorded during the scoring procedure. For the application of this document, the focus is on the scoring of translocations in stable cells so that this method can be applied to retrospective analysis of exposures that have occurred in the past. Therefore, it is recommended that unstable aberrations detected in counterstained chromosomes should also be recorded to determine whether the translocation occurs in a stable or unstable cell. To avoid slowing down the scoring, the analysis of all the counterstained chromosomes can be performed only in cells with stable aberrations visible in the painted chromosomes.

The service laboratory shall choose which chromosome pairs and type of aberrations to score for the purpose of assessing absorbed dose estimates and shall be consistent throughout.

Metaphases selected for scoring should be well-spread and appear to be complete.

There are several aberration classification systems currently in use (e.g. PAINT)[3]. For the application of this document, the service laboratory shall choose which type of scoring system to be used and shall be consistent throughout. It is recommended that all visible damage be recorded but only translocations in stable cells are to be counted for generating the calibration curve and providing absorbed dose estimates. The information about the frequencies of all observed aberrations allows an opportunity for further interpretation of the exposure conditions.

4.5 General requirement of the laboratory

The laboratory shall be well-equipped with the required standard laboratory equipment for lymphocyte culture, cell processing, slide preparation, and fluorescence microscopy scoring of cells. The laboratory should maintain QA documents, including those describing periodic calibration and maintenance of the equipment used for cell culture as required.

5 Responsibility of the customer

This clause includes items that are not controlled by the laboratory. Prior to blood sampling, coordination between the customer and the service laboratory should occur. Essential requirements should be explained to the customer and this should be by a standardised instruction sheet as illustrated in Annex A. The essential features are:

a) blood sampling shall use a collection system, containing lithium or sodium heparin as the anticoagulant, which has been sent or specified by the service laboratory;

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b) blood shall be collected (ideally about 10 ml), labelled accurately and unambiguously, maintained between 6 °C and 30 °C and sent to the laboratory as soon as possible (ideally within 48 h);

c) precautions to ensure the integrity of the container and to prevent leakage during shipment shall be observed. Blood samples should be kept between 6 °C and 30 °C during shipping. A temperature recorder should be included to monitor the temperature during shipment. Packaging and labelling shall conform to national and international regulations. If air transportation is involved, a physical dosimeter shall be included to monitor whether the sample was irradiated in transit;

d) a questionnaire provided by the laboratory shall be completed accurately and returned promptly; particularly listing previous medical or occupational radiation exposures (see Annex B). Accurate biological dosimetry is limited for patients who have received a previous unknown medical exposure;

e) the laboratory shall be alerted of biologically contaminated and/or infectious samples.

6 Responsibility of the laboratory

6.1 Setup and sustainment of the QA program

The laboratory shall establish and maintain a QA program (see Clause 14), which covers all aspects of the service. The QA program should address the following issues:

a) the laboratory's QA program shall include periodic internal checks of equipment operations, reagent suitability, and various performance checks (i.e., intra-laboratory comparisons, operator qualifications, sample protocol, scoring, absorbed dose estimations, report generation, etc.);

b) the laboratory's QA program shall include periodic external checks of the laboratory's operations. The external audits shall include a review of the service laboratory's documentation of equipment operations, reagent suitability, and various performance checks (i.e., inter-laboratory comparisons, operator qualifications, sample transport integrity, etc.).

The laboratory shall establish the frequency of these QA checks.

6.2 Responsibility during service

The service laboratory shall provide necessary guidance, procedures, and reporting to provide absorbed dose assessment by cytogenetic analysis in response to a request for service. The service activities shall address the following issues:

a) the laboratory shall have documentation, reviewed and endorsed by a designated, competent person including the following:

   1) an instruction sheet to be sent to the customer describing shipping procedures (see Annex A);

   2) a questionnaire that shall elicit patient consent 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 habit, and significant exposures to any other DNA damaging agents (such as organic solvents or heavy metals) (see Annex B);

   3) step by step procedures for processing the blood sample from receipt of the sample to reporting of the absorbed dose;

b) if required, a blood collection system (10 ml) containing lithium or sodium heparin as the anticoagulant shall be sent to the customer, also including the appropriately labelled and addressed packaging material for the return of the sample to the service laboratory. The packaging shall conform to national and/or international regulations for the transit of potentially infectious pathological specimens (see 14.2.4);

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