PD ISO/TR 22019:2019

BSI Standards Publication

Nanotechnologies — Considerations for performing toxicokinetic studies with nanomaterials

National foreword

This Published Document is the UK implementation of ISO/TR 22019:2019.

The UK participation in its preparation was entrusted to Technical Committee NTI/1, Nanotechnologies.

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

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Published by BSI Standards Limited 2019

ISBN 978 0 580 97439 7

ICS 07.120

Compliance with a British Standard cannot confer immunity from legal obligations.

This Published Document was published under the authority of the Standards Policy and Strategy Committee on 31 August 2019.

Amendments/corrigenda issued since publication

Date	Text affected

PD ISO/TR 22019:2019

TECHNICAL REPORT

ISO/TR 22019

First edition
2019-05-24

Nanotechnologies — Considerations for performing toxicokinetic studies with nanomaterials

Nanotechnologies - Considérations pour réaliser des études toxico cinétiques de nanomatériaux

Reference number
ISO/TR 22019:2019(E)

Contents

Page

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 of 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 www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 229, *Nanotechnologies.*

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

Nanomaterials (NMs) are a family of chemicals that, like any other chemicals, can exert a range of toxicities. Toxicokinetics can support the safety evaluation of compounds including NMs by identifying potential target organs, and especially for NMs, the potential for persistence in organs (including cellular uptake and compartmentalization). Also, toxicokinetic information can be used to evaluate if a NM behaves differently from a similar NM or bulk material with the same chemical composition, e.g. with regard to barrier penetration. As for all studies with NMs, a proper characterization of the NM dispersions or aerosols used in the toxicokinetic studies is essential.

Importance of toxicokinetic information for risk assessment (of nanomaterials)

Toxicokinetics describes the absorption, distribution, metabolism and excretion (ADME) of foreign compounds in the body with time. It links the external exposure with the internal dose and is thus a key aspect for toxicity. If a NM is absorbed by the body through any of the potential exposure routes (oral, respiratory, dermal) it can enter into the blood or lymph circulation. Subsequent distribution to internal organs determines potential target tissues and potential toxicity. Alternatively, NMs can be intravenously administered (e.g. as nanomedicine) thus directly entering the blood circulation, potentially resulting in wide spread tissue distribution. Toxicokinetics therefore aids in the design of targeted toxicity studies and in identifying potential target organs and can thus also provide relevant information for justification or waiving of toxicity studies. In addition, toxicokinetic information can be useful as basis for grouping and read-across of NMs. Risk assessments based on internal concentrations, determined using toxicokinetic information, can be more realistic than risk assessments based on external doses, as nanoparticles (NPs) can show specific tissue distribution and accumulation. Toxicokinetic studies can be used to build toxicokinetic models, especially physiologically based pharmacokinetic (PBPK) models, which then can be used to extrapolate experimental toxicity data to other species, tissues, exposure routes, exposure durations and doses. Due to the accumulation of some NPs, the ability to extrapolate to longer exposure durations is of special importance for NMs.

Why a technical report specifically for nanomaterials?

A considerable body of published literature, including many national and international guidelines, exists on the use of toxicokinetic methods to study the fate of chemicals in the body. In addition, OECD Test Guideline (TG) 417 on Toxicokinetics (latest update dated 2010) gives an extensive description for evaluation of the toxicokinetic profile of chemicals but excludes NMs specifically. ISO 10993-16:2017 *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*, provides an overview for toxicokinetic studies for leachables of medical devices. Furthermore, the European Medicines Agency's ICH S3A (Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies) and ICH S3B (Pharmacokinetics: Repeated Dose Tissue Distribution Studies) give guidance on the design and conduct of toxicokinetic studies to assist in the development of new drugs.

Guidelines also exist on toxicokinetic modelling, especially the development and application of physiologically-based pharmacokinetic (PBPK) models. For example, the United States Food and Drug Administration's Draft Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry, provides the standard content and format of PBPK study reports while the United States Environmental Protection Agency's Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment, addresses the application and evaluation of PBPK models for risk assessment purposes. The European Medicines Agency (EMA) has published a "Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation" in 2016[1]. WHO has published the "Characterization and application of physiologically based pharmacokinetic models in risk assessment"[2].

As stated, the current OECD toxicokinetics TG 417 explicitly states that the guideline is not intended for the testing of NMs[3], as the toxicokinetics of NMs are different from dissolved ions/molecules and large particles. This was confirmed in a report on preliminary review of OECD Test Guidelines for their applicability to NMs[4]. Additionally, the PBPK models described in the current and mentioned guidance documents are not suitable for NMs, as the processes governing the distribution of NPs is different from those of the dissolved (molecular/ionic) substances addressed by the current guidance documents (e.g. Reference [5]).

New guidelines or specific additions to existing guidelines about the case of NMs are thus necessary. A review of the current knowledge on the specific toxicokinetic characteristics of NMs and the issues around toxicokinetic testing is a practical preparative step to ensure the best possible understanding of testing needed to obtain relevant information on toxicokinetics of NMs.

How are nanomaterials different from dissolved ions/molecules and large particles?

Nanomaterials (NMs) present a unique family of chemicals that, by their particulate nature and reduction in size, acquire specific physical chemical properties not present for their bulk or soluble counterparts, that might or might not be accompanied by specific toxicity as discussed previously in many reports (e.g. References [6], [7], [8], [9], [10]).

Toxicokinetics of NPs is of special interest because, in comparison to larger sized particles, the small size of NPs could enable an increased rate of translocation beyond the portal of entry, to the lymphatic fluid and blood circulation, from where they can reach potentially all internal organs[11]. In addition, smaller sized NPs can show a more widespread organ distribution than larger sized particles[12]. For the same reason, transport across barriers such as the blood-brain barrier and placenta can occur (e.g. References [13] and [14]).

Other notable differences between the toxicokinetic behaviour of dissolved molecular/ionic substances and NMs can be understood within the context of the principles that govern the absorption, distribution, metabolism and excretion (ADME) of a substance. For dissolved molecular/ionic substances, toxicokinetics is driven by 1) passive transport, which includes simple diffusion and filtration or 2) special transport, which includes active transport, carrier-mediated transporter systems and facilitated diffusion through cellular membranes, enzymatic metabolism and passive or active excretion. For NMs, toxicokinetics involves aggregation, agglomeration, protein corona formation, active cellular uptake, distribution through macrophages, and for certain NMs degradation, and excretion[15]. In addition, the surface chemistry/composition affects the toxicokinetics of NPs by its potential of binding a variety of biomolecules on the surface (also designated the “protein” corona). As excretion is often limited, bioaccumulation can occur similar to other poorly metabolized molecules. Thus, the requirements for the testing and modelling of the toxicokinetics of NMs can differ significantly from those identified for dissolved substances. In this respect, especially the potential for accumulation and persistence in organs needs to be evaluated, for example in repeated dose and prolonged toxicokinetic studies.

Nanotechnologies — Considerations for performing toxicokinetic studies with nanomaterials

1 Scope

This document describes the background and principles for toxicokinetic studies relevant for nanomaterials.

Annex A shows the definitions for terminology with respect to toxicokinetics as used in OECD TG 417:2010.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in the ISO 80004 series Nanotechnologies Vocabulary and the following apply.

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

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

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

3.1
agglomerate
collection of weakly or medium strongly bound *particles* (3.12) where the resulting external surface area is similar to the sum of the surface areas of the individual components

Note 1 to entry: The forces holding an agglomerate together are weak forces, for example van der Waals forces or simple physical entanglement.

Note 2 to entry: Agglomerates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO 26824:2013, 1.2]

3.2
aggregate
particle (3.12) comprising strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of surface areas of the individual components

Note 1 to entry: The forces holding an aggregate together are strong forces, for example covalent or ionic bonds, or those resulting from sintering or complex physical entanglement, or otherwise combined former primary particles.

Note 2 to entry: Aggregates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO 26824:2013, 1.3, modified — Note 1 adapted.]

