ICS 07.030
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NATIONAL STANDARD OF THE PEOPLE'S REPUBLIC OF CHINA

GB/Z 43193-2023

Nanotechnologies - Considerations for performing toxicokinetic studies with nanomaterials

Issued on: September 7, 2023 **Implemented on: April 1, 2024**

Issued by: State Administration for Market Regulation, China National Standardization Administration

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Foreword

This document complies with the provisions of GB/T 1.1-2020 "Standardization Work Guidelines Part 1.Structure and Drafting Rules of Standardization Documents"

Drafting.

This document is equivalent to ISO /T R22019.2019 "Research Elements of Toxic Metabolism Kinetics of Nanotechnology and Nanomaterials", file type

The ISO technical report was adjusted to my country's standardized guiding technical document.

This document has made the following minimal editorial changes.

---Delete Note 2 of 3.5 in ISO /T R22019.2019;

---Correct "ISO /T S80004-2.2017" in 3.9 in ISO /T R22019.2019 to "ISO /T S80004-2.2015";

---Correct "3.12,3.13" in ISO /T R22019.2019 to "3.10,3.11".

Please note that some content in this document may be subject to patents. The publisher of this document assumes no responsibility for identifying patents.

Introduction

Nanomaterials (NMs) are a class of chemicals that, like other chemicals, can produce a range of toxicities. Carry out toxic metabolism activities

Mechanics (also called toxicokinetics) studies are important for evaluating the safety of nanomaterials and identifying the persistence of nanomaterials in different organs (including cells).

It is of great significance to evaluate the similarities and differences between nanomaterials and powder materials of the same chemical composition (such as barrier penetration). exist

In all nanomaterial toxicokinetics studies, proper characterization of the nanomaterial dispersions or aerosols used is critical.

need.

The importance of toxicokinetic information in nanomaterial risk assessment.

Toxicokinetics describes the absorption, distribution, metabolism, and excretion (ADME) of foreign compounds in the body over time.

This situation, which relates exposure dose to in vivo dose, is a key aspect of toxicity assessment. On the one hand, nanomaterials can be used in many ways

(oral, respiratory, skin) is absorbed into the body and enters the blood or lymph circulation. Subsequent distribution in the internal organs will determine its potential target tissues and

toxicity. On the other hand, nanomaterials can directly enter the blood circulation through the intravenous route (e.g., as nanomedicines), leading to widespread differentiation in tissues.

cloth. Toxicokinetics can help to design toxicity studies and identify potential target organs, and can also provide guidance for rational implementation or timely termination.

Antitoxicity studies provide relevant information. In addition, toxicological metabolism information can provide a basic basis for the grouping and cross-comparison of nanomaterials.

Since nanoparticles have specific tissue distribution and accumulation properties, toxicokinetic information is used to perform internal concentration-based analysis.

Risk assessments may be more realistic than those based on exposure dose. Toxicokinetic study results can be used to establish toxicant

Metabolic kinetic models, especially physiologically based pharmacokinetic (PBPK) models, can be used to predict other species, tissues, and exposure routes.

Toxicity experimental data on diameter, time and dose. Since some nanoparticles can accumulate in the body, it is speculated that the impact of long-term exposure on nanoparticles

Materials are particularly important.

Why is it necessary to establish technical standards for toxicant metabolokinetics for nanomaterials?

A large amount of literature, including many national and international guidelines, has used toxicokinetic methods to study the effects of chemical substances in vivo.

The final destination of the inside. TG417 "Guidelines for Toxicokinetic Testing" of the Organization for Economic Co-operation and Development (OECD) (last updated on

2010) provides a detailed description of the evaluation of toxicokinetics of chemicals, but does not include nanomaterials. ISO 10993-16.2017

"Biological Evaluation of Medical Devices Part 16.Toxicokinetic Study Design of Degradation Products and Leachables" provides an overview of medical device extractables

Toxicokinetic studies. In addition, the European Medicines Agency's ICHS3A "Toxicokinetics Guidance Principles. Systemic Exposure in Toxicity Studies"

"Assessment of Exposure" and ICHS3B "Pharmacokinetics. Guiding Principles for Tissue Distribution Studies with Repeated Dosing" on toxicokinetic study design

and implementation provides guidance that can aid the development of new drugs.

Toxicokinetic modeling, particularly the development and application of PBPK models, is also introduced in these guidelines. For example, American food and

The Drug Administration's draft "Industry Guidance for Format and Content of PBPK Assays" provides standard content and

Format; the US Environmental Protection Agency's "Methods for Application of PBPK Models and Supporting Data in Risk Assessment" mainly involves the format used for risk assessment.

Application and evaluation of PBPK model. In.2016, the European Medicines Agency issued the Guidance Document on PBPK Modeling and Simulation Qualifications and Reporting.

"Parts"[1]. The World Health Organization published "Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment" [2].

As mentioned above, the existing OECDTG417 clearly points out that nanomaterials are different from dissolved ions, molecules and large particles, and their toxic metabolism

The kinetics are also different, so this guideline is not applicable to testing nanomaterials [3]. This point is reflected in the OECD's preliminary guidance on applicability.

It has also been confirmed in step judgment [4]. In addition, the biodistribution process of nanoparticles is not related to the soluble substances (molecules) involved in the guidance document [5].

or ions), so the PBPK model described in the document is not applicable to nanomaterials either.

Based on this, it is necessary to develop new guidelines or make specific supplements to existing guidelines based on the characteristics of nanomaterials. Toxic to nanomaterials

A review and summary of metabolic kinetic characteristics and current knowledge is

necessary to fully understand the necessity of toxicological metabolic testing of nanomaterials.

Base.

How do nanomaterials differ from dissolved ions, molecules, and large particles?

Nanomaterials are a class of substances with unique properties. Due to their granularity and small size, nanomaterials have corresponding bulk or

The different physical and chemical properties of soluble components make nanomaterials likely to have specific toxicity discussed in many reports [6-10].

Toxicokinetic analysis of nanoparticles is of great significance. Typically, smaller sized nanoparticles are

Particles will enter lymph fluid and blood circulation more quickly, and may reach all organs [11]. Furthermore, smaller size particles are

Smaller nanoparticles have wider organ distribution [12], and may also be transported across barriers such as the blood-brain barrier and placenta [13-14].

There are other significant differences between the toxicant metabolic kinetic behavior of soluble molecules or ions and nanomaterials, including the absorption of substances,

Distribution, Metabolism, Excretion (ADME). For dissolved molecules or ionic substances, the toxicant metabolism kinetics consists of 1) passive transport (including simple

diffusion and filtration) and 2) special transport (including active transport, carrier-mediated transport systems, promoted diffusion through cell membranes, enzyme metabolism,

Passive and active excretion) drive. For nanomaterials, toxicokinetics involves aggregation, condensation, protein corona formation, cellular uptake, and

Biodistribution and degradation and excretion of some nanomaterials due to phagocytosis by macrophages [15]. In addition, the surface chemistry and organization of nanoparticles

(also called protein corona) can affect the binding of biomolecules on their surface, which in turn affects the toxicant metabolism kinetics of nanoparticles. nanoparticles

Excretion is usually very limited and may bioaccumulate like other poorly metabolized molecules. Therefore, nanoparticle toxicant metabolism dynamics

Chemical testing and modeling differ significantly from soluble substances. In this regard, especially in repeated exposure and long-term toxicokinetic studies, it is necessary to

Assess the risk of accumulation and persistence of nanomaterials in organs.

Nanotechnology Nanomaterials Toxicokinetics

research elements