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Nanotechnologies — Considerations for performing toxicokinetic studies with nanomaterials

Nanotechnologies - Considérations pour réaliser des études toxico cinétiques de nanomatériaux



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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.

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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

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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.