Systematic Literature Reviews as a tool to develop Adverse Outcome Pathway landscapes in Nanotoxicology:
case study of ingested Titanium dioxide nanomaterials

Authors: Dora Rolo[1], Ricardo Assunção[1,2], Maria João Silva[1,3] and Henriqueta Louro[1,3]

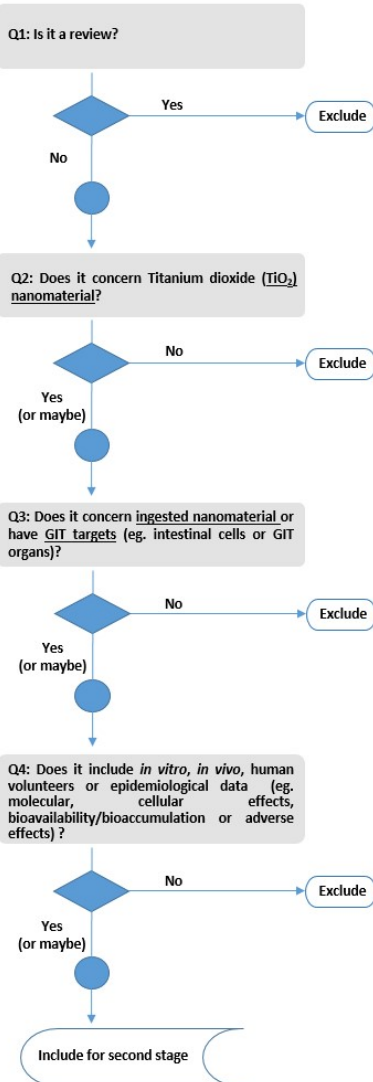[1]National Institute of Health Dr. Ricardo Jorge (INSA), Lisbon, Portugal
[2]CESAM – Centre for Environmental and Marine Studies, University of Aveiro, Aveiro, Portugal
[3]ToxOmics – Centre for Toxicogenomics and Human Health, NOVA Medical School, NOVA University, Lisbon, Portugal

Introduction

Worldwide, Titanium dioxide (TiO_2) nanomaterials are one of the most frequently applied nanomaterials as food additive, pharmaceuticals and toothpastes. Many studies addressed their potential adverse effects considering the nanomaterials primary physicochemical characteristics. However, surrounding matrix can affect their properties and consequently the secondary features may be more relevant for determining the toxicological outcome. In this regard, further research is needed. In fact, the potential of Ingested TiO_2 nanomaterials (Ing-TiO_2) to cause undesirable effects on human health is still unknown. Of major concern is their potential to induce genotoxicity that may contribute to cancer. A valuable tool in predictive nanotoxicology is the establishment of Adverse Outcome Pathways (AOPs) landscapes. However, there is a lack of methodical approaches to assess this issue. A systematic literature review (SLR), that integrates information produced on this topic and provides data for a standardized assessment of the evidence, is necessary.

Decision Tree for inclusion/exclusion criteria of publications in this study.

Q1: Is it a review?

Q2: Does it concern Titanium dioxide (TiO_2) nanomaterial?

Q3: Does it concern ingested nanomaterial or have GIT targets (eg. intestinal cells or GIT organs)?

Q4: Does it include *in vitro*, *in vivo*, human volunteers or epidemiological data (eg. molecular, cellular effects, bioavailability/bioaccumulation or adverse effects)?

Include for second stage

Objectives

The goal of this study was to conduct a SLR evaluating the genotoxicity of Ing-TiO_2, for identifying key cellular and molecular events leading to adverse health outcomes in order to guide future research needs on the assessment of potential AOPs. The present communiication presents results ofSLR stages before data extraction.

Stage I Description:

Using the advanced search string ("Titanium dioxide" OR "Titanium dioxide nanoparticle" OR nanotitanium OR "nano titanium" OR "Titanium dioxide nanomaterial" OR "TiO2 nanomaterial" OR "TiO2 nanoparticles") AND (gastrointest* OR digest* OR oral* OR ingest* OR gavage) AND (Genotoxic* OR Cancer OR Toxic* OR "adverse outcome pathway" OR Epigenetic* OR "DNA damage" OR "Biological effect" OR "Cellular effect" OR "Molecular event" OR "Key event" OR hepatic OR inflammatory OR immunity OR ROS OR "oxidative damage"), a decision tree was designed in order to select the publications to include in this study. Inclusion criteria included English Spelling, not being a review and in a publication timeframe from 2000 to 2020.

Flow diagram in systematic literature reviews

The 213 papers are being analyzed by a panel of 12 reviewers in order to extract data that will support the construction of potential AOPs, associated with Ing-TiO_2 nanomaterials and gastrointestinal effects.

It is expected that a framework of AOPs for Ing-TiO_2, that describes a sequence of causally linked events at different levels of biological organization leading to adverse health effects, may contribute to support risk assessment based on mechanistic reasoning. In addition it will support read cross and grouping of ingested nanomaterials based on common key events and potentially similar health effects