Report

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Task Force: (nano) TiO_2 safety communication

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List of abbreviations

ANSES: Agency for Food, Environmental and Occupational Health & Safety
ATP: Adaptation to Technical and scientific Progress
CARACAL: European Commission's Competent Authorities for REACH and CLP
CLP: Classification, Labelling and Packaging; (EC) No 1272/2008
ECHA: European Chemicals Agency
EFSA: European Food Safety Authority
EUON: European Observatory for Nanomaterials
GHS: Globally Harmonized System
HLEG: High-Level Group of Experts (on disinformation)
NM: Nanomaterial
NSC: NanoSafety Cluster
OECD: Organisation for Economic Cooperation and Development
RAC: Risk Assessment Committee
REACH: Registration, Evaluation, Authorisation and restriction of Chemicals
ROS: Reactive Oxygen Species
SCCS: Scientific Committee for Consumer Safety
SDS: safety data sheets
TiO_2: Titanium dioxide
TF: Task Force
UN: United Nations

The key message

1. Knowledge is the cornerstone of any decision making. The decision-makers must be provided by the necessary information and knowledge needed to make decisions.
2. The open question is which type of knowledge and other elements of data-information-knowledge-wisdom (DIKW) hierarchy are crucial for decision-making.
3. We conclude that it is a role of scientists is to transform an entity at a lower layer of the DIKW hierarchy to an entity at a higher layer to reduce information overload and support decision.

INTRODUCTION

The goal of the **(nano)TiO_2 safety communication task force** of the EU NanoSafety Cluster (NSC) was to provide scientific input to ongoing classification of titanium dioxide. The TF on TiO_2 safety communication ran from January 2018 to January 2019, and this is the summary report. The TF members communicated via mail, Skype and face to face at different scientific meetings. They collected information regarding TiO_2 classification itself and information on TiO_2 hazard potential from available scientific literature.

It turned out that there was no opportunity for intervention with the ongoing procedure during the public consultation (Figure 1). The first public consultation happened before the TF was launched. The second, exceptional public consultation was opened in 2019 and limited to "technical progress of the EU's classification and labelling (CLP) Regulation". This Commission's public consultation attracted 489 responses, which is 40 times higher than the average response rate on similar acts (https://chemicalwatch.com/82285/commission-full-steam-ahead-on-titanium-dioxide-classification-proposal ; https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2019-141469/feedback_en?size=10&page=1&p_id=352721). This shows a great interest in the topic.

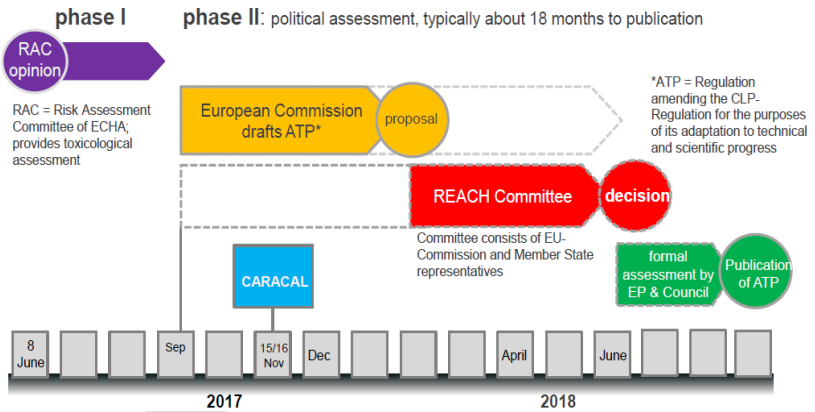

Figure 1. Phases of CLP regulation adoption.

Historic overview

- In **November 2015**, the French government Agency for Food, Environmental and Occupational Health & Safety (ANSES) proposed a dossier to support the classification of TiO_2 as a human carcinogen (**Category 1**).
- The dossier was published by the European Chemicals Agency (ECHA) on **31 May, 2016** (https://echa.europa.eu/harmonised-classification-and-labelling-consultation/-/substance-rev/13832/ter).
- After that, the first public consultation was opened for 90 days.
- **In September 2016,** ECHA's risk assessment committee (RAC) evaluated proposed harmonized classifications by applying hazard criteria adopted in the CLP regulation from the UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as a **Category 2** (Animal) Carcinogen, or a **substance suspected of causing cancer by inhalation** and not in category 1B as proposed due to insufficient evidence.
- In **January 2019**, additional a four-week public consultation as part of the 14th adaptation to technical progress of the CLP was launched.
- The decision on the classification of titanium dioxide as a hazardous substance was expected to be taken on **14 February 2019**, https://www.esma.com/news/dot-news/hsep/887-titanium-dioxide-the-classification-debate.
- In **mid 2019**, the Commission switched to the new procedure for delegated acts. The draft proposal was discussed by experts from the Member States and representatives of the European Parliament at a special CARACAL meeting on **17-18 September 2019** (but not voted).
- On **4 October 2019,** the Commission submitted its adopted act to the European Parliament and Council of Ministers who were given two months to formulate any objections to the act. If no objections were raised, the delegated act enters into force.
- On **3 December 2019**, MEPs voted 19 in favour and 46 against the objection put forward by the European Conservatives and Reformists (ECR), with four abstentions.
- The 14th ATP is expected to be published in **January 2020** and to take effect 18 months later, probably in **July 2021**

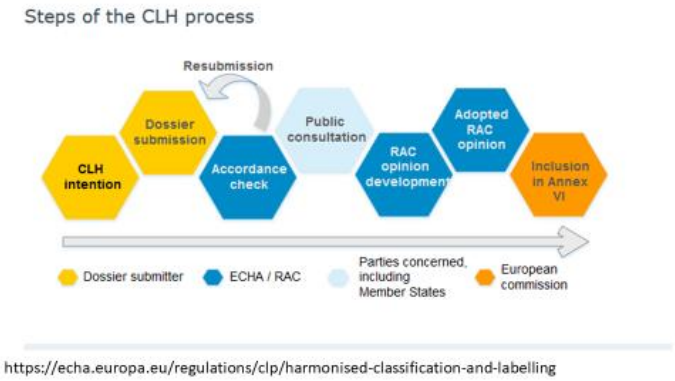

Figure 2. CLP process with details of individual steps.

Problem identification

The European Commission (EC) will be going ahead with its proposal to classify titanium dioxide (TiO_2; CAS 13463-67-7) as a **category 2** carcinogen (a **substance suspected of causing cancer by inhalation)**. The classification is reported to apply to liquids as well as powders "containing 1% or more of titanium dioxide in the form of or incorporated in particles with aerodynamic diameter ≤ 10 µm."

Titanium dioxide will be the first prominent issue the Commission has to deal with under the new rules of the "delegated acts" procedure. The new procedure strengthens the role of the Commission, which in future can classify substances without the approval of the Member States.

The Commission acknowledged that the CLP classification of TiO_2 would have unintended impacts on the circular economy and the efforts to address the issue by proposing an update to the guidance on the classification of waste (CA/23/2019). The guidance is a positive step, but it is not legally binding.

The **real problem** is that the waste and recycling issue created by the classification will not be tackled at EU level.

Additional explanation

The Commission proposal to classify titanium dioxide as a "*substance with a suspected carcinogenic effect in humans through inhalation"* (Category 2) in Annex VI CLP Regulation covers two different categories:
(1.) '**Titanium dioxide in powder form** containing 1% or more of particles with aerodynamic diameter ≤ 10 µm;' and
(2.) '**Mixtures in powder form** containing 1% or more of titanium dioxide which is in the form of or incorporated in particles with aerodynamic diameter ≤ 10 µm.' [underlined = new text in "Note 10"].
The last point has undergone various small but significant changes during the process. In contrast to the previous version it is now clear that not only
a) **titanium dioxide particles ≤ 10 micrometer** but also
b) **all particles ≤ 10 micrometer containing titanium dioxide** [*new*]
lead to a classification, if the total proportion of titanium dioxide in the powder mixture is 1% or more.

All these affected mixtures would have to be labelled with the Pictogram GHS08 and the hazard statement "***Suspected of causing cancer through inhalation***" (H351). In addition, several EU rules explicitly exclude carcinogenic substances from certain products, e.g. toys.
According to the proposal, liquid mixtures (e.g. paints, coatings etc.) in the future would have to be labelled:
"EUH211: **Hazardous respirable droplets** may be formed when sprayed. Do not breathe spray or mist."
*"EUH212: Warning! **Hazardous respirable dust** may be formed when used. Do not breathe dust*".

AIM of (nano) TiO_2 safety communication TF

A task force **"(nano) TiO_2 safety communication"** was proposed at the NanoSafetyCluster (NSC) meeting of October 2017 and approved in December 2017. It was launched in January 2018 (https://www.nanosafetycluster.eu/task-forces/active-task-forces/proposed-task-force-on-tio2.html).

The motivation for the task force was **to contribute** the cumulative scientific knowledge from the NSC projects to the TiO_2 CLP classification procedure, which aims to increase the level of protection of human health and the environment.

The task force (TF) for TiO_2 safety communication set out to **address** the issue of risk communication regarding TiO_2 CLP from a scientific perspective and contribute reflection on TiO2 safety communication.

REPORT

Summary of recent studies on inhalation exposure of laboratory test organisms to TiO_2 (Supplement I)

CLP regulation as a hazard communication tool

CLP regulation is an approach to communicate hazard information across the value chain and along the product life cycle. However, the **TF identified** three types of shortcoming in the CLP as a public communication tool. First of all, CLP classification does not facilitate risk comparisons: substances that show genotoxicity only at very high doses have the same classification as substances that show genotoxicity at very low doses. Secondly, the classification embraces different properties of hazard without making necessary distinctions: for example, in the case of paints, the potential risk of inhalation results from sanding down the paint, or from demolition of the infrastructure but it is not necessarily substance (paint) specific and should be regulated differently. Thirdly, in the case of nanomaterial (NM) regulation and safety communication, different European agencies appear to treat similar NMs differently. For example: ECHA's Scientific Committee on Consumer Safety (SCCS) prohibits use of anatase TiO_2 in sunscreen formulations, while the European Food Safety Authority (EFSA) accepts it as a food additive. ECHA is questioning the industry's use of read-across for different nanoforms. The concept of forms (nanoforms) will appear in updated REACH (and likely CLP) regulations in 2020, with the onus on industry to demonstrate what constitutes a distinct form (e.g. size, shape, surface coating; https://echa.europa.eu/documents/10162/2792271/mb_57_2017_echa_strategy_nanoforms_en.pdf/f913484f-9a21-02bc-d386-8cb68d0027a4).

It is the opinion of the TF that the apparent inconsistencies or divergences may hamper the effectiveness of safety communication with the general public about TiO_2.

Scientific knowledge for evidence - based decision making

Study and Data quality

According to REACH, "*For all available data, an assessment must be made of the adequacy of the available information for arriving at conclusions on hazard assessment, i.e. C&L, PBT/vPvB assessment, and identification of (a) dose descriptor(s) enabling the derivation of (a) DNEL(s) and (a) PNEC(s). DNEL(s) and PNEC(s) are subsequently to be used in the risk characterisation*."

REACH uses the Klimisch score to assess the reliability of individual studies which evaluates reliability, relevance and adequacy (Guidance on information requirements and chemical safety assessment Chapter R.4: Evaluation of available information https://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf). Studies following high scientific standards (scientific reports and academic literature) are not scored as relevant for regulatory purposes unless they are GLP-compliant following internationally accepted specifications for the testing of substances decided on by the OECD or other similar international bodies. There are many initiatives to translate non-standardised tests form non GLP laboratories as equivalent to standardised tests and to integrate the respective scientific information into the regulatory process. The approaches elaborated in different projects (such as the **GUIDEnano** approach including a modified Klimisch scoring, or the **nanoCRED** evaluation criteria, etc.). One aim of new EC

risk governance project **NanoRIGO** is to provide criteria catalogues to support evaluation of data relevance and reliability from non-standardised tests and non GLP laboratories to be used for regulatory decision making.

The ongoing activates within new H2020 risk governance projects will help the decision makers to evaluate the study guilty (fit-for-purpose) in the future.

The **TF members have identified** that **amount of** available scientific publications on the issue, and those considered by the RAC (which was originally prepared back in 2015/2016) are highly **disproportional**.

The RAC recommendation to the European Commission on how to classify TiO2 under REACH was based on four animal studies. This could be explained as follows:

- Only standardised tests from GLP laboratories with Klimisch scores of 1 or 2 were used for regularly decision making (more detailed explanation in the text below)
- the *ECHA Annex I: 3.6.2.2.1.* which stands for classification of a substance as a carcinogen was not taken into consideration . *Guidance on the Application of the CLP Criteria Version 5.0 – July 2017; Annex I: 3.6.2.2.1.* states that *"Classification of a substance as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer - reviewed published studies and additional acceptable data." Page 378.*

Science communication for informed and responsible decision making

The **TF identified** that **science communication** lags behind the scientific knowledge. This gap may hinder the decision process.

For example, the EU's ongoing regulatory classification and labelling process seeks to harmonise the classification of substances on the basis of their hazard properties and provide labels that allow the safe handling and use of the substances. This process only looks at the **inherent, intrinsic properties of the substance**, based on available scientific data, to establish hazard classifications. An intrinsic property is a property of a system or of a material itself. It is independent of how much of the material is present and is independent of the form of the material, e.g., one large piece or a collection of small particles (Guidance on the Application of the CLP Criteria Version 5.0 –July 2017). Already *"RAC acknowledges that the mode of action for the rat lung carcinogenicity in rats can not be considered "intrinsic toxicity" in a classical sense: the deposited particles, but not solutes of TiO_2 molecules can be assumed to be responsible for the observed toxicity."* In line with this, alternative regulations should be found and discussed (https://chemicalwatch.com/74294/ngos-urge-eu-states-to-reject-changed-titanium-dioxide-classification-proposal).

As European nanosafety structures become increasingly formalised (cf. the European Observatory for Nanomaterials EUON, the network of national nanosafety centres as currently supported by the EU project EC4SafeNano, and research infrastructures such as NanoCommons and the new nano-risk governance council established as a result of new H2020 risk governance projects), and a range of international collaborators, will be placed to support fact-checking of high profile or controversial publications and reports related to nanosafety.

In the future, *convergence and networking,* pragmatic consensus-based minimum standards and communication technique could enable translating scientific findings into society. The core issue is in explaining facts and findings to prevent from being misunderstood.

Conclusion and Future challenges

The overall aim of the NSC as scientific community would be to establish **opportunities** for dialogue, discussion and learning, and streamline procedures by which harmonised regulations could be developed, designed and strengthened as necessary to respond to the risks of nanotechnology. NSC can offer opportunities to discuss how regulatory procedures can reflect current and developing scientific knowledge and to communicate as honestly as possible about what we know and what we do not know.

To understand and document the current state of the science on lung particle overload, a workshop was held in Edinburgh Scotland (April 2019; organised by Kevin E. Driscoll and Paul J. A. Borm, to solicit opinions from an Expert Panel on the definition of PSLT; lung particle overload; and, the human relevance of the rat lung response. The Expert Panel on PSLT provided important guidance for conducting and interpreting PSLT inhalation toxicology studies. A recent relevant publication by Bos et al is in press (Pulmonary toxicity in rats following inhalation exposure to poorly soluble 1 particles: the issue of impaired clearance and the relevance for human health 2 hazard and risk assessment).

TF members suggest this paper and the expert opinion from the PSLT workshop to be taken as relevant scientific document when communicating PSLT inhalation toxicity.

Given the ongoing discussion on other PSLT classification and safety, it would be important to re-activate the public debate including experts and stakeholders. There is even a lack of a clear definition of PSLTs. An open discussion would serve to formally document where scientific consensus and differences exist. This could form the basis for the **design of future safety** assessments and decision.

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