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CLP application to nanomaterials: a specific aspect

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Summary. This paper aims at describing some relevant aspects related to the classification, labelling and packaging of nanomaterials. Concerns have been raised about potential adverse effects to humans or the environment as result of impacts of nanomaterials. The new Regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) does not contain any specific definition or provision related to nanomaterials nevertheless they are covered by the definition of substance set in the Regulation. It is recognized that different particle sizes or forms of the same substance can have different classification. Thus, if substances are placed on the market both at nanoscale and as bulk, a separate classification and labelling may be required if the available data on the intrinsic properties indicate a difference in hazard class between the two forms. CLP Regulation requires the manufacturer or importer to ensure that the information used to classify relates to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used. Moreover, CLP demands testing relating to physical hazards to be performed if such information is missing or not adequate to conclude on classification. Further developments of the CLP guidance documents and implementation tools are needed in order to cover nanomaterials more specifically.

Key words: nanomaterial, classification, labelling, substance.

Riassunto *(Applicazione del regolamento CLP ai nanomateriali: aspetti specifici)*. Lo scopo di questo lavoro è descrivere gli aspetti rilevanti connessi alla classificazione, all'etichettatura e all'imballaggio dei nanomateriali. L'impatto dei nanomateriali ha suscitato preoccupazioni legate agli effetti potenzialmente negativi per la salute umana e per l'ambiente. Il nuovo Regolamento CE 1272/2008 sulla classificazione, etichettatura e imballaggio di sostanze e miscele (CLP) non contiene definizioni specifiche o provvedimenti espliciti sui nanomateriali, tuttavia essi ricadono nella definizione di sostanza prevista dal Regolamento. È stabilito che forme e dimensioni diverse di una stessa sostanza possano avere classificazioni differenti. Per le sostanze immesse sul mercato sia in nanoscala che in forma *bulk* sono richieste classificazione ed etichettatura diversificate quando i dati disponibili sulle proprietà intrinseche indicano che esistono differenze nelle classe di pericolo. Il Regolamento CLP impone al fabbricante o all'importatore di assicurare che le informazioni usate per la classificazione si riferiscano allo stato fisico e alla forma con i quali la sostanza è immessa sul mercato ed è ragionevole aspettarsi venga utilizzata. Inoltre, il CLP richiede che vengano effettuati i test relativi al pericolo fisico qualora le informazioni indispensabili per la classificazione risultino inadeguate o mancanti. Successivi sviluppi di guide tecniche e strumenti utili per l'implementazione del CLP sono necessari per garantire ai nanomateriali un quadro legislativo sempre più specifico.

Parole chiave: nanomateriale, classificazione, etichettatura, sostanza.

INTRODUCTION

The new classification, labelling and packaging (CLP) Regulation [1] provides the general framework for the classification, labelling and packaging of chemicals implementing the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) [2]. Nanomaterials are not mentioned in the GHS mainly because knowledge is lacking on the relevance of available test methods for nanomaterials and whenever there is any reason to believe new test methods are required very little is known about how these methods should be designed [3].

In the light of the complexity of nanosciences and nanotechnologies [4, 5] and the wide variety of potential applications, a very broad approach is needed. The possible scientific and economic potential is definitely considered extremely high [6].

Different kinds of nanomaterials have a widespread use in common household items, from sports gear and sunscreens to socks and dresses, from beds and detergents to mobile phones and electronic devices. The characteristics of materials, particularly their colour, strength, conductivity and reactivity, change substantially when their atoms and mol-

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ecules are manipulated. Innovation can bring benefits, but possible risks too. Most nanomaterials are probably perfectly safe for the general public, particularly in solid form, but there is some uncertainty about health risks if, for instance, toxic nanoparticles enter the body through the skin or are inhaled [7], and about environmental risks when nanoparticles are released into soil and water systems.

At present, the debates underway in the European countries and public and private institutions responsible for managing health and environmental risks recognise on one hand the advantages of nanothecnology based innovations and on the other hand the lack of knowledge on risks related to exposure of humans and environment to nanomaterials.

Due to the limited information and resources the regulators are now facing the challenge of adapting an old regulatory framework to a rapidly changing technology.

One of the most recent work on regulatory aspects of nanomaterials in REACH (registration, evaluation, authorization and restriction of chemicals) [8], is being carried out in the framework of Competent Authorities subgroup on nanomaterials, where issues such as substance identification of nanomaterials, information requirements on intrinsic properties (including testing strategies), exposure assessment (including exposure scenarios, evaluation of risk management and mitigation measures and exposure estimation), as well as hazard and risk characterization for chemicals safety assessment are being discussed among Europe Member States experts, industries, NGOs (non-governmental organizations) and Commission representatives. The outcomes of these debates serve as basis for discussions for CARACAL (Competent Authorities for REACH and CLP) where policy decisions on REACH and CLP implementation are being made. A further outcome of those discussions will be the development of guidance documents and implementation tools designed to cover nanomaterials more specifically.

BACKGROUND

What is a nanomaterial and what changes occur at nanoscale

Nanomaterials have extremely small size as their defining characteristic, although there is not yet an agreed international definition for the term "nanomaterial".

Nanomaterials are understood to be either so-called "nano-objects" or "nanostructured materials" according to the UNI CEN ISO/TS 27687:2010 [9].

The current mostly used working definition of nanomaterials is "a material having at least one dimension equal to 100 nanometres or less". To put nanomaterials into perspective, up to 10 000 could fit across a human hair. Nanomaterials can be at nanoscale in one dimension (*e.g.* surface films), two dimensions (*e.g.* strands or fibres), or three dimensions (*e.g.* particles). They can exist in single, fused, aggregated or agglomerated forms with spherical, tubular, and irregular shapes. Common types of nanomaterials include nanotubes, dendrimers, quantum dots and fullerenes.

The 100 nm size boundary used in these definitions, however, only loosely refers to the nanoscale around which the properties of materials are likely to change significantly from conventional equivalents.

Nanomaterials having specific properties may require a different classification compared to the bulk material, also when the nanoform is derived from a bulk substance.

How can a nanomaterial be produced? The manipulation of matter at the nanoscale, can employ either a *top-down* or a *bottom-up* technique. Most nanomaterial manufacturing processes are top-down, which means the material is produced in large primary particles and broken into smaller pieces by grinding or down-cut milling. Depending on the process and the applied forces the final content of particles at nanosize can vary. Any top-down process is likely to result in a certain fraction of nano-objects and their aggregates and agglomerates and it could include a portion of not intentionally produced by-product at nanoscale. On the other hand, bottom-up nanomaterial manufacturing processes are those in which atoms are intentionally controlled during the manufacturing operation to result in nano-objects and their aggregates and/or agglomerates. Both top-down and bottom-up approaches produce materials designed at the nanoscale level to take advantage of their small size and innovative properties which are commonly not identified in their bulk counterparts. Knowledge of the manufacturing process can help to identify and characterize the derived nanomaterial.

The two crucial causes why materials at the nanoscale can display dissimilar characteristics are the resulting amplified specific surface area and new quantum effects. Nanomaterials have a much greater surface area to volume ratio than their bulk forms, which can lead to greater chemical reactivity and influence their strength. Also at the nanoscale, quantum effects can become much more important in regulating the materials properties and characteristics, leading to novel optical, electrical and magnetic behaviors.

The same properties that distinguish nanomaterials may cause possibly human health and environmental hazards. By way of example, the increased surface reactivity is a desired property for many intended applications of nanomaterials, such as catalysts, however, this characteristic can lead to a greater toxicity for cells and living organisms. The physicochemical properties of nanomaterials are determined by the chemical composition, surface structure, small size and associated increase in surface to volume ratio, solubility, shape and aggregation. The influences of physicochemical properties on the toxicological and eco-toxicological profile of nanomaterials are not yet fully understood. Changes

in physicochemical properties can also increase the potential for some nanomaterials to exhibit fire, explosion hazards or catalytic activity. Limited data from preliminary studies in vertebrates have shown that some nanomaterials can accumulate in the lungs and translocate to the blood, cross the blood-brain barrier and produce inflammatory responses [10]. Moreover, direct interaction of nanoparticles with nucleic acids have been shown by *in vitro* studies. Parallels have also been drawn with the incidentally produced nanoparticles (such as combustion products) and their associated adverse effects on human health. Nevertheless, to date there are no confirmed reports on adverse effects to humans or the environment as a result of exposure to engineered nanomaterials.

Nanomaterials definition in the regulatory context

According to REACH and CLP Regulations, substance means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition. REACH and CLP deal with substances, in whatever size, shape or physical state. Therefore this definition includes all physical states, crystal structures, and dimensions of particles of the substance in powder form or in suspension, even if the particle size would go beyond the nanoscale to individual atoms or molecules. ECHA stated on 3 December 2007 at the European NanOSH Conference in Helsinki that REACH treats both the bulk material and the nano-sized material, as the same substance. The Agency added that this, however, does not prevent who is responsible of placing on the market of a chemical from identifying its dangerous properties depending on its size and classify the different types accordingly.

A definition is required in order to provide increased clarity and consistency with respect to the term nanomaterial for use in Regulations laying down provisions on substance. As REACH and CLP are both based on the substance concept, it will be essential for their application to nanomaterials to set up a working definition of the term nanomaterial.

In order to assemble a science-based definition of nanomaterials, the services of the European Commission need clarification on size ranges, physical-chemical properties, relevant thresholds and most appropriate metrics to express such thresholds. The recent draft Recommendation on the definition of the term nanomaterial is based on the work done by the Commission's Joint Research Centre and the input of the Scientific Committee for Emerging or Newly Identified Health Risks (SCENIHR) [11].

The aim of the recommendation is to determine when a material should be considered as a nanomaterial, in particular for legislative and policy purposes in Europe. It should cover all nanomaterials, whether they are of natural, incidental or manufactured origin. In the current draft definition the three following criteria are considered. A material can be considered a nanomaterial if meets at least on of these criteria:

- consists of particles, with one or more external dimensions in the size range 1 nm - 100 nm for more than 1% of their number size distribution;
- has internal or surface structures in one or more dimensions in the size range 1 nm– 100 nm;
- has a specific surface area by volume greater than 60 m^2/cm^3, excluding materials consisting of particles with a size lower than 1 nm.

The draft recommendation came through the public consultation phase and is now under revision in light of the received comments.

CLASSIFICATION AND LABELLING OF NANOMATERIALS

General obligations

According to CLP Regulation, who is responsible of placing on the market of substances and mixtures are obliged to label and package them. Moreover, hazardous substances have to be notified to ECHA, with the purpose of establishing a CLP Inventory which will make the information specified in REACH Article 119(1) and (2) publicly available. According to REACH transitional provisions related to tonnage band and hazard of manufactured or imported substances, a registration dossier must be submitted to ECHA, which includes a classification and labelling section. Independent of volume of manufacture or import, the notifications to the CLP Inventory will provide ECHA with information on hazardous substances and their forms, including nanomaterials, on the market. The information gathered through the CLP Inventory has to be assessed carefully together with other relevant information on nanomaterials, especially related to the definition of nanomaterial, on-going discussion on substance identity of some nanomaterials and information on nanomaterial properties.

The classification and labelling of nanomaterials should follow the rules set out in CLP. It is worth recalling that CLP Article 9(5) states "When evaluating the available information for the purpose of classification, the manufacturers, importers and downstream users shall consider the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used". That is why, the hazard classification should be based on available data that relate to the intrinsic properties of the substance or mixture placed on the market (CLP Article 5(1), 6(1) and 8(6)). Manufacturers, importers and downstream users shall take all reasonable steps available to them to make themselves aware of new scientific or technical information that may affect the classification of the substances or mixtures they place

on the market. When a manufacturer, importer or downstream user becomes aware of such information which he considers to be adequate and reliable, he shall without undue delay carry out a new evaluation and conduct additional testing accordingly.

Ultimately, information on classification and labelling of substances and mixtures as well as instructions for a safe handling have to be communicated to the supply chain via a Safety Data Sheet (SDS). Since many engineered nanomaterials are not currently classifiable as hazardous, it will be no mandatory to prepare an SDS or include information on label. Anyway, SDS should reflect current state of knowledge on chemical safety thus it is extremely important to update it as soon as new information about hazard profile of a nanomaterial is being generated.

Testing nanomaterials for classification purpose

Substances may exist in different forms due to changes in properties such as crystal structure, particle size, homogeneity and viscosity. Other than form, physical state may change depending on agglomeration state, surface treatment, moisture content, residual solvent, activation or stabilisation. It is important to test a sample for classification purpose which is representative for the substance or mixture as it is placed on the market and being aware of changes in its form or physical state carry out evaluation to identify any effects on the classification. If nanomaterials are manufactured/imported both at nanoscale and as bulk a separate classification and labelling may be required if the intrinsic properties at nanoscale lead to a different classification from the one at the bulk. Nickel and nickel powder (particle diameter < 1 mm) is a good example of how a substance with different particle sizes or forms can have different classifications.

The lack of knowledge on the peculiarities of the new nanotechnology applications, in terms of the substance identification and hazard profile, makes very difficult to establish standardized and appropriate criteria in order to evaluate the toxicological properties of nanomaterials (SCENIHR 2006 [12] and 2007 [13]). The Organisation for Economic Co-operation and Development (OECD) and the International Organization for Standardization (ISO) recognise the need for the physical-chemical properties of nanoparticles to be aimed at risk assessment of nanomaterials. The principal physical specifications concerning nanoparticle evaluation are: the size, shape, specific surface area, aspect ratio, agglomeration/aggregation state, size distribution, surface morphology/topography, structure including crystallinity and defect structure and solubility. The most important chemical specifications are: structural formula/molecular formula, composition (including degree of purity, known impurities or additives), phase identity, surface chemistry, charge tension, reactive sites, physical structure, photocatalytic properties, zeta potential and hydrophilicity/lipophilicity (SCENIHR, 2009 [4]).

Furthermore, the SCENIHR affirmed that a general rule does not exist regarding the hazard enhancement of a substance when scaling down in size. Thus the hazard characterisation of nanoforms should be achieved with the case by-case approach.

Another important issue, which has been raised and is already under discussion within the OECD Working Party on Manufactured Nanomaterials (WPMN), is the adequacy of current test guidelines to deliver results for hazard classification of nanomaterials. To date the conclusion is that "Many of the OECD Test Guidelines are applicable, with conditions in some cases, while some are inadequate for testing nanomaterials as measuring, dosing, delivery and tracking nanomaterials are not reliably accomplished at this stage Therefore, the review of OECD Test Guidelines reinforced the need for a guidance document(s) for sample preparation and dosimetry". Accordingly, the modified test guidelines can be used to provide information for the hazard assessment.

With regards to nanomaterials, due to the impact of the increased surface area on physicochemical properties, if information only exists for bulk materials it should be assessed if this information is also applicable to nanomaterials. Information derived when fulfilling the registration requirements in REACH, according to the test methods Regulation (440/2008/EC) [14], will not be sufficient to determine all physical hazards in accordance with CLP. Any evaluation of particulates in the context of CLP Regulation should be conducted in accordance with the principle of using the worst case scenario where the finest relevant fraction of the form and physical states as placed on the market, should be used when testing for physicochemical hazards.

The accordance with the test method Regulation [14] applying the OECD test guidelines and with the Regulation on the good laboratory practice (GLP) is essential for the hazard assessment of substances. Taking into account the evolving situation in testing methods and guidelines as well as scientific opinions from the EU Scientific Committees, the preliminary review of the OECD-WPMN concluded that current test guidelines for human health endpoints, together with the preliminary guidance notes on sample preparation and dosimetry, are considered applicable for nanomaterials. However, additional consideration needs to be given to the physicochemical characteristics of the material tested, including such characteristics in the actual dosing solution. In some cases there will be a need for further modification to the OECD guidelines. This applies particularly to studies using the inhalation route and to toxicokinetics (ADME) studies. There are, however, difficulties with regard to test guidelines for environmental endpoints.

Classification and labelling section of REACH registration dossier

When nanoforms of a known and already registered substance in bulk are commercialized, the registration dossier required by REACH Regulation has to be updated including different classification and labelling of the nanoform [15].

Registrants as intended by REACH Regulation are envisaged to use the following approaches in the classification and labelling of nanomaterials:

- the data sharing within the substance information exchange forum (SIEF) should cover all relevant information including at least sizes, forms and morphologies;
- to determine whether changes in the substance form influence considerably the hazardous properties;
- to evaluate all available information on nanomaterials in the hazard assessment;
- to pay special attention to the appropriateness of the sample preparation and dosimetry used in the testing of nanomaterials;
- classification should be done on a case-by-case basis;
- on the basis of the classification in accordance with CLP, nanomaterials should also be labelled and packaged accordingly.

When approaching a registration dossier the first issue to be solved in case of a nanomaterial appears to be the substance identification. The *Guidance for identification and naming of substances under REACH* [16] recognises that some substances which can be identified by their chemical composition need to be further specified by additional identifiers to get their own substance identification. To give an example, nanomaterials are often surface treated. In fact, surface modifications are relevant for their identification. A physical bonding (*e.g.* van der Waals links) between the nanoparticle and the surface treating agent could be considered as a mixture of two substances. In this case, the two substances would be registered on their own. A chemical bonding instead could be considered as another substance than the untreated particle.

For the identification of nanomaterials two approaches are discussed: one approach is to consider nanomaterials as "substances of defined chemical composition and other main identifiers". There is consensus that the key identifier/characteriser for nanomaterials is the size. Other potential identifiers/characteriser, *e.g.* surface area or optical activity, are linked to size. Primary particle size (and size distribution) and aspect ratio were considered as most important additional identifiers/characterisers. Nature and properties of coating/functional groups/surface chemistry could be an additional identifier/characteriser, (binding) forces/energy between nanoparticle and coating or functional group should be considered. Furthermore, stability/agglomeration/aggregation could be taken into account for the identification/characterisation of nanomaterials. The other approach is to consider nanomaterials as UVCB substances (substances of unknown or variable composition, complex reaction products or biological materials) due to the variability of the additional identifiers, *e.g.* size, chemical composition and surface treatment. Grouping nanomaterials of different size as a UVCB substance could follow the approach for "substances with variations in carbon chain length". The UVCB approach was considered to be more flexible allowing capturing the variability of identifiers values.

IUCLID (International Uniform Chemical Information Database) is a software application to store and exchange data on intrinsic and hazard properties of chemical substances within REACH and CLP context. In particular, the preparation of a IUCLID dossier for nanomaterials is in principle no different from the preparation of a dossier for any other substance with the exception that internationally agreed naming and identification conventions are not yet available for nanomaterials. This can potentially create issues with consistency in the identification information included in the dossier. For cases where the registrant has concluded that the nanomaterial is a nanoform of a substance, it is suggested to include information on the nanoform in the dossier analogously to any other composition of a substance.

There are two new fields in IUCLID version 5.2 [17] which enables the information "nanomaterial" to be included in the dossier. This version has been used for the first REACH registration phase and

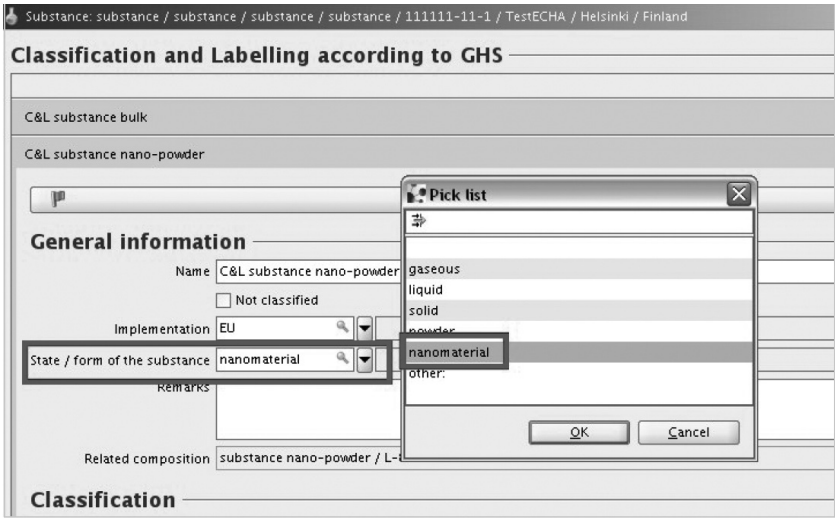

Fig. 1 | *Section 2.1 of the International Uniform Chemical Information Database (IUCLID) dossier in which the form of the substance picklist includes "nanomaterial" [17].*

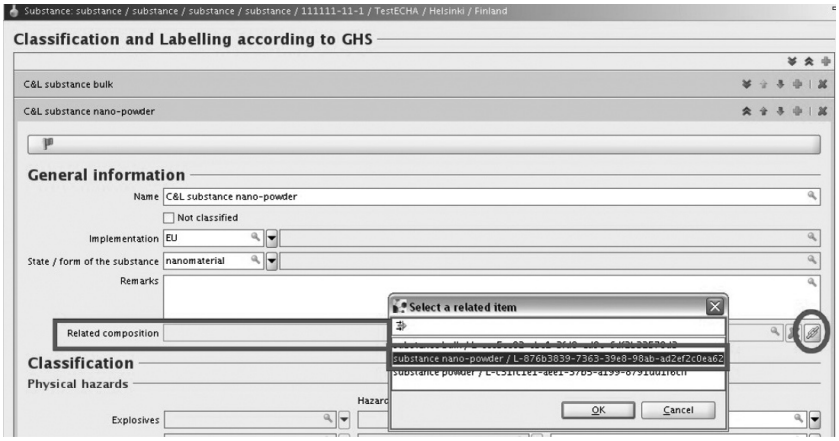

Fig. 2 | *Classification and labelling can be linked to a specific composition available in section 1.2 through the "related composition" field [17].*

for CLP notification. The first new field is in section 2.1 "Classification and labelling according to GHS" where nanomaterial can be selected as the "form of the substance" and the second is the addition of nanomaterial in the list of options for the form of a substance in section 4.1 "Appearance/physical state/colour/" *(Figure 1* and *2)*.

CONCLUSIONS

Majority of nanomaterials currently on the market seems to be produced together with the respective bulk substance. Therefore they are covered by the CLP and REACH obligations. Although there are currently no provisions in EU legislation that refer explicitly to nanomaterials, legislation on chemicals covers in principle the potential health, safety and environmental risks in relation to nanomaterials.

However, since the REACH and CLP Regulations are not designed for nanomaterials, the chemical legal framework needs to be examined and further developed with a view to guarantee a powerful level of protection for human health and environment. To put this into effect, the handling of nanomaterials should be dealt with the REACH revision foreseen in 2012 and the CLP one accordingly. The adequacy of available information is one of the key studies which may provide inputs to the Commission services in the review of both legislations.

It is, for example, essential that criteria which are directly linked to the outcome of the test methods are applicable to nanomaterials. The CLP Regulation has to be modified as regards thresholds applied as soon as new information on nanomaterials becomes available.

The considerable quantity of CLP notifications and REACH registrations submitted to ECHA in 2010 will lend a chance to evaluate in 2011 the accessible information on nanomaterials currently on the market. The CLP notifications provide ECHA, independently on volume of manufacture or import, with information on hazardous substances and their forms, including different nanomaterials. Both Regulations also have an obligation for updates in case of changes in conditions. Accordingly the part provided to ECHA on REACH and CLP will make an important contribution to the overall information. The Commission and the EU Agencies have reviewed and will continue to evaluate the applicability and appropriateness of documents supporting CLP Regulation implementation (*e.g.* technical guidance documents) with the aim of considering the peculiar and distinctive properties of existing and future nanomaterials.

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Conflict of interest statement

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