The ten decrees of nanomaterials regulations

The new revisions of the Annexes of the European Union's chemical legislation with regards to nanomaterials will provide more structure and clarity, but they will also force manufacturers, importers and downstream users to put substantial effort into understanding the details of what should and should not be done.

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In April 2018, European member states approved the European Commission's draft regulation revising the Annexes of the European Union's chemical legislation with regard to nanomaterials[1,2]. The chemical legislation currently includes 17 Annexes that specify many of the technical and scientific details of the legislation and the criteria for when, how and what different actors such as manufacturers, importers, downstream users and regulatory authorities have to do — and not do — with regard to registration and chemical safety assessment. Hence, the Annexes play a significant role in the practical implementation of the legal prerequisites outlined in the main legal text. The draft regulation was released for public consultation in the autumn of 2017 and has now been adopted by the European Commission after a three-month scrutiny review by the European Parliament and Council[3]. The Annex revisions, which aim to clarify registration duties for nanomaterials, come after years of discussion between the European Commission, EU member states and other stakeholders.

In this Comment, we introduce and discuss the new obligations that manufacturers, importers and downstream users "shall" comply with before this regulation applies from 1 January 2020.

Thou shalt register

In essence, we summarize the new Annex revisions into ten decrees aiming at making manufacturers, importers and downstream users register 'nanoforms' and demonstrate safety of all their uses (see Table 1). Under the EU chemical legislation, manufacturers and importers have to register their substances if produced in quantities of 1 tonne or more per year. According to the new regulation, specific minimum characterization information, such as number-based particle number size distribution, shall be provided by the registrant for nanoforms, as these characteristics may influence their (eco)toxicological profile and environmental exposure.

Nanoforms are defined as a form of a natural or manufactured substance containing particles, in an unbound state or as an aggregate or agglomerate, where for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm (ref.[2]). The information provided by the registrant may be applicable to an individual nanoform or to a set of similar nanoforms, and grouping of nanoforms is possible if justification is provided. Notably, molecular structural similarities alone cannot serve as a justification for grouping.

For general registration purposes, the revised Annexes require that information on manufacture and use provided in the registration for regular substances shall also apply to nanoforms or sets of similar nanoforms. Such information includes tonnage used, concentration range used, quantities in articles, human and environmental exposure and waste quantities and composition[2]. When registrants of nanoforms submit joint registration dossiers, they shall justify why information provided is relevant for nanoforms, or they may submit relevant information separately[2].

Thou shalt demonstrate safety

The number of decrees and use of the word "shall" is no more outspoken in the revised Annexes than in sections related to the Chemical Safety Report that has to be provided for substances manufactured or imported in a quantity of 10 tonnes or more per year. According to the new Annexes, the Chemical Safety Report shall first specify whether and which different nanoforms have been characterized as part of the registration, and whether they are covered by the Chemical Safety Assessment. Interestingly, this also applies to producers and importers of articles that are required to prepare a Chemical Safety Assessment as part of their registration[2]. Second, registrants shall describe how information is compiled, adequately document control of risks associated with the uses of their nanoforms and ensure that justifications and conclusions are relevant to these nanoforms along the life-cycle of the substance.

As a general requirement, the nanoform tested shall be appropriately characterized and test conditions documented to allow for adequate assessment of the relevance of any physicochemical, toxicological and ecotoxicological information provided for the different nanoforms[2]. In case the nanoforms of a substance fulfil the criteria for dangerous or hazardous substances, an exposure assessment and risk characterization shall be completed using an appropriate metric, and preferably a multiple-metric presentation of the results shall be considered. It is furthermore repetitively mentioned as a general requirement with regard to classification and labelling that registrants shall indicate and justify actions or decisions taken if information is inadequate to classify a substance and nanoforms thereof as belonging to a particular hazard class or category[2].

When it comes to fulfilling specific information requirements as part of the Chemical Safety Assessment, the revised Annex entails a number of very specific decrees. For instance, for nanoforms that are not soluble nor have high dissolution rate, further degradation tests shall consider morphological transformation, for example, irreversible changes in particle size, shape, surface properties, loss of coating, chemical transformation and other abiotic degradation[1,2]. A range of studies do not need to be conducted depending on the specific circumstances; for example, dustiness does not need to be reported if exposure to a granular form of the substance during its life-cycle can be excluded[2]. It is important that registrants note that high insolubility in water cannot serve as a justification for waiving of a number of information requirements related to the environment, for example, short-term toxicity testing on invertebrates and growth inhibition studies of aquatic plants.

In some aspects, the Annex revisions are very inclusive. In the assessment of persistency, bioaccumulation and toxicity,

Table 1 | The ten decrees of the new Annexes

Decree	Specific information to be provided
Thou shalt register nanoforms and provide information on characteristics that may influence (eco)toxicity and environmental exposure.	Names or other identifiers of the nanoforms or sets of similar nanoforms of the substance as part of the substance identification. Number-based particle number size distribution, surface functionalization or treatment, shape and aspect ratio, specific surface area by volume and/or by mass.
Thou shalt not use molecular structural similarities alone as a justification for grouping different nanoforms.	Characteristics of different nanoforms within a set in the ranges of values clearly defining the boundaries of the set. Justification for why the sets are appropriate and why variation within the boundaries do not affect the hazard-, exposure- and risk-assessment of the individual nanoforms within the set.
Thou shalt justify why safety information provided is relevant for all registered nanoforms.	Adequate justification for each information requirement describing when and how information on one nanoform is used to demonstrate safety of other forms.
Thou shall document safety for all registered nanoforms along the life-cycle.	Demonstration of safety of manufacture, use and exposure to different nanoforms separately considering all stages of the life-cycle of the substance. Consideration of whether specific risk assessment and risk management measures are required.
Thou shalt provide information of test conditions and nanoforms tested.	Documented test conditions and scientific justification for the relevance and adequacy of the utilized test material. Justification of information obtained from means other than testing for the different nanoforms, including a description of the range of the characteristics of the nanoforms to which the evidence can be applied.
Thou shalt fulfil specific ecotoxicity-related test requirements for different nanoforms depending on their dissolution and solubility.	Assessment of potential confounding effect of dispersion when determining water solubility and partition coefficient n-octanol/water. Consideration of long-term aquatic toxicity studies instead of short-term studies if the substance is poorly water soluble or for nanoforms with a low dissolution rate in relevant test media.
Thou shalt fulfil specific toxicity related test requirements for different nanoforms depending on their nature and likely route of exposure.	Acute toxicity study for the oral route or the inhalation route and at least one other route for substances manufactured or imported in 10 tonnes or more per year. Consideration of toxicokinetics, including recovery period and, where relevant, lung clearance in the short-term repeated dose toxicity study and the sub-chronic toxicity study.
Thou shalt consider multiple metric reporting of results for nanoforms that are dangerous or hazardous.	Complete exposure assessment and risk characterization preferably considering a multiple metric presentation of the results. Justification included in the Chemical Safety Report and summarized in the Safety Data Sheet.
Thou shalt provide justification for waiving information requirements.	Adequate justification for relevance of physicochemical property (for example, dissolution rate, dispersion stability) as reason for waiving tests on bioaccumulation in aquatic species and adsorption/desorption.
Thou shalt propose further testing and/or comply with ECHA testing requirements.	Testing proposals regarding short-term repeated dose toxicity studies, studies of sub-chronic toxicity and long-term repeated dose toxicity studies and toxicokinetic studies in specific situations.

registrants have to consider all stages of the life-cycle when making quantitative and qualitative estimates of the dose/concentration of the substance to which humans and the environment are or may be exposed. This includes estimating environmental distribution and fate and performing a characterization of possible degradation, transformation, reaction processes, dissolution rate, particle aggregation and agglomeration and changes in particle surface chemistry.

The Annexes also hold several decrees with respect to further testing. For instance, further studies shall be proposed by the registrant or may be required by the European Chemicals Agency (ECHA) for toxicokinetic studies with regard to nanoforms with high dissolution rate in biological media and for specific additional particle properties "reasonably suspected" to markedly alter the hazard or exposure of the nanoforms of concern.

When downstream users deem additional information necessary for the completion of the Chemical Safety Report, they shall gather the needed information and/or submit a testing strategy proposal, if the required information is pivotal and only obtainable by vertebrate experiments. If waiting for test results, downstream users shall record and ensure relevance of their risk management measures intended to manage the risk for all nanoforms used by the user and any identified nanoforms used further downstream in the supply chain.

The devil is in the detail

The European Commission, EU member states and stakeholders involved in the process of revising the Annexes deserve credit for making it clear that different nanoforms of a substance have to be registered individually or as groups, outlining the Chemical Safety Assessment procedures to be followed and, finally, clarifying when specific information requirements have to be addressed for nanoforms and when these can and cannot be waived.

Nevertheless, manufacturer, importer and downstream users have to be aware of critical facets left to them to decide on, and that the devil lies in the details of many of the decrees outlined in Table 1.

First, manufacturers and importers have to decide whether they have nanoforms that need to be registered and for which data on, for example, particle size distribution, surface functionalization or treatment and shape and aspect ratio has to be provided. To determine whether a nanoform is produced or imported, the number-based particle size distribution has to be characterized, but generally agreed methods and technical standards on how to measure particle size distribution are not yet available[4]. Different methods often provide different results within and outside

the size range of 1–100 nm for the same material. This leaves manufacturers and importers in a dilemma, having to choose between methods that either show that their materials are not nanomaterials, thereby avoiding any registration and Chemical Safety Assessment obligations, or choosing another method that identifies their materials as a nanomaterial, subsequently having to meet a whole range of scientifically and technically challenging registration and test requirements. It is well known that particle size is linked strongly to the manufacturing process[5]. Hence, it could be clearer specified in the Annexes that a combination of methods has to be applied along with a description of the applicability of the chosen methods, sample preparation and the nanomaterial production process[6]. Further complicating matters, there is an on-going process to evaluate the nanomaterial definition proposed by the European Commission back in 2011, as this definition leaves a lot of room for interpretation of terms such as 'particle', 'size' and 'external dimension'[7]. Updates to the definition were expected in mid-2016[8] but have yet to be put forward, which creates regulatory uncertainty and confusion about what a new definition might look like.

The second key decision to be made by manufacturers and importers is whether and how to group different nanoforms, as this decision can be of paramount importance for how much information they subsequently have to provide in the registration dossiers and in the Chemical Safety Report. The revised Annexes clearly state that molecular structural similarities cannot be used alone as a justification for grouping different nanoforms, but they vary in regard to the nature of explanation and justification that has to be provided. With regard to registration, a 'justification' has to be provided for why grouping of nanoforms is appropriate and for why the variation within the boundaries of a set do not affect the hazard-, exposure- and risk-assessment. In contrast, a so-called scientific justification shall be provided in cases where the registrant wishes to use data from one nanoform in the demonstration of the safe use of other nanoforms. ECHA does provide guidance on grouping of nanoforms, making it clear that correct and unambiguous characterization of the nanoforms is a prerequisite for grouping. This raises the question of how manufacturers and importers are to provide justification for forming sets of nanoforms and subsequently not having to provide characterization of all registered nanoforms, when unambiguous characterization of the nanoforms in the first place is considered a prerequisite by ECHA. The second ECHA prerequisite is the development of a grouping hypothesis and a robust scientific justification, including that the hazard characterization is valid for all nanoforms within the group. Three examples of hypotheses provided by ECHA are based on solubility, high aspect ratio and impact of surface treatment on grouping[9]. Here again it seems that the only manner in which manufacturers and importers can truly provide scientific justification of grouping with regard to, for example, hazard characterization and demonstrate safety is by generating information for all registered nanoforms.

Many of the test-specific requirements are hung on vague terms such as 'poorly soluble', 'high insolubility' and 'low' versus 'high' dissolution rate. This is a third important aspect that manufacturers and importers have to be alert to. It is well-established that nanomaterials do not go into solution, but are dispersed[10,11] and as these terms are not clearly defined in the Annexes, whether specific test requirements have to be met will depend on how the registrant interprets such terms. Furthermore, the technical guidance that ECHA currently provides to registrants on how to meet specific test requirements for nanomaterials entail no assistance on how to measure and report on, for instance, irreversible transformations in particle size, shape, surface properties and loss of coating considering all stages of the life-cycle and with regard to assessing the environmental distribution and fate[12–15].

The revised Annexes provided a great opportunity for the European Commission to clarify EU chemical registration duties for nanomaterials and resolve the regulatory uncertainty that has plagued the development and commercialization of nanomaterials since EU's new chemical legislation was adopted in 2006[16]. This opportunity was arguably not fully taken advantage of and there are issues with regards to characterization of nanoforms, grouping of nanoforms and when it is necessary to fulfil specific information requirements that manufacturers, importers and downstream users have to be aware of when trying to comply with the new regulation. ❐

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Competing interests

The authors declare no competing interests.