The ten decrees of nanomaterials regulations

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1 **The Ten Decrees of Nanomaterials Regulations**

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3 **The new revisions of the annexes of the European Union's chemical legislation with regards to**
4 **nanomaterials will provide more structure and clarity, but they will also force manufacturers,**
5 **importers and down-stream users to put substantial effort in understanding the details what**
6 **should and should not be done.**

7

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15 In April of 2018, European Member States approved the European Commission's draft Regulation
16 revising the Annexes of the Union's chemical legislation with regard to nanomaterials^{1,2}. The
17 chemical legislation currently includes 17 Annexes that specify many of the technical and scientific
18 details of the legislation and the criteria for when, how and what different actors such as
19 manufacturers, importers, down-stream users, regulatory authorities have to do - and not do - with
20 regard to registration and chemical safety assessment. Hence, the Annexes play an significant role
21 in the practical implementation of the legal prerequisites outlined in the main legal text. The draft
22 had been out for public consultation in the fall of 2017 and the Regulation has now been adopted by
23 the European Commission after a three-month scrutiny review of the European Parliament and
24 Council³. The Annex revisions, that aim to clarify registration duties for nanomaterials, come after
25 years of discussion between European Commission, EU Member States and other stakeholders.

26 In this commentary, we introduce and discuss the new obligations that manufacturers,
27 importers and downstream users “shall” comply with before this Regulation applies from 1 January
28 2020.

29

30 **Thou shalt register and demonstrate safety**

31 In essence, we summarize the new Annex revisions into ten decrees aiming at making
32 manufacturers, importers and down-stream users register “nanoforms” and demonstrate safety of all
33 their uses (see table 1).

Table 1 The ten decrees of the new Annex

Degree	Specific information to be provided
1. Thou shalt register nanoforms and provide information on characteristics that may influence (eco)toxicity and environmental exposure.	<ul style="list-style-type: none">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.
2. Thou shalt not use molecular structural similarities alone as a justification for grouping different nanoforms.	<ul style="list-style-type: none">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.
3. Thou shalt justify why safety information provided is relevant for all registered nanoforms.	<ul style="list-style-type: none">Adequate justification for each information requirement describing when and how information on one nanoform is used to demonstrate safety of other forms.
4. Thou shalt document safety for all registered nanoforms along the life-cycle.	<ul style="list-style-type: none">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.
5. Thou shalt provide information of test conditions and nanoforms tested.	<ul style="list-style-type: none">Documented test conditions and scientific justification for the relevance and adequacy of the utilised test materialJustification 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.
6. Thou shalt fulfil specific ecotoxicity related test requirements for different nanoforms depending on their dissolution and solubility	<ul style="list-style-type: none">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.
7. Thou shalt fulfil specific toxicity related test requirements for different nanoforms depending on their nature and likely route of exposure	<ul style="list-style-type: none">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 yearConsideration of toxicokinetics, including recovery period and, where relevant, lung clearance in the short-term repeated dose toxicity study and the sub-chronic toxicity study.
8. Thou shalt consider multiple metric reporting of results for nanoforms that are dangerous or hazardous.	<ul style="list-style-type: none">Complete exposure assessment and risk characterization preferably considering a multiple metric presentation of the results.Justification included in the Chemical Safety Report and summarised in the Safety Data Sheet.
9. Thou shalt provide justification for waiving information requirements.	<ul style="list-style-type: none">Adequate justification for relevance of physicochemical property (e.g. dissolution rate, dispersion stability) as reason for waiving tests on bioaccumulation in aquatic species and adsorption/desorption.
10. Thou shalt propose further testing and/or comply with ECHA testing requirements.	<ul style="list-style-type: none">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.

34 Under the European chemical legislation, manufacturers and importers have to register their
35 substances, if produced in quantities of 1 tonne or more per year. According to the new Regulation,
36 specific minimum characterisation information, such as number-based particle number size
37 distribution, shall be provided by the registrant for “nanoforms” as these characteristics may
38 influence its (eco)toxicological profile and environmental exposure.

39 Nanoforms are defined as a form of a natural or manufactured substance containing
40 particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more
41 of the particles in the number size distribution, one or more external dimensions is in the size range
42 1 nm-100 nm². The information provided by the registrant may be applicable to an individual
43 nanoform or a set of similar nanoforms and grouping of nanoforms is possible, if justification is
44 provided. Notably, molecular structural similarities alone cannot serve as a justification.

45 For general registration purposes, the revised Annexes requires that information on
46 manufacture and use provided in the registration for regular substances shall also apply to
47 nanoforms or sets of similar nanoforms including tonnage used, concentration range used,
48 quantities in articles, human and environmental exposure and waste quantities and composition².
49 When registrants of nanoforms submit joint registration dossiers, they shall justify why information
50 provided is relevant for nanoforms or they may submit relevant information separately².

51 The number of decrees and use of the word “shall” is no more outspoken in the revised
52 Annexes than in sections related to the Chemical Safety Report that has to be provided for
53 substances manufactured or imported in a quantity of 10 tonnes or more per year. According to the
54 new Annexes, the Chemical Safety Report shall first specify whether and which different
55 nanoforms have been characterised as part of the registration and are covered by the Chemical
56 Safety Assessment. Interestingly, this also applies to producers and importers of articles that are
57 required to prepare a Chemical Safety Assessment as part of their registration². Second, registrants

58 shall describe how information is compiled, document adequately control of risks associated with
59 the uses of their nanoforms and ensure that justifications and conclusions are relevant to these
60 nanoforms along the life-cycle of the substance.

61 As a general requirement, the nanoform tested shall be appropriately characterised and test
62 conditions documented to allow for adequate assessment of the relevance of any physicochemical,
63 toxicological and ecotoxicological information provided for the different nanoforms². In case, the
64 nanoforms of a substance fulfil the criteria for dangerous or hazardous substances, an exposure
65 assessment and risk characterization shall be completed using an appropriate metric and preferably
66 considering a multiple metric presentation of the results. It is furthermore repetitively mentioned as
67 a general requirement with regard to classification and labelling, that registrants shall indicate and
68 justify actions or decisions taken if information is inadequate to classify a substance and nanoforms
69 thereof for a particular hazard class or category².

70 When it comes to fulfilling specific information requirements as part of the Chemical Safety
71 Assessment, the revised annex entail a number of very specific decrees. For instance, for
72 nanoforms that are not soluble nor have high dissolution rate, further degradation tests shall
73 consider morphological transformation e.g. irreversible changes in particle size, shape, surface
74 properties, loss of coating, chemical transformation and other abiotic degradation^{1,2}. A range of
75 studies do not need to be conducted depending on the specific circumstances e.g. dustiness does not
76 need to be reported, if exposure to granular form of the substance during its life-cycle can be
77 excluded². It is important that registrants note that high insolubility in water cannot serve as a
78 justification for waiving of a number of information requirements related to the environment e.g.
79 for short-term toxicity testing on invertebrates and growth inhibition studies of aquatic plants.

80 In some aspects, the Annex revisions is very inclusive. In the assessment of persistency,
81 bioaccumulation and toxicity, registrants have to consider all stages of the life-cycle when making

82 quantitative and qualitative estimates of the dose/concentration of the substance to which humans
83 and the environment are or may be exposed to. This includes estimating environmental distribution
84 and fate and performing a characterisation of possible degradation, transformation, reaction
85 processes, dissolution rate, particle aggregation and agglomeration and changes in particle surface
86 chemistry.

87 The Annex also holds several decrees with respect to further testing. For instance, further
88 studies shall be proposed by the registrant or may be required by the European Chemicals Agency
89 (ECHA) for toxicokinetic studies with regard to nanoforms with high dissolution rate in biological
90 media and for specific additional particle properties “reasonable suspected” to markedly alter the
91 hazard or exposure of the nanoforms of concern.

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

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99 **The devil(s) in the detail**

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

105 Nevertheless, manufacturer, importer and downstream users have to be aware of critical
106 facets left to them to decide upon and that the devil(s) lies in the details of many of the decrees
107 outlined in table 1.

108 First, manufacturers and importers have to decide whether they have nanoforms that need to be
109 registered and for which, data on e.g. particle size distribution, surface functionalization or
110 treatment and shape and aspect ratio has to be provided. In order to determine whether a nanoform
111 is produced or imported, the number-based particle size distribution has to be characterised, but
112 generally agreed methods and technical standards on how to measure particle size distribution are
113 not yet available⁴. Different methods often provide different results within and outside the size
114 range of 1 nm -100 nm for the same material. This leaves manufacturers and importers in a
115 dilemma having to choose between methods that either show that their materials are not
116 nanomaterials thereby avoiding any registration and Chemical Safety Assessment obligations or
117 choosing another method that identifies their materials as a nanomaterial, subsequently having to
118 meet a whole range of scientifically and technically challenging registration and test requirements.
119 It is well known that particle size is linked strongly to the manufacturing process⁵. Hence, it could
120 be clearer specified in the Annex that a combination of methods have to be applied along with a
121 description of the applicability of the chosen methods, sample preparation and the nanomaterial
122 production process⁶. Further complicating matters, there is an on-going process to evaluate the
123 nanomaterial definition proposed by the European Commission back in 2011 as this definition
124 leaves a lot of room for interpretation of terms such as “particle,” “size” and “external dimension”⁷.
125 Updates to the definition were expected in mid-2016⁸, but has yet to be put forward which creates
126 regulatory uncertainty and confusion about what a new definition might look like.

127 The second key decision to be made by manufacturers and importers is whether and how to
128 group different nanoforms as this decision can be of paramount importance for how much

129 information they subsequently have to provide in the registration dossiers and in the Chemical
130 Safety Report. The revised Annex clearly state that molecular structural similarities cannot be used
131 alone as a justification for grouping different nanoforms, but it varies in regard to the nature of
132 explanation and justification that has to be provided. With regard to registration a “justification” has
133 to be provided for why grouping and sets of nanoforms are appropriate and for why the variation
134 within the boundaries of a set do not affect the hazard-, exposure- and risk assessment, whereas a
135 so-called “scientific justification” shall be provided in cases, where the registrant wishes to use data
136 from one nanoform in the demonstration of the safe use of other nanoforms. ECHA does provide
137 guidance on grouping of nanoforms making it clear that correct and unambiguous characterisation
138 of the nanoforms is a prerequisite for grouping. This raises the question of how manufacturers and
139 importers are to provide “justification” for forming sets of nanoforms and subsequently not having
140 to provide characterization of all registered nanoforms, when unambiguous characterization of the
141 nanoforms in the first place is considered a prerequisite by ECHA. The second ECHA prerequisite
142 is the development of a grouping hypothesis and a robust scientific justification, including that the
143 hazard characterization is valid for all nanoforms within the group. Three examples of hypotheses
144 provided by ECHA are hypothesis based on solubility, high aspect ratio and impact of surface
145 treatment on grouping⁹. Here again it seems that the only manner in which manufacturers and
146 importers can truly provide “scientific justification” of grouping with regard to e.g. hazard
147 characterization and demonstrate safety is by generating information for all registered nanoforms.

148 Many of the test specific requirements are hung on vague terms such as “poorly soluble”,
149 “high insolubility” and “low” versus “high” dissolution rate. This is a third important aspect that
150 manufacturers and importers have to be alert to. It is well-established that nanomaterials do not go
151 into solution, but are dispersed^{10,11} and as these terms are not clearly defined in the Annex, whether
152 specific test requirements have to be met will depend on how the registrant interprets such terms.

153 Furthermore, the technical guidance that ECHA currently provides to registrants on how to meet
154 specific test requirements for nanomaterials entail no assistance on how to measure and report on,
155 for instance, irreversible transformations in particle size, shape, surface properties and loss of
156 coating considering all stages of the life-cycle and with regard to assessing the environmental
157 distribution and fate^{12,13,14,15}.

158 The revised Annex provided a great opportunity for the European Commission to clarify EU
159 chemical registration duties for nanomaterials and resolve the regulatory uncertainty that has
160 plagued the development and commercialization of nanomaterials since EU's new chemical
161 legislation was adopted in 2006¹⁶. This opportunity was arguably not fully taken advantage of and
162 there are issues with regards to characterization of nanoforms, grouping of nanoforms and when it
163 is necessary to fulfil specific information requirements that manufacturers, importers and
164 downstream-users have to be aware of when trying to comply with the new regulation.

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¹ COMMISSION REGULATION (EU) .../...of **XXX** amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annexes I, III, VI, VII, VIII, IX, X, XI, and XII to address nanoforms of substances (European Commission 2018);

http://ec.europa.eu/transparency/regcomitology/index.cfm?do=Search.getPDF&ds_id=56122&version=2&AttLang=en&db_number=1&docType=DRAFT_MEASURE

² ANNEX (European Commission, 2018);

http://ec.europa.eu/transparency/regcomitology/index.cfm?do=Search.getPDF&ds_id=56122&version=2&AttLang=en&db_number=2&docType=DRAFT_MEASURE

³ REACH: Member States vote for more clarity in nanomaterials registrations. (European Commission, 2018);

http://ec.europa.eu/environment/chemicals/news_en.htm

⁴ Roebben, G. *et al.* *Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 2: Assessment of collected information concerning the experience with the definition* (European Commission Joint Research Centre, 2014); http://publications.jrc.ec.europa.eu/repository/bitstream/JRC91377/jrc_nm-def_report2_eur26744.pdf

⁵ Christensen, F.M. *et al.* NANO SUPPORT (European Commission Joint Research Centre, 2012); http://ec.europa.eu/environment/chemicals/nanotech/pdf/jrc_report.pdf

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- ⁶ Hansen, S.F. Registration, Evaluation, Authorisation, Categorisation and Tools to Evaluate Nanomaterials – Opportunities and Weaknesses (REACT NOW) (DTU, 2018); http://orbit.dtu.dk/files/147141535/19_04_2018_REACT_NOW_SFH.pdf
- ⁷ Rauscher *et al.* Towards a review of the EC Recommendation for a definition of the term “nanomaterial”: Part 3: Scientific-technical evaluation of options to clarify the definition and to facilitate its implementation. (European Commission Joint Research Centre, 2015); http://publications.jrc.ec.europa.eu/repository/bitstream/JRC95675/towards%20review%20ec%20rec%20def%20nanomaterial%20-%20part%203_report_online%20id.pdf
- ⁸ Roberts, G. Commission rejects idea of EU nano register. *Chemical Watch* (2016); <https://chemicalwatch.com/45776/commission-rejects-idea-of-eu-nano-register>
- ⁹ **Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals** Version 1.0 (ECHA 2017); https://echa.europa.eu/documents/10162/23036412/appendix_r6_nanomaterials_en.pdf/71ad76f0-ab4c-fb04-acba-074cf045eaaa
- ¹⁰ Skjolding, L.M., Sørensen, S.N., Hartmann, N.B., Hjorth, R., Hansen, S.F., Baun, A. *Angew. Chem. Int. Ed. Engl.* **55**, 15224-15239 (2016).
- ¹¹ Hartmann *et al.* *J Toxicol Environ Health B Crit Rev.* **18**, 299-326 (2015).
- ¹² **Appendix R7-1 for nanomaterials applicable to Chapter R7a Endpoint specific guidance** Version 2.0 (ECHA 2017); https://echa.europa.eu/documents/10162/13632/appendix_r7a_nanomaterials_en.pdf/1bef8a8a-6ffa-406a-88cd-fd800ab163ae
- ¹³ **Appendix R7-1 for nanomaterials applicable to Chapter R7b Endpoint specific guidance** Version 2.0 (ECHA 2017); https://echa.europa.eu/documents/10162/13632/appendix_r7b_nanomaterials_en.pdf/6eca425a-ede1-4c9e-8151-af77973caf32
- ¹⁴ **Appendix R7-2 for nanomaterials applicable to Chapter R7c Endpoint specific guidance** Version 2.0 (ECHA 2017); https://echa.europa.eu/documents/10162/13632/appendix_r7c_nanomaterials_en.pdf/c2d8e0ce-2ab4-4035-a05f-e2dec924d87a
- ¹⁵ **Chapter R.11: PBT/vPvB assessment** Version 3.0 (ECHA 2017); https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf/a8cce23f-a65a-46d2-ac68-92fee1f9e54f
- ¹⁶ Bowman, D.M., van Calster, G., Friedrichs, S. *Nat. Nanotech.* **5**, 92 (2010).