Effects of EU definitions for nanomaterials (June 2022) on dental materials

1. Comparison of definitions of nanomaterials

The first EU definition of nanomaterials was adopted 18.11.2011 as a Recommendation of the EU Commission[1]. A revision of this definition was also adopted 10.06.2022 as a Recommendation of the EU Commission and published 14.06.2022 in the Official Journal[2]. In the meanwhile, the Medical Device Regulation (MDR)[3] relevant for dental materials entered into force, which to a large extent contains in Article 2 (18 – 21) the same text as the definition of nanomaterials from 2011.

The aim of this statement is to examine the effects of the new definition for nanomaterials (2022) on medical devices and specifically on dental materials, and to prepare recommendations for the application of the new definitions.

For this purpose, in Table 1 the texts of the three definitions (Recommendation of 2011, MDR and Recommendation of 2022) are compared and the differences discussed.

Table 1. Comparison of the nano definitions of the EU from 2011, 2022 and in the Medical Device Regulation

Statement	Description	Recommendation of 2011	MDR, Art. 2	Recommendation of 2022
1	Source	2.'Nanomaterial' means a natural, incidental or manufactured material containing	18. 'nanomaterial' means a natural, incidental or manufactured material containing	1. 'Nanomaterial' means a natural, incidental or manufactured material consisting of
2	Form	particles	particles	solid particles,
3	Relevant particle	in an unbound state or as an aggregate or as an agglomerate and where	in an unbound state or as an aggregate or as an agglomerate	that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates,
4	Dimension	and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.	and 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	and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions: a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm; b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm; c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm.
5	Variability of the limit	In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.	-	-
6	Additional inclusion criteria	3. By derogation from point 2, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials..	Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials	-
7	Exclusion criteria 1	-	-	In the determination of the particle number-based size distribution, particles

Statement	Description	Recommendation of 2011	MDR, Art. 2	Recommendation of 2022
				with at least two orthogonal external dimensions larger than 100 µm need not be considered
8	Exclusion criteria 2	-	-	However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial.
9	Definition Particle	4 a) 'particle' means a minute piece of matter with defined physical boundaries	19. 'particle', […], means a minute piece of matter with defined physical boundaries	2 a) ‚particle' means a minute piece of matter with defined physical boundaries;
10	Exclusion criteria „molecule"	-	-	single molecules are not considered 'particles';
11	Definition Agglomerate	4 b) 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components	20. 'agglomerate', […], means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components	2 c) 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components.
12	Definition Aggregate	4 c) 'aggregate' means a particle comprising of strongly bound or fused particles.	21. 'aggregate', […], means a particle comprising of strongly bound or fused particles	2 b) 'aggregate' means a particle comprising of strongly bound or fused particles;
13	Volume specific surface (VSSA) as inclusion criteria	5) […]A material should be considered as falling under the definition in point 2 where the specific surface area by volume of the material is greater than 60 m^2/cm^3 . However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition in point 2 even if the material has a specific surface area lower than 60 m^2/cm^3 .	-	-

Regarding the statements of the three definitions, the following picture emerges:

Statement 1 is identical in all three definitions.

Statement 2 contains an addition to the aggregate state of the particles in the definition of 2022. The term particle describes a solid body per se. The addition in the definition of 2022 is therefore simply the explicit naming of a fact, that was already implied in the definitions of 2011 and the MDR. In Recital 10 it is indicated that fluid or gaseous structures are characterised by dynamically changeable dimensions, which make inclusion per se impossible.

Statement 3 specifies in the definition of 2022 that agglomerates or aggregates must contain "identifiable constituent particles". This version thus describes the real situation of particle measurement, that there can be cases, in which particles are so strongly aggregated or agglomerated that their boundaries are not clearly vcisible by electron microscopy. Identification of such particles as agglomerates or aggregates was also not possible technically under the definitions of 2011 and MDR, so that this limitation was already implied in these definitions (see also Recital 14).

Statement 4 appears in the definition of 2022 to be considerably more comprehensive than in previous versions due to the additions b) and c). These additions, however, are simply a generalisation of the additional inclusion criteria (Statement 6) and consequently do not represent any significant extension of the definition.

Statement 5 in the definition of 2011 was not adopted neither in the definition of the MDR nor in that of 2022. In the two newer definitions case-by-case variability of the central inclusion criterion (50% of the particles in the nano range) was omitted. According to Recital 13 this was done to guarantee regulatory uniformity and coherence. As the MDR had already waived this variability, this adaptation in the definition of 2022 does not have any influence on medical devices.

Statement 6 contains an additional inclusion criterion for certain material groups in the definitions of 2011 and the MDR. This criterion was replaced and generalised in the 2022 version by criteria b) and c) in the definition (Statement 4). The definition of 2022 should therefore be regarded as more broadly formulated than the older definitions, despite missing this inclusion criterion.

Statement 7 in the 2022 definition contains a new exclusion criterion from the general definition that is missing in the previous versions. In Recital 18 reference is made to the fact that during measurement such particles are usually not recognised as nanomaterials and are therefore excluded in this version of the definition for practical reasons. Based on the measuring process it can be assumed that this exclusion was already implied in the previous definitions.

Statement 8 in the 2022 definition contains further new exclusion criterion from the general definition that is missing in the previous versions. Recital 20 indicates that this criterion has validity to a large extent and consequently only enables a simplified measurement as a decision criterion. It can therefore be assumed that this exclusion was already implied in the previous definitions.

Statements 9, 11 and 12 are factually identical in all three versions.

Statement 10 in the 2022 definition excludes individual molecules as particles. Classification of macromolecules (e.g. proteins) should thus be avoided in the definition of particles. An obvious ambiguity of previous definitions is consequently eliminated in this version.

Statement 13 is only found in the 2011 definition and describes the inclusion criterion for materials with a volume-specific surface area of $60 m^2/cm^3$. Recital 19 explains that the same volume-specific surface area can also be achieved based on an internal nanostructure, so that "that the related option provided in point 5 of Recommendation 2011/696/EU was not appropriate and should be removed from being a qualifier in the definition of a nanomaterial." As this criterion is already missing in the definition of the MDR, the omission in the definition of 2022 does not have any impact on medical devices. Recital 11, which is still to be discussed, also deals with the exclusion of nanostructured materials from the definition.

In summary, it can be stated that the definition of 2022 eliminates some errors of the definition of 2011 and essentially only specifies certain statements or now explicitly includes statements implicitly available. It can therefore be assumed that the definition of 2022 can be regarded as a specification of the definition, which was included in the MDR based on the 2011 definition, and can consequently be used for medical devices under the Medical Devices Regulation.

Particular attention should also be given to statement 11. "The definition should not cover large solid products or components, even when they have an internal structure or a surface structure at the nanoscale, such as coatings, certain ceramic materials and complex nanocomponents, including nanoporous and nanocomposite materials. Some of these products or components may have been manufactured by using nanomaterials and may even still contain them.".

This Recital is not present explicitly in the definition section. It contains the exclusion of large (macroscopic) products, also "when they have an internal structure or a surface structure at the nanoscale". If the definitions of ISO 80004-1[4] and 80004-4[5,6] are taken into consideration, such products correspond to "nanostructured materials"[a] . This Recital indicates that the EU definition of 2022 only relates to nano-objects ("nano-object: discrete piece of material with one, two or three external dimensions in the nanoscale")[4,6], unlike the standard, that includes nano-objects and nanostructured materials ("nanomaterial: material with any external dimension in the nanoscale or having an internal structure or surface in the nanoscale")[4,6]. This clarification is already implied included in all three definitions, as all statements always relate to nanoparticles. It can therefore be

[a] **ISO 80004-1: 2015** defines **nanostructure** as: composition of inter-related constituent parts in which one or more of those parts is a nanoscale (2.1) region. - Note 1 to entry: A region is defined by a boundary representing a discontinuity in properties: and **nanostructured material** as: material having internal nanostructure (2.6) or surface nanostructure. - Note 1 to entry: This definition does not exclude the possibility for a nano-object (2.5) to have internal structure or surface structure. If external dimension(s) are in the nanoscale (2.1), the term nano-object is recommended.
ISO/DIS 80004-1: 2021 gives the following modified definitions: **nanostructure**: surface or internal feature with one or more dimensions in the nanoscale (3.1.1) - Note 1 to entry: A feature includes but is not limited to nano-objects, structures, morphologies or other identifiable areas of nanoscale dimensions. – Note 2 to entry: for example, the nanostructure can be a nanopore or a solid feature on an object: and **nanostructured material**: material having internal nanostructure (3.1.6) or surface nanostructure - Note 1 to entry: This definition does not exclude the possibility for a nano-object (3.1.5) to have internal structure or surface structure. If external dimension(s) are in the nanoscale (3.1.1), the term nano-object is recommended.

assumed that this addition is also not in contradiction of the MDR definition and can be used for medical devices.

As support for application of the definition, two new OECD guidelines were published in June 2022, which deal with determination of the particle size and size distribution[7], and determination of volume-specific surface area[8]. Further guidelines for application of the 2022 definition are in preparation under the aegis of the Joint Research Centre of the EU.

2. Statements of the Medical Devices Regulation on nanomaterials

The Medical Devices Regulation[3] makes statements in several areas on the use of nanomaterials and particles in general. It should be noted that there are not only statements on the classification of medical devices but also on risk management of products incorporating nanomaterials.

a. Classification of medical devices incorporating nanomaterials

Rule 19 (MDR Annex VIII, 7.6) should be observed for medical devices incorporating nanomaterials. This rule states:
All devices incorporating or consisting of nanomaterial are classified as:
— class III if they present a high or medium potential for internal exposure;
— class IIb if they present a low potential for internal exposure; and
— class IIa if they present a negligible potential for internal exposure

For application of this rule under reference on the SCENIHR Opinion[9] there is additional information in the MDCG guidance for classification[10]. It is essential that the products incorporate nanomaterial in accordance with the MDR definition and the nanomaterials present a potential for internal exposure.

b. Risk management of medical devices incorporating nanomaterials

Recital 15 MDR specifies that: “There is scientific uncertainty about the risks and benefits of nanomaterials used for devices.”. A high level of health protection should be ensured.

Article 2 MDR contains the definition of nanomaterials.

In Annex I, the “Basic safety and performance requirements”, the requirements for products incorporating particles are defined under 10.6 as follows: „Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.“

3. Evaluation of changes to the definition of nanomaterials by the 2022 Recommendation

Premise of this evaluation is that the definition of 2022 (as presented in the first part of the statement) is simply a correction or substantiation of the original definition of 2011 and the definition present in the MDR, and can consequently be used without restriction for medical devices.

This means that there are certain changes of the previous approach, which could be used on individual dental materials. The effects on the two aspects of the MDR (classification and risk management) will therefore each be examined.

Table 2: Effects of the changes to the definitions on medical products

Change	Effect on	
	Classification	**Risk management**
Only solid particles should be taken into consideration	if fluid, gaseous particles or molecules were taken into consideration	
Molecules are not particles	Rule 19 is now no longer applicable	Requirement 10.6 is not applicable
Boundary of the particles is not discernible	Rule 19 no longer applicable	No change, as requirement 10.6 relates to all particles
Exclusion of materials with volume-specific surface < 6 m^2/cm^3 (example: highly aggregated particles; layered silicates)		
Point b) or c) of the size definition is applicable, although it does not involve fullerenes, graphene flakes and single-wall carbon nanotubes	Products that incorporate the corresponding particles must be considered under Rule 19	No change, as the corresponding particles were already relevant under requirement 10.6
Exclusion of particles with at least two orthogonal external dimensions larger than 100 µm (example: layered silicates such as mica)	Regulation 19 is no longer applicable on such particles	No change, as requirement 10.6 relates to all particles
Omission of inclusion criterion volume-specific surface > 60 m^2/cm^3	Nano character should be checked using other criteria	No change, as requirement 10.6 relates to all particles

An interesting example for possible interpretation of the rule is the exclusion of particles with at least two orthogonal external dimensions larger than 100 µm, whereby implicitly the 3rd dimension is in the nano range (1 – 100 nm). Materials such as diverse layered silicates would consequently be excluded, if whole platelets are used (e.g. mica plates as electrical or thermal insulation). If corresponding plates are milled and the length and/or width of the particle dimensions is < 100 µm, the definition regarding the size of nanomaterial takes effect and these milled layered silicates are regarded as nanomaterial. There is, however, an exception to this approach: if the platelets are so firmly aggregated that the volume-specific surface is < 6 m^2/cm^3, the corresponding exclusion rule would take effect and the milled silicate would be excluded from classification as nanomaterial.

Omission of the volume-specific surface > 60 m^2/cm^3 as exclusion criterion in the new definition is based on Recital 19 because also internal or surface nanostructures can lead to a specific surface > 60 m^2/cm^3. Otherwise powders can be nanomaterials according to the definition, independent of their internal or surface structure if their particle size (1 – 100 nm) and particle distribution ($\geq$ 50% in the nano range) meet the definition.

Particular attention should be given to Recital 11 of the 2022 definition, as this excludes nanostructured materials from the definition of nanomaterials. Some examples are given, whose influence on dental materials will be discussed in the following:

Basically, this exclusion relates to “large, solid products or components”. Pastes, solutions or powders are therefore exempt from this exclusion, so that the previous approach remains valid for these types of products with the changes named above.

Excluded are now nanoporous materials, which in certain circumstances were previously included based on the criterion of the volume-specific surface > 60 m^2/cm^3. If it involves particles, these must be reassessed based on their size. If it does not involve nanomaterials, classification according to Rule 19 no longer applies, but they should still be taken into consideration in risk management compliant with Annex 1, Paragraph 10.6. Nanoporous, macroscopic bodies (e.g. blocks) are excluded from both aspects of the MDR.

Coatings are cited as an example of surface structures in the nanoscale. For illustration a hydroxyapatite-coated dental implant is considered here as an example. The implant has a highly specific surface that characterises it as nanostructured material. Due to the exclusion, this type of implant will now not be regarded as nanomaterial according to the 2022 nanomaterial definition. As, however, the Medical Devices Regulation in Rule 19 refers to products incorporating nanomaterials and the coating is part of the product, the Rule is nevertheless applicable, in the same way Annex 1, Paragraph 10.6 also remains applicable due to the surface particles. However, in the case of a titanium implant in which a nanostructured surface is not produced by coating but by physical treatment of the titanium itself, so that the product (implant) despite its high surface does not contain any nanoparticles, Rule 19 and Annex 1, Paragraph 10.6 are not applicable.

Ceramic materials can be produced by sintering of (nano)particles. If the primary particle boundaries are not clearly defined, neither Rule 19 nor Annex 1, Paragraph 10.6 is applicable to such blocks. In contrast, ceramic powders used as fillers for example must be examined regarding their size pursuant to the definition and can be regarded as nanomaterial, so that Rule 19 and Annex 1, Paragraph 10.6 remain applicable for corresponding products.

Nanocomposites are defined according to ISO 80004-4[5] as: nanocomposite: solid comprising a mixture of two or more phase-separated materials, one or more being nanophase. Note 1 to entry Gaseous nanophases are excluded (treated in the category nanoporous material). Note 2 to entry Materials with nanoscale phases formed by precipitation alone are not considered to be nanocomposite materials. Also polymer-based nanocomposites, which most closely correspond to dental composites, are defined[5] as: polymer matrix nanocomposite: nanocomposite (3.2) with at least one major polymeric phase.

Using these definitions polymerised dental composites do not fall within the scope. However, as these are marketed unpolymerised as a medical device Rule 19 and Annex 1, Paragraph 10.6 are still applicable. Blocks, crowns, inlays etc. which are fabricated using such composites, can be regarded as nanocomposite materials according to this definition. However, since the Medical Devices Regulation in Rule 19 refers to the fact that the product contains nanomaterial and the fillers used are part of the product, the Rule is still applicable, in the same way Annex 1, Paragraph 10.6 remains applicable due to the particles used.

4. Conclusion

Based on the comparison of the nanomaterial definitions of the EU from 2011, 2022 and in the Medical Devices Regulation, it is assumed that the definition of 2022 is simply a correction and explanation of unclear facts compared to the two previous definitions. It also represents a new state-of-the-art. It can therefore be assumed that this definition can be used on medical devices, despite the extensive inclusion of the definition of 2011 in MDR.

Taking the 2022 definition into consideration, there will be no change in the classification and risk management requirements for dental materials in most cases. Adaptations may be required in some concrete cases. This requires a specific, case-by-case analyisis.

References

[1] Comission Recommendation of 18. October 2011 on the definition of nanomaterial (2011/696/EU) (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011H0696&qid=1667922456654&from=DE)

[2] Comission Recommendation of 10. June 2022 on the definition of nanomaterial (2022/C 229/01) (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022H0614(01)&qid=1667922696162&from=DE)

[3] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5. April 2017 on medical devices amending Directive 2001/83/EC, Regulation (EC) Nr. 178/2002 and Regulation (EC) Nr. 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&qid=1667922812875&from=DE)

[4] ISO/TS 80004-1:2015 Nanotechnologies — Vocabulary — Part 1: Core terms (https://www.iso.org/obp/ui/#iso:std:iso:ts:80004:-1:ed-2:v1:en)

[5] ISO/TS 80004-4:2011 Nanotechnologies — Vocabulary — Part 4: Nanostructured materials (https://www.iso.org/obp/ui#iso:std:iso:ts:80004:-4:ed-1:v1:en)

[6] ISO/DIS 80004-1: 2021 Nanotechnologies – Vocabulary — Part 1: Core terms and definitions (https://www.iso.org/obp/ui#iso:std:iso:80004:-1:dis:ed-1:v1:en) ; combines ISO 80004-1, -2, -4, -11 in one document; contains an amendment oft he definition for nanostructured materials

[7] OECD (2022), *Test No. 125: Nanomaterial Particle Size and Size Distribution of Nanomaterials*, OECD Guidelines for the Testing of Chemicals, Section 1, OECD Publishing, Paris, https://doi.org/10.1787/af5f9bda-en.

[8] OECD (2022), *Test No. 124: Determination of the Volume Specific Surface Area of Manufactured Nanomaterials*, OECD Guidelines for the Testing of Chemicals, Section 1, OECD Publishing, Paris, https://doi.org/10.1787/abb72f8f-en.

[9] SCENIHR Opinion. Guidance on the Determination of Potential Health Effects of Nanomaterials Used in Medical Devices, 6.01.2015

[10] MDCG 2021-24. Guidance on classification of medical devices. Oct. 2021

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