National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Status and challenges in regulation of graphene

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Introduction

- Industrial chemicals regulation in Europe - REACH
- Since 2006

- Concerns started to emerge on safe use of nanomaterials
- OECD Working Party on Manufactured Nanomaterials (WPMN) established in 2006

- OECD Council recommendation (2013):

  "[...] apply the existing international and national **chemical regulatory frameworks** or other management systems, **adapted to** take into account the specific properties of **manufactured nanomaterials** [...]"

Lessons learned from nanomaterials

- Uncertainty about specific legal obligations (applicability of data requirements)
- Uncertainty on appropriateness of the conventional hazard and risk assessment tools
  - increased **importance of the physical properties** of nanomaterials in their fate and behaviour

- These uncertainties could hamper society's ability to ensure responsible development of nanotechnologies
  - This will delay innovations

Nanoforms in REACH

- REACH adaptations in 2018 (Regulation (EU)2018/1881)
  - Definition of "nanoform" of a substance
  - Additional characterisation of nanoform
  - Additional requirements
    - Separate assessment of the nanoform
    - Some additional physicochemical parameters
    - Some adjustments in waivers

- Name
- Particle size distribution
- Surface chemistry
- Shape
- Surface area

http://data.europa.eu/eli/reg/2018/1881/oj

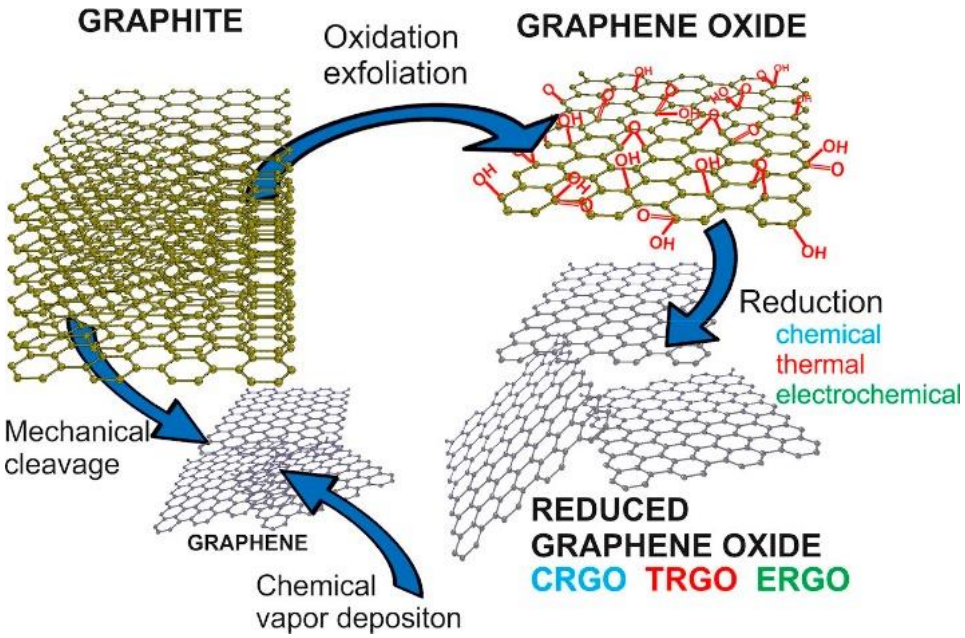
Graphene in REACH

- *"a **nanoform** is a form of a natural or manufactured substance containing particles, in an unbound state or as an aggregate or as an agglomerate 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, including also by derogation fullerenes, **graphene flakes** and single wall carbon nanotubes with one or more external dimensions below 1 nm."*
- Nanospecific requirements apply
- New recommendation on nanomaterial definition (2022):
  - [...] (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. [...]

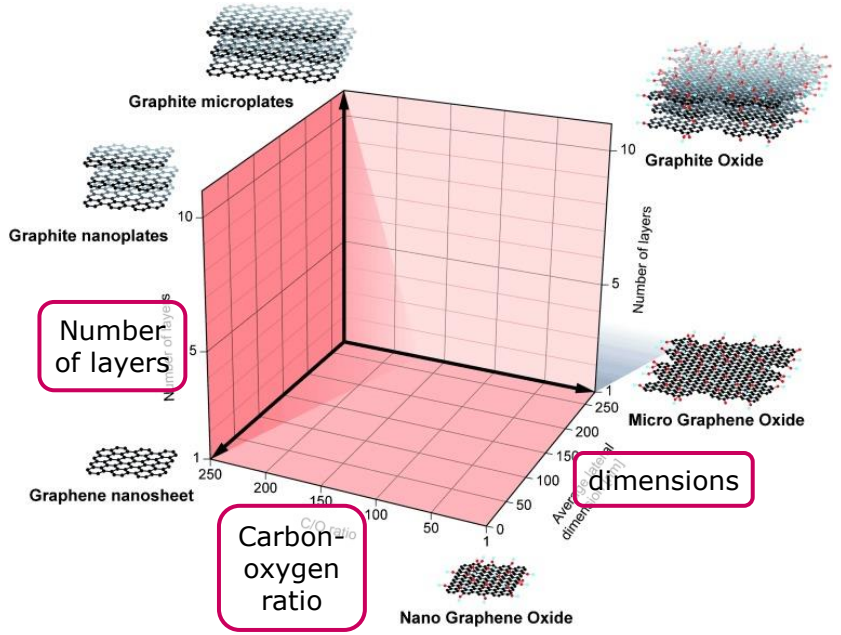
Commission Recommendation 2022/C 229/01: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32022H0614(01)

Graphene – (not) just a carbon compound

- Different from other carbon compounds – often platelets
- Huge range of different 'forms' – 2D material



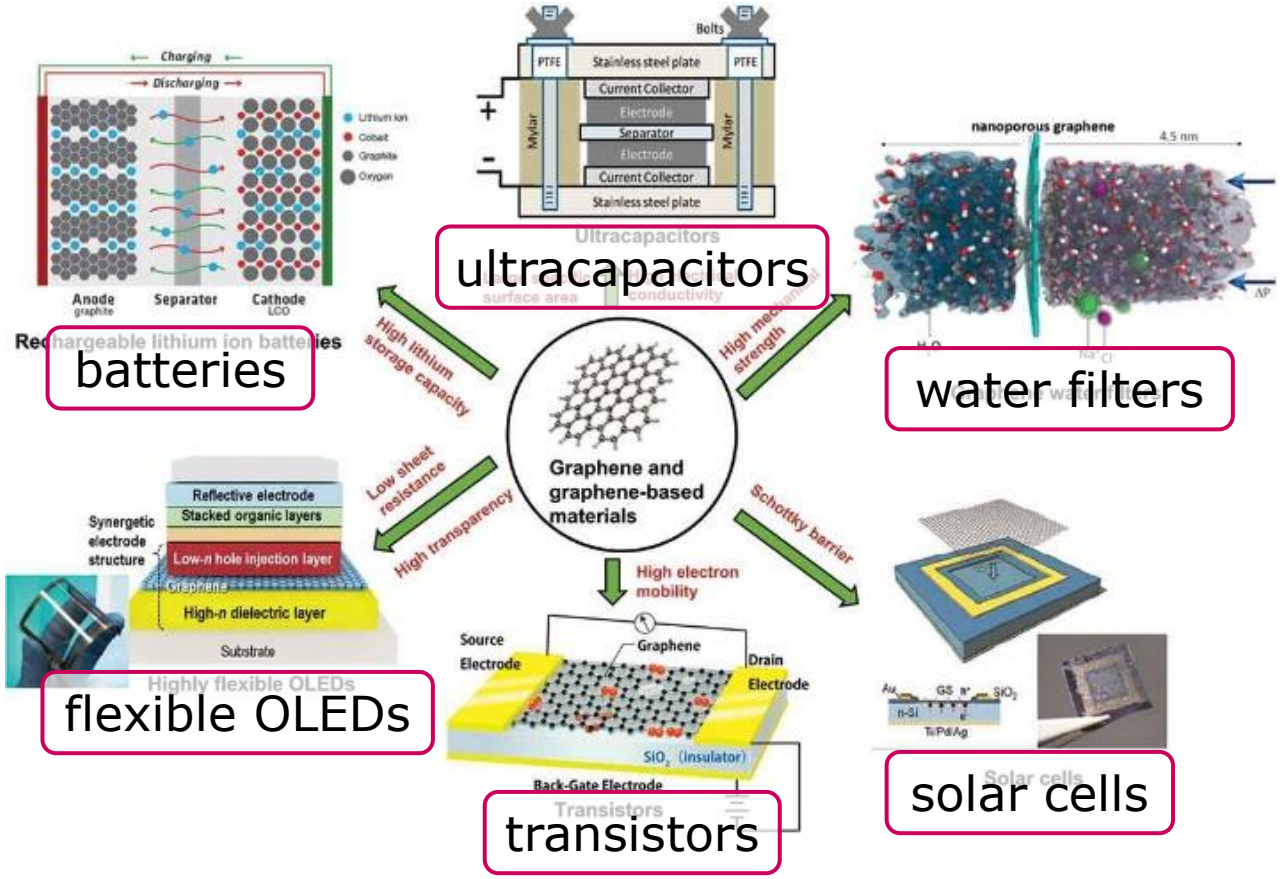
Rowley-Neale et al. 2018
10.1016/j.apmt.2017.11.010



Wick et al. 2014
10.1002/anie.201403335

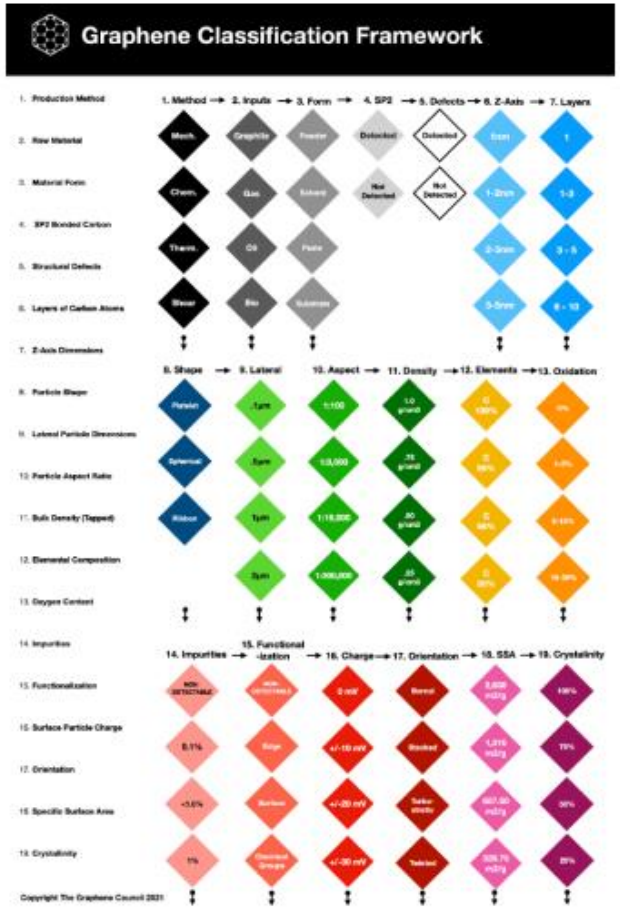
Graphene – (not) just a carbon compound

- Many (potential) applications that may benefit from graphene
- Behaviour and effects in humans and the environment are difficult to predict based on known nanoforms



Yang et al. 2018: 10.1080/14686996.2018.1494493

Identification complex

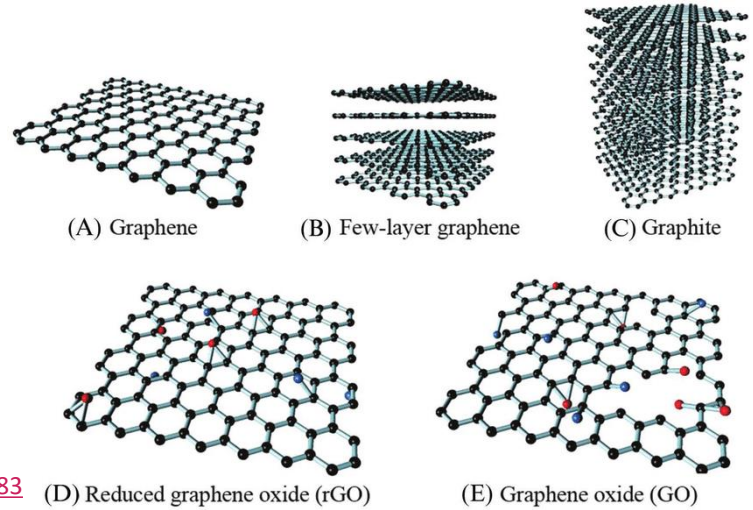


- e.g. Graphene Council:
  Graphene Classification Framework:

  19 parameters to describe the graphene form produced, e.g. production process, shape, number of layers, oxidation, functionalisation, etc. (www.thegraphenecouncil.org/page/GCF)

REACH:

- Name
- Particle size distribution
- Surface chemistry
- Shape
- Surface area



Zhang et al. 2018: 10.1002/smll.201801983

Registration at ECHA

Search for chemicals / regulated substances

graphene

Search for chemicals

15 November 2023

Name	EC / List no.	CAS no.	BP	OBL	
Graphene	801-282-5	[illegible]	BP		REACH registration
Graphene nanoplatelets having a predominant thickness of 1-10 layers with lateral dimension predominantly less than 2 microns	-	-			Import notification
Graphene nanoplatelets having a predominant thickness of 1-10 layers with lateral dimension predominantly less than 2 microns	-	-			Import notification
graphene oxide	942-699-3	-			CLP notification
Graphite IUPAC name: Graphene Nanoplatelets	231-955-3	7782-42-5	BP	OBL	REACH registration
Reaction product of Graphite, acid-treated and potassium permanganate Public name: Graphene oxide	947-768-1	-	BP		REACH registration

Registrations

	Graphene	Reaction product of Graphite, acid-treated and potassium permanganate	Graphite
Total t.p.a.	≥ 10 to < 100	≥ 10 to < 100	≥ 100.000 to < 1.000.000
Individual t.p.a.	≥ 1 to < 10	≥ 1 to < 10	≥ 1.000
Requirements	Annex VII	Annex VII	Annex X
Composition	(set of) nanoform(s) Monoconstituent / inorganic	(set of) nanoform(s) UVCB / inorganic	Bulk / Solid powder Monoconstituent / inorganic
Shape	Platelet	Platelet	No data

- Generally broad boundaries for (set of) nanoforms
- Acute toxicity appears limited, but lack of long-term toxicity data

Graphene related materials – Toxicity

- Most research on graphene oxides
- Toxicity influenced by:
  - Agglomeration of material
  - Density of the material
  - Size, shape
  - Oxidation state
  - Way of interaction with (human) cells

- EUON report: "Assessment of the potential impact of graphene, graphene oxide and other 2D materials on health, and the environment"
  → 8 recommendations on risk assessment of 2D materials

2D materials beyond graphene

- Studies on the health and the environmental impact involving 2D materials beyond graphene are still very limited

ECHA
EUROPEAN CHEMICALS AGENCY

Overall results divided by group of materials

Materials	Toxicity	Ecotoxicity
Graphene, few layer graphene, graphene nanosheets and graphene nanoflakes	Extensive information found	Extensive information found
Graphene oxide	Extensive information found	Extensive information found
Reduced graphene oxide	Extensive information found	Extensive information found
Graphene nanoribbons	Limited information found	No information found
MXenes	Limited information found	Limited information found
2D boron nitride	Limited information found	No information found
Transition metal dichalcogenides	Limited information found	Limited information found
Black phosphorus	Limited information found	Limited information found
Graphitic carbon nitride	Limited information found	No information found

Graphene related materials – Toxicity

In vitro and *in vivo* studies on toxicity of graphene materials have revealed that the toxic effects are induced by

- the extent of material aggregation
- the mode of interaction of graphene with the cells
- the density of graphene (i.e. graphene nanoplatelets more toxic)
- the size, particulate state, oxygen content, or surface charge of graphene
- the nature of cells (i.e. the same dose of graphene oxide is more toxic to fibroblasts than to epithelial cells)

8 recommendations (euon.echa.europa.eu/documents/2435000/3268573/echa_2021_286_graphene_study.pdf)

1. The application of the definitions and available documentary standards should allow to **clearly identify the type of graphene** and 2D materials used for the different applications and to evidence potential toxicity issues and risks.
2. **Multiple characterization techniques** should be applied to clearly identify and quantify graphene materials in cells, tissues, organs and the environment.
3. **Conclusions on toxicity and ecotoxicity should not be generalized** and need to be associated to a precise description of the material used in the tests.
4. When health and environmental risks are reported or identified for a specific graphene or 2D material, **doses and exposure scenarios should be considered** for their manipulation and use.
5. To assess **chronic toxicity** of graphene and 2D materials protocols for repeated-dose studies should be considered.
6. To assess potential toxicity of graphene and 2D materials relevant **immune suppressed or diseased animal models** should be considered.
7. To assess the **potential genotoxic risks**, reliable testing methods should be developed; response mechanisms associated with genotoxicity should be evaluated in depth; appropriate description of the type of graphene and 2D material tested should be reported; and different dosages and exposure times should be applied.
8. The solvents and the molecules used to exfoliate bulk materials into single- or few-layer graphene or 2D materials might remain as residues in the end-product, likely affecting the (eco)toxicity results. It is recommended to consider and include these **potential impurities in the tests** to exclude their implication and responsibility on (eco)toxicity.

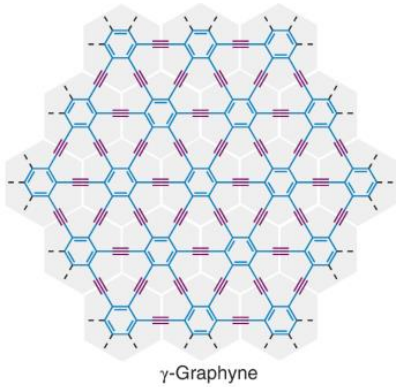
8 recommendations - summarised

- Importance of detailed identification and characterisation (also in test systems)
- Dosimetry and exposures in test systems (relevance in risk assessment)
- Importance of data on chronic toxicity, immunotoxicity, genotoxicity (test methods used, reporting on methods and results)
- Role of impurities in toxicity testing (residues from production processes)

Does this require method adaptations?

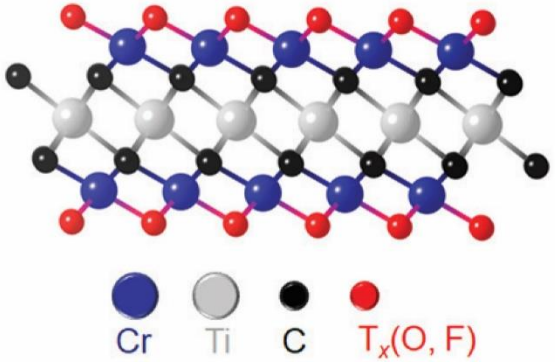
Regulatory challenges

- Diversity and complexity of these materials
  - Characterisation
- Current regulation may not align with complexity
  - Mixture toxicity?



Hu et al. 2022: 10.1038/s44160-022-00068-7

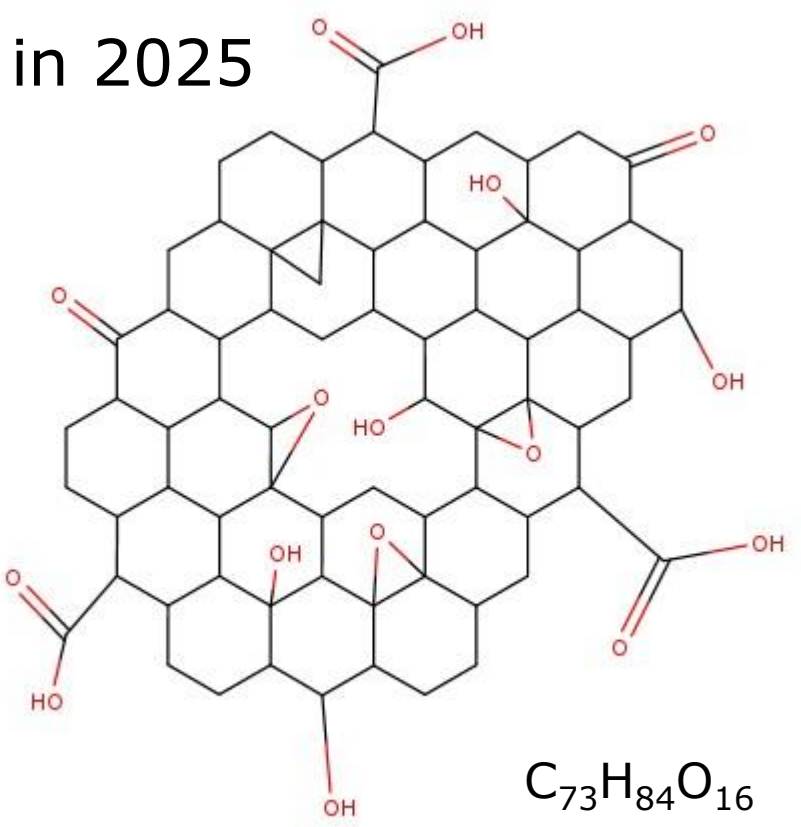
- Keep pace with innovation
  - New materials entering the market
  - Foresight system for regulatory preparedness
    - Need for method adaptations? Need for new methods?
    - Most important data gaps?
    - What would be the most important next steps?



MXene, Cr2TiC2Tx: als.lbl.gov/2d-mxene-shows-evidence-of-a-magnetic-transition

Next steps

- NL intends to start a substance evaluation in 2025
  - Reaction product of Graphite, acid-treated and potassium permanganate
- ECHA will do a Compliance Check
  - Substance identity
- Identify test method needs
  - New/adaptation of Test Guidelines?
- Raising awareness in regulatory arena
  - Regulatory preparedness



$C_{73}H_{84}O_{16}$

representative structure(s)
echa.europa.eu/nl/substance-information/-/substanceinfo/100.260.251

Thank you for your attention!