# REACH Evidence requirements, and how does the Clickable Framework help answer routine consultancy questions?

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## Overview

- What questions do Scientific & Regulatory Consultancies need to address?
- How does the Clickable Framework help?

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II

*(Non-legislative acts)*

REGULATIONS

**COMMISSION REGULATION (EU) 2018/1881**

**of 3 December 2018**

**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**

(Text with EEA relevance)

# "Routine" Consultancy Questions

## REACH Annex relevant questions

1. What substance (nanoform) is it anyway?
2. Does it form part of a "set"?
3. Is there literature available on the nanoform or a similar nanoform(s)?
4. Are there alternative sources for the information needed for REACH (e.g. QSARs, read-across, in vivo, in vitro, epidemiological)?

- Can we justify the use of fulfilling data-gaps using (Q)SAR methods or other non-testing methods? (**Annex VII-XI**)

5. Is there information on exposure, use and risk management measures (including effectiveness)?

~~7. N-octanol water Partition coefficient~~ …. What is more useful then?

8. Will there be exposure to particular compartments or not?

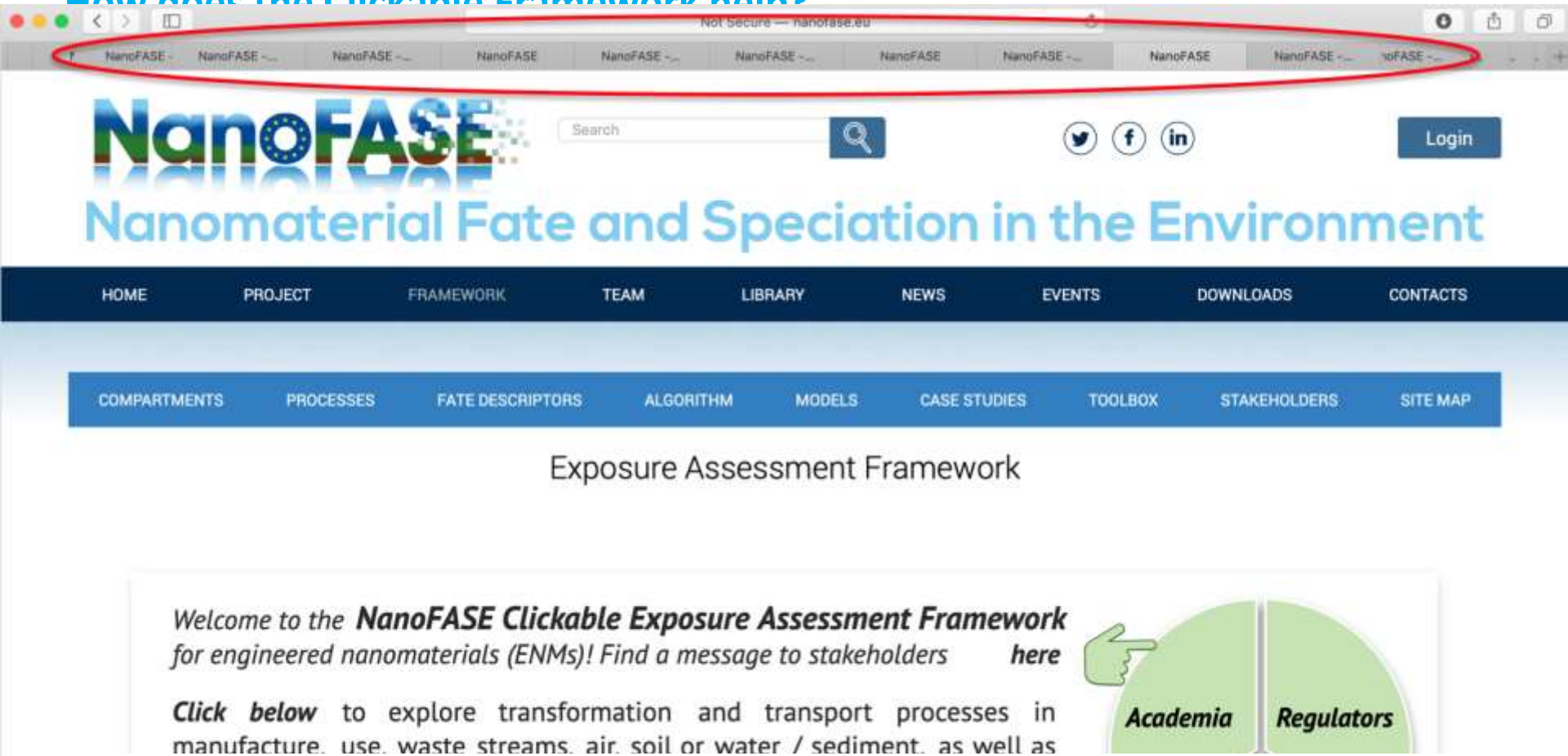
## "Routine" Consultancy Questions

**REACH Annex relevant questions**

9. Can we prove acceptable risk at Tier 1, if not are there models or information that can make our environmental exposure assessment more realistic?
10. What is the bioaccumulative potential of the nanoform?

- **Data-gap analysis/ITS**
- **Endpoint fulfilment**
- **Exposure assessment during chemical safety assessments**

## How does the Clickable Framework help?




*N.B. it is also a good idea to use existing guidance to aid what you are looking for e.g. the new Guidance on how to register*

## Question 1

### 1. What substance (nanoform) is it anyway?

Under REACH or any other regulation it is imperative to know what the substance is.

**Areas of the framework that can help:**


Under the **Characeterisation** tab a **suite of techniques** used by the NanoFASE scientists are available.

Clicking on the relevant techniques gives further breakdown, accompanying references and, when available relevant guidelines.

For example Clicking on DLS returns the relevant **ISO guideline ISO22412 (2017) Particle size analysis - Dynamic Light Scattering (DLS)**.

Could be more though considering the advancements and guidance available…

## Question 2, 3 & 4

2. **Does it form part of a "set"?**
3. **Is there literature available on the nanoform or similar a nanoform(s)?**
4. **Are there alternative sources for the information (e.g. QSARs, read-across, *in vivo*, *in vitro*, epidemiological)?**

**Areas of the framework that can help:**

***Almost all of it – therefore it must be a focused search!***

Generally, any information on physical-chemical, fate and bioavailability from **relevant and reliable** research which shows the nanoform(s) act in the same or a similar manner can be used as evidence to conclude they form part of a set or used for read-across.

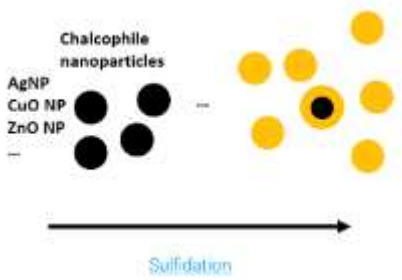
Or perhaps you find research that can directly fulfil and endpoint… or **protocols** to help determine ITS.

The experimental data along with the characterisation should be used in a weight of evidence.

## Question 2, 3 & 4

For example:

After Ag NM release to the environment it is now well known that the nanomaterial's (unless highly protected by a specific coating) main transformation products is $Ag_2S$.




Within the framework several references can be used to support this. This may mean conducting a hazard(incl. testing)/safety assessment on the most relevant form is needed e.g. $Ag_2S$. Or that you are able to find sufficient data to show that this form does not present a hazard (not bioaccumulative/bioactive).

If you can prove your nanomaterial to be within this group using relevant ITS (e.g. using a "Functional Fate Assay"), you may be able use any other information which are from nanoforms within this group (Functional Fate Group). Thus also literature from NanoFASE in a W.o.E or for endpoint fulfilment e.g. transformation.

 N.B. Acceptance of tests that are not done by international guidelines (i.e. fully validated and accepted is case-by-case)

## Question 5

**5. Is there information on exposure, use and risk management measures (including effectiveness)?**

During safety assessment and submission of a dossier for > 10 tonnes data must be provided on nanoform use and their subsequent levels in the environment. During exposure assessment it is possible to refine the release of a substance by accounting for either risk management measures or the substances expected life-cycle. This helps lead to the conclusion of acceptable risk, based on more “real-life” scenarios.

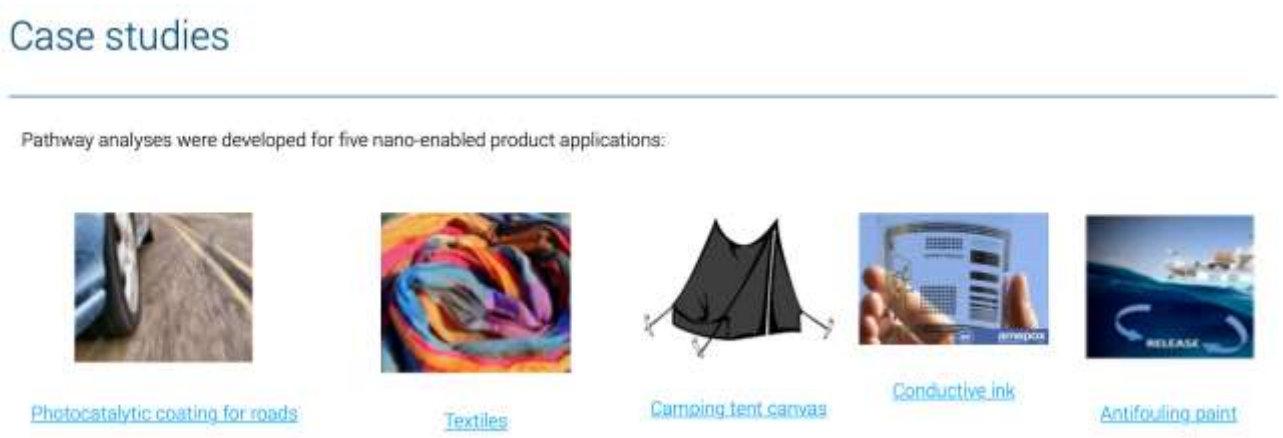
**Areas of the framework that help:**


For example: Pilot studies conducted during NanoFASE have showed that up to 95 % of silver nanomaterials are lost to sludge. Therefore during modelling of fate and exposure it may it could be possible to refine the environmental release factors for Ag NM.

## Question 5

5. **Is there information on exposure, use and risk management measures (including effectiveness)?**

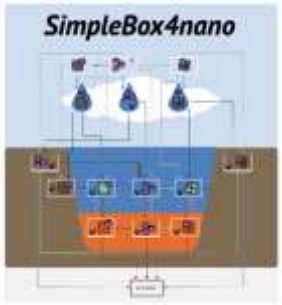
**Areas of the framework that help:**




The case studies may also help refining environmental release category default factors. For example for ERC10a/11a **Widespread use of articles with low release (outdoor/indoor).**

## Question 6

### 6. Partition coefficient n-octanol water…. What is more useful then?




The SimpleBox4nano button, leads to information on the driving forces behind some of landscape modelling for nanoforms and their eventual fate.

e.g. thermodynamic equilibrium is replaced by rate constants such as

- Dissolution
- Aggregation

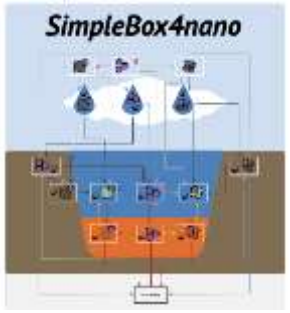
By knowing the workings of the model it begins to highlight the most critical endpoints for accurate exposure assessment…. What about EPM…? Should we test on worms and how?

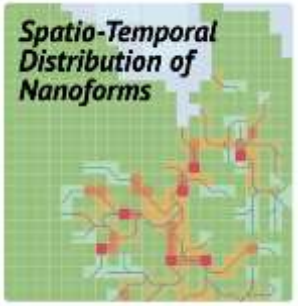
## Question 7

### 7. Will there be exposure to particular compartments or not?

Part of the risk assessment also involves highlighting compartments of concern or those areas/processes for which you do not believe relevant as the substance is unlikely to end up.

**Areas of the framework that may help:**


Once the relevant inputs for the models have been acquired, these models may highlight areas of concern. This will lead to appropriate risk mitigation strategies or highlight the need for more information.

Is regional really Tier 1? Or just regional? How do we best apply regional and local?

## Question 7

**7. Will there b**

**Areas of the fra**

| CASE STUDY | ENMs | LCS STUDIED | RELEASE RATE | RELEASE FORM | COMPART-MENT |
|---|---|---|---|---|---|
| **Camping tents (1 coating)** | Ag-PEI NPs | End of life (leaching) | 183 ± 3 (Ag µg / textile $m^2$) 1.07 ± 0.02% | Ionic ($Ag^+$): 41 ± 0% <20 µm: 37 ± 6% >20 µm: 22 ± 2% | Soil |
| **Camping tents (2 coatings)** | Ag-PEI NPs | End of life (leaching) | 161 ± 7 (Ag µg / textile $m^2$) 0.53 ± 0.02% | Ionic ($Ag^+$): 45 ± 4% <20 µm: 36 ± 2% >20 µm: 19 ± 4% | Soil |
| **Curtains** | $TiO_2$ | Use (washing) | 9 ± 2 % (in 10 washings) | Aggregate | WWTP |
| **Antibacterial textile** | Ag-PVP NPs | Use (washing) | 70 ± 2 % (in 10 washings) | $Ag^+$ | WWTP |
| **Antibacterial textile** | Ag-PVP NWs (~3 µm) | Use (washing) | 59 ± 9 % (in 10 washings) | $Ag^+$ and free NWs | WWTP |
| **Antibacterial textile** | Ag-PVP NWs (~30 µm) | Use (washing) | 73 ± 2 % (in 10 washings) | $Ag^+$ and free NWs | WWTP |
| **Antifouling paints** | Nano-$Cu^0$ | Use (immersion in marine water) | Cu: 0.00026 ± 0.00004% Zn: 0.00235 ± 0.00101% | $Cu^{2+}$ and malachite $Zn^{2+}$ | Water |
| **Antifouling paints** | Nano-$Cu_2O$ | Use (immersion in marine water) | Cu: 0.00050 ± 0.00029% Zn: 0.00681 ± 0.00915% | $Cu^{2+}$ and malachite $Zn^{2+}$ | Water |

It is also importa e of the material release ycle processes, they can also (sc , will be present after th

## Question 8

**8. Can we prove acceptable risk at Tier 1, are there models or information that can make our environmental exposure assessment more realistic?**

Risk assessment is a tiered process. It is, therefore, critical we have tools at varying "tiers". Each further building on the realism of the scenario, but usually also requiring further information either experimental or on such things as RMMs and OCs.

**Areas of the framework that may help:**


The model catalogue presents a suite of exposure models that are of varying levels of complexity including one based on the regulatory accepted SimpleBox. This reduces the need for monitoring or can be used prior to production/use.

Further the breakdown of the varying algorithms allows, an appropriate expert, to manipulate the model by inputting known parameters of their nanoform in place of those that are predicted. For example if release to air is known, but no others….

## Question 9

**9. Can we prove acceptable risk at Tier 1, are there models or information that can make our environmental exposure assessment more realistic?**

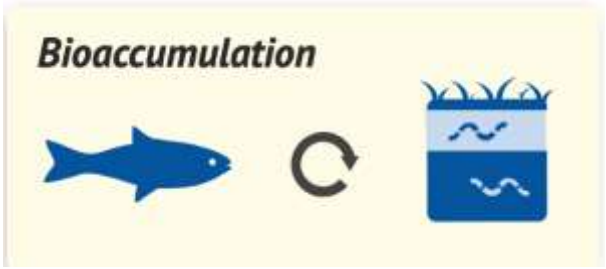
Further to that previously stated, the refinements may also consider those aspects covered in question 5 e.g. refinement of releases, which could ultimately feed into these models…. nanoERCs?

## Question 10

**10. What is the bioaccumulation potential of the nanoform? (also Annex XIII)**

Bioaccumulation is a standard endpoint requirement at higher tonnages (> Annex IX; 100-1000 T), but also a PBT assessment (which may not be fully possible) must be made from Annex VIII (10-100 T) onwards. Information on bioaccumulation can also be used in a WoE for classification and labelling.

**Areas of the framework that may help:**




This area of the framework presents algorithms for uptake and depuration, and together the steady state concentration…. But what constitutes bioaccumulative… BCF/BLM/PBPK? The need for detoxification mechanism inclusion. Current metal frameworks rely bioavailability and bioactivity (i.e. dissolved vs. relevant effect level).

What is the measure and the cut-off?

# Conclusion

## Good bits

- Can the Clickable exposure framework help consultancies? Yes;
- User friendly/ good first principles – but best to enter with a specific purpose;
- Plethora of information;
- Important for Consultants to remember that the tool does not directly provide answers but can lead you to:
    - Critical principles (aiding in ITS etc., algorithms and there inputs);
    - Critical research (perhaps for use as read-across or directly?);
    - Protocols (including internationally recognised guidelines and more bespoke or not yet validated protocols);
    - Models (Tier 1 and higher);
    - Refinement possibilities;
    - Best used in conjunction with other guidelines.

# Conclusion

## Cons/Improvements

- A few less Clicks to get you there would be good in some areas;
- Tabulation of key results (e.g. release factors) and references after the initial Click;
    - Including perhaps breakdown of recognised techniques and how they worked or didn't (some reviews available… when you can find them)
- More references under the first Click including the relevant draft/final international guideline when available;
- More in the protocols section – along with future plans to feed into IGs (first click!)
- Data could be maximised e.g. nano spERCs
- Protocols section could be better & knowledge base access;
    - E.g. transformation protocols? How do we measure in complex matrices?
- Some areas felt unfinished/left wanting more.

## Conclusion

**Good for research – there are still questions!**

- Guidelines needed e.g. worms, bioaccumulation;
- Collating the data -> specific release categories;
- Cut-offs e.g. bioaccumulation/ classification;
- EPM (transformation rate modelling for effect) for nano – is it possible to use aquatic tox. endpoints to estimate sediment and soil tox. endpoints… or is there no relationship.

…..Hopefully it stays live.

## Thank you for Listening…

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