
# Safety and regulation of graphene –

# An overview spring 2019

Erik Nilebäck, Chalmers Industriteknik

2019-06-19

Med stöd från

VINNOVA
Sveriges innovationsmyndighet

Energimyndigheten

FORMAS

Strategiska innovations-program

## Introduction

The development of nanotechnology during the last decades have increased the number of nanomaterials that are used in a wide range of applications from consumer products and beyond. This technological advancement also has the effect that humans and the environment are more exposed to nanomaterials today. To ensure a safe development of nanotechnology, regulatory bodies have started to enforce registration of nanomaterials used in industry and companies are required to stay up-to-date and follow these new directives. Safe handling and use of new materials and products containing such materials is a prerequisite for successful innovation.

The goal of this report is to give a brief overview of the current status regarding safety and regulations of graphene-based materials and products containing graphene. Focus will not be on details of the field of nanosafety research but rather to give some insight into what safety regulations a Swedish company producing graphene containing products or using graphene in their processes should consider. Some background on safety assessment of graphene is also provided.

During the preparation of this report, as well as in the communication with companies using graphene, it has become evident that the information from regulatory bodies on how to implement nanomaterial safety requirements can be challenging to interpret. This can lead to uncertainties from actors using nanomaterials to know how to act and what is required from them. In this report we attempt to address some of the sources of this uncertainty by consulting directly with the Swedish Chemical Agency (KEMI) concerning the compulsory declaration of nanomaterials in notifiable products active from 1 February 2019.

In addition to the national nanomaterial registration this report will also cover the upcoming amendment of the EU regulation on nanomaterials that be in force from 1 January 2020 which all companies producing or importing nanomaterials (including graphene) in amounts > 1 ton need to fulfill.

# Table of contents

# 1. Safety of graphene

Due to their unique properties, graphene and its derivatives are considered to be one of the keys for the future technological development of advanced materials. Therefore, graphene materials are more common today in both products and in industrial processes. Humans and the environment are thus more exposed to graphene, and the potentially toxic effects of graphene production and use are being investigated. Here the main results from a recent review on graphene safety will be presented to set the current status on the effect of graphene on human health and the environment.

## 1.1 Graphene Flagship

The EU funded program Graphene Flagship is the largest research collaboration in the EU, focusing on all aspects of applying graphene in a scientific and industrial environment.[1] One such aspect is the safety assessment of graphene and recently a comprehensive review was published by researchers in the Graphene Flagship that are investigating the safety of graphene with regards to human health and the environment.[2]

This review summarizes the main aspects of the current status on graphene nanosafety and an interview (in Swedish) with one of the main authors, Prof. Bengt Fadeel from the Karolinska Institute, can be found on the SIO Graphene website.[3]

The main points from the review and interview are summarized below:

- For safety assessment graphene should be considered as a *class* of materials (graphene-based materials) since they can differ in terms of lateral dimensions, number of layers, and carbon-to-oxygen ratio (e.g., graphene *versus* graphene oxide).
- The heterogeneous character of graphene-based materials makes detailed and careful characterization of graphene crucial. Without detailed data it is impossible to draw any conclusions when comparing safety assessment studies. This is the main message from the review, **characterization is key**!
- In the characterization it is important to use validated assays that have been agreed upon by the scientific community (and have acquired regulatory acceptance) to further increase the quality of data and the possibility to find activity-structure relationships.

[1] www.graphene-flagship.eu
[2] Fadeel, Bengt et al. 2018. "Safety Assessment of Graphene-Based Materials: Focus on Human Health and the Environment." *ACS Nano* 12(11): 10582–620. http://pubs.acs.org/doi/10.1021/acsnano.8b04758 (December 14, 2018).
[3] https://siografen.se/intervju-med-bengt-fadeel-om-sakerhetsutvardering-av-grafenmaterial/

- **Toxicological screening methods for graphene are still being developed**. The hydrophobic nature of graphene makes it very difficult to use in e.g. regular cell toxicity tests and this needs to be investigated further. This is one of the main challenges in terms of investigating the effect of graphene on human health and the environment.
- Safety aspects needs to be thoroughly assessed in the production and use of graphene. How can the exposure to humans and the environment be reduced to a minimum? In general, more work has focused to date on *hazard* assessment, but information is lacking in terms of *exposure* assessment. Risk is a function of both hazard and exposure.
- Graphene can be contaminated with bacterial endotoxin because of the non-sterile production and difficulty to sterilize the material and this may cause problems in medical applications.
- Water-soluble graphene oxide (GO) has been investigated in many toxicological studies presented in the review on different test systems. In general, graphene oxide shows low toxicity compared to other nanomaterials such as carbon nanotubes. Though, the authors emphasize that more studies are needed where the structure of the nanomaterial is more thoroughly characterized to find structure-activity relationships.

In conclusion:

The safety aspects of graphene-based materials need to be investigated further with well-structured studies aimed at defining structure-activity relationships. Many studies have been performed, mainly on water-soluble graphene oxide, though these studies often lack detailed characterization of the material. By increasing the amount of characterization data on graphene-based materials used in safety assessment, a safe-by-design principle could be considered where the adverse impact of graphene-based materials on human health and the environment is kept at a minimum.

## 2. Regulation of nanomaterials

The increased use of nanomaterials has led to many national and international initiatives to define laws, rules and regulations to ensure a safe development and use of nanomaterials.

### 2.1 Regulation in Europe

In the European Union, the European Chemical Agency (ECHA) is the European governing authority when it comes to chemical safety, which also include nanomaterials. The Swedish competent authority (CA) carrying out the legislation from ECHA, governed by the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, is the Swedish Chemical agency (Kemikalieinspektionen, KEMI). REACH is a regulation adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals.

Recently, in May 2019, a free web tool called eREACHNano was launched to help companies with registration of nanomaterials.[4] This web tool is a joint effort by the Nordic Council of Ministers and developed together with the software and engineering consultant firm DHI. This is a good resource for introducing the concepts of nanomaterials, risk and EU regulation to small and medium sized companies that may lack dedicated regulatory resources in-house. With this tool supported with this report companies are well-equipped to increase their knowledge in the field of nanomaterial safety and regulation.

The establishment of a European register of nanomaterials produced in, or imported to, Europe under ECHA has been processed for many years. Due to slow progress, many countries, including Sweden have set up national registries. These registries (so far Denmark, France, Belgium, Sweden, The Netherlands, Germany, Italy and Norway) varies in terms of information needed. Since this report is part of SIO Grafen we will here focus on the Swedish registry.[5]

[4] http://ereachnano.dhigroup.com/
[5] https://swenanosafe.se/kunskapsbank/dansk-rapport-jamfor-register-for-nanomaterial-i-europa/

For registration both to KEMI and ECHA under REACH, companies in the EU (researchers are generally excluded[6]) need to identify themselves into one of the following categories[7]

> **"Manufacturer:** If you make chemicals, either to use yourself or to supply to other people (even if it is for export), then you will probably have some important responsibilities under REACH.
>
> **Importer:** If you buy anything from outside the EU/EEA, you are likely to have some responsibilities under REACH. It may be individual chemicals, mixtures for onwards sale or finished products, like clothes, furniture or plastic goods.
>
> **Downstream users:** Most companies use chemicals, sometimes even without realizing it, therefore you need to check your obligations if you handle any chemicals in your industrial or professional activity. You might have some responsibilities under REACH."

Most companies using graphene in their production are most likely identified as "downstream user" according to the above definition and therefore has no obligation to register to ECHA or KEMI. Though they are obliged to follow all safety recommendations from the supplier and to inform they supplier on their intended use of the chemical products or nanomaterials.

All Swedish *producers* or *importers* of chemical or biotechnical notifiable products must register their activity if the annual production exceeds 100 kg to KEMI. More details regarding the registration procedure can be found here: https://www.kemi.se/produktregistret. If the amounts exceed 1 ton a year, the registrant must also register at ECHA.[8]

If you find any of the components in your product in the list[9] from the Ministry of the Environment and Energy you need to register at KEMI.

Today, graphene is not included in this list with an exclusive toll number. However, KEMI claims that graphene containing products should be registered, using for instance one of the codes for graphite:

[6] https://echa.europa.eu/regulations/reach/registration/research-and-development
[7] https://echa.europa.eu/regulations/reach/understanding-reach

[8] https://echa.europa.eu/sv/regulations/reach/registration
[9] http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/forordning-2008245-om-kemiska-produkter-och_sfs-2008-245#Bilaga

”3801 Konstgjord grafit; kolloidal och halvkolloidal grafit; preparat på basis av grafit eller annat kol, i pastaform eller i form av block, plattor eller andra halvfabrikat; registreringsplikten omfattar endast:

3801 10 Konstgjord grafit.

3801 20 Kolloidal eller halvkolloidal grafit.”

**How does this translate to nanomaterials?**

The question as to the definition of a nanomaterial is something that has been debated in the EU and elsewhere for a long time. The Joint Research Centre (JRC) of the European Commission published a report with a summary of the (legal) definitions of a nanomaterial.[10]

It is important to note that graphene flakes and single walled carbon nanotubes with one or more dimensions below 1 nm are included in the European definition of a nanomaterial.[11]

If the nanomaterial itself is imported or produced in yearly quantities exceeding 100 kg or is part of products that are produced or imported in those amounts, then it must be registered to KEMI and the following characterization data needs to be provided:

- classification according to the CLP regulation 1272/2008
- function of the nanomaterial
- particle size
- form
- crystalline state
- surface area
- coating
- surface charge
- if the nanomaterial is present in agglomerated or aggregated state (assembly of materials) the mean size should be stated.

As there is not yet a standardized procedure on how to measure all of these properties in 2D materials, this might be a challenge. The complexity of knowing what to do in this area can be seen in the CLP regulation 12/2008[12] (CLP stand for “classification, labeling and packaging).

[10] https://ec.europa.eu/jrc/sites/jrcsh/files/jrc_reference_report_201007_nanomaterials.pdf
[11] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC113469/kjna29647enn.pdf
[12] https://eur-lex.europa.eu/legal-content/SV/TXT/PDF/?uri=CELEX:32008R1272&from=SV

It is a 1355-page document including the desired classification information on included substances at the end of the document. This list consists of chemicals, and "graphene" or "graphene oxide" cannot be found. To our knowledge there is no CLP regulation for graphene. Materials such as "MWCNT", "nanotube" and "fullerene" are not included either. Since the decision process of adding chemicals to the CLP list is long process ECHA provides a database called Public Activation Coordination Tool (PACT[13]), where information regarding activities under REACH that might lead to future regulation can be found. Interestingly, "Multi-Wall Carbon Nanotubes (MWCNT), synthetic graphite in tubular shape" are listed in PACT, which might indicate future regulation of this material. Graphene is not on the PACT list (yet).

## 2.2 Implication for Swedish companies using graphene

All regulation under ECHA and KEMI target companies. Academic researchers are not covered by this regulation and it is very unlikely that any academic production reaches the volumes that are regulated (>100 kg). Every company producing or importing chemicals needs to stay up-to-date and informed if their products needs to register the inclusion of intentionally added nanomaterials, such as graphene.

One **important exception to be aware of is that** if the company has a yearly turnover <5 MSEK, or if the nanomaterial only is a pigment, then they only need to notify KEMI that the nanomaterial is included in the product (without the characterization data listed in 2.1).

If the turnover of the company is > 5 MSEK and the products must be registered, then the characterization data for the included nanomaterial must be provided. The source of that data should ideally be the nanomaterial producer (if not the registering company itself) and therefore it is recommended to require material datasheets from the producer.

## 2.3 CASE – graphene in an industrial process

SIO Grafen was contacted by a Swedish company using graphene in their processes for guidance, whether they need to register to KEMI or not. This company has a turnover > 5 MSEK and would therefore need to provide the characterization data stated above. The process of collecting this data would then potentially lead to increased costs and delays in production.

[13] https://echa.europa.eu/sv/pact

After reading regulations and discussing with KEMI, the company got a verification from KEMI that since their processes include less than 100 kg graphene per year, they do not need to register to KEMI. The company was thus classified as a "downstream user" and not an importer as it would have been if they bought more than 100 kg graphene/year from outside of EEA/EU.

This company case has served as inspiration for sections 2.1-2.2 and hopefully this report can be used as some guidance for companies in a similar situation.

## 2.4 Short guidance list for Swedish companies

First line of information on registration of chemical products should be KEMI[14]. Always turn to them first for updated information even though the information below can be used for guidance.

- You must notify of added nanomaterial in your notifiable products to KEMI if:
    - You include > 100 kg nanomaterial (e.g. graphene) annually in your products that you produce or import. This also implies if you import 100 kg of nanomaterial annually. If the amount produced or imported exceeds 1 ton you also must register at ECHA.
    - You produce or import products including nanomaterials with a total product volume > 100 kg annually. Bear in mind that the amount of nanomaterial in the product can still be in low amounts.
- You only need to notify KEMI of the nanomaterial in your products (no characterization data) if either:
    - Your company has an annual turnover below 5 MSEK.
    - Your nanomaterial is used only for pigments.
- Again, if unsure, contact KEMI to get first-hand information.

[14] www.kemi.se

### 2.5 SweNanoSafe

Following a decision by the Swedish Government, SweNanoSafe[15] was established in 2016 as a platform for national information and collaboration regarding nanosafety. The background to this decision was an investigation carried out on the behalf of the Swedish Government that was presented in 2013.[16] SweNanoSafe is an excellent resource for information on nanosafety related questions both for industry and academia.

## 3. REACH amendment and future EU regulation

The reason for the considerable effort to register and keep track of nanomaterials, is to avoid situations where nanomaterials becomes a case in a "late lessons from early warning"-report. [17]

These reports have been highly acknowledged and describes different scenarios where early warnings of toxicity were ignored and later had severe consequences, this was the case for e.g. DDT, asbestos, radiation and halocarbons. For nanotechnology, the "precautionary principle" is adapted to instead turn this into "early lessons from early warnings", by carefully screening new nanomaterials to greatly reduce the risk of creating the next asbestos. [18] (Foss Hansen et al. 2008)

A considerable undertaking of ECHA has been the process to prepare the regulation Registration, Evaluation, Authorization and Restriction of Chemicals, known as REACH, that entered into force in 2007.

REACH was adopted to decrease the impact of the use of all chemical substances on the environment and human health and at the same time increase the control and quality of the European chemical industry. REACH is the underlying framework for all the registration procedures covered in section 2.1 – Swedish regulation.

[15] www.swenanosafe.se
[16] https://www.regeringen.se/49bba7/contentassets/9b5e3cd243354810a54fb230576bf7fb/saker-utveckling---nationell-handlingsplan-for-saker-anvandning-och-hantering-av-nanomaterial-sou-201370

[17] https://www.eea.europa.eu/publications/late-lessons-2
[18] Foss Hansen, Steffen, Andrew Maynard, Anders Baun, and Joel A. Tickner. 2008. "Late Lessons from Early Warnings for Nanotechnology." *Nature Nanotechnology* 3(8): 444–47. http://www.nature.com/articles/nnano.2008.198

On December 3rd, 2018, ECHA approved a revision of REACH covering the information requirements by companies registering nanomaterials to ECHA that will significantly increase the test burden on the registrant from 2020. [19] **Companies producing or importing nanomaterials in volumes > 1 ton need to register their nanomaterial** (called nanoform) to ECHA and follow the new amendments from 1 January 2020. This is essentially different from the Swedish registry where the volume of produced or imported nanomaterial or product containing nanomaterial is only 100 kg.

It is important to note that when acquiring graphene in quantities above 1 ton, you do not need to register if the producing company resides within the EU. Then the task to register to ECHA and to comply with REACH lies with the producing company and you as a downstream user do only need to follow their safety data sheet and do not need to register again to ECHA.

Clausen and Hansen describe the amendments and their effects in detail in a recent publication, clarifying that this will be costly for companies using amounts above 1 ton of nanomaterials, such as graphene.[20] There is especially a larger number of toxicity tests to be performed and documented. Since these tests are in general more time-consuming than regular material characterization careful planning will be needed.

Together with member states, industry, NGOs and expert panels ECHA has prepared practical guidelines on how to register nanoforms.[21]

The guidance was published in 2017 and is under revision to be aligned with the amendments of the Annexes and will hopefully be published in good time before 1 January 2020.

[19] https://echa.europa.eu/sv/-/companies-to-provide-more-information-on-nanomaterials

[20] Clausen, Lauge Peter Westergaard, and Steffen Foss Hansen. 2018. "The Ten Decrees of Nanomaterials Regulations." *Nature Nanotechnology* 13(9): 766–68. http://www.nature.com/articles/s41565-018-0256-2 .

[21] https://echa.europa.eu/sv/-/reach-guidance-for-nanomaterials-published