INN PRESSME
Open Innovation Test Bed

D8.5 Generic nanosafety guidelines for project partners

Report

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Technical References

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[1] PU = Public
PP = Restricted to other programme participants (including the Commission Services)
RE = Restricted to a group specified by the consortium (including the Commission Services)
CO = Confidential, only for members of the consortium (including the Commission Services)

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Document history

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Summary

The nanosafety studies performed in the frame of INN-PRESSME project aim at ensuring operators' nanosafety throughout the production, processing, and transformation of bio-based materials on the sixteen pilot lines.

The first eighteen months are dedicated to providing the generic guidelines to the whole consortium, the selection of the 3 pilot lines where the measurement campaigns will be performed, and the continuous support for all the pilot lines. Therefore, a nanosafety workshop was held in November 2021 during the consortium meeting. This two-hour presentation aimed at introducing nanosafety concerns and raising awareness of nanosafety guidelines for all INN-PRESSME partners. The main information is detailed in this report. Additionally, nanosafety questionnaires were circulated among pilot line owners at the beginning of the project. The information collected allowed us to perform a preliminary nano-risk assessment based on a chemical risk assessment approach. According to the assessment results, three pilot lines have been selected for the nano-measurement campaigns:

- PL6 because powder nanoparticles are handled;
- PL8 due to the large number of tasks/chemicals with a medium inhalation potential priorities;
- PL16 because unintentional release of nanoparticles could occur during the printing.

The release, emission, and occupational exposure assessment for three pilot lines will be performed in the second half of the project and will be the subject of D8.6.

Disclaimer

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Glossary

ATEX: Explosive Atmosphere

CLP: Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures…

CNC: Cellulose nanocrystals

CNF: Cellulose nanofibrils

ECHA: European Chemicals Agency

HEPA: High-Efficiency Particulate Arrester

IARC: International Agency for Research on Cancer

INCO: Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers…

INRS: Institut National de Recherche sur la Sécurité au Travail

MSDS: Material Safety Data Sheet

NOAA: Nano-Object, their Aggregates and their Agglomerates.

PL: Pilot line

REACH: Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)…

SOBANE method: Screening, Observation, Analysis, Expertise

STOP principle: Substitution, Technical, Organisational, Personal

ULPA: Ultra Low Penetration Air filter

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1 Definitions

1.1 Scale

The nanometric scale characterises the infinitely small, "nano" coming from the Greek "nanos" meaning "dwarf". One nanometre equals 10^{-9} metres or one billionth of a metre, i.e. approximately 1/50000 of the thickness of a human hair. For comparison, there is the same difference in size between a particle of 1 nm diameter and an orange as there is between an orange and the planet Earth (Figure 1).

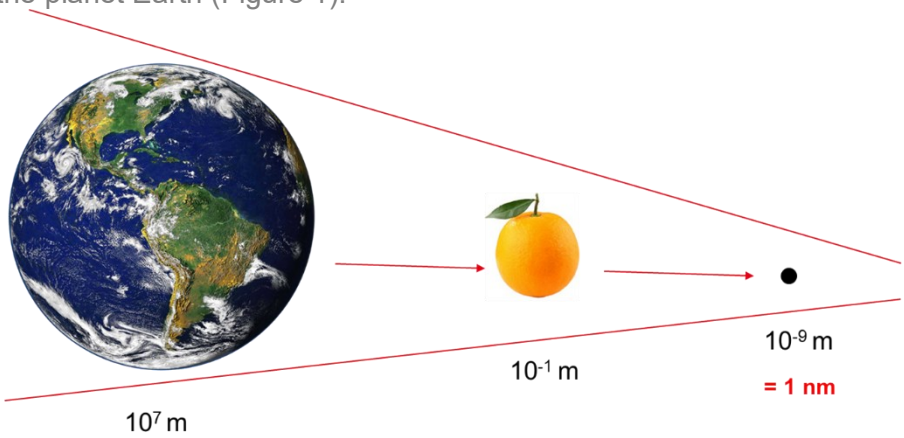

Figure 1. Nanoscale

At the nanometric scale, substances no longer respond to the laws of macroscopic physics but to the laws of quantum physics. This scale imparts unique physical, chemical, magnetic, and electrical properties to materials or objects, distinct from those observed at the micro or macroscopic scale, offering substantial innovation potential. At the nanometric scale, the surface-to-volume ratio increases considerably, as does the exchange surface. This results in greater reactivity of the substances, potentially giving rise to new properties and risks.

According to the ISO/TS 80004 - 1 standard, a nanomaterial is a material with an external dimension at the nanoscale or with an internal structure or surface structure at the nanoscale. A distinction must be made between nanomaterials of natural origin and nanomaterials of anthropogenic origin, either manufactured or unintentionally produced. Manufactured nanomaterials include nano-objects and nanostructured materials, as shown in Figure 2. Legislative definitions are presented in section 2 related to Nanosafety EU legislation.

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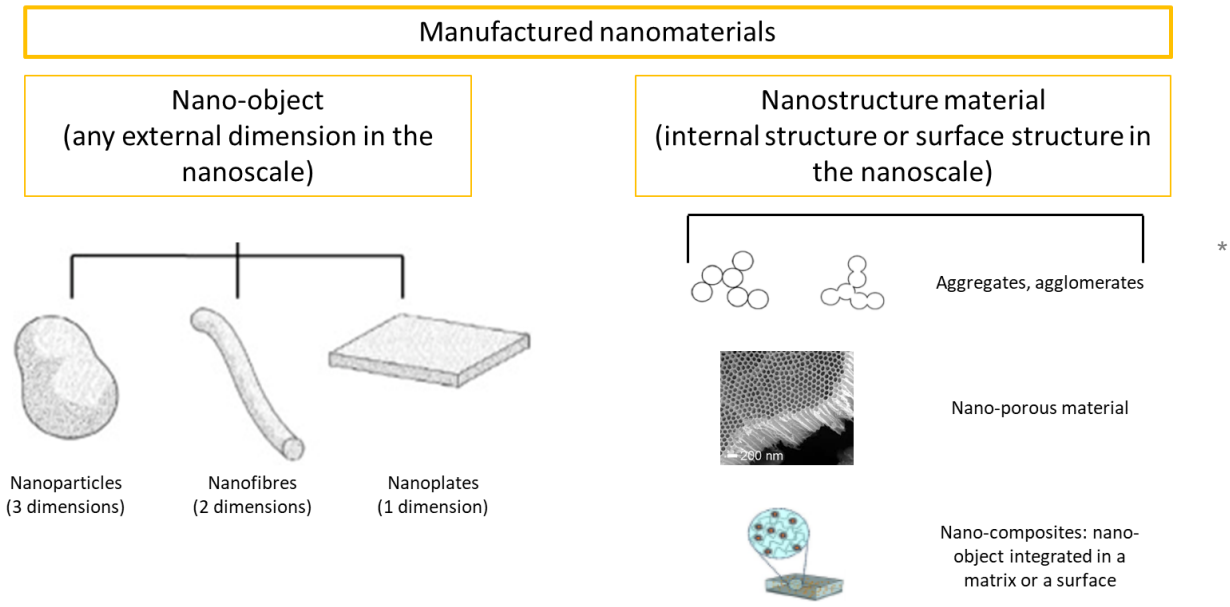

Figure 2. Manufactured nanomaterial definitions

(*) An aggregate is a particle comprising strongly bonded or fused particles, where the resulting external surface area may be significantly smaller than the sum of calculated surface areas of the individual components.
(*) An agglomerate is a collection of weekly bound particles or aggregates or a mixture of the two where the resulting external surface area is similar to the sum of the surface areas of the individual components.

In this report, NOAA will be used to mention the nano-objects, their aggregates, and their agglomerates.

Manufactured nanomaterials can be synthesised according to two main principles:

- The "bottom-up" approach consists of constructing nanomaterials atom-by-atom, molecule-by-molecule or aggregate by aggregate. The assembly or positioning of atoms, molecules or aggregates is carried out in a precise, controlled, and exponential manner, thus allowing the development of functional materials whose structure is completely under control.
- The "top-down" approach consists of reducing and miniaturizing bulk materials by fractionating them until they reach nanometric dimensions.

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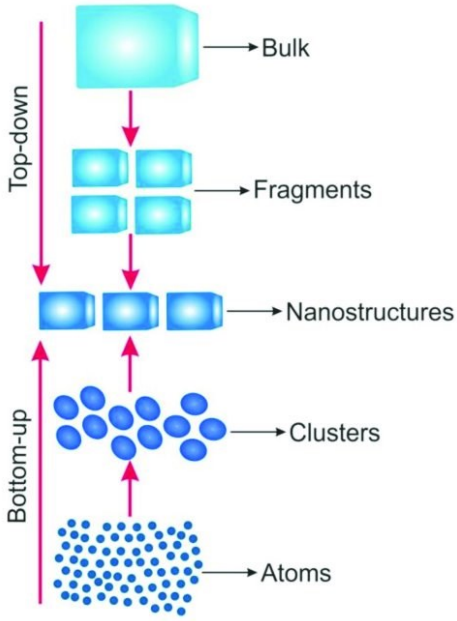

Figure 3. Schematic representation of the top-down and the bottom-up approaches for the fabrication of metal oxide nanostructures [1].

1.2 Prevention vocabulary

The words are defined below with the scope of chemical risk (including NOAA risk).

Hazard refers to the inherent properties of a substance that make it capable of causing harm to human health or the environment.

Exposure describes both the amount of and the frequency with which, a chemical substance reaches a person, group of people or the environment.

Risk is the possibility of a harmful event arising for instance from exposure to a chemical or physical agent, under specific conditions. *It thus represents the combination of hazard and exposure.*

2 Nanosafety EU legislation

This chapter sets out the main legislative texts applicable at the time the report was drawn up. Other regulatory texts (chemicals, noise …) may also be applicable depending on the actual activities carried out.

European law takes precedence over national law. Five categories of legal acts may be published in the Official Journal of the European Union: regulations, directives, decisions, recommendations and opinions. Regulations and decisions are directly applicable, without transposition into national law. They are legally binding acts. Directives must be transposed into national law within the prescribed time limit. These are objectives to be achieved by the member countries. Recommendations and opinions are not binding, they do not have the force of law. They are tools for the preparation of national legislation.

Since 2009, the term nanomaterials, or more recently nanoforms, appears explicitly in European legislation. Figure 4 shows the chronology of the consideration of these new materials.

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Figure 4. Chronology of nanomaterials consideration in EU legislation

Given the fields of activities of INN-PRESSME partners and their interest in specific subjects, the following sections therefore develop the INCO and REACH regulations. Regulations concerning cosmetics (Regulation (EC) No 1223/2009), biocides (Regulation (EU) No 528/2012) and novel foods (Regulation (EU) No 2015/2283) are not developed in this report.

INCO

On October 25th 2011, Regulation (EU) No 1169/2011 was published in the Official Journal of the European Union. This regulation defines "engineered nanomaterial' as follows: "*any **intentionally produced** material that has **one or more dimensions of the order of 100 nm or less** or that is composed of **discrete functional parts**, either internally or at the surface, many of which have **one or more dimensions of the order of 100 nm or less**, including structures, **agglomerates or aggregates**, which may have a size above the order of 100 nm but retain **properties that are characteristic of the nanoscale**.*
Properties that are characteristic of the nanoscale include:

(i) those related to the large specific surface area of the materials considered; and/or
(ii) specific physicochemical properties that are different from those of the non-nano form of the same material."

This regulation stipulates also how crucial consumer information is. Indeed article 18.3 states: *"All ingredients present in the form of engineered nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets."*

REACH

On December 3rd 2018, Regulation (EU) 2018/1881 was published in the Official Journal of the European Union. It amends Annexes I, III, VI, VII, VIII, IX, X, XI, and XII of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) to cover nanoforms of substances. This amendment concerns substance registrants (import > 1 tone/year). The information to be provided in the registration dossiers is clarified for the nanoforms of substances. The REACH Regulation places the burden of proof on companies. To apply it, companies must identify and manage the risks associated with the substances they manufacture and market in the EU. They must show to ECHA (European Chemicals Agency) how the substance can be used safely and communicate risk management measures to users.

This regulation is based on the definition of nanomaterials of the European Commission's recommendation of 18 October 2011, which states: *"Nanomaterial means a **natural, accidentally formed or manufactured material** containing free particles, in aggregate or agglomerate form, of which **at least 50% of the particles, in numerical size distribution**, have **one or more external dimensions between 1 and 100 nm**".* It is stated, *"In specific cases, where justified for reasons of environmental protection, public health, safety or competitiveness, the 50% threshold may be replaced by a threshold between 1% and 50%".* Any material, which has a specific surface area in volume greater than 60 m^2/cm^3, is also considered to fall under this definition. Despite a revised version expected since 2014, the definition has been included as it stands in REACH (2018).

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LEGISLATIONS DEALING WITH SAFETY

All the legislations dealing with safety at work apply to NOAA, even if NOAAs are not mentioned. Indeed, the NOAA-related risks must be managed as any other chemical risks.
Regulation (EC) No 1272/2008 published in 2008 in the Official Journal, known as CLP (Classification, Labelling, Packaging), sets out rules for the classification, labelling and packaging of chemicals. Since 2007, the obligation to draw up a Material Safety Data Sheet has come under Title IV and Annex II of the REACH regulation. In this case, the MSDS contains the hazard statements (H) and the precautionary statements (P). Particular attention must be paid to sections 7 "handling and storage" and 10 "stability and reactivity" which provide information on specific storage methods, storage temperatures or inert atmosphere.

Directive 2012/18/EU of the European Parliament and of the Council of 4 July 2012 on the control of major-accident hazards involving dangerous substances, amending and subsequently repealing Council Directive 96/82/EC. It is known as the SEVESO Directive.

Generally, the more the material is divided, the more its reactivity is increased (by increasing the exchange surface). Physical risks cannot be ignored (flammability, explosion, etc.). Concerning the risk of explosive atmospheres (ATEX), two directives apply:

- Directive 1999/92/EC, published in 1999 in the Official Journal, on minimum requirements for improving the safety and health protection of workers potentially at risk from explosive atmospheres (ATEX).
- Directive 2014/34/EU published in 2014 in the Official Journal, on the harmonisation of the laws of the Member States concerning equipment and protective systems intended for use in potentially explosive atmospheres.

In conclusion, there are a few legislations explicitly dealing with NOAA. However, the current "safety at work" legislations apply. NOAA risk must be managed in the same way as chemical risk.

3 Nano risk prevention

This chapter firstly details the generic risk prevention scheme (section 3.1). How to identify the risk related to NOAA (section 3.2) and to mitigate it (section 3.3) are then presented.

3.1 Global risk prevention

Usually in risk prevention (e.g. chemical risks), knowledge of the effects on health comes from epidemiological studies (Figure 5). Firstly, the substance is launched on the market. When health effects appear, clinicians then entrust these cases to epidemiologists. They highlight the common point between all the patients. Once the substance at the origin of these conditions has been identified, the epidemiologists pass on the information to toxicologists. The toxicologists define how the substance acts on living organisms and establish occupational exposure limits. Health and safety officers in their risk prevention policy use these values, once confirmed and validated by standards and/or regulations.

Figure 5. Classic prevention scheme

To date, no pathology has been identified or attributed to the exposure to NOAA.

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The prevention scheme is evolving, among other things via REACH, where predictive toxicology is required. Toxicologists, epidemiologists, metrologists, government agencies, etc. have joined their efforts to gain a better understanding of the possible effects of NOAA (Figure 6). As the risk assessor does not always have the information concerning the hazard of nanoforms, he must focus the action on exposure.

Figure 6. Joint action by prevention stakeholders in the case of NOAA

3.2 Identification of the risk related to NOAA

The general strategy of risk management SOBANE [2] describes a strategy for risk prevention in four levels: Screening, Observation, Analysis and Expertise. This strategy aims to coordinate the cooperation between workers, management, and internal and external Occupational Health practitioners and to implement adequate risk prevention faster and more cost-effectively. It follows the diagram of Figure 7 and the criteria is defined in Table 1.

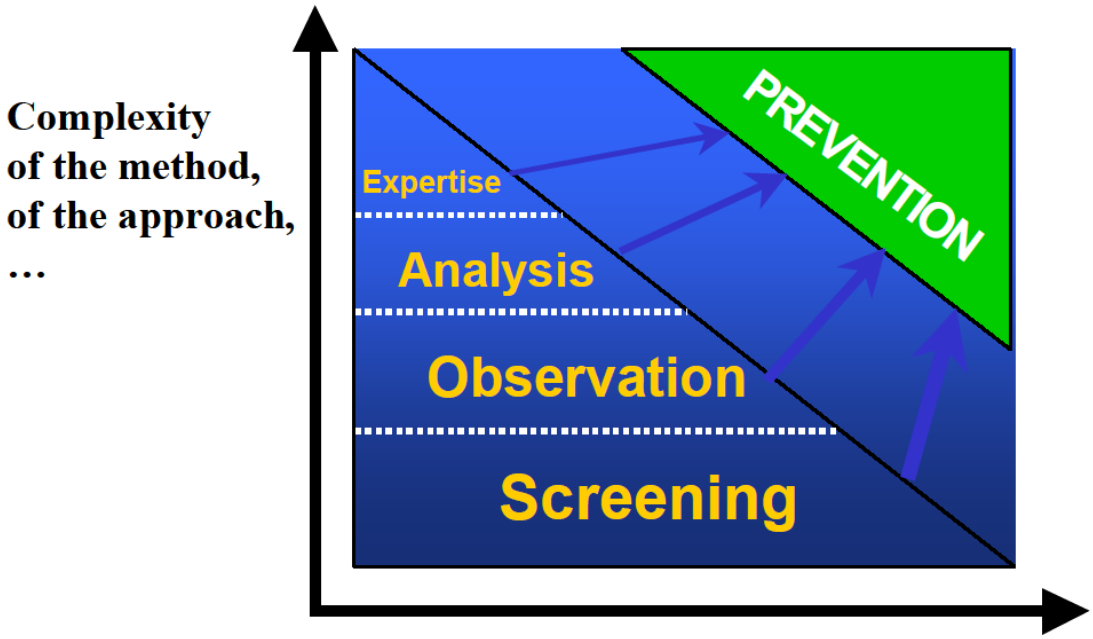

Figure 7. General outline of SOBANE strategy in risk management [2]

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Table 1. Characteristics of the four levels [2]

	Level 1 SCREENING	Level 2 OBSERVATION	Level 3 ANALYSIS	Level 4 EXPERTISE
When?	All cases	If problem	In difficult cases	In complex cases
How?	Simple observations	Qualitative observations	Quantitative observations	Specialised measurements
Cost?	Very low 10 minutes	Low 2 hours	Medium 2 days	High 2 weeks
By whom?	People of the company	People of the company	People of the company + OH practitioners	People of the company + OH practitioners + Expert
Qualifications *work situation *health at the work	Very high Low	High Overage	Average High	Low Specialised

The screening and observation steps are crucial for companies, such as the INN-PRESSME partners. Thus, these two levels are developed in this section.

The screening level aims to identify the main problems and to immediately solve the easiest ones. People who are thoroughly familiar with the work situation, even if they have no formal qualifications in safety theories, must conduct this identification internally. The method at this level must seek to identify the problems in all work circumstances. At this first level, some problems will already be solved; others will simply be identified and will be the subjects of study at level 2: Observation. The ED6174 from INRS (Institut National de Recherche et de Sécurité), which takes the form of a datasheets repository, is a support for identifying the manufactured nanomaterials handled in companies and for taking into account the potential associated risks [3].

The observation level aims to study in more detail the problems that were not solved at the screening level. This observation level requires a deep understanding of the work situation. The depth of the study will be variable according to the risk factor and the company size. The method should not require any quantification and therefore any measurements. Currently, finding a NOAA-specific observation tool is not easy. All the control banding or assessment tools specific to NOAA are intended for people with high knowledge in risk prevention (and in particular in chemical risk prevention). Thus, these tools are more in line with the SOBANE step 3: Analysis. However, the control banding tool developed by ANSES [4] or the method exposed by A. Groso [5] could be used to broadly discriminate the risk in several workstations.

The analysis level is performed in Chapter 6. The expertise levels will be performed with the support of CEA for 3 pilot lines.

3.3 Reduce the exposure to mitigate the risk

Risk is a combination of hazard and exposure (Figure 8). Even if nanoform hazards are still mostly unknown, means of prevention to be implemented to reduce workers' exposure are well established [6]. By reducing the level of exposure, the level of risk decreases even if no consensus exists on the hazard (Figure 8).

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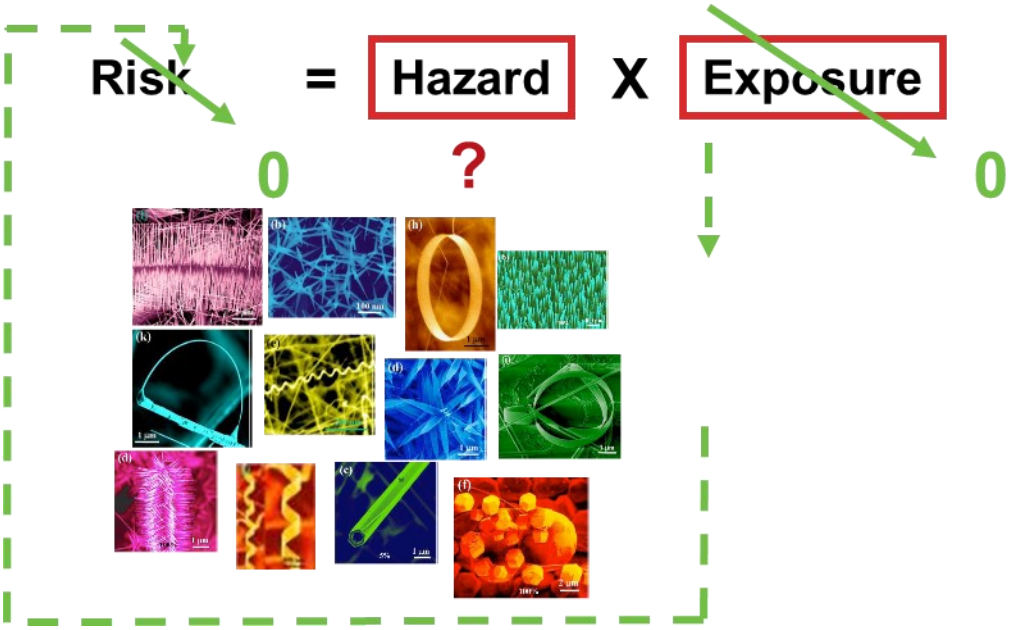

Figure 8. Risk is a combination of hazard and exposure

In occupational health and safety, the "STOP principle" is applied. It defines the hierarchy of protective measures and groups them. This principle can also be applied to the handling of nanomaterials. The safeguards in the handling of nanomaterials must be generally comparable to the handling of conventional materials (and dust in particular). The abbreviation STOP stands for Substitution, Technical measures, Organisational and Personal protective equipment.

The two following chapters develop the hazard effects and the exposure mitigation according to the STOP principle.

4 Health effects

This chapter focuses on the knowledge status regarding NOAA health effects.

Currently, there is no consensus on the toxicity of manufactured nanomaterials on humans. Most of the data comes from experimental studies carried out on cell cultures or animals. The results are difficult to extrapolate to humans [6] [7].

However, the effects of ultrafine particles from air pollution (e.g. produced by diesel engines, wood burning) or emitted during certain industrial activities (e.g. during welding processes) have been widely studied [8]. Epidemiological studies and human trials under controlled exposure conditions on this type of particles have proved the respiratory (inflammatory reactions, reversible obstruction of the small airways) and cardiovascular (myocardial ischaemic affections) effects, particularly in vulnerable people. Such effects are also suspected in case of exposure to certain manufactured nanomaterials.

Adverse effects on human health have already been widely documented for specific nanomaterials [9] such as fullerenes [10] or carbon nanotubes [11]. Furthermore, even if it is impossible to generalise this principle to all nanomaterials, more severe effects of nano-sized particles have been noted compared to particles of the same chemical nature in larger size [12]. The effects are inflammation, oxidative stress, fibrosis and the formation of granulomas and lung tumours.

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4.1 Entry pathway

In the workplace, inhalation is the main route of penetration of nanomaterials into the human body (ahead of transcutaneous and ingestion). Once inhaled, nanomaterials can either be exhaled or deposited in the different regions of the respiratory tract which are:

- the upper airways (the nasal fossae, mouth, pharynx and larynx),
- the trachea-bronchial tract (the trachea, bronchi and bronchioles),
- the pulmonary alveoli.

This deposition is usually not uniform throughout the respiratory tract. It varies considerably depending on the diameter, degree of aggregation and agglomeration and the behaviour of nanomaterials in air. Particles with a diameter between 10 and 100 nm are deposited mainly in the deep lung (in the pulmonary alveoli), in a much higher proportion than micrometric particles (Figure 9). Smaller particles, on the other hand, are deposited mainly in the upper airways and, to a lesser extent, in the tracheobronchial region (Figure 9).

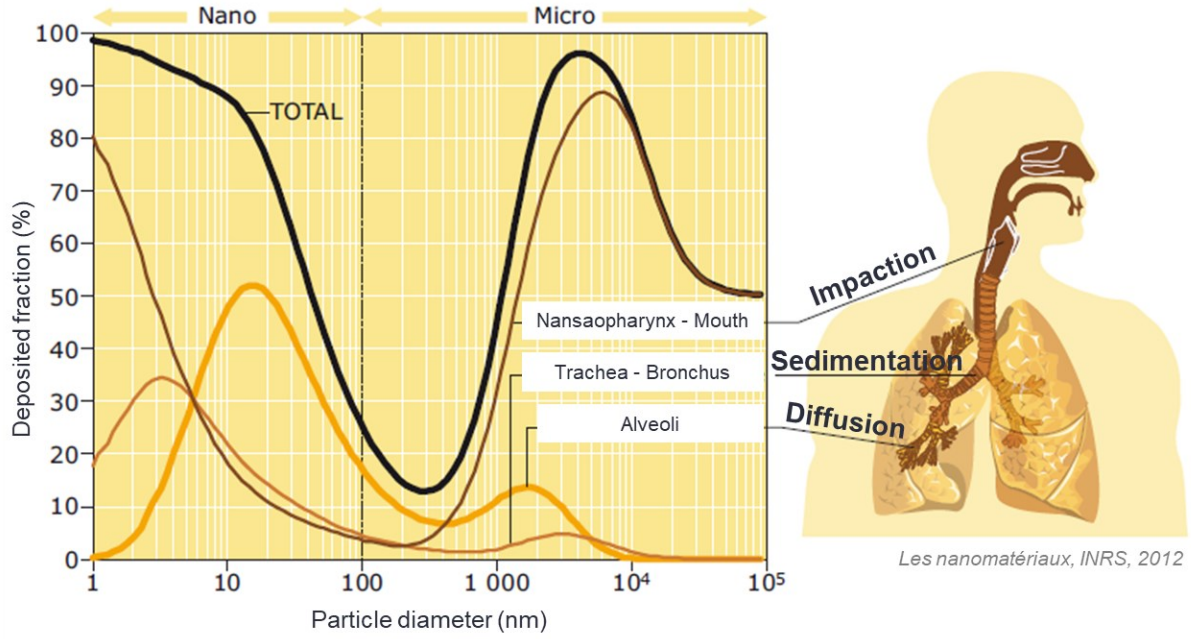

Figure 9. Airborne particle deposition fraction as a function of size and respiratory track location [7]

The transcutaneous passage of nanomaterials is a hypothesis that is still under study. Many parameters are likely to influence the penetration of particles through the skin (size, elasticity and surface properties of the particles, skin condition, mechanical stress, presence of sweat, etc.). This absorption can be a major exposure route for the NOAA in colloidal form. However, no consensus exists on this topic, so it is not possible to formally exclude any risk of transcutaneous passage [6].

4.2 Distribution in the organism and potential health effect

The toxicity of inhaled NOAA depends partly on their deposition in the respiratory tract (region, quantity, etc.) but also on the capacity of the respiratory tract to eliminate them partially or totally (clearance process). Two processes are involved:

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- chemical elimination, which consists of the dissolution of nanomaterials soluble in biological fluids. Chemical elimination processes occur in all regions of the respiratory system.
- physical elimination, which consists of the transport of insoluble or poorly soluble nano-objects to one or more other sites in the body and in particular to the mouth and nose. The mechanisms involved in physical elimination differ according to the regions of the respiratory system considered.

Mucociliary transport mainly eliminates the insoluble nano-objects deposited in the upper airways and the tracheobronchial tract towards the nose and mouth (Figure 10). They can then either be swallowed (and gain access to the digestive system) or discharged to the outside (sneezing, blowing nose).

Figure 10. Mucociliary transport (dynamic purification)

At the level of the pulmonary alveoli, the elimination of insoluble nano-objects is performed by purifying immune cells called macrophages (Figure 11) thanks to a digestion mechanism called phagocytosis. However, individual nanomaterials, i.e. non-aggregated and non-agglomerated, do not appear to be efficiently phagocyted by macrophages. This can result in a significant accumulation of nanomaterials in the pulmonary alveoli. The persistence of particles in the lungs is likely to cause inflammation, which may lead in the long term to the development of respiratory pathologies.

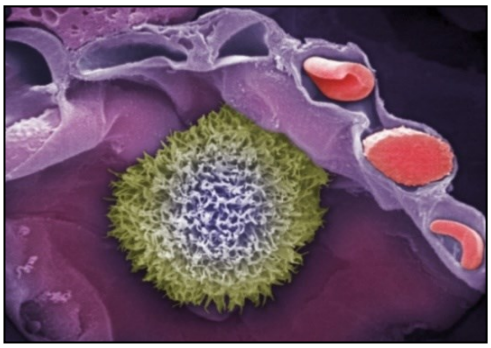

Figure 11. Alveolar macrophage (immunological purification)

Some inhaled nanomaterials are also capable of crossing the alveolar wall, migrating to the pleura, and the ganglion structures, reaching the blood and lymphatic systems and reaching various organs such as the liver, heart, or spleen. In some cases, they can also pass through the nasal mucosa and the nerves transport them to the brain.

4.3 Causes of the toxicological effects

All the available data show that it is not possible to make a general hypothesis on the toxicity of nanomaterials. Each nanomaterial, even for the same chemical composition, has its own

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toxicological profile. It is currently impossible to predict the potential effects of a nanomaterial because of the multiplicity of physicochemical parameters influencing toxicity (Figure 12). In the fields of toxicology and eco-toxicology, the effect of a substance is usually related to the mass absorbed. However, in the case of NOAA, mass is not the most appropriate parameter. It is not yet possible to figure out the determining parameters for predicting the toxicity of a NOAA.

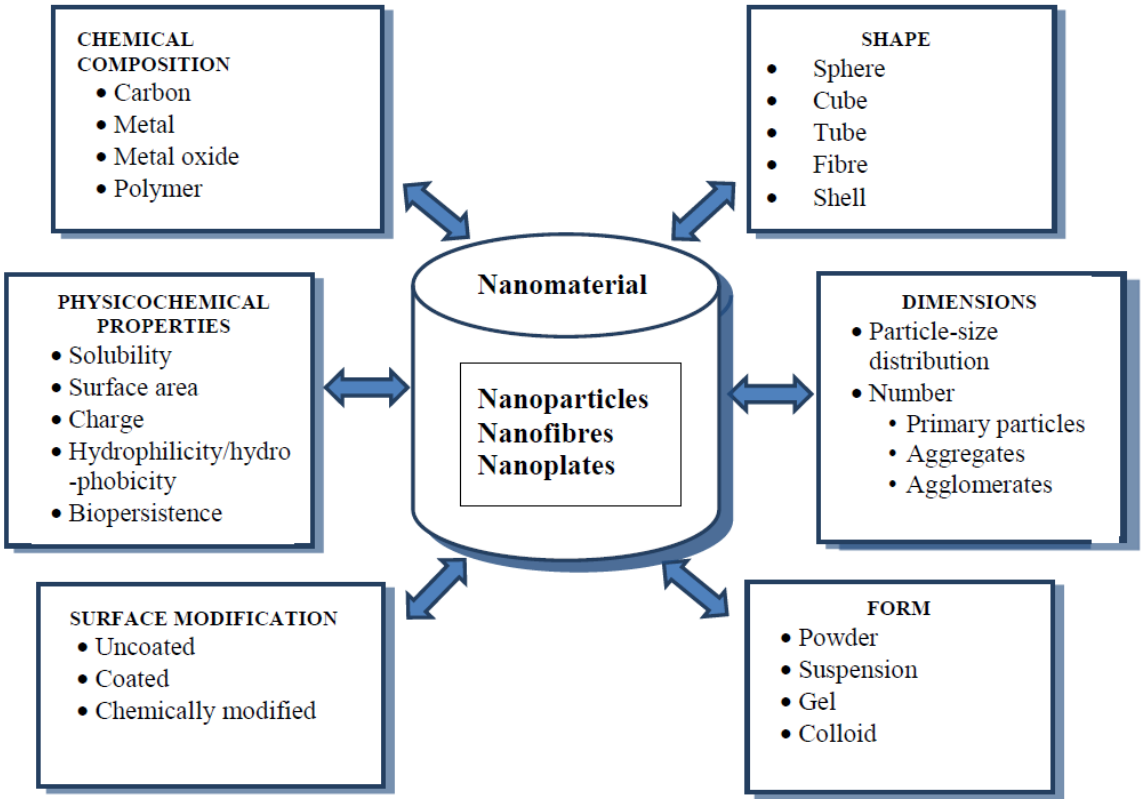

Figure 12. Physicochemical characteristics of nanomaterials [6]

In addition to physicochemical parameters, other factors can determine the toxicological effects of nanomaterials on the organism [7]:

- Exposure-related factors: routes of entry into the organism, extent, and duration of exposure,
- Factors related to the exposed organism: individual susceptibility, physical load, biokinetic parameters (deposition, distribution, and migration of particles in the organism),

In conclusion, to date, there is no generic consensus on the NOAA health effects. This is mostly due to the wide variety of physicochemical factors, which determine the toxicological effects on NOAA.

5 Exposure mitigation

This chapter firstly details the nanomaterial-specific behaviour (section 5.1). Then exposure mitigation ways (sections 5.2 to 5.5) are exposed according to the STOP principle hierarchy (section 3.3) both for health and safety risk.

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5.1 Nanomaterial behaviour

As inhalation is the most common route of occupational exposure, the behaviour of nanomaterials as solid aerosol, (airborne particles) must be understood. Three main forces determine the airborne particles' behaviour: diffusion, gravitational and inertia. The diffusion increasingly dominates as the particle size diminishes. The solid particles start to behave like a vapour or a gas. Diffusion is thus the main mode of transport of nanomaterials.
The following sections present field solutions to mitigate the exposure.

5.2 Substitution (safe-by-design) approach

Eliminating or reducing risks before they are introduced into the workplace is the most effective way for mitigation management. Both products and processes could be safe-by-design. For example, it is possible to replace hazardous substances with less hazardous ones, to replace powders with pellets or to replace manual by automatic process…

5.3 Technical (engineering) control

Any local exhaust ventilation system proven effective for vapour or gas can protect workers from NOAA by preventing their dispersion in the workplace. The nine ventilation principles settled by INRS (Institute National de Recherche et de Sécurité) [13] should be followed for NOAA as well:

- Surround the NOAA production zone as much as possible
- Capture emissions as close to the source as possible
- Place the hood so that operators are not between it and the pollution source
- Utilise the pollutants' natural movements
- Induce sufficient air speed
- Distribute air speed uniformly within the capture zone
- Compensate air exhaust by equivalent air input
- Avoid drafts and thermal discomfort
- After filtering, exhaust polluted air outdoors, away from fresh air intake areas.

The air containing NOAA must be treated before being discharged into the environment. HEPA (High-Efficiency Particulate Arrester) filters or ULPA (Ultra-Low Penetration Air) filers should be installed.
The guide ED6181 from INRS exposes advice on this topic [14].

5.4 Organisational control

The organisational controls aim to reduce accident risk thanks to optimal work methods. The following items should be settled:

- Information, training and regular refresher courses for both workers and managers.
- Formalised procedures both for work (including housekeeping and maintenance) and for emergencies (spills, fire …).
- Minimising the duration of exposure and the number of workers involved.
- Access restriction to the NOAA areas.
- Regular housekeeping (HEPA vacuum cleaner, wet cleaning - broom should be banished) and preventive maintenance.
- Designing non-porous surfaces, reducing the angle of baseboard or glove boxes… so that equipment is easy to clean
- Transport of dry NOAA in closed containers (double bagging)

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- Regarding specific medical surveillance, the current level of knowledge is insufficient to recommend specific medical screening. However, NIOSH has recommended specific medical tests for workers exposed to some NOAA. The following references could help to develop an occupation of medical surveillance: [6] [15] [16]
- Changing rooms for workers with double locker rooms to avoid the contamination of street clothes.
- Labelling each piece of equipment dedicated to NOAA (vacuum cleaner, safety cabinet, bin, container…).
- Storage of NOAA in sealed containers or double bagging.
- Waste management [17]

5.5 Personal protective equipment

Wearing Personal Protective Equipment (PPE) can only be considered when all other risk mitigation measures are insufficient or impossible to implement.

5.5.1 Respiratory protection

For the less emissive phases with a sufficient concentration of dioxygen (>19% in volume), a tight-fitting respirator with a particulate-removing air-purifying element is recommended. For a short task (less than one hour), a quarter or a half mask with a P3 filter should be worn. For longer tasks (more than one hour), a powered respirator TM2P, TM3P or TH3 is advised.
For the most emissive phases, loose-fitting respirators are recommended [7].

5.5.2 Skin protection

Chemical protection suit category 5 is recommended for the body. Hands should be protected by barrier gloves (for example: nitrile, vinyl or neoprene). In case of repeated or prolonged exposure, two pairs of gloves should be worn [7].

6 NOAA risk assessment for the 16 pilot lines

In addition to the generic nanosafety guidelines provided above, the nano-risk is assessed for the 16 INN-PRESSME pilot lines. This chapter aims to define the three pilot lines where a measurement campaign should be performed as explained in section 3.2.

6.1 Method

The nano risk assessment is based on a chemical risk assessment approach and is carried out in two steps, as shown in Figure 13. Firstly, a provisional risk is assessed based on the hazard, the quantity involved and the frequency of the exposure. It is followed by an inhalation potential assessment based on the collective protection, the process type and the physical state of the material. Combining provisional risk assessment and inhalation potential data, the relevant pilot lines, where the measurement campaigns will be performed, are selected.

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Figure 13. Risk assessment steps

A nanosafety questionnaire is distributed among partners to collect the data needed to perform this assessment.

First, a provisional risk level is assigned to each of the combinations (products and tasks). Table 2 from the INRS ND 2233 method [18] is used to define the hazard levels of each product according to the hazard statements for each substance in the MSDS, on the ECHA (European CHemicals Agency) and the IARC (International Agency for Research on Cancer).

Table 2. Chemicals hazard levels

Chemicals hazard levels	1	2	3	4	5
Hazard sentences	none	H315 H319 H335 H336	H302 H304 H312 H317 H332 H371 H373	H301 H311 H314 H318 H331 H334 H341 H351 H361 H362 H370 H372	H300 H310 H330 H340 H350 H360

This hazard level is then multiplied by the potential exposure level resulting from the data concerning the quantity of materials used and the frequency of exposure. The result of this multiplication is the provisional risk level. Table 3 presents the three provisional risk priorities established in this study according to the provisional risk level.

Table 3. Provisional risk priority

Provisional risk priority	***Provisional risk level***
Weak	< 100
Medium	100 - 10 000
Strong	(≥ 10 000)

In the workplace, inhalation is the main route of entry of nanomaterials into the human body (section 4.1). For this reason, the second part of this assessment deals with the level of inhalation potential. This is a combination of the physical state of the material, the level of collective protection in place and the type of process. Table 4 shows the three levels of priority for inhalation potential.

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Table 4. Inhalation potential priority

Inhalation potential priority	***Inhalation potential level***
Weak	0-0,1
Medium	0,1-100
Strong	100-10000

Based on these two priorities (provisional risk and inhalation potential), the pilot lines, where the measurement campaigns are needed, are selected.

6.2 Results

This section presents the results of the nanosafety questionnaire analysis for the 16 pilot lines. **These results are based on the information provided by the pilot line owners during the first six months of the INN-PRESSME project. All the chemicals at stake in the project were not known when this analysis was performed.** Besides, it was difficult for some pilot line owners to estimate the frequency of exposure and the quantity of products handled at this state of the project.

The materials and processes analysed in this report may have evolved during the project but were used as a basis to select the PL where the measurement campaign needs to be conducted.

6.2.1 Questionnaires' generic analysis

This section presents the main generic conclusions of the nanosafety questionnaire analysis. 167 task/chemical combinations are analysed for 15 pilot lines. Indeed, this nanosafety questionnaire is not applicable for the pilot line 3 POL PHA because no nanomaterials are used in this pilot line.

Figure 14 highlights the number of task/chemical combinations in each of the three categories (strong, medium, weak) of both the provisional risk priority and the inhalation potential priority. The majority of combinations have a medium provisional risk (50% - 83 combinations) or/and a medium inhalation potential (59% - 99 combinations). Figure 14 also shows that no task/chemical combination has both a strong provisional risk and a strong inhalation potential. Furthermore, 56% of the 167 combinations have mixed priorities regarding these two assessments (i.e. different strong, medium or weak priorities). The following analysis focuses first on the ten strong provisional risk priorities.

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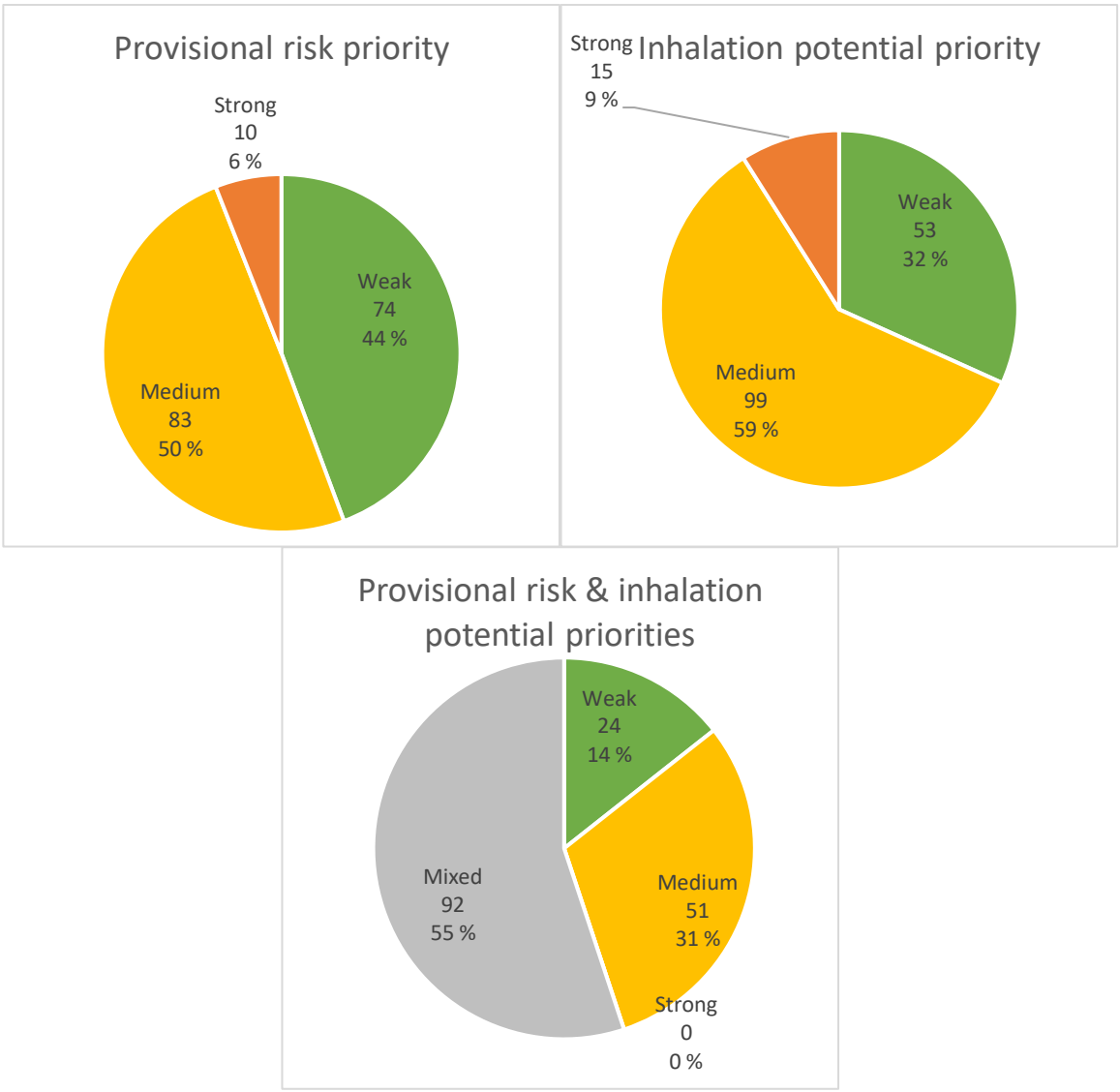

Figure 14. 167 task/chemical combinations are analysed for 15 pilot lines

The ten strong provisional risk priorities shown in Figure 14 are detailed in Table 5. These strong priorities apply to the five pilot lines mentioned below. These strong priorities are mostly due to the hazard of classical chemicals.

Table 5. Ten strong priorities are identified for the preliminary risk

PL + processes	Tasks	Chemicals	Hazard
PL2 RISE CNC (cellulose nanocrystals) synthesis	Whole process	Sodium hydroxide (CAS 1310-73-2)	**4**
PL2 RISE CNC (cellulose nanocrystals) synthesis	Whole process	Sulfuric acid (CAS 7664-93-9)	**4**
PL5 CID INK	Screen-printing mixtures from step 1	Mixture of products from step 1	**3**
PL5 CID INK	Screen-printing mixtures from step 1	Poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) CAS: 155090-83-8	**4**

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PL6 GNA CNM - Manufacturing carbon-based nanocomposites in powder form	3. Base addition. Precipitation	Sodium hydroxide solution 1310-73-2	**4**
PL8 CEA POUDR'INOV -1. Nanocomposite formulation by internal mixer	Internal mixing: NP introduction	Potassium permanganate	**5**
PL8 CEA POUDR'INOV -1. Nanocomposite formulation by internal mixer	Internal mixing: NP introduction	Acetic anhydride	**5**
PL8 CEA POUDR'INOV -2. Nanocomposite formulation by twin-screws extruder	Hopper loading +NPs addition into TSE	Potassium permanganate	**5**
PL8 CEA POUDR'INOV -2. Nanocomposite formulation by twin-screws extruder	Hopper loading +NPs addition into TSE	Acetic anhydride	**5**
PL10 FISC NP - hybrid coating process	Wet chemical synthesis of lacquer by sol-gel reaction	Tetraethylorthosilicat 78-10-4	**3**

This report aims to analyse the nanosafety and to determine whether a nano-aerosol measurement campaign is needed. Thus, the following analysis only focuses on the inhalation potential priorities. Figure 15 summarises the number of task/chemical combinations in each of the three categories (strong, medium, and weak) for the inhalation potential priority. Pilot lines 2, 4, 10 and 13 do not require further nanosafety analysis as all their tasks/chemicals combinations present only weak inhalation potential priorities. The nano-aerosol measurement campaign will be performed for three pilot lines. To have a vision of the entire production process, these campaigns will be carried out for one PL in each of the three INN-PRESSME stages (i.e., synthesis, formulation, and processing).

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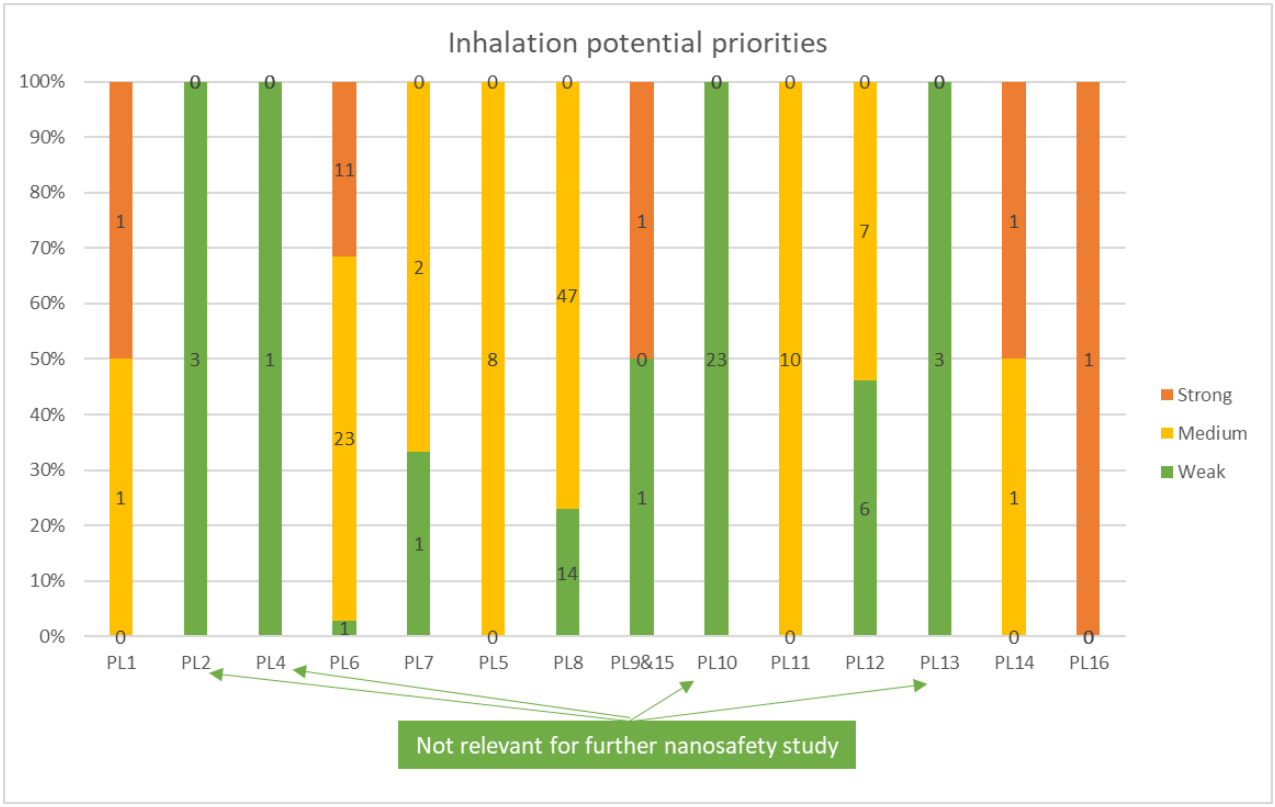

Figure 15. Inhalation potential priorities for the 15 pilot lines

To conclude this section, four pilot lines (PL2, PL4, PL10 and PL13, marked green in Figure 15) have only weak inhalation potential. Therefore, the inhalation potential assessment is further analysed for the other pilot lines: PL1 & 14, PL5, PL6, PL7, PL8, PL9 & 15, PL11, PL12 and PL16. These are discussed in the following sections.

6.2.2 Questionnaires' detailed analysis

This section presents the nanosafety questionnaire analysis of the eleven pilot lines identified in section 6.2.1.

6.2.2.1 PL1 VTT CNF & 14 VTT SUTCO

Pilot lines 1 VTT CNF and 14 VTT SUTCO are strongly linked. The cellulose nanofibrils are produced in the first pilot line while the fourteenth is the coating machine. The nanosafety questionnaire is filled with the two pilot lines constituting only one process. Figure 16 presents the different steps of this process: from dispersion to coating via pre-grinding, fibrillation, and the associated wet cleaning, packing and shipping. The cellulose pulp (powder) is the only NOAA for both PL1 and PL14.

All the provisional risk priorities are weak. Two steps have a strong inhalation potential priority: the fibrillation and the coating of the cellulose pulp. These are highlighted in Figure 16. The two medium inhalation potential priorities identified in Figure 15 are linked to the use of water and are not taken into account as priorities.

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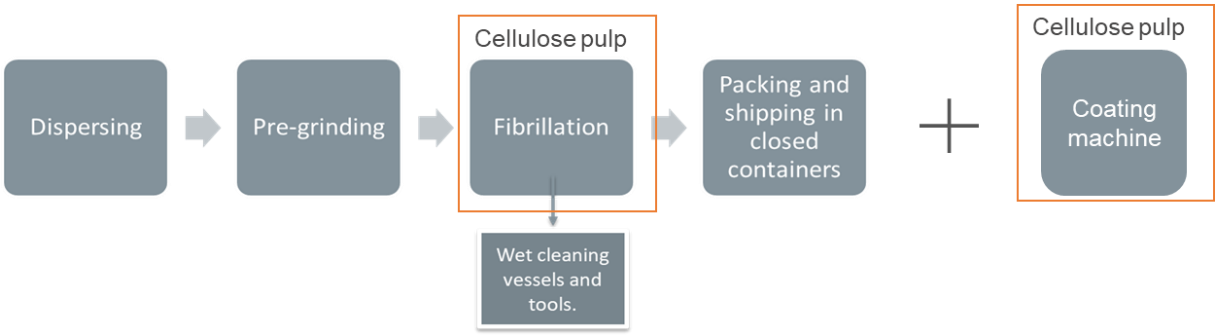

Figure 16. PL1 VTT CNF and PL 14 VTT SUTCO process and associated strong priorities.

Both PL1 and PL14 could be potential candidates for the measurement campaign. However, after comparison with the others (presented in the following sections), **they are not selected.**

6.2.2.2 PL5 CID INK

Pilot line 5 CID INK develops bio-based printable inks based on commercial cellulose derivatives for use as electrolytes in printed batteries and displays. The process of ink formulation and printing is divided into 3 main tasks. Firstly, the raw materials (different nanomaterials pre-dispersed in water - supplied by VTT- and a small proportion of another component(s) (as powder) are weighted by the operator wearing face piece protection and mixed in a closed vacuum-sealed container. After reaching the target properties for the mixture (measured with integrated in-line sensor systems), a high-viscosity water-based ink is printed on paper substrates by screen printing in a ventilated room. The substrates with the printed patterns are exposed to UV light in a UV chamber in the same ventilated room to cure the inks.

All the combinations tasks/chemicals of pilot line 5 CID INK have a medium inhalation potential priority as shown in Figure 15. Figure 17 exposes for each step of the process, the chemical used.

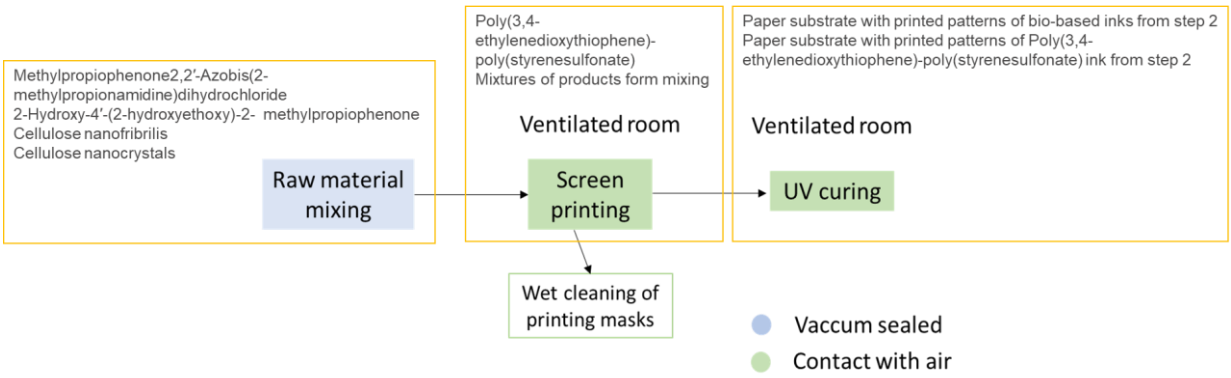

Figure 17. PL5 CID INK process and associated medium priorities

Table 6 lists the NOAA identified for PL5. They all are in liquid dispersions.

Table 6. List of NOAA used or produced identified by PL5

NOAA	State
Cellulose nanofibrils	Liquid
Cellulose nanocrystals	Liquid
Mixture of products from mixing	Liquid

All the NOAA handled or produced during the PL5 process are in liquid dispersion, thus **this PL is not a priority for the measurement campaign.**

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6.2.2.3 PL6 GNA CNM

Pilot line 6 GNA CNM has developed a novel technology for the generation of a new family of nanomaterials based on graphene and other forms of carbon from different biosources, combined with metal/metal oxide nanoparticles allowing the manufacturing of this family of nanomaterials at a preindustrial scale, using different dispersion systems. This process of manufacturing carbon-based nanocomposites in powder form is divided into 7 main tasks. Firstly, the raw materials are weighted. In the second step, they are added manually to the reactor and dissolved. In the third step, the carbon material, weighted, is added manually to the reactor. The mixture is dispersed in line with an ultrasonicator probe or high-shear mixing. After dispersion, an alkaline solution is added to the reactor to obtain the final product. The alkaline is added with the help of a peristaltic pump. The precipitated product is then transported to the filtration reactor. Once the filtration is finished, the filtered powder is recovered manually. The powder is then dried overnight, milled, and packaged.

Thirty-five combinations of tasks/chemicals are studied for the pilot line 6 GNA CNM. The inhalation potential priorities of all of them are presented in Figure 18. Approximately one-third have a strong inhalation potential priority while two-thirds have a medium one.

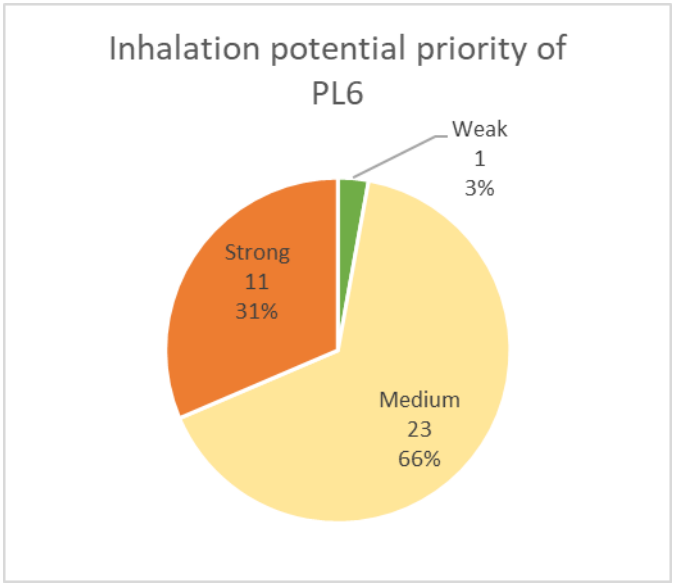

Figure 18. Inhalation potential priority of PL6 GNA CNM

Figure 19 presents the PL6 process steps and the associated eleven strong inhalation potential priorities. The hot spots are the dissolution, the carbon addition and dispersion and the drying. The associated chemicals are graphite, the metal oxides (silver nitrate, copper dinitrate, dicopper oxide, triiron tetraoxide, diiron trioxide and zinc oxide), the mixtures of these oxides and the graphene copper oxide nanocomposites. Table 7 lists the NOAA identified by PL6.

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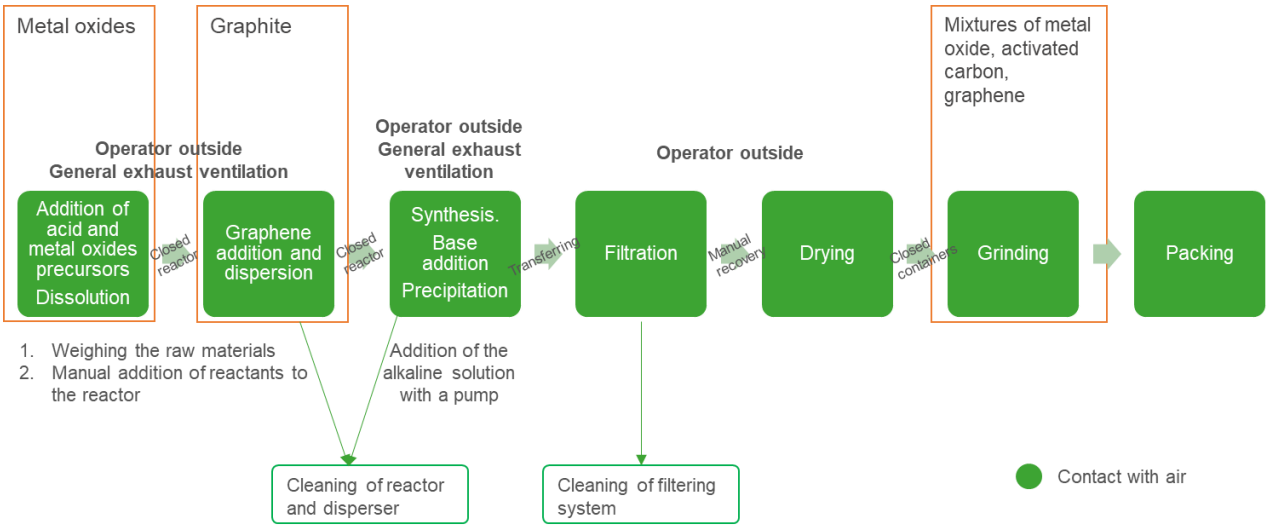

Figure 19. PL6 GNA CNM process and associated strong priorities

Table 7. List of NOAA used or produced identified by PL6

NOAA	State
Metal oxide precursor: dicopper oxide	Powder
Metal oxide precursor: triiron tetraoxide	Powder
Metal oxide precursor: diiron trioxide	Powder
Metal oxide precursor: Trimanganese tetraoxide	Powder
Metal oxide precursor: ZnO	Powder
Carbon Graphite	Powder
Carbon metal oxide composite - mixtures of metal oxides and carbonaceous materials (INN-PRESSME material)	Liquid
Carbon metal oxide composite - mixtures of metal oxides and carbonaceous materials (INN-PRESSME material)	Powder
Carbon metal oxide composite - graphene metal oxide nanocomposites	Liquid
Carbon metal oxide composite - graphene metal oxide nanocomposites	Powder

The variety of nanopowders used during this process and the high number of strong inhalation potentials make the **PL6 a good candidate for the nano measurement campaign**.

The list of chemicals and materials at stake will be updated in D8.6.

6.2.2.4 PL7 VTT PLAX

Pilot line 7 VTT PLAX helps customers to develop, scale up and demonstrate industrially viable scalable and environmentally friendly process solutions. It includes testbeds for catalyst development, and chemical and polymer synthesis. The process of PLAX dispersion is divided into 5 main tasks. Firstly, the raw materials are weighted and charged. The dispersion is then mixed in a closed reactor. Dispersion is formulated in the same reactor. Additives are added to the reactor at last.

Three combinations of tasks/chemicals are studied for the pilot line 7 VTT PLAX. Indeed, the whole process is described as one task for three chemicals: CNC, polyvinyl alcohol and polyactic acid. The inhalation potential priorities of all of them are presented in Figure 20. Two-

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thirds have a medium inhalation potential priority while one-third of the combinations of tasks/chemicals have a weak inhalation potential priority.

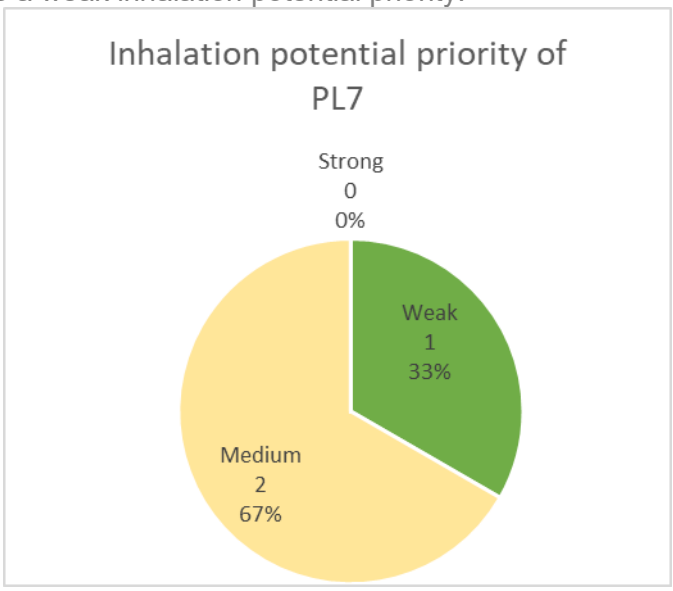

Figure 20. Inhalation potential priority of PL7 VTT PLAX

Figure 21 presents the PL7 process steps and the associated two medium inhalation potential priorities. These are linked to the use of CNC and polyvinyl alcohol. The CNC is a NOAA in liquid dispersion.

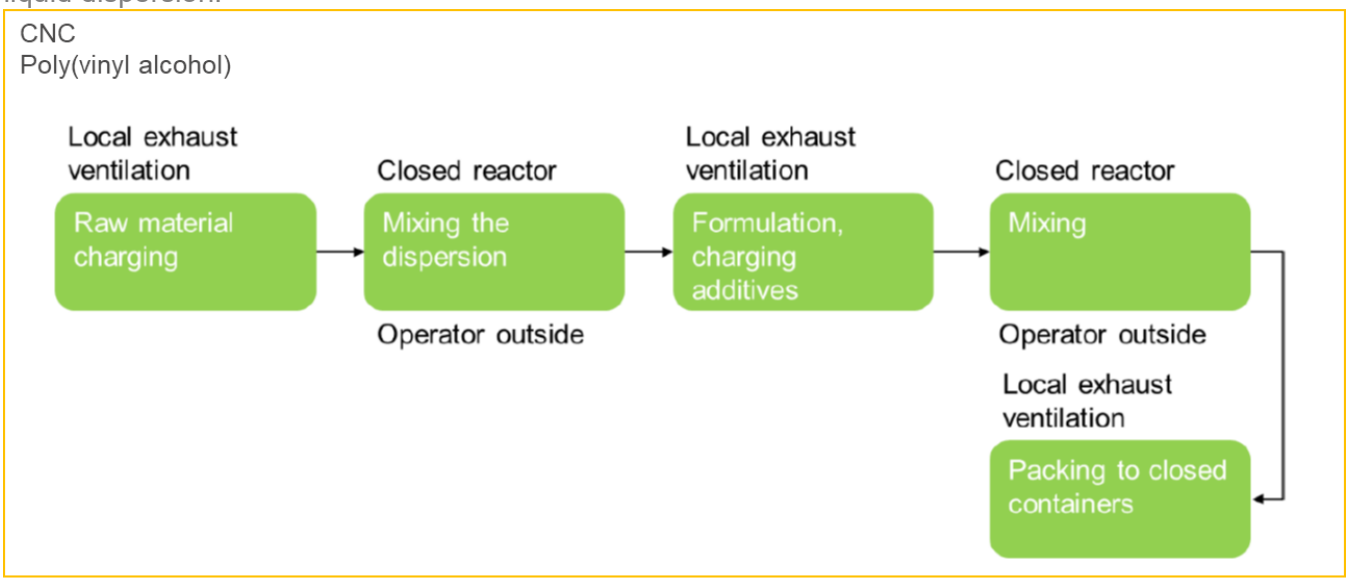

Figure 21. PL7 VTT PLAX process and associated medium priorities

Only one NOAA is used during this process. Therefore, **PL7 is not a priority for the measurement campaign.**

6.2.2.5 PL8 CEA POUDR

PL8 CEA POUDR offers three different processes in the frame of INN-PRESSME. First the nanocomposite formulation by an internal mixer, then the nanocomposite formulation by a twin-screw extruder and lastly the casting of the nanocomposites into films.

Sixty-one combinations of tasks/chemicals are studied for pilot line 8 CEA POUDR. No strong inhalation potential but a large number of medium priorities have been identified. Indeed, more

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than three-quarters (forty-seven) of combinations of tasks/chemicals have a medium inhalation potential priority as shown in Figure 22.

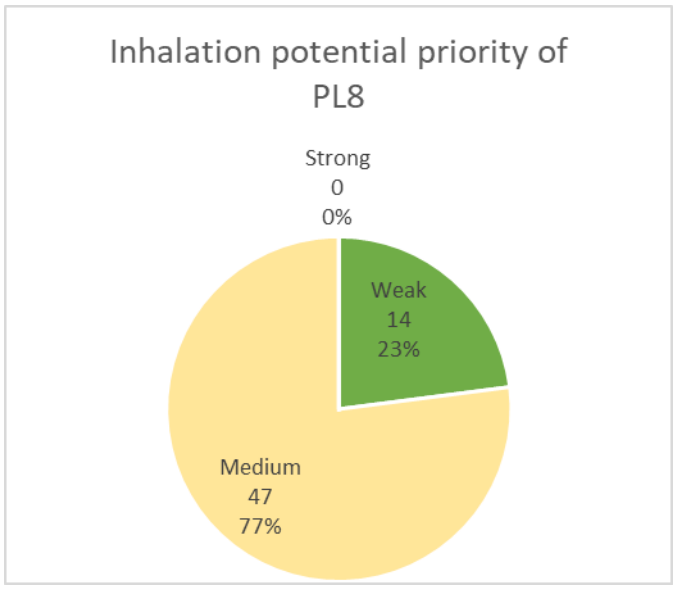

Figure 22. No strong priorities for the PL8 inhalation potential but a large number of medium

6.2.2.5.1 Nanocomposite formulation by an internal mixer

The process of nanocomposite fabrication is divided into 6 main tasks. First, the raw materials are dried before the nanocomposite development process. Secondly, polymer pellets are introduced into the internal mixer and then the NPs are gradually and manually introduced into the internal mixer. To recover the nanocomposite, it is necessary to open the internal mixer completely. The nanocomposite is recovered using a spatula. The nanocomposite is in the form of a block of material that looks like a stone. These “nanocomposite stones” are obtained and crushed into pellets.

Figure 23 illustrates the steps involved in the PL8 nanocomposite formulation, presented as an internal mixer process, along with twenty medium inhalation potential priorities. These priorities are linked with drying some of the products before their introduction, mixing in the internal mixer, crushing the nanocomposites to obtain pellets, and cleaning. The products involved are listed in the figure. Table 8 presents the NOAA used or produced in this process.

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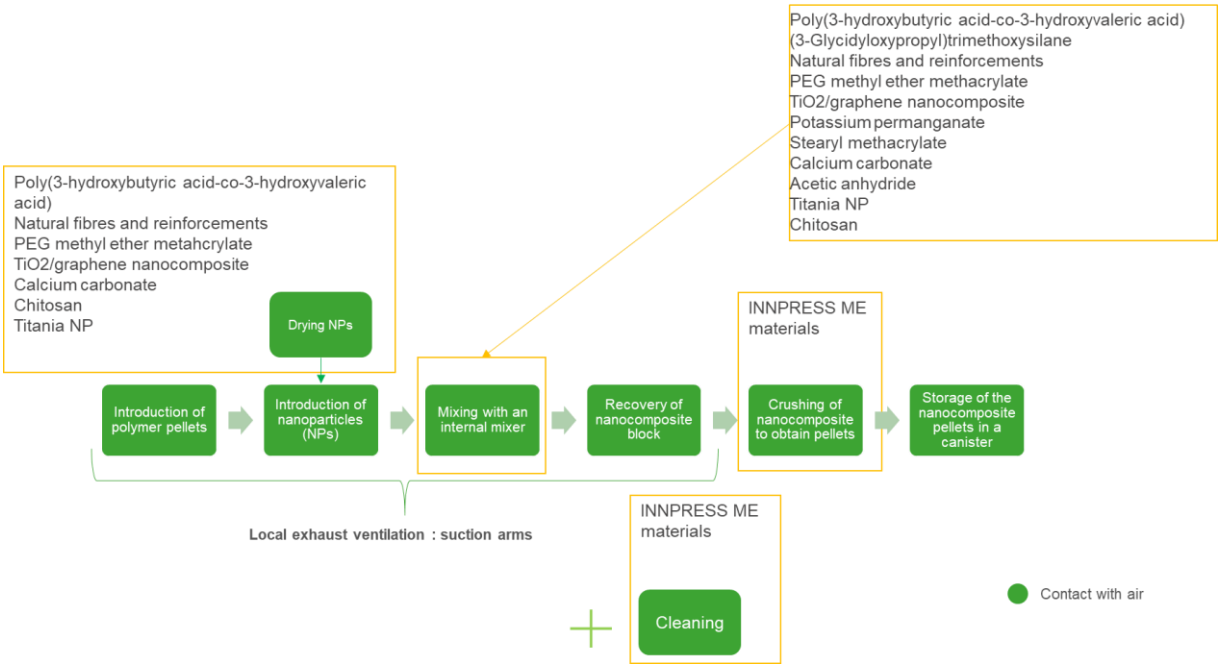

Figure 23. PL8 POUDR'INOV - Nanocomposite formulation by an internal mixer process and the associated medium priorities

Table 8. List of NOAA used or produced identified by PL8 for the nanocomposite formulation using an internal mixer process.

NOAA	State
TiO2/graphene nanocomposite, 10 mg/mL, dispersion in acetone	Liquid
Chitosan	Powder
Calcium carbonate	Powder
Natural fibres and reinforcements	Powder
Titania nanoparticles	Liquid
Natural fibres and reinforcements	Powder
INN-PRESSME materials (graphene, nanocellulose …)	Solid
INN-PRESSME materials (graphene, nanocellulose …)	Powder

6.2.2.5.2 Nanocomposite formulation by a twin-screw extruder

The process of nanocomposite fabrication is divided into 6 main tasks. First, the raw materials are dried before the nanocomposite development process. Next, the polymer pellets are introduced into the hopper and then introduced automatically into the twin-screw extruder by the hopper. In the third task, the nanoparticles (NPs) are introduced into the side feeder and NPs are introduced into the twin-screw extruder by the side feeder. The side feeder doses and weighs the nanofillers, which are transferred from a first hopper to a second hopper employing an endless screw. This passage is done in direct contact with the air of the part. Then from this second hopper (still in direct contact with the air of the part), two augers drive the nanoparticles into the extruder where the polymer is melted. In the fourth task, the material passes through a die in the form of a ring to obtain a filament. Fifth, this filament is drawn into a cold water cooling bath (which operates in a closed loop). Finally (sixth task), the filament is cut with a granulator to obtain pellets.

Figure 24 presents the steps in the PL8 nanocomposite formulation using a twin-screw extruder process and the associated twenty-three medium inhalation potential priorities. These priorities are linked to the drying of NP before introduction, their introduction, filament cooling, filament cutting, and cleaning. The products involved are listed in Figure 24. Table 9 presents the NOAA used or produced in this process.

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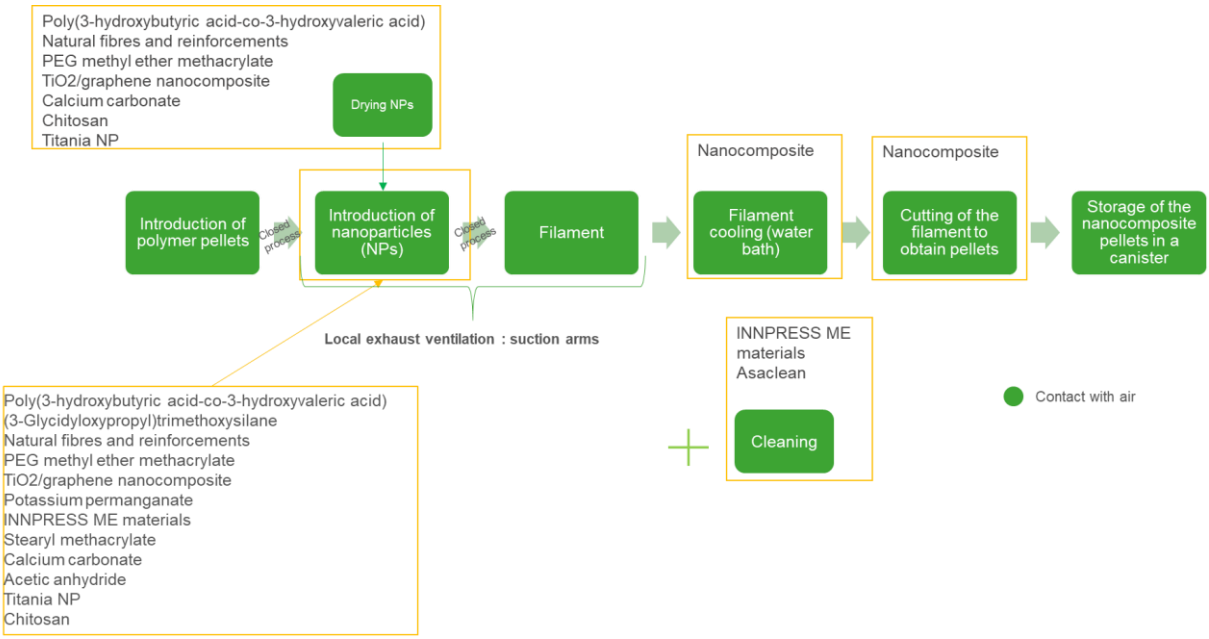

Figure 24. PL8 POUDR'INOV - Nanocomposite formulation using a twin-screw extruder process and the associated medium priorities.

Table 9. List of NOAA used or produced identified by PL8 for the nanocomposite formulation by twin-screws extruder process

NOAA	State
TiO2/graphene nanocomposite, 10 mg/mL, dispersion in acetone	Liquid
Chitosan	Powder
Titania nanoparticles	Liquid
Calcium carbonate	Powder
Natural fibres and reinforcements	Powder
INN-PRESSME materials (graphene, nanocellulose …)	Powder
Nanocomposite (polymer +NP)	Solid

6.2.2.5.3 Casting of nanocomposite films

Nanocomposite pellets obtained using the two processes presented before, are added into a mono-screw extruder, where the flat die at the extrusion end produces a flat film. The lateral edges of the film are cut out to ensure perfect control of the film width.

Figure 25 presents the nanocomposite film-casting process steps of PL8 along with the associated four medium inhalation potential priorities. These priorities are linked to the drying of the NP before processing, nanocomposite pellet addition, edge cutting, and cleaning. For each medium priority, the INN-PRESSME materials are involved. These materials are solid NOAA and they are the only NOAA involved in this process.

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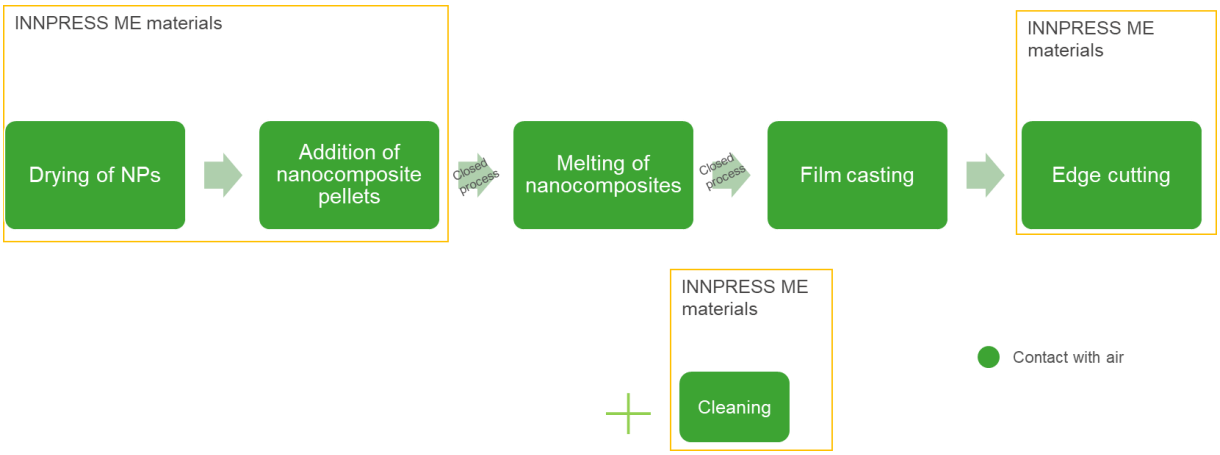

Figure 25. PL8 POUDR'INOV – Process for casting nanocomposite films and the associated medium priorities

The variety of processes and tasks developed in the PL8, and the high number of medium inhalation potentials make the **PL8 a good candidate for the nano measurement campaign.**

6.2.2.6 PL9 IPC METEOR & PL15 IPC MULTINANO

Pilot line 9 IPC METEOR is dedicated to compounding and converting new formulations based on recyclable, bio-based, or biodegradable materials. Pilot line 15 IPC MULTINANO is based on multinano layering for the micro and nano co-extrusion of films with high gas barrier and optical properties. The co-extrusion line consists of three extruders (a fourth can possibly be added) and the configured line is modular.

The compounding can be performed in Oyonnax or Alençon; while the film casting is performed in Alençon. The whole process in Alençon has a strong priority because the process is dispersive and there is no general mechanical ventilation nor collective protective equipment. The whole process in Oyonnax has a weak priority. Figure 26 presents the process.

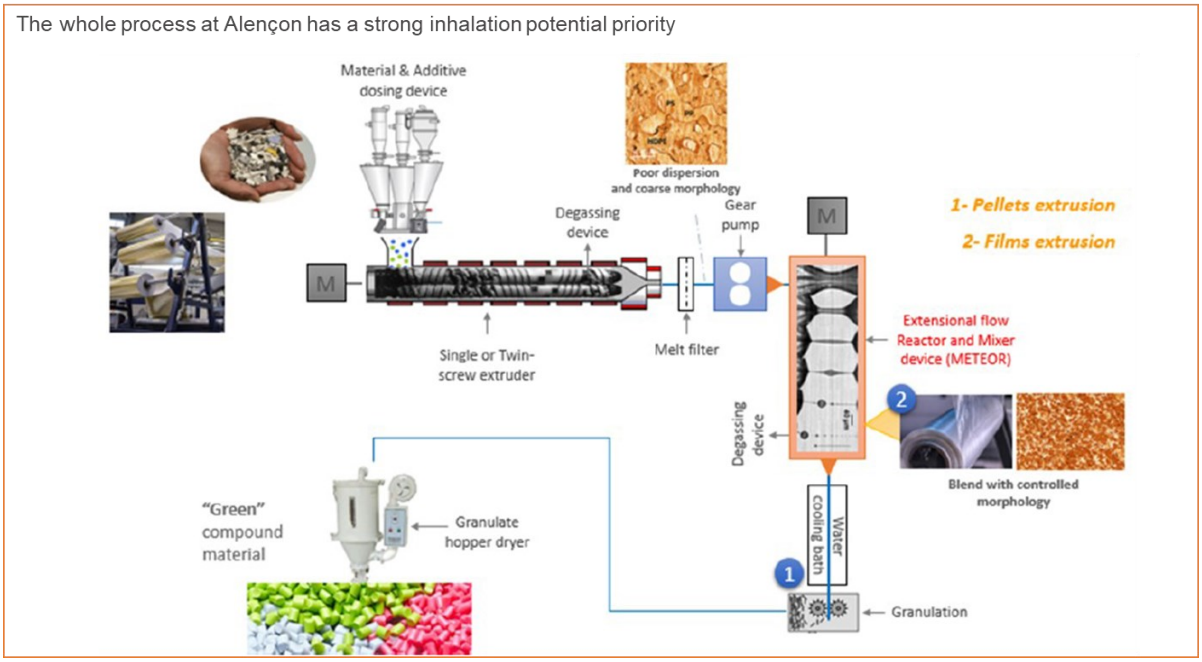

Figure 26. PL9 IPC METEOR & PL15 IPC MULTINANO process and associated strong priority.

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The priority is to secure the pilot lines. **Measurement campaign is not the priority at this stage.**

6.2.2.7 PL11 FICT FOAM

The process of particle foaming carried out in pilot line 11 FICT FOAM is divided into 3 steps. Firstly, the raw materials are handled to fill the dosing units of the extruder. The materials are then loaded with a blowing agent and extruded (twin-screw extrusion with subsequent underwater pelletizer). After this process, expandable polymer granules are available. These granules are then pre-foamed to foam beads in a prefoamer (steam-based) and subsequently moulded to the final product.

All the ten task/chemical combinations have a medium inhalation potential priority. Figure 27 presents these medium priorities. The nano masterbatch is the only NOAA used in this process and it is a solid product.

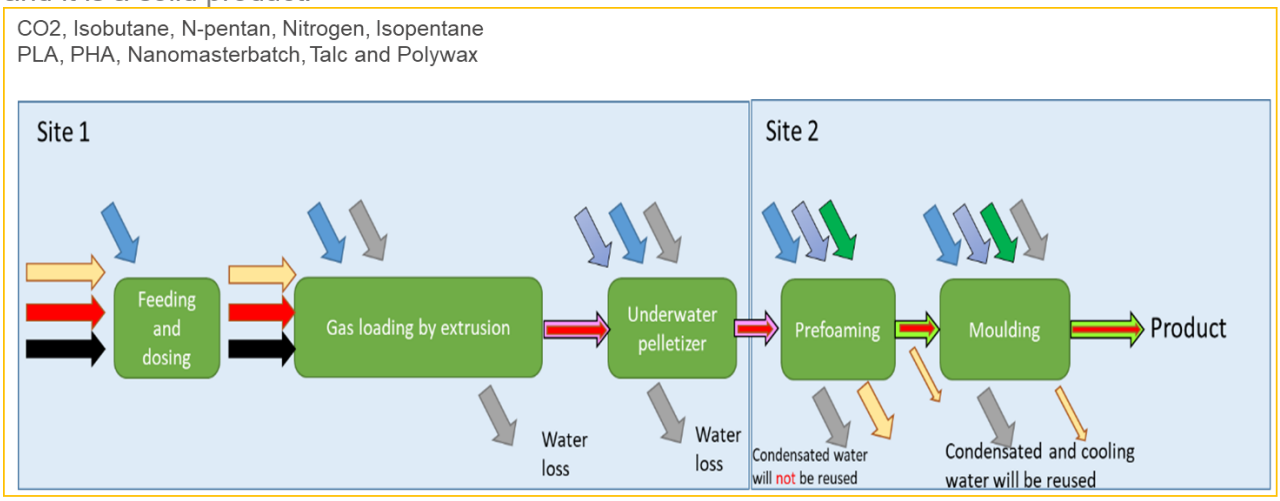

Figure 27. PL11 FICT FOAM process steps and associated medium priorities.

The whole process has a weak inhalation potential priority if a local exhaust is installed. **This pilot line is not selected for the measurement campaign.**

6.2.2.8 PL12 CID COAT

Pilot line 12 CID COAT is dedicated to the production of electrodes for energy storage devices. This pilot plant is equipped with very flexible application systems, which allow working with different materials and different ink formulations including biomaterials and water-based processing. The process of roll-to-roll electrode manufacturing is divided into 3 main tasks. Firstly, the aluminium foil is coated with the slurry (previously prepared in the ink pilot line (P-L5)). For that purpose, the slurry is automatically fed from a container to the coating head. Next, the wet film is automatically moved to a three-zone oven system with an integrated exhaust and is dried. Once the electrode is dried, it is rolled and transferred to the calendaring unit. There, it is densified to the target density.

Thirteen task/chemical combinations are studied for pilot line 12 CID COAT. No strong inhalation potential has been identified. The inhalation potential priorities are approximately half medium and half weak, as shown in Figure 28.

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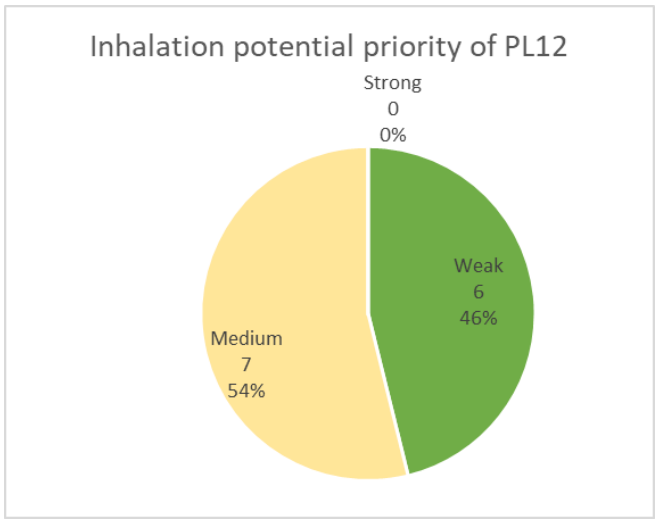
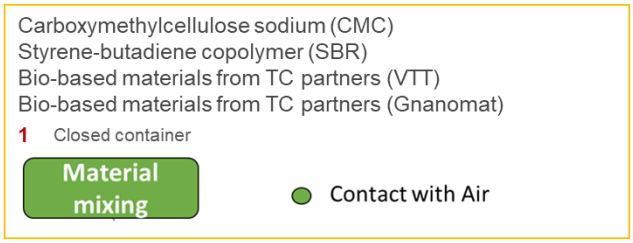


Figure 28. PL12 CID COAT inhalation potential priorities

Figure 29 presents the process steps and the associated medium priorities from pilot line 12 CID COAT. The process steps include the mixing of CMC, SBR, the bio-based materials from VTT and Gnanomat, the electrode coating and drying of the bio-based materials from Gnanomat and the electrode calendaring of the final product. The NOAA involved in this process are bio-based materials from VTT (liquid) and from Gnanomat (powders) and the final product (solid), which are shown in Table 10. The mixing step is closed but open regularly without any CPE while the electrode coating and drying is open with a LEV. The electrode calendaring is open without any CPE.



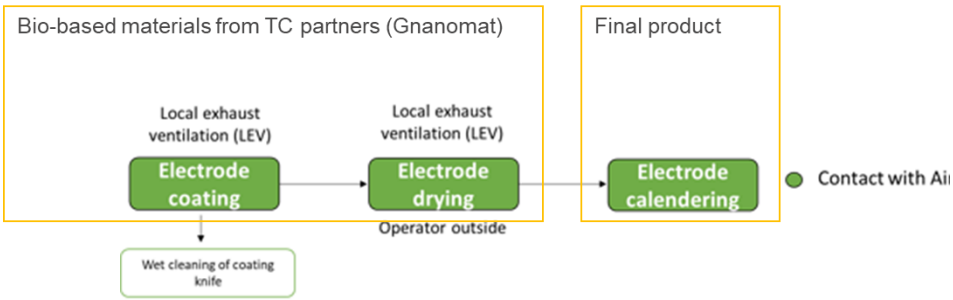


Figure 29. PL12 CID COAT process steps and associated medium priorities

Table 10. List of NOAA used or produced identified by PL12

NOAA	State
Bio-based materials from VTT	Liquid
Bio-based materials from Gnanomat	Powder
Final product	Solid

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6.2.2.9 PL16 AITP 3DP

The whole PL16 process is described as one task with only one material: the one produced during the INN-PRESSME project. As seen with the previous assessments, NOAAs are used and produced in the other PLs. Thus, the PL16 raw materials could be considered as NOAA. Besides additive manufacturing is known to release unintentional nanoparticles during printing [19].

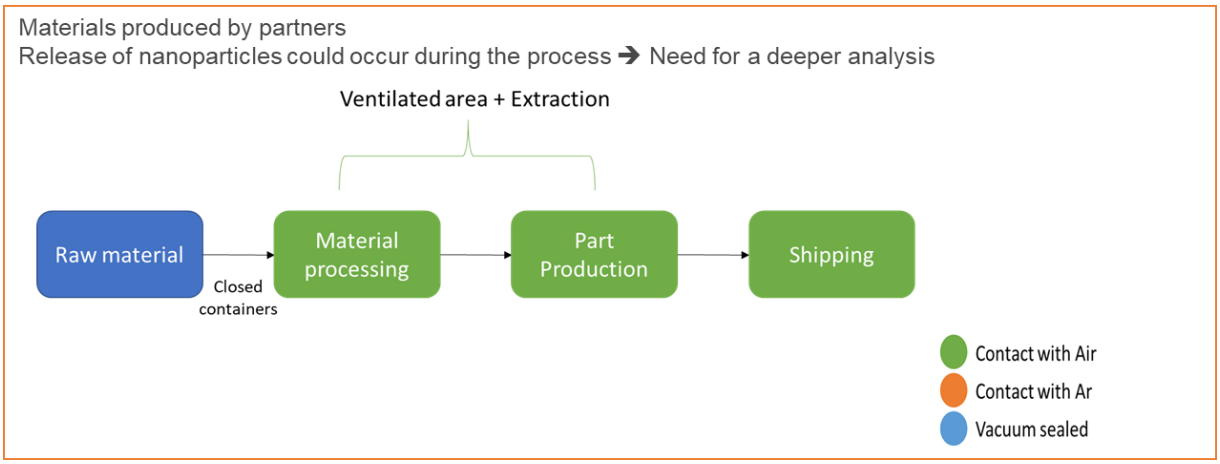

Figure 30. PL16 AITP 3DP process and the associated strong priorities

In conclusion, **performing a measurement campaign in PL16 seems interesting.**

6.2.3 Questionnaires' analysis conclusions

In conclusion, none of the task/chemical combinations have both a strong provisional risk and a strong inhalation potential. Most of the task/chemical combinations have a medium provisional risk and/or a medium inhalation potential priority. According to the provisional risk assessment results, three pilot lines have been selected for the nano-measurement campaigns (Figure 31):

- PL6 because powder nanoparticles are handled;
- PL8 due to the large number of task/chemical combinations with a medium inhalation potential priorities;
- PL16 because unintentional release of nanoparticles could occur during the printing.

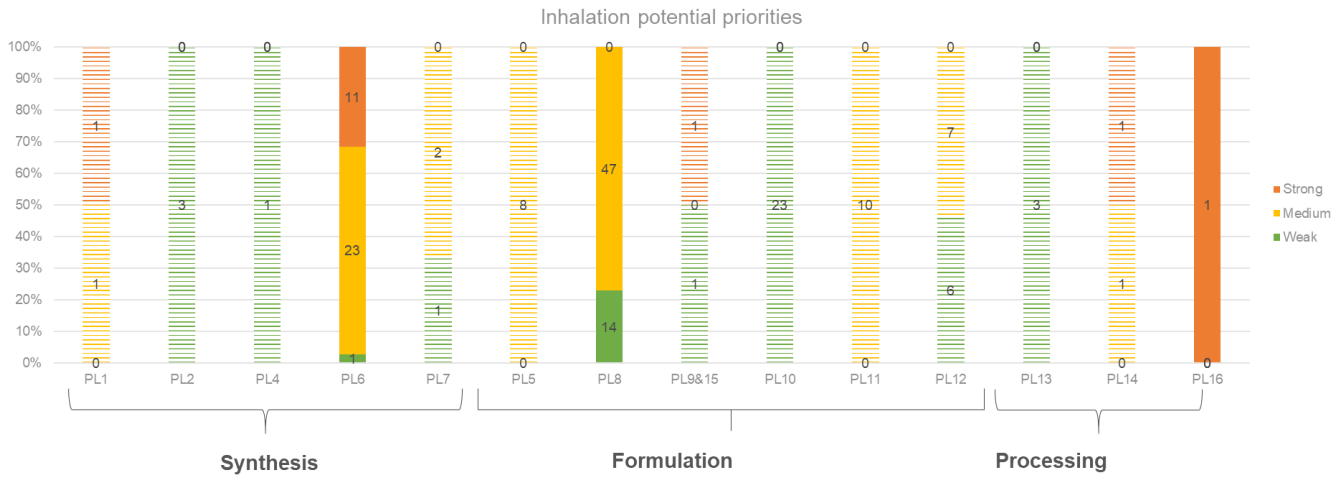

Figure 31. Three pilot lines have been selected for the measurement campaign: PL6, PL8 and PL16.

In conclusion, CEA prepared in autumn 2022 the measurement campaigns with PL6, PL8 and PL16 and conducted them in spring 2023.

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