Practical Methodological Guide for Assessing Substitution Solutions

November 2017

MEDEF/INERIS Working Group for the
Ministry for the Ecological and Inclusive Transition

Foreword

On February 8, 2016, the Director General for Risk Prevention (DGPR) of the French Ministry for the Ecological and Inclusive Transition sent an engagement letter (Appendix 1) for the attention of Philippe Huber (INERIS) and Patrick Levy (MEDEF), asking them to form a working group to create a methodology to assess substitution solutions, as a practical guidance document.

As requested in the engagement letter, an ad-hoc working group was created based on a call to the members of the French Health and Environment Group, which is charged with monitoring the PNSE3 (Plan National Santé Environnement 3 [3rd National Health and Environment Plan]), and the road map from the environmental conference (see the group members in Appendix 2).
The working group, consisting of industry representatives, stakeholders in civil society, public authorities and experts, met on 4 occasions (April 7, May 12, June 22 and December 6 of 2016), and the drafting work continued into June 2017. At this time, a proofreading process was implemented and concluded in September 2017 with a final proofreading by Working Group 4 of the PNSE3's Health and Environment Group.

At the conclusion of this process, this guide was submitted to the Director of the DGPR of the Ministry, who approved it.

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1 INTRODUCTION

The reason for substituting hazardous chemicals is to protect human health and the environment. It is encouraged by the EU Member States, and it is explicitly mentioned by EU regulations[1]. It is also the focus of voluntary processes undertaken by businesses. However, businesses need assistance on all of the factors to be considered: health, environment, technology, the economy and society.

This guide on chemical substitution is intended to guide businesses in this process, as well as other stakeholders (non-profits) and public authorities that may have reason, in particular, to help them compare different potential alternatives and identify a substitute. This guide is presented as a documented review of all the stages leading to the final qualification of the substitution options.

This guide is based on the idea that a substitution process has been decided. It will not be useful for examining the reasons for initiating a substitution process for a specific substance.

On the contrary, it is intended to assist in choosing a substitution solution.

Substitution is part of a logic aimed at controlling a risk, a logic in which the pure and simple elimination of the risk is prioritised in any substitution process. In particular, one may sometimes stop using a substance that is revealed to have had no real benefit for the end users. Substitution may also go so far as to adjust or abandon a functionality, in accordance with user demand.

2 PRINCIPLES AND MODE OF WORKING

This guide aims to go above and beyond existing processes by developing a notion of functionality associated with the use of a substance, by providing ways of assessing hazards that have not yet been classified, by expanding the list of criteria to be considered in determining the correctness of a choice and by suggesting organisational elements to steer the process within the entity implementing it.

This guide is based on documentation that provides an overview of the substitution approaches suggested by international bodies[2].

Two hearings have been held by the working group:

- An ANSES (French Agency for Food, Environmental and Occupational Health & Safety) hearing, which has developed a method for comparing alternatives as part of a case on formaldehyde, in order to ensure complementarity and coherence in the ANSES expert report and this operating guide

- A hearing with Ms. Antonia Reihlen, of the German company Ökopol, who presented a guide on the sustainable use of chemicals created by the Germany Environmental Agency, and "Substool," a tool for assisting with substitution.

[1] In particular the European regulations referred to as "REACH" 1997/2006 (Registration, Evaluation, Authorization of Chemical Substances, "biocides" 528/2012 (making available on the market and use of biocidal products, and "phytopharmaceuticals" 1107/2009 (making available on the market and use of phytopharmaceutical products)).

[2] The main documents are available at https://substitution.ineris.fr/fr/documentation-gt-substitution.

The notion of the functionality to be replaced, is the entry point to this guide. This term was preferred
to very similar ones such as "**use**" and "**service rendered**."

The need to specify the functionalities targeted by the substitution owe to the fact that it is rare for a substance to be replaced in the same way for all the different functionalities that it can provide. For example, the alternatives to BPA as a developing agent in thermal paper are not the same as those for BPA as a resin hardener.

A substance can have a **direct functionality** (for example insecticide, food coloring, cleaning agent). It can be **part of the manufacturing process** of a material or a product (for example as a hardener) or it can be **incorporated into a product or a material** to give it particular properties (examples: hardener, flame retardant, UV resistance).

It follows that the functionality does not necessarily concern an end user that would be the consumer. The use may be part of an industrial activity that precedes the manufacture and distribution of the final product.

In this last case, not only is the functionality assessed differently, but the same goes for assessing a hazard and the emergence of a risk. For example, inhalation toxicity or an explosion hazard may be controlled vis-à-vis their effects on health and the environment for certain industrial applications in a well-controlled production environment[3],[3] whereas they would be of very high concern for use by the public at large.

Moreover, the notion of **an alternative is not limited to a chemical alternative, rather it also includes resorting to different procedures**, different technological approaches, organizational measures or changes to the product in which the substance is used. In these cases, it is necessary to monitor whether new types of hazards appear.

The substitution may go so far as to **adjust or abandon a functionality in accordance with user demand.** This last case is not explored in detail in this guide, as changing or abandoning a functional service is a specific process to be developed on a case-by-case basis with the sector in question. Even if a scientific and technical analysis has been carried out, this form of substitution requires working on the use, the perception of the use and the reasons justifying its use (for example, the opinions of municipalities on the usefulness of phytosanitary products for weeding and promoting biodiversity).

Once a functionality has been targeted, the **proposed method** rests, according to the majority of guides published on the subject, on **assessing the different criteria linked to the hazards, risks and impacts of the substitution and to the social, technical and economic impacts** it would involve.

This guide thus proposes a methodological process equipped with tools to implement it, without hiding the problem of potential missing information needed to assess and compare an alternative to the substance to be replaced. For example, because it is rare to successfully replace a well-known substance with a substance the properties of which are also well documented in data bases (standard or non-standard), ways are provided for finding information on a new substance by way of less "official" data sets, or even by way of "rapid screening" methods with studies on the substance.

[3] For example, an industrial process using a toxic substance in a totally enclosed process that totally consumes it over the course of a chemical reaction.

Due to the relative lack of knowledge and feedback on unused or seldom used alternatives, any substitution may give rise to regrettable consequences (replacing lead with benzene as a detonating agent in gasoline, substituting trichlorethylene with tetrachlorethylene in dry cleaning processes) that may eventually require further intervention, or even taking a step backward. This guide thus presents a process for anticipating, to the extent possible, all the consequences of a substitution (transfer of undesirable risks, subsequent resurgence of analogous hazards, other harmful socio-economic impacts, etc.) in order to prevent an unsatisfactory, or even "regrettable," substitution.

This guide not only addresses the method but also the **substitution process,** which must be viewed as a continuous process.

To succeed, the substitution process must be propagated all along what one could call the value or functionality chain, in other words the ensemble of operations (manufacturing, processing, supply, distribution, etc.) leading to the manufacture of a substance used in the manufacture of a product, its sale and subsequent use by the consumer, and its end of life (or its recycling or reuse). Limiting the analysis to a link in this chain may result in difficulties, or even a "regrettable substitution".

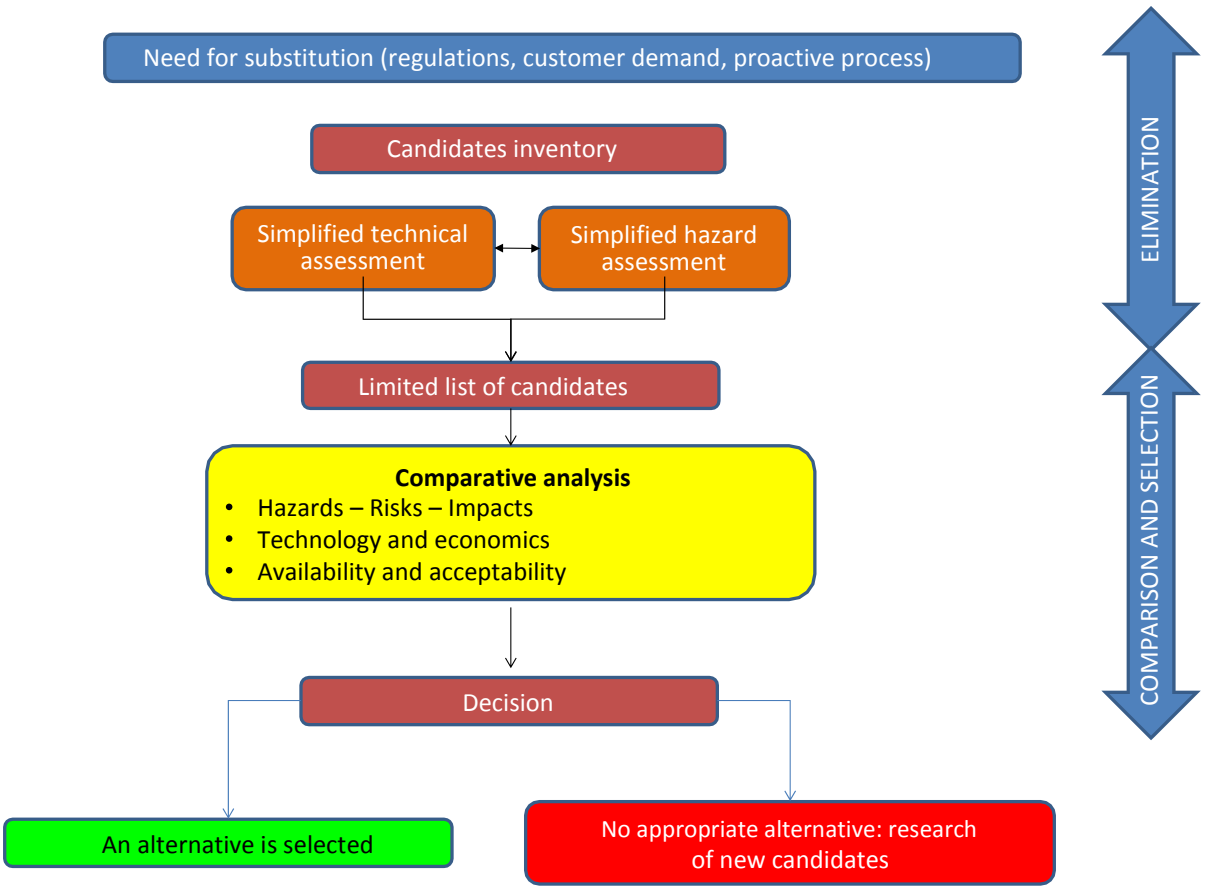
While in principle it is assumed that substitution is first and foremost an issue for businesses that use chemical products, particularly those that put products on the market aimed at the public at large, the goal of this guide is to help any actor in the value chain by indicating which data to collect and which assessments to make such as: impacts on supply chains, all the costs to be considered, etc.

In any case, it is clear that the substitution process associated with a functionality should be revisited from time to time if there are changes in technology or company processes, or substitution innovations in its relevant sectors. Aside from this occasional revisiting, the process should be re-evaluated and updated on a regular basis (a frequency of every 5 years can be given as an example but should be determined on a case-by-case basis).

This guide is structured in the following manner: an introductory paragraph provides an overview of the logic of the process advocated in this guide. It requires that an organization plan be implemented according to the recommendations summarized in the following paragraph. The following paragraphs address the methodological aspects of targeting functionalities, documenting assessment criteria (direct impacts on health and the environment; global and indirect impacts; operational feasibility) and decision-making. A summary presentation is provided to illustrate the conclusion.

3 PROCESS OVERVIEW

The substitution process as a whole can be summarized in by the following diagram:



An initial survey of potential alternatives is undertaken by mobilizing the business's internal knowledge and also by researching outside information (technical guides and works, chemical suppliers and technical centers, a list of which appears in Appendix 3).

The substitution process thus unfolds in two stages.

First, it is necessary to quickly **eliminate alternatives that are not acceptable** based on their hazards (alternatives the hazard level of which is unacceptable in and of itself[4]) or their performance, which may be judged inadequate.
If no alternative remains at this stage, it is necessary to look at the survey again, to examine it more in depth and verify that no other potential solution has been overlooked. If this is not the case, reflect on the necessity of the intended performance for the targeted functionality (is the current level necessary?), or build an R&D program to identify new candidates, or even modify and more thoroughly rethink the functional need, or even reduce the ambitions of the targeted functionalities.

[4] The group's discussion clearly focused on this point, and the conclusion was that one does not "replace a PE with a PE" even if it is less hazardous, not even with a category 1 CMR.

The **second step consists of selecting the alternative(s) to be implemented** in accordance with a comparative analysis of preselected alternatives based on several criteria, which are described in Section 6. It is possible that the more in-depth analysis will reveal that no alternatives are appropriate (revising the opinion at the second stage based on the more in-depth study). In this case, one may start the process over at the initial research and development phase.

The stages of a substitution plan are as follows:

1. Define the substitution plan and the functionalities concerned.
2. Research the potential alternatives, and the related documentation.
3. Eliminate unacceptable alternatives.
4. Define the criteria for analyzing and comparing the alternatives.
5. Assess and compare the alternatives.
6. Decide and select an alternative (including final testing and validation).
7. Implement the alternative.
8. Feedback, monitoring.

The process must also fit within the context of global innovation, in particular the energy and ecological transition and the circular economy for which reference documents are developed.

The "Green Growth Commitment" (GGC) ["Engagements pour la Croissance Verte" (ECV)] is a new contractual instrument in France for facilitating innovation for the ecological transition – it can also concern substitution.

As an experiment, the French Ministries of Environment and Economy (CGDD, DGPR, DGE) have created, in partnership with financial networks, a new contractual instrument supporting innovation (technological and organizational) focused on the circular economy. Inspired by the "Green Deals" experience in the Netherlands, the GGC is a flexible, non-binding legal tool.

GGC Example: Reverplast Project: new channel for recycling acrylic glass.

Initiated by Arkema, in partnership with the technological platform Canoe, the recyclers Paprec and Indra, and PME plastics processor Plastinov, the project aims to develop applications for recycled acrylic glass to substitute non-recyclable materials (e.g. Plexiglas) in the automobile (headlights), sailing, and renewable energy (solar panels and wind turbines) industries.
The professionals have agreed to conduct a techno-economic feasibility study to create a new recycling channel.
The French State has agreed to provide a network and a federation of actors for this emerging channel, as well as awareness-raising measures.

Changes to formulas, materials and mixtures.

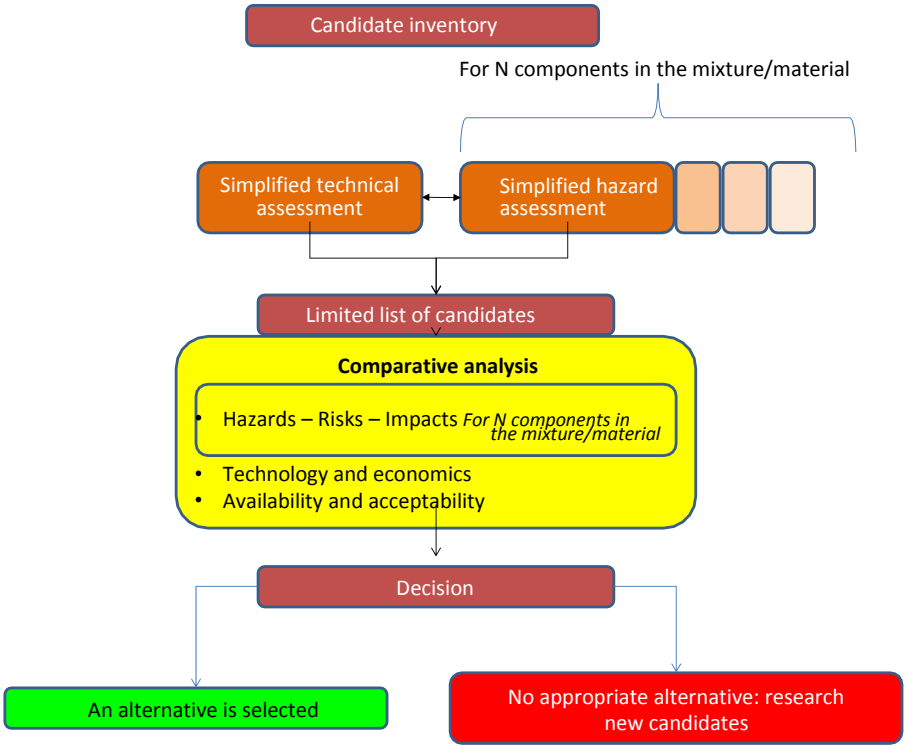
Chemical substances are often used as part of a specially formulated mixture of substances.

Substitution, then, often involves replacing a mixture with another potentially complex mixture.

In theory, each criteria in this guide should thus be applied to the different initial components of the mixture (or material), and alternative mixtures (or materials). In practice this task can prove to be long and tedious. It requires an accurate analysis of the mixture so as to correctly deal with the compounds that present a potential hazard, and it must be subject to evaluation and additional analysis:

- Obtain information on the composition of the mixtures or materials involved in the substitution process
- Identify the main components of the mixtures, being mindful of the proportion and the type of hazard (in particular if the components are "no-threshold" substances, it is necessary to bear them in mind even if they are present in small proportions)
- Perform a comparative analysis according to the hazard criteria for each of the components selected
- Present the results of the comparison between the substance and the alternatives by summarizing the hazards resulting from the initial solution and the alternative solutions. It is necessary to classify, regardless of the hazard criteria, a mixture as "category 1"[5] if one of the primary components selected is “category 1” itself.

The general framework of the substitution process is only slightly different, then, and is as follows:



[5] See the description of the hazard criteria.

4 IMPLEMENTING AN ORGANIZATION PLAN FOR SUBSTITUTION IN THE SUPPLY CHAIN

The substitution process is a key project of a business, and it requires to implement an organization compatible with the intended goal and the means available.

To do so, one must have a checklist of actions that must be verified during the substitution process.

A brief sample checklist is provided in Section 8.

SMEs may be more dependent on outside resources compared to larger groups that can draw on more consistent internal means. In any case, a project manager must be named; he must coordinate the project and make sure it follows the action plan; he reports to the people at the relevant persons in the business who are responsible for making decisions on the product(s) involved (the president if a SME).

The project group involves all or part of the following functions/resources, which are to be mobilized or not based on the size of the business and the scope of the project:

The following matters must be addressed without fail:

- Company representative with decision-making power.
- R&D.
- Industrial Processes.
- HSE (Health Safety Environment).
- Quality.
- Purchasing.
- Sales.
- Regulations.

Optional functions/resources:

- HR.
- Legal Affairs/ Regulations – intellectual property.
- Consultants.
- Marketing.
- Customers.
- Suppliers.
- Occupational health and safety committee (CHSCT).

As with any business plan, the project needs to have a schedule, intermediate deliverables, budget oversight and human resources assigned to the project. To ensure the accuracy of the supporting documentation to be provided to customers and stakeholders (including the authorities and, if applicable, the shareholders), and as necessary in the event of mandatory substitution because of regulation, there must be a tracking system for stage notes and reports. All decisions regarding the project must be well reasoned.

At the end of the project, when the alternative solution is selected, monitoring must be implemented, which consists of periodically updating the information available about the selected alternative, in the same way as may be done for any new process implemented by a business. The scope and scale of the monitoring must then be adjusted according to the project's stages.

Most SMEs are not capable of developing a personalised, internal monitoring structure. In this context, a solution may consist of joining a group monitoring system capable of detecting the most significant alerts on the availability of potential new alternatives.

To facilitate this process, a business can draw on a certain number of external resources:

For assistance with substitution:

- French and international websites on substitution (SNA Substitution INERIS[6], Substitution - CMR ANSES[7], INRS-FAS (Substitution Fact Sheets)[8], SUBSPORT[9],[9] OECD SAAToolbox[10], the Massachusetts Toxics Use Reduction Institute website – University of Massachusetts Lowell[11]).
- The ECHA website: Information present in the registration files and in applications for authorization or restriction under REACH (by way of alternative assessments).

For information on alternatives:

- Inter-professional technical centers (see sample list in Appendix 3[12]).
- CRITTs (Centres Régionaux d'Innovation et de Transfert de Technologie [Regional Centers for Technology Transfer and Innovation]).
- Innovation centers (see http://competitivite.gouv.fr/ the innovation center search engine to search by sector of activity).
- Occupational Health Services and their partners in preventing occupational risks.
- Contract Research Organizations, CARSATs (Caisses d'Assurance Retraite et de la Santé au Travail [Occupational Health and Retirement Insurance Funds]). Subcontractors and consultants specializing in processing, recycling, product safety, chemical risk assessments, etc.

Monitoring and feedback particularly help detect changes in the knowledge that has the most impact on potential alternatives (in terms of hazards, innovations, and costs).

Indeed, aside from being a project that substitutes one particular substance with another, substitution is a permanent process that affects all of the chemicals used by the business. Monitoringmust be permanent therefore and open to receive alerts from all stakeholders and supply chains, particularly by comparing credible lists of hazardous substances (drafted by regulators, sector businesses or professional centers, NGOs), and substances concerning the business.

For a list of scientifically recognized substances, see Appendix 4 hereof.

[6] INERIS SNA Substitution: https://substitution.ineris.fr/fr
[7] ANSES CMR Substitution: https://www.substitution-cmr.fr/
[8] INRS FAS (Substitution Fact Sheet): http://www.inrs.fr/media.html?refINRS=FAS%200
[9] SUBSPORT: http://www.subsport.eu/?lang=fr
[10] OECD SAAToolbox: http://www.oecdsaatoolbox.org/
[11] Massachusetts Toxics Use Reduction Institute: http://www.turi.org/
[12] A complete up-to-date list is available at www.legifrance.gouv.fr, the list in Appendix 3 contains a list of these centers.

5 IDENTIFYING AND TARGETING FUNCTIONALITIES IN THE SUBSTITUTION PROCESS

The process's point of departure rests on identifying and assessing the substance's functionality(-ies).

Assessing the link between the substance and the service rendered provides the technical performance criteria.

As pointed out above, this not only applies to a functionality (or functionalities) of a substance itself, but also to the product or products that are manufactured with this substance or contain it.

An initial point of view consists of looking at the substance's intrinsic functionality (or the intrinsic properties it gives to a material and, subsequently, a product or item). The alternatives are then essentially judged by their capacity to reproduce this functionality identically (or in a similar fashion), and by their capacity to transfer similar properties to a material and then to an item.

For example, a biocidal product is used to disinfect the surfaces of clean rooms in the agro-food industry. The active substance must be active on certain micro-organisms (bacteria, fungus...). Substitute biocidal products must respond to an equivalent spectrum of activity.

A second point of view will endeavor to consider the substance based on the end user's operational functionality: functional duration, flexibility, color, resistance, recyclability and end of life (hazardous waste, non-hazardous waste, biodegradable waste, etc.). This is, by definition, more subjective than the point of view focused on the substance's intrinsic properties but will influence how the economic and societal criteria are assessed (for example, a product may lose consumers who are potentially dissatisfied by the new color or texture).

Thus, the discussion of the technical performance of an alternative must take into account these two aspects (intrinsic "functioning" and "service" from the point of view of the intermediate or end user), either of which may have greater weight in assessing alternatives based on the situations. The project team will be responsible for determining the weight to give to each factor in the evaluation.

A specific, detailed knowledge of the function(s) of the substance to be substituted and the conditions in which this (these) function(s) operate in the different use(s) allows one to research other means of achieving the same or equivalent function in a process or well-defined application. It is however necessary to bear in mind that a sequential replacement considerably limits the field of research and innovation; the use of another substance, technology or finished product may achieve the same functionality.

The function accomplished by the substance requires a full understanding of its use, including **a description of the manufacturing process in which it takes part, and a description of the use and distribution chain.**

The following questions may help to identify and describe the conditions and constraints linked to a substance's replacement:

1. *What is the **exact function** and the essential properties of the substance to be replaced?*

   This question calls for a response that is as specific as possible. The exact function determines to what extent replacement solutions can be identified. For example, a solvent used in a plant extraction process may be replaced by a certain number of substances and replacement techniques. However, the physical and chemical conditions imposed by the process, the output and the quality controls may restrict the number of actual conceivable solutions. The substance's essential properties are those directly linked to its function: for example, it may be a solvent's extraction capacity, or, for a grease remover, the capacity to dissolve grease.

2. *Do the **technical specifications of the finished product** significantly limit selecting a replacement solution?*

   A customer's specification for a finished product may impose certain selection criteria for a replacement solution: for example: if a customer has a process that requires a temperature of 190° C and a pressure of 15 bars, this significantly limits the replacement solution choices. This may also concern the impurities profile required by the current standards, that impose additional purification stages to achieve the same quality.
   Thus, it is important to understand how the function is connected to the customer's final requirements and to what extent they may be re-assessed (for example, if a substitution entails a change in color reflected in a specification, is this color really functional or implicitly interpreted by the customer as proof that the function is fulfilled?)

3. *What are the substances **secondary properties?***

   These properties are important but not essential to the function, and it is necessary to assess the need to preserve them at all costs in a substitution process. For example, it may be a physical property such as the flash point, the steam pressure or even the "recyclability."

4. *What are the requirements in terms of **durability**?*

   The function's technical performance may be subject to time constraints. Must the function be performed one time, at a particular moment, or must it be performed for a minimum or maximum period of time? Certain coatings must resist weather for the entire life of a specific product. For example, replacing a substance that guarantees anti-rust protection for an aircraft part must take into account the expected duration of service (considering, as necessary, the need to have to provide spare parts during a given period) and overall safety (approval procedures and/or a regulatory framework).

5. *What are the quality requirements in terms of **final product quality**?*

   Is the alternative solution capable of fulfilling the customer's quality requirements as stipulated in the required specifications? For example, within the context of a pharmacy, changing a synthesis step to eliminate the use of a substance must achieve a satisfactory output and an acceptable purity from the point of view of the standards and the specifications.
   Conversely, the demand for a very high level of purity is obviously required for cosmetic and pharmaceutical applications, but it is much less so for less demanding applications, for which it is conceivable to slightly downgrade the quality of the product with a substitution solution without compromising the functionality. For example, an extraction solvent in pharmacy must respond to the pharmacopoeia and achieve a very high level of purity; the same solvent used in a grease remover will not have the same purity level requirements, provided the impurities do not generate new risks. Other examples: the quality requirements for long-term chromium plating that resists different physical and chemical aggressions and has a shiny or mat appearance greatly influences the field of acceptable alternatives.
   It must also be highlighted that the substitution is also an opportunity to engage with customers about the need for the required technical performance levels, especially if they hinder a substitution solution from being implemented.

At the end of this analysis, the substance's function must be able to be described in simple terms, for example: *solvent used in the phases of producing, purifying and isolating a synthetic intermediate for a biocidal active substance.*

5.1 Examples of simple functionalities in a short supply chain

The following examples illustrate the concept of functionality and show that the definition of the function is a delicate stage that requires specific analytical work:

- *Solvent for degreasing machined mechanical parts*:

The substance's functionality clearly appears (degreasing), as does the purpose (removal of oils from parts cut in a mechanical operation (piercing, milling, boring, detaching, etc.). Discontinuing use of the substance without a replacement and the ensuing lack of degreasing could render the piece unusable in later stages of production. The impact would fall directly on the actor performing the degreasing and have consequences down the chain. For example: the stoppage of an assembly or motor production line, etc.

In this example, one can imagine a different design for the final item (a cam shaft of a motor, for example) in which the degreased piece is no longer used. In this case, the new motor design could consider the limitation on degreasing metal parts or resort to non-metal or non-machined materials based on other techniques.

- *Processing solvent:*

Substituting a processing solvent occurs in a more complex context (example: extraction solvent with very low solubility in water used in synthesizing caprolactam from cyclohexanone).

On one hand, the actors involved are many: the manufacturer or importer of the solvent's substance, the industrial user in the caprolactam synthesis process with integrated recycling, external recycling, waste management.

Moreover, substitution can be envisaged in several ways:

- **By replacing the solvent** considering only the step for which it is required,
- **by changing several steps of the process**, which would lead, as applicable, to replacing the solvent but also to changing steps up and down the process chain. Eliminating steps could make changing the solvent problematic. On the other hand, the step under consideration could be divided into several sub-steps leading to changing the solvent (for example, replacing the solvent with a less effective solvent that requires adding a purification step),
- **changing the synthesis in its entirety**, which could lead, for example, to a form of physical extraction without using a solvent to produce the same end molecule,
- **changing the process to produce another molecule** providing an equivalent functionality,
- **replacing the end molecule with another technique**.

5.2 Example of complex functionality in a long supply chain

The typical example is replacing a PVC plasticizing agent to produce items that join PVC parts to others (example: toys, home appliances, floor covering, packaging, luggage, rain clothing, etc.).

The substance is used to soften the PVC, allowing it to be more easily processed (example: manufacturing a toy), which may lead to several production stages (primary and secondary processing, simple and complex assembly).

Here, the intrinsic functionality is the softening of the PVC, allowing it to be processed and to ultimately be used in the assembled items.

But the supply chain, which determines the substance's operational functionality, includes the following actors:

- The manufacturer or importer of the plasticizing agent.
- The formulator: the producer of the PVC premix or compounds.
- The primary processor: processing the plasticized PVC by calendering, extrusion, blow molding, etc.
- The assembler of the item (for example: assembling the different components of a suitcase).
- The distributer.
- A large or small-scale retailer.
- The end user (professional or public at large).

The life cycle must be considered as a whole by integrating different options, particularly for end-of-life management: recycling (EPR[13][13] with a certifying body), incineration, etc.

[13] EPR: Extended Producer Responsibility.

In this situation, substitution may be more difficult if it is only encouraged by one actor in the supply chain. The substitution process can only develop with the collaboration of all the chain's actors, who must think together and implement working groups or a consortium[14], which increases the complexity of the project process.

6 CRITERIA FOR ANALYZING ALTERNATIVES

The comparative analysis of alternatives is conducted based on several criteria. Besides a definition, there must be a value scale (quantitative or qualitative) for measuring each criterion and sources of information allowing a specific value to be assigned to each alternative. The value scale adopted must be adapted to the concrete information available.

6.1 Technical performance

The technical performance of an alternative is based on its capacity to perform or replace the original substance's function. It is closely linked to the conditions in which the function must be performed.

The technical performance evaluation can be quite simple if the replacement is of the "substance for substance," or "drop-in," type; in other situations, changes must be made to the process or the conditions of use, to allow the replacement solution to be used, and must be evaluated.

Moreover, performance evaluations may also take into consideration bibliographical information that will be supplemented by experimental or digital studies. Indeed, assessing the technical performance will require testing in general and may call for a more detailed analysis that could lead to research activities aimed at evaluating the replacement solution.

Technical performance indicators.

The substance's technical performance description may require several performance indicators. These indicators may contain some tolerances (ranges concerning the purity or the mechanical features required or about the physical and chemical properties that must be transmitted to the finished product).

Determining the technical performance indicators includes a series of stages, which appear hereunder:

1) **Based on the expected functions, make a list of the relevant performance characteristics that may be evaluated qualitatively and quantitatively.**

2) **Create a performance value scale for each relevant indicator** to determine the objective of the evaluation of the replacement solution(s) and to compare them against each other and against the substance to be replaced. This may be qualitative, or even binary (acceptable/unacceptable performance).

[14] In this arrangement, it will be important to respect the right to competition.

Below, we provide a sample list of criteria to consider when replacing a processing solvent use in the synthesis of an active substance:

1. The solvent must aprotic.
2. Dissolving properties, for which the range of acceptability is defined according to two aspects:
- High dissolution of the raw material.
- Weak dissolution in the finished product, allowing it to crystallize.
3. Inert in relation to synthesizing reagents.
4. Stability in an acidic or basic medium, at a high temperature, etc.
5. Capacity to absorb certain impurities formed over the course of the reaction.
6. Non-miscible in water, allowing cleanings during synthesis.

6.2 Hazards to living organisms

A first comparison criterion concerns the hazards of the substance and its alternatives. In other words, the phenomena linked to the toxic, ecotoxic, physical and chemical properties intrinsic to the substance or alternative processes.

The hazard is the principal criterion for comparing, in a simplified manner, the risks linked to the chemicals within the context of a substitution process. However, the hazard criteria may not be enough to discriminate among alternatives, and we may then need to resort to additional criteria concerning exposure and risk (cf. 6.3 and 6.4), which assist in making a more accurate comparison but present the inconvenience of making the process more complex and increase the need for data (or models eventually).

Concerning the hazards to living organisms, a limited number of hazard categories are considered below: .

In general, three substance categories should be considered:

1. substances for which a voluntary or standard classification is available in literature or regulations,
2. substances for which information is available that allows them to be classified,
3. substances for which information is not available and for which there is a lack of knowledge regarding their toxicity or ecotoxicity.

In the first case, the ranking in the different categories will be based on the classification given based on the criteria presented in the various tables hereinafter.

In the second case, the position in the different categories will be based on the indicators presented in the relevant tables.

In the last case, an assessment must be performed either by way of testing or by way of alternative predictive approaches (see below).

6.2.1 Substances having a known classification.

The following tables summarize different classification criteria available in regulations which one can use to classify a substance.

Environment

PBT, vPvB, POP and other highly toxic substances for the aquatic environment are considered here. Their different properties are all included in one
criterion.

	Category 1	Category 1bis[15]	Category 3	Category 4
Toxicity to the environment	Substance listed in REACH Appendix XIV Substance listed on the POP list of the Stockholm Convention.	List of substance candidates for the authorization process. Substance proposed to appear on the POP list of the Stockholm Convention.	Substance very toxic to the aquatic environment.	Substance not classified in the previous categories.
Indicator	PBT, vPvB properties	PBT, vPvB properties	Classification: H400 substance very toxic to aquatic organisms. Or H410 substance very toxic to aquatic organisms with long lasting adverse effects.	Substance not presenting any of these properties.
Source:	FDS Sections 2, 9, 12 INERIS: http://www.ineris.fr/substances/fr/ ECHA: http://echa.europa.eu/fr/ Stockholm Convention: http://chm.pops.int/Home/tabid/2121/mctl/ViewDetails/EventModID/871/EventID/230/xmid/6921/Default.aspx Regulation No. 850/2004 of 04/29/04 on persistent organic pollutants and amending Directive 79/117/CEE.			

[15] The number proposed is coherent with that of regulatory texts.

Acute toxicity

	Category 1	Category 2	Category 3	Category 4
Criterion Acute oral/dermal/inhalation toxicity	FATAL	TOXIC	HARMFUL	Substance not classified in the previous categories
Indicators	H300 Fatal if swallowed or H310 Fatal in contact with skin H330 Fatal if inhaled	H301 Toxic if swallowed H311 Toxic in contact with skin or H331 Toxic if inhaled	H302 Harmful if swallowed or H312 Harmful in contact with skin H332 Harmful if inhaled	
Source:	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment			

Specific target organ toxicity - single exposure

	Category 1	Category 2	Category 3	Category 4
Criteria chronic toxicity				Substance not classified in the previous categories
Indicators	H370: Known risk of serious damage to organs following a single exposure	H371: presumed risk of serious damage to organs following a single exposure	H335: May cause respiratory irritation following a single exposure or H336: May cause drowsiness or dizziness following a single exposure	Substance not presenting any of these properties
Source:	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment			

Corrosion/Irritation/sensitization

	Category 1	Category 2	Category 3
Criterion Corrosion/Irritation/ sensitization	BURNS/SERIOUS INJURY	IRRITATION	Substance not classified in the previous categories
Indicators	**H314** Causes severe skin burns and eye damage **or** **H318** Causes serious eye damage	**H315** Causes skin irritation **or** **H319** Causes serious eye irritation	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment		

Respiratory sensitization

	Category 1	Category 2
Criterion Respiratory sensitization	SENSITISATION/ALLERGY	Substance not classified in the previous category
Indicators	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment	

Skin sensitization

	Category 1	Category 2
Criterion Skin Sensitization	SENSITIZATION/ALLERGY	Substance not classified in the previous category
Indicators	H317: May cause an allergic skin reaction	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically: http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment	

Chronic toxicity

	Category 1	Category 2	Category 3
Criterion Chronic toxicity			Substance not classified in the previous categories
Indicators	H372: known risk of serious damage to organs following prolonged or repeated exposure	H373: presumed risk of serious damage to organs following prolonged or repeated single exposure	Substance not presenting any of these properties
Source:	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment		

Carcinogens

	Category 1	Category 1 bis	Category 2	Category 5
Criterion Carcinogen	1A / 1B 'CLP) May cause cancer	1A/1B other than CLP (IARP, ACGIH)	2 Suspected of causing cancer (cat. 2 CLP)	Substance not classified in the previous categories
Indicators	H350		H351	
Source	SDS Sections 2, 9, 11 NTP https://ntp.niehs.nih.gov ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment IARC: http://monographs.iarc.fr/ENG/Monographs/suppl7/index.php US EPA (IRIS): https://www.epa.gov/iris INERIS : http://www.ineris.fr/substances/fr/			

Mutagens

	Category 1	Category 2	Category 5
Criterion Mutagen	1A /1B (CLP) May cause genetic defects	2 (CLP) Suspected of causing genetic defects	Substance not classified in the previous categories
Indicators	H340	H341	
Source	SDS Sections 2, 9, 11 ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment INERIS: http://www.ineris.fr/substances/fr/		

Reprotoxicity

	Category 1	Category 2	Category 4
Criterion Reprotoxic	1A /1B (CLP) May damage fertility or the unborn child	2 (CLP) Suspected of damaging fertility or the unborn child	Substance not classified in the previous categories
Indicators	H360	H361	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment		

6.2.2 Substances not having a classification but with data available.

Environment

	Category 2	Category 3	Category 4
Toxicity to the environment	Substance not listed in Reach Appendix XIV but meeting the criteria of Appendix XIII Substance not listed on the Stockholm Convention's POP list but meeting its criteria	Substance very toxic to the aquatic environment	Substances presenting a negligible effect
Indicator	Persistence: degradation half life: ➢ >60 days seawater ➢ Or > 40 days estuary or fresh water ➢ Or > 180 days marine sediment ➢ Or > 120 days estuary or fresh water sediment ➢ Or > 120 days soil bioaccumulation Aquatic specimen bioconcentration factor > 2,000 Toxicity NOEC <0.01 mg/l or Cat. 1 or 2 Carcinogenic Substance Cat. 1 or 2 Mutagen Or Reprotoxic Cat. 1, 2 or 3 Either STOT-RE cat. 1 or 2 or: Persistence: degradation half life ➢ 60 days fresh water ➢ > 180 days in soil ➢ > 180 days in sediment ➢ Or other evidence of sufficient persistence Bioaccumulation Aquatic specimen bioconcentration factor > 5,000 or Log Kow > 5 Long-distance propagation Measures Modeling (in particular T1/2 air > 2 days)	CL50 96 h (for fish) ≤ 1 mg/l and/or CE50 48 h (for crustaceans) ≤ 1 mg/l and/or CEr50 72 or 96 h (for algae and other aquatic plants) ≤ 1 mg/l	Substance not presenting any of these properties

Source:	SDS Sections 2, 9, 12 INERIS: http://www.ineris.fr/substances/fr/ ECHA: http://echa.europa.eu/fr/ Stockholm Convention: http://chm.pops.int/Home/tabid/2121/mctl/ViewDetails/EventModID/871/EventID/230/xmid/6921/Default.aspx Regulation No. 850/2004 of 04/29/04 on persistent organic pollutants and amending Directive 79/117/CEE: http://www.ineris.fr/aida/consultation_document/447

Acute toxicity.

	Category 1	Category 2	Category 3	Category 4
Criterion Acute oral/dermal/inhalation toxicity	FATAL	TOXIC	HARMFUL	Substance not classified in the previous categories
Indicators	0 < DL50 oral < 50 mg/kg bw or 0 < DL50 dermal < 200 mg/kg bw or 0 < DL50 Inhalation < 500 ppmV (gas) or 0 < DL50 Inhalation < 2 mg/l (vapor) 0< DL50 Inhalation < 0.5 mg/l (dusts)	50 < DL50 oral < 300 mg/kg or 200 < DL50 dermal < 1,000 mg/kg bw or 500 < DL50 Inhalation < 2,500 ppmV (gas) or 2 < DL50 Inhalation < 10 mg/l (vapor) 0.5< DL50 Inhalation < 1 mg/l (dusts)	300 < DL50 oral < 2,000 mg/kg pc or 1,000 < DL50 dermal < 2,000 mg/kg bw or 2,500 < DL50 Inhalation < 20,000 ppmV (gas) or 10 < DL50 Inhalation < 20 mg/l (vapor) 1< DL50 Inhalation < 5 mg/l (dusts)	Substance not presenting any of these properties
Source:	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ US EPA (IRIS): https://www.epa.gov/iris ATSDR: http://www.atsdr.cdc.gov/toxprofiles/index.asp OMS: http://www.inchem.org/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment			

Organ toxicity following single exposure

	Category 1	Category 2	Category 3	Category 3
Criterion Organ toxicity following single exposure				Substance not classified in the previous categories
Indicators	Substances producing noticeable toxic effects in human beings or for which there is reason to suspect that, based on data from animal studies, they can be extremely toxic to human beings following single exposure. The substances classified in category 1 are specifically toxic to target organs (single exposure) based on: a) reliable, data of good quality obtained from human case studies or epidemiological studies; or b) appropriate animal studies allowing observation of significant and/or serious toxic effects transposable to human beings resulting from exposure to generally weak concentrations	Substances from animal studies that suggest they can be harmful to human health following single exposure The substances classified in category 2 are specifically toxic to certain target organs (single exposure) based on appropriate animal studies allowing observation of significant and/or serious toxic effects transposable to human beings resulting from exposure to generally moderate concentrations.	Transient effects on certain target organs This category does not include narcotic effects and irritation of airways. These effects on target organs are caused by a substance that does not meet the criteria of categories 1 or 2. These effects alter a human function during a short period of time following exposure from which a human being can recover in a reasonable period of time without any remaining significant functional or structural change.	Substance not presenting any of these properties
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment			

Irritation /sensitization

<table>
<tr><th></th><th>Category 1</th><th>Category 2</th><th>Category 3</th></tr>
<tr><td>Criterion
Corrosion/Irritation</td><td>BURNS/SERIOUS INJURY</td><td>IRRITATION</td><td>Negligible effects</td></tr>
<tr><td>Indicators</td><td>Corrosive for at least 1 animal out of 3
<table><tr><th>Exposure</th><th>Observation</th></tr><tr><td>< 3 minutes
Or > 3 m - <1 h
Or 1 h - < 4 h</td><td>< 1 hour
< 14 days
< 14 days</td></tr></table>Or
A substance that, applied to the eye, produces
- an irreversible or partially irreversible effect on the cornea, iris or conjunctiva in an animal for at least 21 days or corneal opacity > 3 and/or iritis > 1.5</td><td>A substance that causes erythema, eschar or edema (average value between 2.3 and 4) in 2 out of 3 animals tests in 24, 48 and 72 h.
or persistent inflammation in at least 2 animals after 14 days or
lower values observed in just 1 animal but with significant variation from one animal to another
or
A substance that, when applied to the eye, causes a positive reaction in at least 2 out of the 3 test animals (corneal opacity > 1 and/or iritis > 1 and/or reddening of the conjunctiva > 2 and/or conjunctival edema > 2, after 24, 48 and 72 h following instillation and reversible effects in 21 days</td><td></td></tr>
<tr><td>Source</td><td colspan="3">SDS Sections 2, 9, 11
INERIS: http://www.ineris.fr/substances/fr/
US EPA (IRIS): https://www.epa.gov/iris
ATSDR: http://www.atsdr.cdc.gov/toxprofiles/index.asp
OMS: http://www.inchem.org/
INRS: http://www.inrs.fr/
ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment</td></tr>
</table>

Respiratory sensitization

	Category 1	Category 2
Criterion Respiratory sensitization	SENSITIZATION/ALLERGY	Substance not classified in the previous category
Indicators	These substances are classified as respiratory sensitizers (category 1) according to the following criteria: there are data showing that the substance can induce a specific respiratory hypersensitivity in human beings, and/or an appropriate animal test has produced positive results.	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ US EPA (IRIS): https://www.epa.gov/iris ATSDR: http://www.atsdr.cdc.gov/toxprofiles/index.asp OMS: http://www.inchem.org/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment	

Skin sensitization

	Category 1	Category 2
Criterion Skin Sensitization	SENSITIZATION/ALLERGY	Substance not classified in the previous category
Indicators	These substances are classified as skin sensitizers (category 1) according to the following criteria: there are data showing that the substance can induce sensitization by skin contact in an elevated number of human beings, or appropriate animal tests have produced positive results.	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ US EPA (IRIS): https://www.epa.gov/iris ATSDR: http://www.atsdr.cdc.gov/toxprofiles/index.asp OMS: http://www.inchem.org/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically: http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment IFRA: http://www.ifraorg.org/en-us/standards	

Organ toxicity following repeated or continued exposure

	Category 1	Category 2	Category 3
Criterion Organ toxicity following repeated or continued exposure			Substance not classified in the previous categories
Indicators	Substances producing noticeable toxic effects in human beings or for which there is reason to suspect that, based on data from animal studies, they can be extremely toxic to human beings, following repeated exposure. The substances classified in category 1 are specifically toxic to certain target organs (repeated exposure) based on: — reliable, data of good quality obtained from human case studies or epidemiological studies; or — appropriate animal studies allowing observation of significant and/or serious toxic effects transposable to human beings resulting from exposure to generally weak concentrations	Substances from animal studies that suggest they can be harmful to human health following repeated exposure. The substances classified in category 2 are specifically toxic for certain target organs (repeated exposure) based on appropriate animal studies allowing observation of significant and/or serious toxic effects transposable to human beings resulting from exposure to generally moderate concentrations.	Substance not presenting any of these properties
Source	FDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ US EPA (IRIS): https://www.epa.gov/iris ATSDR: http://www.atsdr.cdc.gov/toxprofiles/index.asp OMS: http://www.inchem.org/ INRS: http://www.inrs.fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment		

Carcigenesis

	Category 1	Category 2	Category 5
Criterion Carcinogen	1A / 1B 'CLP) May cause cancer	2 Suspected of causing cancer (cat. 2 CLP)	Substance not classified in the previous categories
Indicators	Known or presumed human carcinogens A substance is classified in category 1 for carcinogenicity on the basis of epidemiological and/or animal data. **Category 1A**: Substances known to have carcinogenic potential for humans. Classification in this category is largely based on human data. **Category 1B**: Substances presumed to have carcinogenic potential for humans. The classification in this category is largely based on animal data. The classification in categories 1A and 1B is based on the probative force of the data and other considerations (see point 3.6.2.2). The data can come: — from human studies that appear to show a causal link between human exposure to a substance and the onset of cancer (known human carcinogen). Or — animal studies the results of which are sufficiently convincing (1) to demonstrate the carcinogenic potential for animals (presumed human carcinogen).	Suspected human carcinogens The classification of a substance in category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in category 1A or 1B, and takes into account the probative force of the evidence and other considerations It can be based on information (1) from human and animal studies on carcinogenicity.	
Source	SDS Sections 2, 9, 11 NTP https://ntp.niehs.nih.gov ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment IARC: http://monographs.iarc.fr/ENG/Monographs/suppl7/index.php US EPA (IRIS): https://www.epa.gov/iris INERIS : http://www.ineris.fr/substances/fr/		

Mutagenesis

	Category 1	Category 2	Category 5
Criterion Mutagen	1A /1B (CLP) May cause genetic defects	2 (CLP) Suspected of causing genetic defects	Substance not classified in the previous categories
Indicators	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans. **Category 1A**: The classification in category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans. **Category 1B**: The classification in category 1B is based on: — positive results from in vivo heritable germ cell mutagenicity tests in mammals; or — positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolites to interact with the genetic material of germ cells; or — positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed humans.	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. Classification in category 2 is based on: — positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments obtained from: — somatic cell mutagenicity tests in vivo, in mammals; or — other in vivo somatic cell genotoxicity assays which are supported by positive results from in vitro mutagenicity tests.	

Source	SDS Sections 2, 9, 11 ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment US EPA (IRIS): https://www.epa.gov/iris INERIS: http://www.ineris.fr/substances/fr/

Reprotoxicity.

	Category 1	Category 2	Category 4
Criterion Reprotoxic	1A /1B (CLP) May damage fertility or the unborn child	2 (CLP) Suspected of damaging fertility or the unborn child	Substance not classified in the previous categories
Indicators	Known or presumed human reproductive toxicant. Substances are classified in category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans **Category 1A:** Known human reproductive toxicant **Category 1B:** Presumed human reproductive toxicant The classification of a substance in category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects.	Suspected human reproductive toxicant. Substances are classified in category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in category 1. If deficiencies in the study make the quality of evidence less convincing, category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.	
Source	SDS Sections 2, 9, 11 INERIS: http://www.ineris.fr/substances/fr/ ECHA: http://echa.europa.eu/fr/ and more specifically:http://echa.europa.eu/fr/about-us/who-we-are/committee-for-risk-assessment US EPA (IRIS): https://www.epa.gov/iris		

6.2.3 Substances not having a classification due to lack of data.

In the absence of a classification or any of the studies referenced in the tables, one can collect a minimum amount of data using the following techniques:

- QSAR[16] modeling, which attempts to deduce the properties hazardous to living organisms from the molecular structure, if the hazardous properties of neighboring molecules are known experimentally.
- These "read across" techniques also attempts to predict a characteristic of a molecule (physical/chemical property, toxicity, ecotoxicity, behavior in the environment) based on information available for another molecule determined to be similar.
- If these methods are not applicable, it is possible to conduct a series of rapid toxicological assays to collect an initial amount of information.

In any case, it is necessary to have access to a specialist in the field to mobilize additional resources.

Examples of software for estimating acute toxicity	
By ingestion	**By inhalation**
http://www.epa.gov/nrmrl/std/qsar/qsar.html (Free software) http://www.acdlabs.com/products/pc_admet/tox/tox/ (Free software) http://www.simulations-plus.com/ (Paid software) http://www.multicase.com/products/prod01.htm (Paid software) http://www.terrabase-inc.com/ (Paid software) http://accelrys.com/solutions/scientific-need/predictive-toxicology.html (Paid software)	http://accelrys.com/solutions/scientific-need/predictive-toxicology.html (Paid software)

Examples of software for estimating irritation/sensitization
http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree (Free software) http://accelrys.com/solutions/scientific-need/predictive-toxicology.html (Paid software) http://www.terrabase-inc.com/ (Paid software) https://www.lhasalimited.org/derek_nexus/http://www.acdlabs.com/products/pc_admet/tox/tox/ (Paid software)

[16] The principle of QSAR methods (Quantitative Structure Activity Relationship) consists of implementing a mathematical relationship assisted by data analysis methods correlating molecular properties called "descriptors" to an experimental effect (biological activity, toxicity, affinity for a receptor) for a series of similar chemical compounds; they take into account the information on the molecules' structure and physical and chemical properties.

Examples of software for estimating respiratory sensitization	
Free software http://www.vega-qsar.eu/ http://www.caesar-project.eu/ http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree	Paid software https://www.lhasalimited.org/derek_nexus/ http://www.compudrug.com http://molcode.com/) http://oasis-lmc.org/?section=software&swid=4 http://accelrys.com/solutions/scientific-need/predictive-toxicology.html

Examples of software for estimating carcinogenicity	
Free software http://apps.ideaconsult.net:8080/ToxPredict http://www.vega-qsar.eu/ http://www.caesar-project.eu/ http://lazar.in-silico.de http://www.epa.gov/oppt/sf/pubs/oncologic.htm http://www.organic-chemistry.org/prog/peo/ http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree	Paid software http://www.simulations-plus.com/ http://www.prousresearch.com/spage/technology/testpage/pageid-79/epage/BioEpisteme.aspx http://www.biobyte.com/bb/prod/cqsarad.html https://www.lhasalimited.org/derek_nexus/ http://www.compudrug.com http://www.leadscope.com/ http://www.multicase.com/ http://molcode.com/ http://accelrys.com/solutions/scientific-need/predictive-toxicology.html

Examples of software for estimating mutagenicity	
Bacterial genetic mutation Free software http://www.vega-qsar.eu/ http://www.caesar-project.eu/ http://www.organic-chemistry.org/prog/peo/ http://lazar.in-silico.de http://www.epa.gov/nrmrl/std/qsar/qsar.html http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree **Mutagenicity of mammalian cells in vitro** Free software http://apps.ideaconsult.net:8080/ToxPredict **Mutagenicity in vivo** Free software http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree	Paid software http://www.acdlabs.com/products/pc_admet/tox/tox/ http://www.biobyte.com/bb/prod/cqsarad.html http://www.multicase.com/ https://www.lhasalimited.org/derek_nexus/ http://www.compudrug.com/ http://molcode.com/ http://oasis-lmc.org/?section=software&swid=4 http://accelrys.com/solutions/scientific-need/predictive-toxicology.html Paid software https://www.lhasalimited.org/derek_nexus/ http://molcode.com/

Endocrine disruptors

Endocrine disruptors[17] are particularly important, and it is essential to ensure that the alternative selected as a substitute is not also an endocrine disruptor.

For example, if Bisphenol A (BPA) is being replaced in the composition of thermal paper, one must prevent it from being replaced by Bisphenol S (BPS) and/or Bisphenol F (BPF), which, having a similar chemical structure to BPA, could also raise fears of an estrogenic potential identical to that of the substituted molecule.

Categorizing the hazards linked to substances "labeled" as "endocrine disruptors" (ED) is particularly difficult, owing on one hand to the lack of current, clear regulatory criteria defining endocrine disruptors and, on the other hand, to the scientific controversy on this subject.

Furthermore, there is no H-statement (a phrase attributed to a hazard class or hazard category that describes the nature of the hazard in the substance) associated with the notion of endocrine disruption nor are endocrine-disrupting substances classified in different categories (as is the case for CMR substances), and ultimately the notion of potency (endocrine disrupting potential) still remains vague and very controversial.

Nevertheless, most EU regulations on chemical products have already taken this problem into account. For example, in REACH[1818] an endocrine disruptor is recognized as a SVHC (substance of very high concern) and may be added to the candidate list (list of substances of very high concern), or even Appendix XIV, and its use may be prohibited after a period of time.

What are the steps to follow to make sure a substance isn't an endocrine disruptor?

1. First, it is possible to consult the different available lists of potential endocrine-disrupting substances. These are provided for reference purposes. Some are from governmental organizations, others from non-governmental organizations. It is important to remain critical and verify the validity of the information provided. The most commonly used lists appear below: (non-exhaustive list):

   Lists focused on potential endocrine disruptors:

- Lists from the European Commission: (http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm#priori ty_list)
- The TDEX list: (http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/chemicalsearch)
- The JRC EASIS database: (https://eurl-ecvam.jrc.ec.europa.eu/databases/eas_database)

[17] The definition of an endocrine disruptor most commonly admitted is that established by the WHO in 2002: "A Potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations."

[18] Regulation (EC) No. 1709/2006

Other lists not solely focused on endocrine disruptors:

- The ChemSec SIN List:
  (http://www.chemsec.org/images/stories/2014/New_SIN_substances_October_2014.pdf

- The CORAP list:
  (https://echa.europa.eu/fr/information-on-chemicals/evaluation/community-rolling-action-plan/corap-list-of-substances)

- The REACH Candidate list:
  (https://echa.europa.eu/fr/candidate-list-table)

These lists and some other examples of very-high-concern lists, which may include potential endocrine disruptors, are included in Appendix 4.

2. If, after consulting the lists, it is not possible to come to a clear conclusion (for example, an alternative appearing on only one of the consulted lists, with insufficient data), one can nevertheless determine the endocrine disrupting potential. To do so, it will be necessary to collect all the available information about the substance (physical and chemical properties, epidemiological studies, available (eco)toxicological studies, etc.), then eventually categorize it by way of (eco)toxicological testing. For example, we can cite two well-codified approaches permitting a scientific process that advances stage by stage: that of the EPA (the Environmental Protection Agency) and that of the OECD:

- **The EPA approach** consists of two stages[19]. First, there is an initial screening phase to identify substances that may potentially disrupt the endocrine system, then a second phase to determine the hormonal effects and to establish a dose-response curve.

  The first stage includes in vitro and in vivo (eco)toxicological tests, of which some are on non-mammalian organisms. The second stage involves more elaborate, long-term testing on the organisms' entire life cycle, or on multiple generations.

[19] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-battery-assays

- **The OECD approach: Conceptual framework for testing and assessing endocrine disruptors.**

This stage-based approach consists of the five levels described below:

Level 1. Collecting existing general data:

Physical and chemical properties, (eco)toxicological data tests available on the substance, read across, chemical categories, QSARs and other in silico predictions, and ADME model predictions (absorption, distribution, metabolism and excretion).

Level 2. In vitro assays providing data about the mechanism of action of endocrine disruption.

Level 3. In vivo assays providing more specific data about the supposed mechanism of action.

Level 4. In vivo assays providing data on adverse effects and their correlation with a suspected endocrine disrupting mechanism.

Level 5. In vivo assays providing more comprehensive data on the effects on endocrine relevant endpoints over the entire life cycle of the organism.

Note 1: The testing guidelines are available at the OECD website.

Note 2: In 2012, the OECD published guidelines on assessing data from standardised tests for endocrine disruptors. Its objective is to facilitate the interpretation of results by proposing possible scenarios while guiding the user toward additional tests to provide evidence whether a substance does or does not have endocrine disrupting properties.

Conclusions:

Despite the foregoing highlighted difficulties, categorising hazards linked to the endocrine disrupting nature of a substance is essential to a substitution. It is important to draw on internationally known definitions and criteria that provide reference, such as those by the WHO. Then, proceed methodically stage-by-stage and checking at each stage if it is possible to proceed to the next stage, based on (eco)toxicological data and an expert opinion on the subject. Naturally, these guidelines are for reference and simply intend to guide the reader by providing some initial points of reflection.

6.3 Accidental Hazards[20]

Besides these criteria on hazards to living organisms, other physical and chemical hazard criteria should be taken into consideration, such as flammability, explosivity, or self-heating, oxidizing or pyrogenic properties. Substances presenting such hazards may actually endanger the safety of workers, or require safety measures that make the work harder. In addition, they can also endanger production facilities, the public and consumers.

The substances can be categorized according to their classification under CLP regulation[21], with (at most) four accidental hazard categories:

Flammability

Liquids

	Category 1	Category 2	Category 3	Category 4
Criterion	Extremely flammable	Very flammable	Flammable	Not classified
Indicator	H224	H225	H226	
Source	See note 20	See note 20	See note 20	

Solids

	Category 1	Category 2
Criterion	Flammable	Not classified
Indicator	H228	
Source	See note 20	See note 20

[20] http://clp-info.ineris.fr/sites/clp-info.gesreg.fr/files/documents/tableau_cl_fr.pdf

[21] the European Chemicals Agency maintains an updated table of all the harmonized classifications available under the CLP regulation: https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp. See also http://clp-info.ineris.fr/sites/clp-info.gesreg.fr/files/documents/tableau_cl_fr.pdf

Aerosols

	Category 1	Category 2
Criterion	Extremely flammable	Flammable
Indicator	H222	H223
Source	See note 20	See note 20

Explosion

	Category 1	Category 2
Criterion	Explosion	Not classified
Indicator	H200/201/203/204/205	
Source	See note 20	

Heating may cause explosion (self-heating mixtures or substances)

	Category 1	Category 2	Category 3	Category 4
Criterion	Heating may cause an explosion	Heating may cause a fire or explosion	Heating may cause a fire	Not classified
Indicator	H240	H241	H242	
Source	See note 20	See note 20	See note 20	

Self-heating or pyrophoric materials or liquids

	Category 1	Category 2
Criterion	Catches fire spontaneously if exposed to air / Self-heating material may catch fire	Not classified
Indicator	H250/251/252	
Source	See note 20	

Substances or mixtures that release flammable gases when in contact with water

	Category 1	Category 2	Category 3
Criterion	In contact with water releases flammable gases which may ignite spontaneously	In contact with water releases flammable gases	Not classified
Indicator	H260	H261	
Source	See note 20	See note 20	

Oxidizers

	Category 1	Category 2	Category 3
Criterion	May cause fire or explosion; strong oxidizer	May intensify fire; oxidizer	Not classified
Indicator	H271	H272	
Source	See note 20	See note 20	

Metal Corrosion.

	Category 1	Category 2
Criterion	May be corrosive to metals	Not classified
Indicator	H290	
Source	See note 20	

If data is lacking, one can resort to:

- ✓ QSAR[22] modeling, which attempts to deduce the accidental hazard properties of the molecular structure, if the accidental hazard properties of neighboring molecules are known experimentally.
- ✓ One can conduct a series of rapid toxicological assays to collect an initial amount of information.

[22] The principle of QSAR methods (Quantitative Structure Activity Relationship) consists of implementing a mathematical relationship assisted by data analysis methods correlating molecular properties called "descriptors" to an experimental effect (biological activity, toxicity, affinity for a receptor) for a series of similar chemical compounds; they take into account the information on the molecules' structure and physical and chemical properties.

6.4 Hazard summary

The criteria listed for hazards include classification and their corresponding codes. There are **three information access levels** described in the foregoing paragraphs (6.2 and 6.3). For a **substance having a known classification** (REACH, or other regulation: biocides, phytosanitary products, etc.), it is possible to see all the information from the table below.

For non-classified substances, it is possible to classify it based on a **knowledge of its properties and available data.** Lastly, with very little data, one must generate **preliminary or temporary classifications with the screening tools** or testing software described previously.

Two important points must be highlighted:

The codes do not represent a criteria "value." The same code (1 for example) for flammable or for carcinogenic does not have the same value in a decision analysis. Assigning a value will have to be addressed during the decision analysis.

If a substance is known and registered under REACH, and if the substance is not classified **for a hazard criterion**, this means that it does not present the hazard under consideration. Conversely, if only partial data exist, one cannot assume "not classified" means "non-hazardous" because it may be that it has not been studied from this angle. This possibility warrants a certain vigilance.

Hazard	Classification based on CLP codes				
ENVT toxicity [École Nationale Vétérinaire de Toulouse (National Veterinary School of Toulouse)]	1	1 bis	3	4 not classified	
Acute toxicity	1	2	3	4 not classified	
Acute specific target organ toxicity	1	2	3	4 not classified	
Irritation	1	2	3 not classified		
Respiratory sensitization	1	2 not classified			
Skin sensitization	2	2 not classified			
Chronic toxicity	1	2	3 not classified		
Carcinogenic	1	1bis	2		5 Not classified
Mutagens	1	2			5 Not classified
Reprotoxic	1	2		4 not classified	
Flammable liquids	1	2	3	4 not classified	
Flammable solids	1	2 not classified			
Flammable aerosols	1	2 not classified			
Explosion	1	2 not classified			
Heating may cause explosion	1	2 not classified			
Pyrophoric liquids	1	2 not classified			
In contact with water releases flammable gases	1	2	3 not classified		
Oxidizers	1	2	3 not classified		
Metal corrosion	1	2 not classified			
Endocrine disruptor	Refer to lists, even launch studies				

6.5 Exposure and risk assessment

When other criteria do not clearly allow for an alternative to be discarded, and the hazard criterion proves to be particularly insufficient to discriminate among them, one can refer to additional exposure and risk criteria.

Indeed, for the same hazard, two substances may (due to their physical and chemical properties or the different conditions in which they are used) generate very different exposures, which may constitute an additional criterion for differentiating them in the analysis.

In this case, it is a matter of determining the different human populations (general, workers, sensitive populations, etc.) or the ecosystems exposed (in terms of number of individuals, routes and durations of exposure).

The human and environmental exposure of a substitute must be assessed at all stages of the substitute's life, production, formulation, use and elimination.

It is important to be attentive to the potentially different exposure patterns between a substance and its alternatives: for example, the replacement of a substance used in a surface treatment processing solution, and emitted in an aqueous effluent, may significantly change the route and targets of exposure compared to a process performed with atmospheric deposition.

Different populations, route and situations of exposure resulting from the types of emission the substance and its alternatives release into the environment must, thus, be considered based on their particular context. These populations are to be considered separately and are described below.

To assess exposures and risks, the regulatory dossiers compiled under EU regulations, and particularly registration dossiers for REACH, are valuable sources of information, the data of which may be, with the assistance of a specialist, adapted to a specific substitution under study. However, in the absence of existing usable data, specific assessments and measures are to be conducted with the help of specialists and the tools proposed in the following sections in which, just like the organization adopted in REACH registration dossiers, in which different exposure categories are identified.

6.5.1 Workers' exposure

Workers are a group that is often subject to a very specific type of exposure that strictly depends on the work conditions, the industrial process they participate in, the safety measures they benefit from and the effectiveness of these measures vis-à-vis chemical substances, all at the same time. Workers are also subject to specific exposure regulations. In fact, there are specific tools for assessing exposures and risks to workers.

Many different-tiered tools are proposed by INRS[23] to assess the exposure and risk resulting from the use of a chemical product.

[23] National Safety Research Institute [Institut National de Recherche sur la Sécurité] - www.inrs.fr

The SEIRICH application, a tier-1 tool, allows an assessment of the risk via the skin and inhalation exposure routes. The exposure is estimated by taking into account the physical and chemical properties of the substance, the implementation process and the means of collective prevention. The level of exposure is combined with one of 5 hazard groups derived from the classification. The risk is then categorized into one of three levels: moderate, high, very high. The "simulation" module allows a comparison of the risks of different alternatives.

The IHMOD software developed by AIHA (American Industrial Hygiene Association) and translated into French by the INRS is a tier-3 modeling tool. It allows one to calculate the exposure as an atmospheric concentration. Based on a probabilistic approach, it is adapted to calculate the exposure of a substance, the application to a product (mixture or substances) needing additional calculations from an expert.

There are simpler approaches based on experimental evidence which can be transposed to the case under study. The INRS makes available on its website databases (Solvex, Fibrex) of results of exposure measures that allow, for similar alternatives (physical and chemical properties, sector of activity, etc.) to the substances under study, to estimate the exposure to workers.

Moreover, different tools such as ECETOC TRA, Stoffenmanager or Chesar allow one to estimate the exposure linked to the use of chemicals.

Stoffenmanager (https://stoffenmanager.nl) combines information on a substance's or product's hazard properties and an employee skin contact/inhalation exposure assessment to assess a risk indicator.

CHESAR (https://chesar.echa.europa.eu/) is a chemical safety assessment tool developed by the European Chemicals Agency (ECHA) to help registrants under REACH. This application allows exposure assessments to be conducted and to categorize the risk based on different exposure scenarios.

6.5.2 Consumer exposure

Even if used upstream, a chemical substance may be found in consumer goods and give rise to consumer exposure in many ways. To assess this exposure, one must identify the consumer goods and the modes of exposure: e.g. skin contact, via mouthing, product handling, or emissions of substances to indoor air or in aquatic environments during its use or end of life.
There are tools (free) that allow a calculation of consumer exposure, for example:

- ECETOC TRA, available at www.ecetoc-tra.org.
- ConsExpo, a mathematical model for assessing exposure to chemicals present in consumer products, developed by the RIVM (National Institute for Public Health and the Environment of the Netherlands).

6.5.3 Sensitive human groups

Before implementing exposure and risk assessment tools, it will be necessary to identify the eventual groups sensitive to the substance to be replaced or one of its alternatives. For these sensitive groups, more specific and accurate risk exposure calculations may be necessary. Indeed, certain human groups may prove to be more sensitive if exposed to chemicals, and in such cases the effects may either be specific or occur at weaker doses than for the rest of the population. For endocrine disruptors in particular, the fetus (and thus pregnant women), young children and adolescents at puberty are sensitive groups, since these molecules can cause effects that have long-term adverse consequences on their health (child development, etc.).

Another example, allergic or asthmatic populations will be sensitive to certain allergens more quickly and at weaker doses.

6.5.4 Human exposure via the environment

This is exposure that results from pollution in environmental media: air pollution (pollution in the atmosphere from a neighboring production site, etc.), and water and land pollution (substances released in the water or ground leading to human exposure via underground or surface aquatic environments, if the substance reaches a drinking water system or food). In the event the substance to be replaced or the alternative are released into the environment, the possibility of causing exposure to the surrounding population should be assessed. If it appears necessary to go beyond a qualitative exposure assessment, it is possible to use, for example, the EUSES model available free of charge (https://ec.europa.eu/jrc/en/scientific-tool/european-union-system-evaluation-substances).

6.5.5 Exposure of organisms in the environment

Chemical substances also lead to the exposure of fauna and flora, in or via all environmental media: aquatic species via water pollution, the diverse species of the soil (particularly micro-organisms), as well as generally exposed mammals such as humans via all environmental media. Reference values are available for certain substances, particularly on the INERIS's chemical substance portal (www.ineris.fr/substances/fr).

6.5.6 From exposure to risk assessment

Risk is defined as the probability that an adverse effect will occur after exposure. It is, thus, the combination of an exposure in a given situation and its hazard level.

Risks concern both humans (consumers, workers, sensitive populations) and the environment (risk to ecosystems, even impacts on biodiversity).

In the event that assessing risk does not always permit one to clearly compare alternatives (for example, if exposure routes and hazards of different natures are in play for each of the alternatives), the notion of risk may allow one to achieve this phase (for example, to conclude whether an alternative presents a significant risk and another does not, even though the hazards and exposures are difficult to compare).

The simplest approach consists of qualitatively assessing the risks by referring to the estimated hazard criteria and exposure levels (which may also be qualitative) according to the approach described in the foregoing paragraphs.

A simple quantitative approach consists of calculating a risk ratio between the exposure of the population under consideration and a toxicological and ecotoxicological reference value.

For "threshold" substances, i.e. substances for which there is a concentration under which the substance does not induce an adverse toxicological effect, one will consider that a risk ratio under 1 translates to an acceptable risk level while a risk ratio over 1 will be interpreted as an unacceptable risk level.

For "non-threshold" substances, i.e. substances for which the toxicological effect is observed regardless of dose (such as carcinogenic or mutagenic substances), the risk will be quantified by calculating the excess risk. This corresponds to expected risk of a given pathology following continued exposure (24h/24h) over the span of a life (70 years) at a concentration of 1 unit of the substance under consideration.

The doses can sometimes be assessed by their concentration: thus, for a substance to which one is exposed by an atmospheric route (by inhalation), it will be possible to work more easily with the atmospheric concentration values (values to which the people are exposed, and a reference toxicological concentration).

Toxicological reference values for a wide variety of chemical substances are accessible on the following websites:

- www.ineris.fr/substances/fr/,
- https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de- r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses.

The Health Risk Assessment (HIA) [’Evaluation des Risques Sanitaires (ERS)] methods allow one to fine tune the quantitative risk estimate correlated to a substance or alternatives when more than just a simple risk ratio needs to be calculated. The concept is similar to the risk ratio but the methods specifically focus on taking into account more carefully all of the multiple exposure routes, different effects on health and the environment, or even the environment's pre-existing state of pollution. The HIA allows one to create a spatial distribution (geographical) of the risk and, in particular, to take into account location-specific information if the substitution concerns potential impacts that are defined and limited by geography (for example, if the substitution principally has implications on a process at a specific industrial site).

A resource guide on assessing health risks offered by INERIS is available at the following address: http://www.ineris.fr/centredoc/drc-guide-ers-2013-v4d-complet-lienscompact- 1378197912.pdf.

6.5.7 Risk of accident

It is important to define scenarios based on functionalities and processes, and to develop a risk analysis.

A general guide for analyzing risks generated by an industrial facility has been developed by INERIS and is a good introduction to the methods.

However, this guide does not specifically concern accidental risks generated by chemicals (see particularly the INERIS guide on risks related to thermal runaway phenomena.)

6.6 Health and environmental impacts

An impact is the concrete result of a risk that is actually borne out by society. It must be expressed such that it makes sense in terms of public health and environmental health: increases in asthmatic pathologies, for example, in male cases of infertility or the disappearance, even locally, of a species, etc.

Health impacts are characterized by two main factors: the nature of the pathologies, and for each of them, their scope (the number of persons affected and the severity of the impact).

AHealth Impact Assessment is a method that continues where the Health Risk Assessment left off by using the correlations between doses and responses to calculate the cases of pathologies.

Resorting to this additional and potentially useful criterion is necessary when the risk and hard-to-compare exposure criteria are insufficient to discriminate between two solutions. The impact study will thus allow one to estimate potential adverse health effects and to more concretely compare alternatives.

It may also be necessary to utilise economic tools that allow one to classify, or even monetize the adverse health effects, which will help render them quantitatively comparable. For this purpose, the WHO proposes measuring the severity of pathologies in terms of DALY (*Disability Adjusted Life Years http://www.who.int/healthinfo/global_burden_disease/me*). The ECHA offers a guide applied to chemicals for socio-economic analysis (*Guidance on Socio-Economic Analysis – Restrictions, ECHA May 2008*).

Health impacts are characterized by two main factors: the nature of the pathologies, and for each of them, their scope (the number of persons affected and the severity of the impact).

Based on these examples, it appears the impact prolongs the risk:

- By transposing more relevant indicators onto a societal scale.
- By taking into account the size and characteristics (sensitivity, etc.) of a specific population and of a globally affected population.

For a substance, the notion of risk is sometimes too dependent on a regulatory framework (exposure level ratio expected in scenarios correlated to toxic reference values), or too correlated to the "critical effects" (the effect criterion retained in an assay) in toxicology. The table below indicates the transpositions that it is desirable to make.

Converting risk data into desirable health and environmental impact estimates. Indicator and calculation logics		
	Risk assessment **In a regulatory logic**	**Impact assessment**
Hazard (examples)	Classification: toxic to reproduction/fertility. Sensitizer	Extends the time needed to conceive. Assisted reproduction need.
Exposure	Estimate based on a worst-case exposure scenario	Average exposure of the population, or even target or vulnerable populations.
Risk indicators (human health)	Risk ratios: No effect Dose /calculated exposure.	The probability that a disease will appear in an individual. Number of cases of the disease in a population.
Risk indicators (environment)	Specific ratios for a species (predicted no-effect concentration/exposure at a calculated concentration).	Decrease or disappearance of a species Loss of biodiversity.

Responding to this type of question with quantified estimates of the impacts is rarely possible. The examples are often the exception (cases of atmospheric pollution[24], cases of chemicals managed under the restriction and authorization procedures in REACH with assessments not only of the global health impact but also the economic impact). **But the question of the impact estimates remains relevant in the proposed process for at least two reasons**:

- It is often possible to classify adverse effects to health or species beyond toxicological classifications.
- Some substitution estimates and values may be accessible.

The process is as follows:

Stage 1: *Classify the health and environmental stakes* for individuals and society and the related adverse effects if a (eco)toxicological classification exists. If there is no existing classification, create one.
Examples:
H370 classification: Known risk of serious effects to organs following single exposure:
identify the organ, the pathology and what the consequences are for the person.
Examples: Skin sensitization... other sensitizations, phototoxicity.

[24] Report from the Senate Investigative Committee on the economic and financial cost of air pollution. Report 610, July 2015.

NB: Information on the types of cancer (or malformations from reprotoxic substances impacting the fetus) are in principle not relevant because these substances are to be immediately discarded for potential alternatives, but they may appear if one integrates changes to the process generating pollution differentials.

Data sources:

Existing data and dossiers mentioned previously for hazards. They may not provide sufficient information and will require resorting to technical specifications sheets and monographs (INERIS, EPA, OSHA, INRS, Cal EPA, Health Canada, NIH, etc. specification sheets).

Stage 2: *Build potentially simplified indicators on the collective impact.*

Principle of calculation:

A comprehensive assessment should succeed, in estimating real exposures, dose-effect ratios and in providing an estimate of the expected adverse effects in different populations. It is obviously extremely rare for this to be feasible, so simplified processes have been developed.

In practice, some very simplified processes are available. We give two examples below.

The first process is that of Eurostat, which measures REACH's effectiveness with **risk scores**. Comparative risk ratios (hazard/exposures thresholds and RCRs) are weighted by indicators of very cursory population sizes with some classes (the population modifiers, PMR).

Risk score = comparative ratio x population modifier.

The estimate is made for four categories:

1. environment,
2. humans in the environment,
3. consumers,
4. humans at work.

Values have been estimated for more than 300 substances.

As part of an exercise classifying priority substances for the PNSE [Plan National Santé-Environnement, French National Plan for Environmental Health], INERIS has worked on a complementary approach by applying the principles above to estimate a "collective risk indicator" for 319 substances, by calculating a **collective risk index**[25].

This is defined as a product of the magnitude of the exposed population (PExp) multiplied by the estimated risk (the sum of the (exposure by inhalation/toxic dose by inhalation) ratios, same for ingestion).
Both methods proceed in the same spirit, but in the classification exercise the substances are sometimes different, and the exposure values are more specific to France.

[25] Guillaume Karr, Bénédicte Pecassou, Céline Boudet, Martine Ramel. "Assistance in selecting priority substances for the future national health and environment plan: Building and implementing a collective risk indicator." *Environment Risks and Health*, Vol. 13, No. 3 May-June 2014 ["Aide au choix des substances prioritaires du futur plan national santé environnement : Elaboration et Mise en œuvre d'un indicateur de risque collectif." *Environnement Risques et santé*, volume 13 n°3 Mai Juin 2014.]

Data sources:

For the full exercise: no specific sources. The hazard data come from previously mentioned sources. The risk assessment exercise can be based on HIA methods and EUSES software.

For the Eurostat "risk score": *REACH Baseline study - a tool to monitor the new EU policy on chemicals - REACH Eurostat 2009. And the REACH baseline study - 5 year update - Comprehensive study report, EUROSTAT 2012.*

For the collective risk indicator built for the PNSE: *Defining a method to identify and classify substances of concern – Applying in the present case the preparation for the third National Health and Environment Plan. No. INERIS-DRC 12-125943-04682A. INERIS 2013. See also, specifically, Appendices 14, 34 and 37.*

Stage 3: *Identify the multi-dimensional nature of the impacts.* Principle of calculation:

Also as part of the work performed by INERIS to rank the priorities of action on pollutants, a list of quantification rules and criteria have been established (not to be confused with the criteria described in 6.4 for the substitution process):

1. Natural / anthropic sources.
2. Dispersion of the exposure.
3. Sensitive groups.
4. Environmental risk.
5. Health risk (need to act on).
6. Permanence of the impregnation in the media.
7. Intrinsic hazard to health.
8. Technical difficulty and cost of reducing emissions.

The first criteria can play a non-negligible role in the acceptability of substitutes but does not fall directly under the impact.

Data sources:

EUROSTAT provides in its report the values and the calculating methods used. For the INERIS classification exercise, estimates have been made for 319 substances of concern. The estimate rules are provided for each criterion, as well as the accessible data sources.

Processing asymmetrical information:

All of the data necessary for a quantitative impact assessment is generally not available and requires a completely new study. Simplified indicators and scores may be available and may be rebuilt (for ex., if there are existing REACH dossiers).

In other cases, it is important to note that patchy data is accessible, sometimes on hazards (cf. § on hazards), sometimes on exposures (for example, a substitution for a well-documented use). A brief survey can always be conducted.

6.7 Other impacts

The review of hazards, risks and impacts in the foregoing paragraphs focuses on the toxicological and ecotoxicological properties of substances or other alternatives. The substitution process will take into consideration the criteria related to other kinds of impacts that are still important to assess in a sustainable development process. For example, the expected impact of alternatives on air quality, global warming (and the emission of greenhouse gases), water pollution, natural resource management, waste management, etc.

Assessing these types of impacts will consider the life cycle of the substance and its alternatives. If, based on this examination, one foresees significant impacts at certain stages of this life cycle other than those expected from using the substance and its alternatives, it may be useful to conduct a simplified life cycle assessment.

Some criteria proposals for these impacts are described in this section. These criteria can be considered optional and should be omitted unless they can demonstrate a significant difference between certain substances. There may be some situations without impacts that allow one to disregard them, hence the need to use reason on a case-by-case basis. They can also help distinguish between different alternatives that might be difficult to decide between based solely on other criteria.

6.7.1 Climate/Greenhouse gases (GHG) and energy.

This impact is characterized by greenhouse gas emissions induced by the use of the substances under study, regardless of whether the emissions are direct or indirect. The aspects we will examine include:

- Increased energy use that is automatically accompanied by growing greenhouse gas emissions.
- An increased need to transport substances and goods.

If the above is possible, for example using available data on a company's carbon footprint or sustainable development criteria, for example,
it is necessary to estimate indicators such as:

- The amounts of greenhouse gas emissions (equivalent to CO_2) emitted per ton of substance produced or used (if a chemical alternative)[26].
- The nature of the energy resources associated with the alternative: share of renewable energies compared to fossil energies.
- The energy use associated with implementing the alternative (a proxy will allow one to determine the greenhouse gas emissions based on the indicator for the share of renewable energies) including resource transport (cf. below).

[26] The website http://www.bilans-ges.ademe.fr/fr/accueil/contenu/index/page/giec/siGras/0 provides the global warning potentials (allowing emissions to be converted into CO_2 equivalents) of the main greenhouse gases.

6.7.2 Consumption of natural resources.

The consumption of resources concerns the use of the material resources needed to implement a process and includes the water needed and its eventual impact on this resource.
The material resources are the ones need to replace a substance with an alternative. The origin of the resources and transporting them is a matter that will be consider in the part on GHGs. In this part we are more interested in the impact on water resources or on non-renewable resources such as rare earth in particular (for example, an alternative that would necessitate resorting to a catalyst such as platinum and would thus contribute to the consumption of this rare, non-renewable earth metal).

6.7.3 Transfers and impacts on the environment.

The alternatives contemplated may have varying impacts on air, water and soil quality, with respect to substances emitted directly or indirectly. This not only depends on the toxicological or ecotoxicological properties of the substances, which have already been discussed in the preceding paragraphs, but also depends on their capacity to disperse in different environmental compartments and on their accumulation and persistence potential.

This potential problem is considered in the "environment" criterion, but only partially (only for substances already identified in the regulatory framework). Beyond the regulations, it is possible to verify whether the substance to be replaced or the alternatives may be persistent, bioaccumulative and toxic (PBT) without being officially recognized as such.

Some databases allow one to identify them, but there are not many. A good example is the work carried out by the RIVM[27], which has identified and categorized a great number of substances. There are also some online tools, some of which are available for free (www.pbtprofiler.net).[28]

6.7.4 Waste Management.

Alternatives can differ from the substance to be replaced in terms of the amount of waste generated, and the ways of managing it (recycling may be affected, for example).

6.8 Availability assessment.

The availability of an alternative may not be guaranteed if it is not produced in a quantity sufficient enough to satisfy a business's demand, or if secure supply is not certain. This can be the case if the alternative is new on the market and the production capacity is still limited until higher demand can be confirmed.

Another issue is accessibility: this means knowing, for example, whether an alternative is being proposed by actors to which the business actually has access (who aren't, for example, bound by exclusive contracts with competitors or protected by patents). Some information concerning the origin and the origin of the alternatives (sustainable production, renewable substance or fossil, etc.) will also help assess their availability.

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[27] Rorije, E., Verbruggen, E. M. J., Hollander, A., Traas, T. P., & Janssen, M. P. M. (2011). Identifying potential POP and PBT substances. Development of a New Persistence/Bioaccumulation Score, Report 601356001/2011.

[28] Some QSAR models have also been especially developed for this purpose when the necessary data is not available (see in particular, the Prometheus model https://www.vegahub.eu/portfolio-item/prometheus/)

6.9 Statutory and regulatory constraints.

When assessing alternatives, it is important to consider statutory and regulatory barriers, or certification and validation constraints. It is possible to take them into account in a specific criterion, or incorporate them into the economic feasibility assessment, if figures on the costs of compliance with laws, regulations or certifications arising from the move to an alternative are available.

If regulations absolutely ban an alternative, there is little chance
they will change, and it will be necessary to strike this alternative from the assessment.

Aside from this extreme case, the description of the substance's regulatory obligations is a point of departure and an element that can be compared with replacement substances and techniques.

The sector's principal regulatory fields appear below:

- AMM (Pharmaceuticals, Biocides, Phytopharmaceuticals, etc.).
- Medical devices.
- Electrical and Electronic equipment(RoHS).
- Toys.
- Cosmetics.
- Textiles.
- Food.
- Food contact.
- Waste.
- WFD.
- The Seveso Directive.

There are also related regulatory areas:

- ICPE (Installation Classée pour la Protection de l'Environnement [Facility Classified for Environmental Protection]).
- PIC.
- Occupational health and safety.
- Transport.
- Waste.

6.10 Economic feasibility of alternatives.

The purpose of the economic feasibility assessment is to compare the costs of an alternative to those of the substance to be replaced. The costs can be positive (investments to be made, more costly alternatives, etc.) or negative and represent, thus, savings (less costly alternatives, energy savings, etc.).

The following are the different cost components of a substitution process:

- The investment costs associated with changing to an alternative technology, owing to the acquisition of machinery and equipment. If an alternative substance, investment may also be necessary to adapt the process.

- The recurring costs associated with using the replacement substance or the technology. For an alternative substance, these costs correspond to maintaining a consistent supply of said substance, for a replacement technology, they correspond to maintenance. Other eventual differences between an alternative and the substance, in terms of consumables, may also need to be considered: energy consumption, the productivity of the technical process, the labor required, additional consumable material, etc.
- Other non-recurring costs may also need to be considered: the cost of R&D activities – including reformulating, testing, reclassifying a substance or regulatory dossiers of products or processes, including training. If the regulatory and certification costs are considered at this stage, they will not need to be taken into account for the "statutory and regulatory constraints" criterion.

Two points of view can be adopted for cost comparison purposes:

- The total substitution cost (the difference between the cost of an alternative solution and that of implementing the initial substance). This consists of comparing the financial resources outlaid (or saved) for each of the alternatives. A tool that can, as needed, be used to do this comparison is calculating the Net Present Value of the substitution project.
- The cost of substitution can be expressed in a ratio with the price of a downstream product, which allows an assessment of the feasibility of the costs being passed downstream in the supply chain.

Some basic scenarios must be common to all of the calculations made for the alternatives and the substance to be replaced: a reference year common to all of the prices, including inflation data for eventual price corrections, the duration of the scenarios, and the discount rates of correction eventually used.

Some qualitative elements will conclude the cost assessment for each substitution solution, in particular concerning the expected impact on the business's competitiveness: the impact on product quality and on market positioning (particularly through innovation and an eventual competitive or regulatory advantage in the future permitted by a substitution). As opposed to the substitution costs, which are relatively easy to determine, these substitution benefits are difficult to quantify, but are important to consider in order to have a comprehensive outlook on the economic consequences.

6.11 Acceptability assessment

6.11.1 By the supply chain

This part will qualitatively assess the positives and negatives on the substitution solution's supply chain and logistics, if they have not already been considered in the economic feasibility assessment of the alternatives.

It is important to focus on the following issues:

- The overall acceptability of the new solution, based on the efforts to be made regarding information, training and changing work habits.
- The impact on the "quality" control system: changing procedures, internal audits to be conducted, etc.
- The impact on the supply chain organization.
- The impact on waste management, or potential problems associated with the "recyclability" of the business's products.

6.11.2 By the public

Acceptability can be linked to:

- Increased costs to consumers, which will depend on the type of product and the amount of the increase.
- Possible increase in costs to the business (marketing, advertising).
- If the function of the final product (or its shelf life, or another property indirectly related to the substitution effected) is changed in a perceptible manner, an impact on the product's acceptability is possible.
- Consumer habits, traditions and local culture.

Acceptability, and in particular acceptability vis-à-vis the public, may be subject to verification by way of a survey – to ensure that the substitution solution implemented presents no significant inconvenience in the eyes of consumers – which may have evaded a follow-up assessment based on this guide.

A successful substitution may naturally be part of communications efforts in order to take part in informing the public and raising awareness of best practices in the industry.

7 FINALISING A DECISION

A first decision is made at the initial stage selecting alternatives by elimination. Alternatives the technical performances of which are unsuccessful, or of which the hazards are clearly too high, are eliminated.

A second decision stage comes after the comparative assessment of the preselected alternatives. At this stage, the decision will also be simple in certain cases:

- If one of the alternatives presents a better performance than the others and the substance to be replaced, for all of the criteria assessed, it will be selected.
- If, after in-depth analysis, all the alternatives present a higher hazard level than the substance to be replaced, none are suitable (and the search for potential alternative must start over again).

Besides these simple cases, two main difficulties arise when comparing and selecting alternatives: conflicting criteria and insufficient information.

7.1 Multi-criteria management.

Inevitably, certain alternatives will perform better on certain criteria than the substance to be replaced, and perform worse on other criteria. For example, alternative A may be preferred over alternative B for hazard criteria, but alternative B may be preferred over alternative A in terms of performance and cost. For example, the summary overview in the criteria tables from paragraph 6.4 raises a certain number of issues regarding the importance and the priorities one wishes to assign to the criteria.

7.1.1 Simple, deliberative methods.

Comparing alternatives and making a decision will generally be based on developing an overall vision of the alternatives, for example, by using a simple comparison table that shows, for each alternative, the score (or the grade, as applicable) for each criteria.

A comparison table clearly shows the conflicts to be resolved in selecting an alternative (for ex., an alternative better in terms of technical performance, yet presenting a worse hazard profile, than another). The basic elements are what allow the project's actors to deliberate on the alternative's respective merits and decide on a choice. It is possible to resort to structured methods for organizing the collective discussion, which can help arrive at a consensus more quickly and surely (DELPHI methods[29]).

To limit these difficulties, it is recommended that the number of comparison criteria be limited as much as possible when presenting the alternatives (maximum 6-8 criteria seeming desirable), while also maintaining the comprehensive nature of the criteria under consideration. A rule that helps limit the criteria and sub-criteria is to verify ahead of time that they present certain required qualities: independence and non-redundance. It is particularly important to verify prior to the final comparison stage that certain impacts have not been accounted for multiple times for several criteria. Ultimately, choosing the criteria must allow the stakeholders to decide from among the hazards identified, even if this aspect constitutes one of the difficulties of decisional analysis.

[29] Iterative forecasting method relying on a panel of experts that shows the consensus, the areas of conflict and the uncertainties while progressing toward a collective decision

7.1.2 Multi-criteria methods.

A numerical scoring system is a possible solution for resolving conflicts. However, it is not proposed that a numerical scoring system is always used because this may be unsuitable or difficult to implement for many cases. If a numerical scoring scale is used, it is preferable to avoid mixing qualitative and quantitative scales in the same comparative approach, because quantitatively assessed criteria have a tendency to implicitly receive more attention.

If a scoring system is being used, weighting the different criteria could also be an issue. The absence of weighting means that the criteria are of equal importance, which should normally be the case. Determining the weighting is always very delicate because it implies prioritizing different impacts (health, economic, technical, etc.) and one person alone is rarely in a position to decide. Instead, choosing how to weigh the criteria should be decided by all representative stakeholders, following the rules of the art on the matter.

Another inconvenience of scores (with or without weighting) is that they can automatically bring about offsets among criteria. Such offsets are often acceptable or not, based on point of view (paying a little less for an alternative that also doesn't perform as well may depend on one's position in the supply chain). Scores should only be used after verifying and making certain all the offsets induced are acceptable.

Solutions other than scoring systems are available for decision-making actors:

- Collective discussion and deliberation tools (for ex., DELPHI method[30]) provide an interesting complementary support for the tools described below.
- Setting preference rules in advance, which can, for example, be rules for prioritizing or eliminating criteria (such as the primacy given to the hazard criterion, as previously mentioned).
- Introducing new criteria may facilitate decision-making (for example, risk or exposure criteria, if they haven't been introduced at the start). Limiting the number of criteria to what is strictly necessary at the start is also a way of facilitating the implementation of this method.
- Ranking methods, which compare all alternatives two by two and establish an order of preference, without resorting to score calculations.

7.2 Managing insufficient data and information on alternatives.

Uncertain data can affect the validity of a comparison of alternatives. In particular, there is often much less information on the hazards of the alternatives than the substance to be replaced (asymmetrical information). It is thus recommendable to identify the most uncertain and the most critical data, and verify whether different data within the range of uncertainty lead to a change in the outcome of the alternative selection process. If the outcome is influenced too noticeably by uncertain data, it will probably be better to research how to better assess the data before making any decisions.

The alternatives summary table can be designed in a way that also shows uncertainties (see example below), making them obvious and requiring them be taken into consideration.

Several strategies are possible for managing uncertainties, particularly:

- excluding alternatives presenting too high uncertainty,
- downgrading the values of criteria, if the underlying information is too uncertain,
- searching for additional information.

Insufficient information is different from uncertain information and may make comparing alternatives unfeasible. In particular, a significant lack of data on the hazards of an alternative or an unknown variable regarding the technical feasibility must lead the assessment to be discarded or make acquisition of additional information imperative. It is also recommendable to make the missing information explicitly clear on the alternative comparison tables.

Example (simplified) of an alternatives summary table showing uncertain and missing data

	Cost			**Technical Performance**			**Toxicity to humans**		
	Low	**Average**	**High**	**Low**	**Average**	**High**	**Low**	**Average**	**High**
Substance to be replaced									
Alternative A									
Alternative B									
Alternative C									
	Low uncertainty								
	Average uncertainty								
	High uncertainty								
	Absence of data								

8 SUBSTITUTION PROCESS SUMMARY

The substitution process is divided into four main parts:

- A preparation phase that specifies the project to be implemented, assigns a team to it, defines the project goal, and determines how the project will operate.
- A rather technical phase for identifying and selecting the criteria used to choose the alternative(s).
- An assessment and decision-making phase.
- A longer feedback phase that also includes scientific and technological monitoring.

The main stages are summarized below:

Defining the substitution project.

- Define the project team, the stakeholders and their form of involvement.
  It is important to identify the internal resources at the business (e.g. individuals knowledgeable on the performance and costs, and the resources that perhaps might need to be procured outside the company ((eco)toxicological competencies).
- Define the use and the function (intrinsic functionality and operational functionality) of the chemical product.
- Document the performance levels of the defined function(s).
- Identify the uses contemplated for substitution.

Research and assess potential alternatives.

- Conduct research.
- Consult experts and resource centers.
- File relevant documentation.
- Define the criteria for assessing and comparing alternatives.
- Out of all the criteria, retain and list the relevant criteria (at a minimum, hazards, performance and costs).

To frame this qualification phase one can divide criteria into different families.

Performance

⇨ *Assessments [i.e. scoring] to be conducted by the developer's engineers and sales teams.*

Direct impacts on Health and the Environment

- The hazard properties of a substance.
- Exposures to the substance and risk ratios.
- Impacts on public health and the environment.

⇨ *Elements developed in this guide use frequently shared data and competencies from regulations or specific studies (cf. REACH, toxicology, ecotoxicology). Based on the complexity of the substance (or mixture) and its alternative, and the degree of investigation desired (on the hazards and impacts), outside experts will sometimes need to be called upon.*

Indirect and global impacts

- Climate.
- Consumption of natural resources.
- Transfers in the environment.
- Waste management and life cycle.

⇨ *Assessments to be conducted on an ad hoc basis, based on existing literature, without the need for specific competencies.*

Operational feasibility

- The availability of a substance and feasibility of its supply.
- Regulatory acceptability.
- Economic interest.
- Ease of flow: from the supply chain to the consumer.

⇨ *Assessments to be coordinated by a "product stewardship" manager.*

Assessment and Decision-Making

Eliminate irrelevant alternatives:

- Discard alternatives with hazard levels greater than or equal to the substance to be replaced.
- If the alternatives have a lower performance level than the substance to be replaced, for each one:
  - ⇨ Research whether the performance level can be adjusted.
  - ⇨ Research whether the functionality can be modified.
  - ⇨ Modify the performance, the function, or reject the alternative.

Assess and compare the alternatives:

- Establish an accurate list of comparison criteria (including, at a minimum, the hazard, performance and cost criteria).
- Define the method for comparing the alternatives.
- Collect data to identify the criteria and, if possible, determine their uncertainty.
- Identify the criteria and proceed with the comparison.

Select an alternative (including testing and final validation):

- Inform, consult, deliberate with members of the project team and the stakeholders as initially determined.
- Take their comments into consideration and, if necessary, revise the foregoing process.

Feedback and monitoring

Implementing the selected alternative:

- Collect information, particularly on performance and costs.
- Compare implementation to the initial estimate.

Feedback, monitoring:

- Obtain a first round of feedback after implementation.
- Define the how and when comprehensive feedback will be obtained and
- how and when the substitution process will be revised/updated.

9 APPENDIX

Appendix 1: Engagement Letter

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

MINISTÈRE DE L'ÉCOLOGIE, DU DÉVELOPPEMENT DURABLE
ET DE L'ÉNERGIE

Direction Générale de la Prévention des Risques

Service des risques sanitaires liés à l'environnement, des déchets et des pollutions diffuses

Sous-direction santé-environnement, produits chimiques, agriculture

Bureau des produits chimiques

Nos réf. : SPC-16-003

Affaire suivie par : Jordane WODLI
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Tél. : 01 40 81 86 99 – Fax : 01 40 81 20 72

Paris, le 08 FEV. 2016

Le Directeur général de la prévention des risques

à

Monsieur le Directeur Général de l'INERIS
Monsieur le Président du MEDEF

A l'attention de :
Philippe Hubert, INERIS
Patrick Levy, MEDEF

Objet : Mandat pour la définition d'une méthodologie d'évaluation des solutions de substitution tenant compte des principaux critères décisionnels

Monsieur le Directeur Général, Monsieur le Président,

Les risques liés à la santé, à l'environnement ou la sécurité constituent souvent, au-delà de l'amélioration continue des procédés et des obligations réglementaires, la première motivation à engager un processus de substitution visant les substances extrêmement préoccupantes, dont les perturbateurs endocriniens.

L'action 66 de la feuille de route résultant de la conférence environnementale 2014 précise, en ce qui concerne la substitution des perturbateurs endocriniens, qu'un groupe de travail définira une méthodologie d'évaluation des solutions de substitution tenant compte des principaux critères décisionnels.

En effet, le retour d'expérience des substitutions réussies ou regrettables montre qu'elles doivent suivre un processus logique. Celui-ci doit tenir compte de l'objectivation des propriétés de dangers et de risques associés aux substances ou procédés pressentis pour substituer et suivre les différentes étapes de qualification : le respect du cahier des charges technique, l'évaluation bénéfices/risques, l'impact socio-économique, la capacité à être déployée dans la chaine de distribution et notamment auprès du public.

Un groupe de travail « GT substitution » sera mis en place formellement en ce début d'année 2016. Comme cela a été évoqué avec mes services, l'INERIS et le MEDEF coprésideront ce groupe. Il comprendra des membres des parties prenantes impliquées dans le suivi du PNSE3 et de la feuille de route résultant de la Conférence environnementale de 2014.

www.developpement-durable.gouv.fr

Ministère de l'Ecologie, du Développement Durable et de l'Energie
92055 - LA DEFENSE – CEDEX
Tél. : 01.40.81.21.22

Son objectif est d'élaborer un guide méthodologique conçu comme un outil d'aide à la décision à destination de l'ensemble des acteurs (décideurs, parties prenantes, entreprises) permettant une revue critique de l'ensemble des étapes conduisant à la qualification finale – éventuellement comparative – des options de substitutions.

Ce guide abordera notamment les points suivants :

- Screening des propriétés de danger : physico-chimie, toxicologie et écotoxicologie,
- Faisabilité technologique et opérationnelle,
- Enjeux économiques et socio-économiques.

La démarche conduite par le groupe de travail sera présentée au groupe de suivi du plan national santé environnement ainsi que le projet de guide avant son adoption finale prévue mi 2016.

Le guide sera mis en ligne, en particulier sur le site de l'Ineris, et pourra constituer un cadre pour les demandes de soutien à l'innovation industrielle concernant la substitution des substances chimiques.

Je vous prie d'agréer, Monsieur le Directeur Général, Monsieur le Président, l'expression de ma considération distinguée.

Le Directeur général de la prévention des risques

Marc Mortureux

Appendix 2: Working Team Members

Representatives of:

ANSM	*Agence Nationale de Sécurité du Médicament et des Produits de Santé [National Agency for Medicines and Health Products Safety]*
CIRAD	*Centre de coopération internationale en recherche agronomique pour le Développement [International Center for Agricultural Research and Development]*
CLCV	*Association Consommation, logement et cadre de vie [Consumer, Housing and Environment association]*
CGPME	*Confédération Générale des Petites et Moyennes Entreprises [Association of Small and Medium Enterprises]*
DGS	*Direction Générale de la Santé du Ministère des Solidarités et de la Santé [Department of Health of the Ministry of Health and Welfare]*
DGT	*Direction Générale du Travail du Ministère des Solidarités et de la Santé [Department of Labor of the Ministry of Health and Welfare]*
FEBEA	*Fédération Professionnelle des Entreprises de la Beauté [Beauty and Cosmetic Product Trade Association]*
FNE	*France Nature Environnement [French Nature and Environment Federation]*
Générations Futures	*Générations Futures [Future Generations]*
INERIS	*Institut National de l'Environnement Industriel et des Risques [National Institute for Industrial Environment and Risks]*
INRS	*Institut National de Recherche sur la sécurité [National Safety Research Institute]*
INVENTEC	*Inventec Performance Chemicals*
MICHELIN	*MICHELIN*
MEDEF	*Mouvement des Entreprises de France [French network of Entrepreneurs]*
Mouvement Générations Cobayes	*Mouvement Générations Cobayes [Guinea Pig Generations Movement]*
Ministère chargé de la recherche / DGRI	*Direction Générale de la Recherche et de l'Innovation du Ministère chargé de la recherche [Department of Research and Innovation of the Ministry of Research]*
MTES/DGPR	*Direction Générale de la Prévention des Risques du Ministère de la Transition Ecologique et Solidaire [Department of Risk Prevention of the Ministry of Ecological Transition and Welfare]*
SFSE	*Société Française de Santé-Environnement [French Health and Environment Society]*
UIC	*Union des Industries Chimiques [Chemical Industries Union]*
UIPP	*Union des Industries de la Protection des Plantes [Union of Plant Protecting Industries]*
Université Paris 8	*Université Paris 8 [Paris University 8]*
WECF	*Women Engage for a Common Future*

Appendix 3: List of Inter-Professional Technical Centers

Technical center	Industrial sectors covered
ACTA (Association de Coordination Technique Agricole [Association for Technical and Agricultural Coordination])	Agricultural Technical Institutes
CETIAT (Centre Technique des Industries Aérauliques et Thermiques [Thermal and Aeraulic Industry Technical Center])	Industrial manufacturers of heating, ventilation, air conditioning, dedusting, filtration, humidifying and drying materials
CETIM (Centre Technique des Industries Mécaniques [(Mechanical Industry Technical Center)])	Mechanics businesses
CTC (Centre Technique Cuir Chaussure Maroquinerie [Footwear and Leather Goods Technical Center])	Businesses from the leather goods, glove and footwear industry
CTCPA (Centre Technique de la Conservation des Produits Agricoles [Agricultural Product Preservation Technical Center])	Businesses that produce preserved food products, i.e. products of vegetable or animal source that have been processed
CTDEC (Centre Technique de l'industrie du DEColletage [Bar Processing Industry Technical Center])	Bar Processing Businesses
CTICM (Centre Technique Industriel de la Construction Métallique [Metal Construction Industry Technical Center])	Businesses from the metal construction sector: buildings, bridges, pylons, silos, chimneys
CTIF (Centre Technique des Industries de la Fonderie [Smelting Industry Technical Center])	Industrial businesses from the smelting sector
CTIPC https://www.poleplasturgie.net/ipc.html	Plastics manufacturing
CTMNC (Centre Technique de Matériaux Naturels de Construction [Natural Construction Materials Technical Center])	Manufacturers of natural construction materials, terra cotta and stone
CTP (Centre Technique du Papier [Paper Technical Center])	Businesses from the pulp, paper, cardboard and other associated industries (printing, packaging - processing, suppliers, builders, etc.)
CTTN-IREN (Centre Technique de la Teinture et du Nettoyage [Dye and Cleaning Technical Center])	Businesses from the industrial cleaning and maintenance sector, particularly textiles

Technical center	Industrial sectors covered
Institut Technologique FCBA [FCWF Technological Institute (Forest, Cellulose, Wood – Construction, Furniture)]	Forest, paper, wood and furniture industries: forestry, paper pulp, logging, lumber, framework, carpentry, structuring, wood paneling, furniture, packaging and miscellaneous products
Institut des Corps Gras [Institute of Fats and Oils]	Businesses of the fats and oils industry and users of lipids: agro-food, green chemistry, cosmetics, pharmacy, etc.
LRCCP Laboratoire de recherches et de contrôle du caoutchouc et des plastiques [Rubber and plastics research and control laboratory]	Businesses of the rubber industry

Appendix 4: Lists of Substances of Concern

European lists

List name	Origin	Content	Address
List of endocrine disruptors classified by the European Commission (priority list)	European Commission	List of endocrine disruptors (the substances cited in these lists are ones that should, according to the Commission, but subject to in-depth studies regarding their ED properties).	http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm https://ec.europa.eu/health/endocrine_disruptors/impact_assessment_en https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/2016_impact_assessment_en.pdf
REACH (**R**egistration, **E**valuation, **A**uthorization and **R**estriction of **C**hemicals)	European Union	Candidate List substances Substances submitted for authorization	https://echa.europa.eu/fr/candidate-list-table https://echa.europa.eu/fr/addressing-chemicals-of-concern/authorisation/recommendation-for-inclusion-in-the-authorisation-list/authorisation-list
RoHS Directive	European Union	Substances presenting environmental and human health risks	http://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32002L0095&from=EN
Water Framework Directive (WFD)	European Union	Substances representing a significant hazard to or via the aquatic environment	http://www.bulletin-officiel.developpement-durable.gouv.fr/fiches/exboenvireco/200202/A0020013.htm
List of emerging environmental substances	NORMAN network	List of substances detected in the environment but not included in routine monitoring programs at a European level	http://www.normandata.eu/sites/default/files/files/Emerging_substances_list_Feb_16/NORMAN%20list_2016_FINAL.XLSX

NGO lists

List name	Origin	Content	Address
SIN List	CHEMSEC	REACH Substances of very high concern (SVHC), i.e. substances presenting an environmental and/or human health risk	http://chemsec.org/business-tool/sin-list/
List of the European Trade Union Confederation	European Trade Union Confederation (ETUC)	List of substances of extreme concern according to REACH among substances of high production volume (HPV) (Substances presenting a health and/or environmental hazard)	https://www.etuc.org/IMG/pdf/TUListREACH.pdf

International lists

List name	Origin	Content	Address
List of substances classified as carcinogens - IARC	IARC	Substances classified as carcinogens	http://monographs.iarc.fr/ENG/Classification/ClassificationsCASOrder.pdf
The OPAR convention list	OSPAR (15 European western coastal and island governments)	List of PBT substances or substance groups	https://www.ospar.org/
Persistent organic pollutants (POPs) identified by the Stockholm Convention or the Aarhus Protocol.[71]	Aarhus Protocol / Stockholm Convention: international accords	Aarhus Protocol: long-range transboundary pollution Stockholm Convention: list of persistent organic pollutants (substances harmful to human health and the environment)	Aarhus Protocol: http://www.unece.org/fileadmin/DAM/env/lrtap/full%20text/1998.Pops.f.pdf Stockholm Convention: http://chm.pops.int/TheConvention/ThePOPs/ListingofPOPs/tabid/2509/Default.aspx

French lists

List name	Origin	Content	Address
List ranking reprotoxic substances (and their TRVs)	ANSES	Potential reprotoxic (CMR) substances	https://www.anses.fr/fr/system/files/CHIM2003etAS03Ra.pdf
Pollutants of interest to the interior air quality (and their reference values)	ANSES / CSTB (Centre scientifique et technique du bâtiment [Scientific and Technical Center for Building])	List of indoor air pollutants of interest, which includes a restricted list of substances to be prioritized for study	https://www.anses.fr/fr/system/files/AIR2004etVG001Ra.pdf
Substances ranked by the Indoor Air Quality Monitor [Observatoire de la Qualité de l'Air Intérieur (OQAI)].	Indoor Air Quality Monitor	Pollutants present in indoor air and in the dusts of buildings	http://www.oqai.fr/ObsAirInt.aspx?idarchitecture=236
Substances from the second French Comprehensive Food Study (EAT 2, June 2011	ANSES	Chemical substances present in foods for which the risk has not been assessed as of no concern	https://www.anses.fr/fr/content/les-%C3%A9tudes-de-lalimentation- totale-eat https://www.anses.fr/fr/system/files/PASER2006sa0361Ra2.pdf
Pesticides classified as priority$_{70}$ by: • The ORP (Observatoire des Résidus de Pesticides [Observatory for Pesticide Residues]) concerning foods; • Sph'air concerning ambient air	ORP: AFSSA (Agence française de sécurité sanitaire des aliments (French Health and Food Safety Agency]) Sph'air: LCSQA (Laboratoire Central de Surveillance de la Qualité de l'Air [Central Air Quality Monitoring Laboratory]) / INERIS (Institut Nationale de l'Environnement Industriel et des Risques [National Institute of Environmental and Industrial Risks])	ORP: pesticides prioritized in terms of monitoring chronic food exposure Sph'air: national list of pesticides prioritized for air monitoring	ORP: https://www.anses.fr/fr/system/files/PASER-Fi-ORPresume.pdf Sph'air: http://www.lcsqa.org/rapport/2007/ineris/pesticides-air-ambiant-rapports-sph-air-metrologie

List of substances of concern specific to a sector of activity (examples)

List name	Origin	Content	Address
Substances in OEKO-TEX labeled textiles subject to regulation	OEKO-TEX	Substances presenting human health and environmentalrisks	https://www.oeko-tex.com/en/business/certifications_and_services/ots_100/ots_100_limit_values/ots_100_limit_values.xhtml
Substances in APPLE brand products/accessories and packaging subject to regulation	APPLE	Substances presenting human health and environmental risks	https://images.apple.com/supplier-responsibility/pdf/Apple-Regulated-Substance-Specification.pdf
Substances in SCANIA brand products subject to regulation (manufacturer of heavy trucks and buses)	SCANIA	Substances presenting human health and environmental risks	https://public.mdsystem.com/documents/10906/17094/STD4400en.pdf