Dealing with uncertainty in REACH

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1. Abstract

In 2008, the European Chemical Authority (ECHA) has published a chapter of its "Guidance on information requirements and chemical safety assessment", entitled "Uncertainty analysis". This chapter provides guidance on dealing with uncertainty in the chemical safety assessment to be accomplished as part of REACH[1] implementation. Three "uncertainty groups" are highlighted in this guidance chapter, namely scenario, parameter and model uncertainty.
The question asked in our paper is if the conceptual and methodological support offered in this guidance chapter relevantly addresses uncertainty in the chemical risk assessment envisaged in REACH.

We build our approach on extensive literature study of typologies proposed for addressing the different classes of uncertainty in environmental science for policy, and particularly in chemical risk assessment. The various types of uncertainty reported in the literature are analyzed using an original methodological framework. This method is based on the ideas of "knowledge life-cycle" (framing, production, communication and use of knowledge) and differentiation between substantive, contextual and procedural dimensions of the stages of this life-cycle.

Our results offer a structured approach of uncertainty relevant for the process of REACH implementation, and highlight several dimensions which were previously involved in sociotechnical controversies.

2. Introduction

The "existing and new chemicals" regulatory framework preceding REACH required an assessment of the substance for any "new" chemical (i.e., put on the market after 1981), a producer or importer wanted to put on the market. For the "existing" chemicals (i.e., put on the market before 1981), the public authorities had to determine whether any of them were a priority for being examined, and if so, were required to conduct this assessment.
However, from 1993 to 2001, only 141 high-volume chemicals were prioritized and risk assessment was accomplished for only 27 (KPMG Business Advisory Services, 2005a,b). By 2004, only 4 assessments were implemented in the Community legislation. In 1999, only 14% of substances had data publicly available at the level of the base set, 65% had some data but less than the base set and 21% had no data whatsoever (Koch and Ashford, 2005, European Commission, 2006).
REACH was mainly intended to solve the inefficacy of this past regulatory regime. Its final text has been adopted on 18th December 2006 and became effective on 1st June 2007. It consists of the following elements:
- **Registration**, requiring manufacturers and importers of chemicals to obtain, document and present, the relevant information on the properties of their substances and their safe use;
- The information provided by companies is **evaluated** by the European Chemicals Agency (ECHA);

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[1] Acronym for Registration, Evaluation, and Authorization of Chemicals. REACH is an European Regulation which became effective in 2007, and which has three goals: 1. improving knowledge of the properties and uses of individual chemical substances, 2. increasing the speed and efficiency of the risk assessment process and 3. making producers and importers responsible for this process.

- Substances found to be of "very high concern" (SVHC) shall be subject to **authorization**. These substances are: category 1 or 2 CMR (carcinogenic, mutagenic or toxic to reproduction), PBT (persistent, bioaccumulative and toxic), vPvB (very persistent and very accumulative) and substances identified as having serious effects on humans and the environment, such as endocrine disrupters;
- **Restrictions** may consist of risk-reduction measures or of bans.

The regulation covers most of the chemical substances which are manufactured or imported in Europe, excepting some substances which are the object of other regulatory frameworks, like radioactive, waste and food substances, pesticides or substances subject to custom supervision. Substances used in the interest of defense are also excluded.

REACH applies to all the other substances produced in quantities bigger than 1 t/y per producer or importer. The following remarks apply to the substances produced or imported in quantities > 10 t/y, for which uncertainty analysis is envisaged in the ECHA guidance. For these substances, industry must provide a Chemical Safety Assessment (CSA), which is documented in a Chemical Safety Report (CSR).

 The objective of the CSA is different, depending on the properties of the substance assessed (ECHA, 2008a):

- ❖ For all substances > 10 t/y, the CSA contains (steps 1 to 4 in Fig. 1):
  - A. the assessment of the intrinsic hazards of the substance => **hazard classification**;
  - B. the characterization of the hazards, including where possible derivation of **DNEL**[2] and **PNEC**[3];
  - C. the assessment of **persistence** (P), of **bioaccumulation** (B) and of **toxicity** (T).

- ❖ For the substances > 10 t/y which, in addition, are classified as dangerous (at phase A) or assessed to have PBT or vPvB properties (at phase C):
  - D. the assessment of the **exposure** of man and the environment resulting from the production and use of the substance throughout all its life-cycle;
  - E. the characterization of **risks** issuing from this exposure;
  - F. the identification and documentation of the conditions of manufacture and use needed for controlling the risks for human health and the environment, i.e., **Operational Conditions**[4] (OC) and **Risk Management Measures**[5] (RMM). This set of information is called **Exposure Scenario** (ES).

This corresponds to steps 5 et 6 in Fig. 1.

Risk is considered controlled if:
- ✓ estimated exposure levels / DNEL or PNEC < 1, i.e., exposure is minimized through the implementation of the ES;
- ✓ if DNEL or PNEC cannot be determined (ex.: the substance is not characterized by a threshold effect), the risk characterization consists of semi-quantitative or qualitative assessment of the likelihood that adverse effects are avoided;
- ✓ the likelihood and severity of adverse events occurring due to the physic-chemical properties are negligible.

STEP 1 consists in classifying the substance according to the rules of Directive 67/548.
STEP 2 consists in further evaluating the physico-chemical properties of the substance.
STEP 3 consists in:

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[2] Derived No-Effect Level, for human health
[3] Predicted No-Effect Concentration, for the environment
[4] Examples of OC: duration and frequency of use, amount or concentration of a substance in an activity, process temperature, etc.
[5] Examples of RMM: local exhaust ventilation, wearing certain type of gloves, etc.

- evaluating in which environmental compartment the substance will predominantly end up (air, water…) and
- evaluating which routes of exposure must be taken into account, depending on uses and the mobility of the substance between compartments (volatility, water solubility, dustiness, etc.)
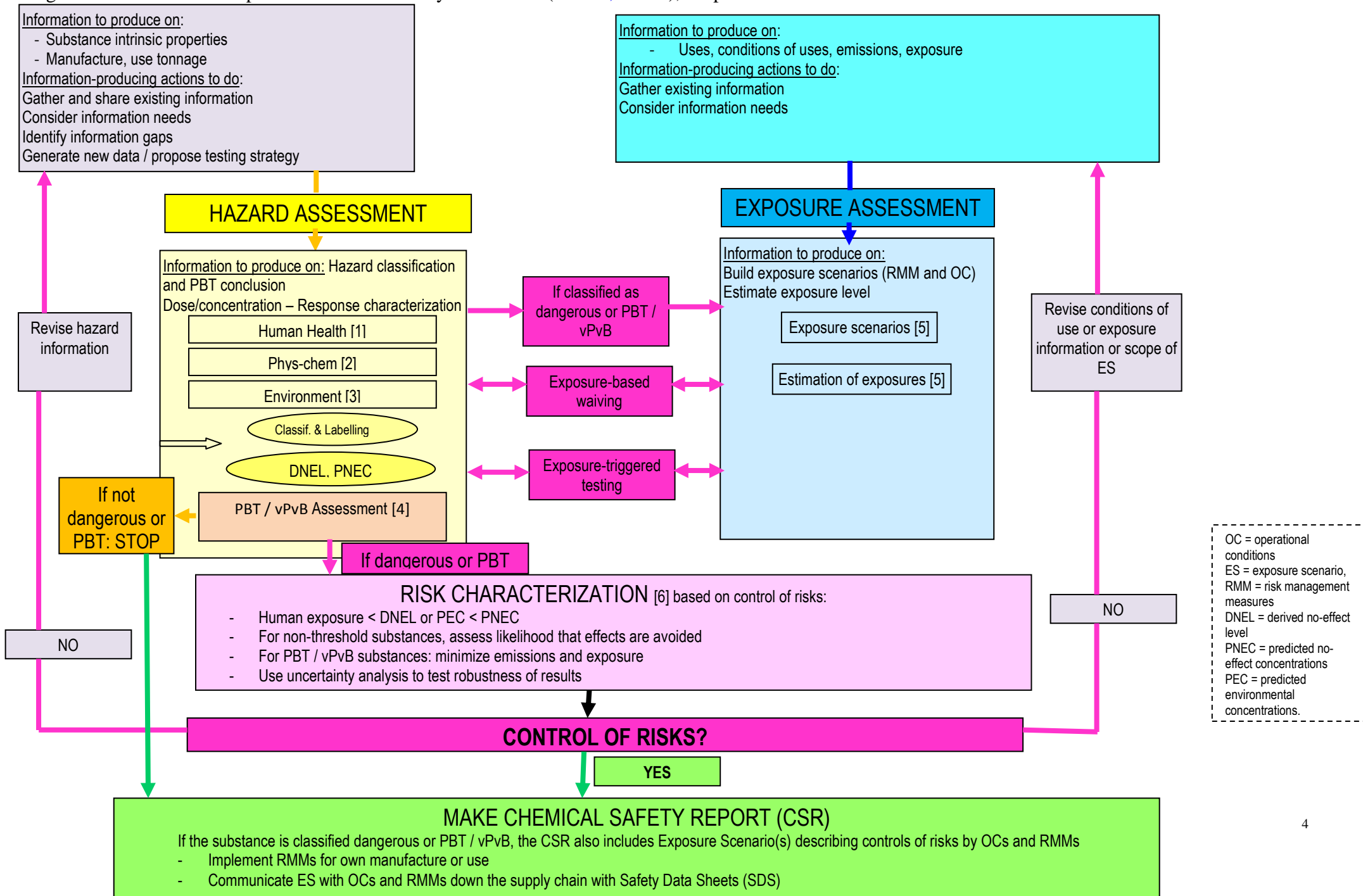
After steps 1 to 3:
- DNEL, PNEC or a semi-quantitative / qualitative characterization of hazards must be derived, from the available testing results on various endpoints.
- P, B and T must be assessed.

If the substance is not classified as dangerous/PBT/vPvB, the CSA stops here and a CSR is produced. However, exposure assessment may also be required in some cases even if the substance has not been classified dangerous or PBT/vPvB.

If the substance is dangerous/PBT/vPvB, a risk characterization is made and an ES is created. If the manufacturer or importer fails to identify realistic measures for controlling the risks of a substance for a certain use, he should advise against that use in the safety data sheet (SDS, which goes to the downstream users).

Fig. 1. Overview of the steps in the chemical safety assessment (ECHA, 2008a), adapted

Information to produce on:
- Substance intrinsic properties
- Manufacture, use tonnage

Information-producing actions to do:
Gather and share existing information
Consider information needs
Identify information gaps
Generate new data / propose testing strategy

Information to produce on:
- Uses, conditions of uses, emissions, exposure

Information-producing actions to do:
Gather existing information
Consider information needs

HAZARD ASSESSMENT

EXPOSURE ASSESSMENT

Information to produce on: Hazard classification and PBT conclusion
Dose/concentration – Response characterization

Human Health [1]

Phys-chem [2]

Environment [3]

Classif. & Labelling

DNEL, PNEC

PBT / vPvB Assessment [4]

Information to produce on:
Build exposure scenarios (RMM and OC)
Estimate exposure level

Exposure scenarios [5]

Estimation of exposures [5]

If classified as dangerous or PBT / vPvB

Exposure-based waiving

Exposure-triggered testing

Revise hazard information

If not dangerous or PBT: STOP

Revise conditions of use or exposure information or scope of ES

NO

NO

If dangerous or PBT

RISK CHARACTERIZATION [6] based on control of risks:
- Human exposure < DNEL or PEC < PNEC
- For non-threshold substances, assess likelihood that effects are avoided
- For PBT / vPvB substances: minimize emissions and exposure
- Use uncertainty analysis to test robustness of results

NO

CONTROL OF RISKS?

YES

MAKE CHEMICAL SAFETY REPORT (CSR)
If the substance is classified dangerous or PBT / vPvB, the CSR also includes Exposure Scenario(s) describing controls of risks by OCs and RMMs
- Implement RMMs for own manufacture or use
- Communicate ES with OCs and RMMs down the supply chain with Safety Data Sheets (SDS)

OC = operational conditions
ES = exposure scenario,
RMM = risk management measures
DNEL = derived no-effect level
PNEC = predicted no-effect concentrations
PEC = predicted environmental concentrations.

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3. How does REACH address uncertainty?

REACH is a 850 pages Regulation. In order to render its understanding and implementation easier, a series of guidelines is produced by the ECHA. Among these, the chapter R.19 of the "Guidance on information requirements and chemical safety assessment" deals with "Uncertainty analysis". This chapter provides guidance on dealing with uncertainty in the chemical safety assessment, based on a tiered approach.

The underlying assumption behind the tiered approach is that the level of uncertainty and its potential impact on risk characterization increase with the amount of information which must be produced during the chemical safety assessment. Indirectly, uncertainty is defined as being synonymous of "lack of knowledge". Indeed, ECHA, 2008b specifies that "*it would not add much practical value to a chemical safety assessment to provide a detailed probabilistic analysis for a substance which has full data set, few dangerous properties, minimal exposure and a risk characterization ratio (RCR) which is significantly less than 1*" (pp. 8). Uncertainty analysis is thus considered "*of most potential benefit*" (ECHA, 2008b, pp. 11) mainly for "problematic" substances, i.e., substances for which it is found that the Risk Characterization Ratio (RCR) is close to the regulatory trigger value, i.e., above or below a RCR of 1.
In other words, uncertainty is understood exclusively under its quantitative dimension, as being insufficient information in a process in which sufficient accumulation of information would necessarily lead to a certain outcome.
Based on this assumption, the use and the level of detail of uncertainty analysis (UA) is "*a matter of judgment for the report authors*" (pp. 8) and increases with the need of the report authors to refine the risk characterization outcomes, for the specific situation where this risk is showed to be > 1. The procedure proposed may include several levels of detail, from a basic qualitative approach to more complex techniques like deterministic and probabilistic analysis.

Three "*uncertainty groups*" are highlighted in this guidance chapter, namely scenario, parameter and model uncertainty.

 a) Scenario uncertainty "*is the uncertainty in specifying the scenario(s) which is consistent with the identified use(s) of the substance*" (ECHA, 2008b, pp. 8), i.e., the level of accuracy of scenario description.

Scenario uncertainty may include:
- Descriptive errors (e.g., wrong or incomplete information, like use of an incomplete or wrong series of estimates for deriving an Exposure Scenario);
- Aggregation errors (e.g., incomplete or wrong approximations for volume and time, like wrong calculated anticipated conditions of use);
- Errors of assessment (e.g., choice of the wrong model);
- Errors of incomplete analysis (e.g., overlooking an important exposure pathway).

 b) Model uncertainty is "*the uncertainty in the adequacy of the model used with the scope and purpose of the assessment*" (ECHA, 2008b, pp. 9).

Indeed, mathematical or statistical models are often used for representing an exposure or hazard process. Model uncertainty can be:
- Extrapolation errors (i.e., use of a model outside the domain for which it was developed);
- Modeling errors (e.g., non-consideration of parameters in the model structure itself, certain assumptions, etc.);
- Dependency errors (i.e., lack of consideration of correlations between parameters).

c) Parameter uncertainty is "*the uncertainty involved in the specification of numerical values*" (ECHA, 2008b, pp. 9).

Parameter uncertainty includes:
- Measurement errors (e.g., influence of the methodology used, errors in the analytical method used to measure chemical concentration, technical inadvertence);
- Sample uncertainty (e.g., lack of representativeness of the data set for the range of values found in reality due to criteria used for taking the sample, averaging methodologies, etc.);
- Selection of the data used for assessing the risk (e.g., use of default data – TGD data are frequently used for exposure assessment, choice of the dose descriptor – uncertainty in choosing one data among others for RA purpose);
- Extrapolation uncertainty (e.g., use of alternative methods – QSAR, in-vitro tests, read-across for similar substances, use of assessment factors – inter-species, intra-species, acute to chronic, route to route, lab to field extrapolation).

Difference is also made in the guide between underlined uncertainty (related to "*limitations in knowledge… as well as biases or imperfections in the instruments, models and techniques used*", ECHA, 2008b, pp. 10) and variability (related to "*variation that exists in the real world*", ECHA, 2008b, pp. 10).
Whereas uncertainty can be reduced, variability cannot, because it is an inherent property of the system. Thus, one can only reduce the uncertainty in the knowledge about the variability. Sources of variability can be: inter-species variability, intra-species variability (e.g., due to age, sensitivity, physiology, behavior, etc.), variability in environmental characteristics (e.g., temperature, wind, homogeneity, etc.), variability in time and space, etc.

The stepwise procedure proposed by the guidance for UA consists in three levels.

Level 1, Qualitative assessment[6], structured in 6 points:

A) Systematic identification of uncertainties - different sources of uncertainty and/or variability are listed.
B) Uncertainty classification – uncertainty is distinguished of variability, and sources of uncertainty are classified in scenario, model and parameter uncertainties.
C) Uncertainties evaluation - main uncertainties are identified, based on (subjective) indications (by the risk assessor) of their direction (overestimation or underestimation of the risk) and magnitude (how much the specific uncertainty source potentially affects the risk outcome).
D) Criteria and scaling for evaluation – Magnitude can be assessed using a qualitative scale (low, medium, high).
E) Evaluation of the overall uncertainty – consists in the subjective consideration of the assessor.
F) Final outcomes - Text discussion of major uncertainties, of their combined effect on the assessment outcome and of the technical means to reduce them.

Level 2, Deterministic assessment

This step generates alternative point estimates, by making a series of "reasonable worst-case assumptions" for the determination of the exposure and by the use of varying factors for the determination of the hazard. It consists in performing a scenario analysis, i.e., changing critical assumptions and/or input parameters and calculating the effect on the assessment outcomes, in order to see if this effect is large enough for influencing the risk management decisions. In other words, it is a sensitivity analysis focused on a limited number of parameters and combined effects chosen by the report author.
For example, the guide mentions previous sensitivity analysis of the EUSES model by Jager et al. (1997, 1998 and 2000) and Verdonck et al. (2005), who showed that key parameters for the estimation of the

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[6] "Qualitative" does not refer here to the assessment of qualitative dimensions of uncertainty (e.g., methodological, epistemological), but to a non-quantified (qualitative, textual) way of expressing uncertainty.

environmental exposure in EUSES are tonnage release scenario, biodegradability, lipophilicity (K_{ow}) and volatility.

Level 3, Probabilistic Risk Assessment (PRA)

PRA aims at "*defining the probability that the RCR is exceeded, given the fact that both the effect and the exposure are probabilistic factors*" (ECHA, 2008b, pp. 26). The idea in PRA is to obtain probabilistic distributions instead of fixed values for risk. These distributions show the most likely impact (expressed as RCR) and its range of values. Whereas deterministic risk assessment provides a single point estimate, probabilistic risk assessment produces a range of risk values, i.e., a probability distribution of the risk.

Several approaches exist for PRA in risk analysis: 1D and 2D Monte-Carlo simulations, bootstrapping, Bayesian analysis, fuzzy arithmetic, probability bounds. Generally, it consists in:
- Probabilistic estimation of the hazard (e.g., using the benchmark dose concept for hazard assessment and the sensitivity species distribution for ecotoxicological data)
- Probabilistic estimation of the exposure (obtaining distributions based on expert judgment + fitting distribution functions to data + Monte-Carlo simulations for understanding the propagation of uncertainty & variability in the model)
- Probabilistic estimation of the risk (through overlapping the hazard and exposure distributions)
- Sensitivity analysis of different input parameters (allowing to rank them based on their contribution to the overall uncertainty).

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4. A background for appreciating the treatment of uncertainty in REACH

The question asked in our paper is if the conceptual and methodological support offered in this guidance chapter relevantly addresses uncertainty in the chemical risk assessment envisaged in REACH.
In order to answer to this question, we will start by making clear why we have asked it in the first time. Indeed, discussions about uncertainty and its role in environmental decision-making initially come from acknowledging the controversial nature of decision-making on complex environmental issues. Addressing uncertainty in such cases become necessary for answering to the problem of credibility of scientific approaches used in a decision-making context (van der Sluijs, 2002).
However, many research developments in the field of uncertainty assessment seem to have forgotten this original purpose, and became more and more positivistic. Uncertainty is represented as a mathematical object that can be quantified in order to obtain a (false) impression of "certainty" (Verdonck, 2007), to the point that today they tend to become themselves part of an increasingly "normal" "uncertainty science". Most of the developments in this area of uncertainty analysis insist on the "objective" nature of uncertainty, only very few also address its "subjective" nature (i.e., related to perception of the existing evidence).
Besides their capacity to improve the precision of the risk assessment, uncertainty analyses must be accessible to the public susceptible to contest or mistrust results produced in REACH. In other words, uncertainty analysis must be itself both scientific and socially relevant.

The current of post-normal science addresses uncertainty as being the "lack of quality" of knowledge related to a given socio-scientific purpose, i.e., a risk assessment in a context of political decision-making (Ravetz, 2006, van der Sluijs et al., 2008). In line with this line of thought, we propose to consider that uncertainty has fundamentally both "objective" and "subjective", quantitative and qualitative dimensions, which can play different roles in different situations, and can be addressed by different analytical approaches and assessment tools.
The consequence of this proposal is to differentiate between the substantive uncertainty – referring to the content of the knowledge itself, and contextual and procedural uncertainty. These last two forms of uncertainty are as important for the social relevancy of knowledge as the substantive dimension is for its technical, methodological and epistemological robustness.

In this view, besides the lack of knowledge, uncertainty can refer to an inappropriate process of knowledge production (e.g., ignoring local knowledge in a situation where it is highly pertinent, unbalanced composition of expert committees among different contrasting interests, etc.) or to an inappropriate contextual setting of knowledge production (e.g., inappropriate risk assessment method promoted through regulation).

We have done an extensive literature study, whose details will be published in a separate paper. This study included 88 references dealing with analysis of uncertainty in environmental research and particularly in chemical risk assessment. It led us to the classification presented in Table 1. We use this classification as a background for appreciating the adequacy of uncertainty assessment proposed in the REACH guidance.

A well-known typology of uncertainties has been proposed by Walker et al. 2003, according to three axes:
- location (where they occur in the knowledge production process),
- level (where uncertainty manifests itself on the gradual spectrum between deterministic knowledge and total ignorance) and
- nature (whether uncertainty primarily stems from knowledge imperfection or is a direct consequence from inherent variability[7]) (Van der Sluijs et al., 2003).

However, the definition of the "level" of uncertainty suggests us the possibility of a continuous "objective" graduation of the lack of knowledge, and by this it does not allow the inclusion of the subjective nature of uncertainty, i.e., the fact that the level of uncertainty can be perceived differently by different experts and/or stakeholders (see for example the certainty trough of MacKenzie, 1990, as well as Assmuth et al., 2007 and Maxim and van der Sluijs, 2010). Furthermore, the "level" of uncertainty suggests necessary quantification of all forms of uncertainty, quantitative and qualitative, and excludes, for example, procedural aspects, communication-related or socially created uncertainty. We adapt and extend this well-known classification for including contextual and procedural dimensions.

> In order to structure the different aspects of uncertainty, we propose four axis of description:
> - The step in the knowledge life-cycle
> - The location in the Chemical Safety Assessment
> - The dimension of knowledge
> - The type of uncertainty

We build on the idea of "***knowledge lifecycle***", consisting in several "***steps***":
- *problem framing*,
- *knowledge production*,
- *knowledge communication* from authorities to stakeholders, or knowledge-based communication between stakeholders (i.e., using the CSA results as arguments),
- *use of knowledge* for action.

We highlight this last step in the knowledge lifecycle, which mainly concerns risk management, but we do not address it in our approach, because it obeys to particular criteria of quality that we cannot develop here. Indeed, this step can have a major importance in transforming knowledge in action, and many failures in risk management are related to it (e.g., the EEA, 2001 report showed well that in many cases knowledge about risks existed long before political action was implemented, e.g., the case of asbestos).

The "problem" on which we focus is the Chemical Safety Assessment, as defined in REACH.

A second axis of uncertainty[8] description can be identified regarding its different "***locations***" in the CSA:

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[7] Arises because the system under study can behave in many different ways; it is a property of a system.
[8] We will make reference to "uncertainty" and to "lack of knowledge quality" as being synonymous.

- the *assumptions* established through Regulation, during the negotiations preceding the adoption of REACH, or made by registrants for proposing new tests
- the *input data* and *parameters* used in hazard assessment and exposure assessment
- the *models* used in hazard assessment and exposure assessment
- the *scenarios* used in exposure assessment and the exposure scenario
- the *methods* used for hazard assessment
- the *modeling technical supports* for hazard assessment, exposure assessment and risk characterization
- the *data management and storage*
- the *risk characterization*
- the *communication* of the outcomes of the CSA through the CSR and the SDS
- the Registration *regulatory process of implementation control*
- the *processes* of Hazard Assessment, Exposure Assessment and Risk characterization.

A third axis of description includes three "***dimensions of knowledge***":
- *substantive* (referring to the content of the knowledge itself)
- *contextual* (referring to the context of knowledge production or use, i.e., "when and where" knowledge is produced or used, in which socio-economic and political background, etc.)
- *procedural* (referring to the processes of knowledge production or use, i.e., "how" knowledge is produced or used, namely the processes of interaction between scientists, and between scientists and society).

Finally, for the fourth axis, we can highlight several "***sources***" of uncertainty:

a) For the contextual dimension:
- the rules established through the Regulation (*regulation-induced* uncertainty)
- *value-ladenness*[9]

b) For the substantive dimension:
- *choice of source* uncertainty
- inexactness (*technical* uncertainty) (Funtowicz and Ravetz, 1990, Van der Sluijs, 2006)
- unreliability (*methodological* uncertainty) (Funtowicz and Ravetz, 1990, Van der Sluijs, 2006)
- ignorance (*epistemological* uncertainty) (Funtowicz and Ravetz, 1990, Van der Sluijs, 2006)
- variability (*stochastic* uncertainty)
- monitoring of real world effects (*validation* uncertainty)
- linguistic patterns (*communication-related* uncertainty)

c) For the procedural dimension:
- the rules established through Regulation (*regulation-induced* uncertainty)
- *transparency*
- *effectiveness*
- availability of human, time and financial resources (*operational* uncertainty)

All of the crossings between these four dimensions cannot be quantified using probabilistic approaches. For example, some can be qualified using (numerical or not) uncertainty scales (e.g., the methodological dimension), or reference to a set of levels of procedural quality (e.g., fair / unfair; strongly influenced by conflict of interest / moderately influenced by conflict of interest / without conflict of interest).

THE CONTEXTUAL DIMENSION

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[9] "*Value-ladenness refers to the notion that value orientations and biases of an analyst, an institute, a discipline or a culture can co-shape the way scientific questions are framed, data are selected, interpreted, and rejected, methodologies are devised, explanations are formulated and conclusions are formulated.*" (Van der Sluijs et al., 2003, pp. 64)

The contextual dimension of uncertainty refers to the set of social, economic and political conditions in which knowledge is produced.

This dimension refers to the influence of the socioeconomic and political contexts on the knowledge quality. In decision-making, scientific knowledge has to be "put in context" for adapting it to the specific problem under discussion, mainly the relevant socioeconomic stakes (child mortality? income losses?) and the options of action (ban? limit uses?). The context also gives sense to a piece of knowledge, allowing data interpretation, measurements, models, to say "what do they mean". For each of these aspects, a piece of knowledge will be perceived as being more or less relevant, in other words having different qualities.

In the framework of REACH, the main form of contextual uncertainty is related to problem framing, i.e., the settings established for the risk assessment through the Regulation (*regulation-induced uncertainty*). These are themselves based on a series of assumptions such as the correlation between the production tonnage and the risk, the representativeness of the species chosen in the standardized tests for the real ecosystems, the assessment of substances excluding aspects related to synergic or antagonistic effects with other chemicals or to multicausality, etc. These are rules established before the knowledge production starts and which cannot be challenged during the CSA.

THE SUBSTANTIVE DIMENSION

In the process of knowledge production, *technical* uncertainty refer to the numerical imprecision of data – which can come from the limited measurement techniques, the ordinary variability of repeated measures, or to the inherent variability of the real world.

The methodological dimension concerns the relevancy (regarding the specific characteristics of the problem addressed) and the scientific robustness of the method chosen for producing the knowledge.

Finally, the epistemological dimension refers to our ignorance, to our limits in understanding the world. One can refer to "active ignorance", when the analyst know which are the limits of his/her knowledge but does not know their importance for the understanding of the problem addressed. One can refer to "passive ignorance" when he/she "does not knows what he/she does not know" (Funtowicz and Ravetz, 1990, Van der Sluijs, 2006).

THE PROCEDURAL DIMENSION

This dimension concerns the processes of:
- framing the problem (e.g., is there enough transparency in framing the knowledge production?, are there enough time, resources and institutional support allowed to knowledge production? etc.) ;
- producing knowledge (disciplinary competence of the scientists or experts involved, their knowledge of the field reality, the robustness of the procedural rules established through regulation for evaluating the quality of knowledge, etc.).

Despite the fact that they do not refer to the content itself of the knowledge, these processes can significantly influence the quality of the risk assessment results.

Presently, several stakeholders (industry, academia, NGOs, interest groups, non-scientific experts, investigation journalists, etc.) produce knowledge involved in decision processes. It is therefore irrelevant to talk about "science" in general, as science is not an undifferentiated "whole". Scientific practices can be, for example, influenced by their local conditions (e.g., the practices of a certain laboratory, Wynne,

1996). The process of knowledge production depends on elements such as the researchers' independency, the source of his/her funding, and the stakes of the institutions employing him/her. These elements are all playing important role in the perception of the level of uncertainty (or quality) associated to a certain piece of knowledge.

Table 1. Uncertainty in REACH

Note: Cells filled in with mauve include types of uncertainty addressed in the REACH uncertainty analysis guidance.

Uncertainty nature / Localization in knowledge life-cycle	Problem framing		Knowledge production		Knowledge communication	
	Type of uncertainty	Localization of uncertainty in RA	Type of uncertainty	Localization of uncertainty in RA	Type of uncertainty	Localization of uncertainty in RA
Contextual	Regulation-induced uncertainty	Assumptions: Choice of production tonnage as substances classification criterion	Value-ladeness	Assumptions: choice of the set of additional tests to be performed		
	Regulation-induced uncertainty	Assumptions: definition of the risk assessment method				
	Regulation-induced uncertainty	Assumptions: standardized tests – choice of species, of the number of essays, of the hazard endpoints for determining the intrinsic properties of the substance, of the criteria for considering a substance as being "dangerous", etc.				
	Regulation-induced uncertainty	Assumptions: choice of the set of tests to be performed				
	Regulation-induced uncertainty	Assumptions - Choice to ignore natural randomness issued, for example, from synergic and antagonistic effects of two or several chemicals, or of chemicals and other environmental factors (e.g., climate change)				
Substantive	Choice of source uncertainty	Input data to Hazard assessment and to Exposure assessment The use of primary data: - Incompleteness of chosen set of sources - Selective use in assessment of some sources, among those available, without using standardized / shared quality validation criteria (data selection, reference coverage) - data selection – citation coverage	Technical uncertainty	Input data to Registration - (incorrect) production tonnage declaration	Communication-related uncertainty	In reporting the results in the CSR: Underreporting uncertainty / bias = incomplete reporting of testing outcomes to authorities, lack of reporting of their results by the industry, to the scientific community, invoking confidentiality
	Choice of source uncertainty	Input data to Hazard assessment, Exposure assessment, Risk characterization - data availability	Technical uncertainty	Input data to Hazard Assessment: - Performance of the measurement techniques used, including establishment of the Detection Limit and Quantification Limit	Communication-related uncertainty	Hazard, exposure and risk communication in the CSR: Robustness : communication of results must include discussion of both « for » and « against » evidence
	Technical uncertainty	Assumptions: lack of consideration for the change of production tonnage over time	Epistemological uncertainty	In conceptual model structure in Hazard Assessment - oversimplification (process error), - dependency errors - uncertainty in causal relationships = functional errors (about the nature of functional relations), - extrapolation errors , - use out of the validity domain	Communication-related uncertainty	Communication of RA outcomes in the CSR: - Linguistic uncertainty : Ambiguity (lack of linguistic conventions regarding the meaning of words) - Linguistic uncertainty : Vagueness (imprecision in meaning) - Linguistic uncertainty : Translational uncertainty (uncertainty in explaining results) - Linguistic uncertainty : contentual, epistemic, conditionalisin, inferential (Levin et al., 2003)

						- Synthesis uncertainty : adequacy of conclusions regarding the main text describing the results
	Epistemological uncertainty	In Assumptions: - form of the dose-response relationship - level of the uncertainty factor (assessment factor) : interspecies, acute to chronic, route to route, lab to field - ecosystem dynamics	Technical uncertainty	Hazard Assessment, Exposure Assessment In modeling technical support - hardware and software errors (bugs) In data management and storage - Database management errors	Communication-related uncertainty	Communication of RA outcomes through Safety Data Sheets : - communication / documentation patterns on risk control
	Technical uncertainty	In Assumptions: choice of the routes of exposure to take into account (based on the identified uses[10] of the substance)	Epistemological uncertainty	In conceptual model structure, in Hazard Assessment, Exposure Assessment: - scale / spatial or temporal resolution errors (looking at one scale, for grasping a phenomenon happening to another scale) - scaling algorithms - statistical uncertainty (use of the wrong statistical method) - aggregation errors (temporal, spatial, ecological) - hardware and software errors (bugs) - uncertainty about model completeness	Communication-related uncertainty	Reporting of UA itself : - for the qualitative UA, unstandardized text discussion of main uncertainties, leading to different practices specific to the risk assessors - for PRA, form of result communication
			Technical uncertainty	Parameters in Hazard Assessment: - Measurement uncertainties (low sample size, measurement errors), i.e. of physico-chemical properties, DNEL / PNEC, bioaccumulation potential, etc.		
			Choice of source uncertainty	Parameters in Hazard Assessment: - Selection of data (e.g., choice of the dose descriptor, default values)		
			Epistemological uncertainty	Parameters in Hazard Assessment: *Extrapolation uncertainty* - from QSAR, QSPR, Read-across, in-vitro-test to tests on real organisms		
			Variability	Input data to Hazard Assessment : - Inherent randomness and unpredictability in all the variables measured HA		
			Methodological uncertainty	In methods for Hazard assessment: - (inappropriate) choice of the RA method, for those hazards for which standardized tests do not exist (ex.: chronic and low-dose effects) - (lack of) inclusion of certain hazards (ex.: chronic and low-dose effects) in the RA - choice of the hazard endpoints to be considered for determining the intrinsic properties of the substance - robustness/validation of the type of test to be used: QSAR, SAR, in vitro, animal testing, read-across, categorization of substances, etc. - developing and implementing the research		

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[10] If a downstream user finds that some uses are not taken into account in the SDS provided by the manufacturer / importer, or that conditions of use specified in the ES do not correspond to its practices, he can: inform the supplier, adapt his conditions of use, conduct his own CSA or replace the substance by an alternative with a more suitable ES.

				protocol: choice of the test species and strains - developing and implementing the research protocol: application of the test system according to the standards - performing the experiment, collecting and recording data: experimenters' bias - Data and results analysis: choice of the statistical method for analyzing data		
			Epistemological uncertainty	In conceptual model structure, in Exposure assessment: *Extrapolation*, e.g.: read-across for similar substances / scenarios *Model uncertainty*: – oversimplification (process error), - dependency /functional errors (about the nature of functional relations), - extrapolation errors , - use out of the validity domain		
			Technical uncertainty	Scenario uncertainty in Exposure assessment: - *Descriptive errors* - *Aggregation errors* - *Errors of assessment* - *Errors of incomplete analysis* - (not exhaustive and/ or incorrect) identification of life-cycle stages of the substance - (not exhaustive and/ or incorrect) identification of emission sources - incorrect measurement of emissions (by source) - (not exhaustive and/ or incorrect) identification of ways of manufacture of the substance - (not exhaustive and/ or incorrect) identification of uses and conditions of use of the substance - (incomplete or incorrect) identification of the exposed population (consumer, children) or ecological community - (incomplete or incorrect) identification of the relevant routes of exposure for humans and for the environment - (incomplete or incorrect) identification of exposure events (magnitude and frequency of the event)		
			Technical uncertainty	Scenario uncertainty in Exposure assessment: - (incorrect) assumed efficacy of risk management measures (e.g., usage) - spatial and temporal setting (short, long term; local, regional) - environment of exposure (conceptual model of working place or natural environment)		
			Technical uncertainty	In the definition of Exposure scenario: - Exhaustive and correct identification of the		

				conditions in which the risk is called "minimized"[11] - Exhaustive and correct identification of operational conditions and of necessary risk management measures		
			Choice of source uncertainty	In parameter of Exposure assessment: *Selection of data*: - Conservativeness in estimation of emissions - Choice of the exposure concentration used for exposure assessment - Adequacy of default values - Assumed effectiveness of risk management measures *Measurement uncertainties*, e.g.: - Low sample size - Measurement error - Instrument error		
			Variability	In parameters of Exposure Assessment: - Environmental variability (temperature, wind, homogeneity, etc.) - Variation in human and societal behavior - Variation in time and space, relating to any of the above (ex: in the evolution of the socio-economic systems, inducing changes in uses[12], ways of manufacturing, etc.)		
			Epistemological uncertainty	Parameters of Hazard Assessment, Exposure Assessment, Risk characterization: Propagation of state (input) and parameter errors		
			Value-ladenness	In Assumptions for Hazard Assessment, Exposure Assessment, Risk characterization: - influence of conflict of interest, of institutional affiliation) - influence of the experts' discipline		
			Value-ladenness	In input data to Hazard Assessment, Exposure Assessment, Risk characterization: - Uncertainty related to the interpretation of the primary data		
			Validation uncertainty	Risk characterization: In results validation - lack of [long-term] monitoring of chemicals in the environment, in relationship with particular hazards		
Procedural	Transparency	Hazard Assessment, Exposure Assessment, Risk characterization processes: - completeness of result communication - opportunities given to stakeholders to feedback - consideration given to stakeholders' feedback - uncertainty analysis and communication - consideration given to value diversity (indeterminacy)	Effectiveness	Registration control : low level of control by authorities = some unregistered substances might still be commercialized		

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[11] Check and feed-back should theoretically be insured by the downstream users for whom these measures are destined.
[12] New identified uses may trigger the obligation to update the exposure scenarios, the CSA and the CSR.

	Operational uncertainty	Hazard Assessment, Exposure Assessment, Risk characterization processes: - Time and resource constraints (situational limitations) - Institutional support	Operational uncertainty	Hazard Assessment process : Influence of testing cost-efficiency on measurements of DNEL and PNEC	
			Value-ladenness	Risk characterization: Interpretation of the results in the CSR, due to different reasons: - socio-political (communication of outcomes may be colored by the political preferences of the analyst, by its conflict of interest, by institutional affiliation) - disciplinary - epistemic (communication of outcomes may be colored by the approach that the analyst prefers)	

In order to highlight the different dimensions of uncertainty potentially important for implementing REACH, we will follow the "life-cycle" of knowledge production stipulated in the regulation and synthesized in Figure 1. We highlight below the aspects (dimensions, types, locations) of uncertainty whose treatment could be improved under REACH.

5.1. QUANTITATIVE AND QUALITATIVE UNCERTAINTY

Regarding the UA procedure proposed by ECHA, 2008b, several problems can be highlighted:

1. Leaving the decision to make or not an UA to the report authors opens the way to strategic use of uncertainty, which is a well-known phenomenon repeatedly treated in the literature (Funtowicz and Ravetz, 1990, 1993, WHO, 2000, Michaels, 2005). Focusing uncertainty analysis only on risk characterizations above or below a RCR of 1 can constitute a bias towards avoiding false positives, whereas no similar provision is taken for avoiding false negatives. Indeed, as described in the guidance, UA allows considering, a-priori, that the information having concluded to an uncontrolled risk is uncertain, but does not allow the same for the information having led to showing that a risk is controlled. The guidance specifies that UA can also be practiced when "*the registrant simply wants to carry out their own uncertainty analysis to improve their characterization of the risk*" (ECHA, 2008b, pp. 11). However, given the cost-efficiency constraints of REACH for registrants, this choice is likely to be made only for very few additional substances.

2. PRA allows the inclusion of variability in input values, by incorporating their probability distributions. Several advantages of the PRA have been highlighted in the literature (Verdonck et al., 2007), i.e., taking into account the inherent variability of effects and exposure characterizations is explicitly taken into account, and the decision on which is the "acceptable" risk is further transferred from the assessment to the management phase.

However, PRA is demanding in terms of data collection and availability, calculation effort and experience of the risk assessor. As well, its communication encounters difficulties. Furthermore, decision on the distribution to use can involve value-ladenness related to expert judgment (see 5.3.4 below) - in defining probability distributions of input variables, and related to political intervention - in deciding the probability of risk triggering concern.

These constraints are important in the framework of REACH:
- PRA needs a lot of data; therefore it is undertaken actually for substances with large data availability. This is opposite to the recommendation of the guide itself, to use UA for those substances having low data availability. It seems therefore that there is a contradiction between the identified need for UA (for substances with few data) and the tool recommended for making UA (needing large data availability).
- PRA is not easy to communicate (Jager, 1998); however, one of the main purposes of UA is to increase transparence regarding the process of risk assessment and the understandability of uncertainty issues by non-specialists, like policy-makers. If UA is too obscure, technical and difficult to understand, the objective of transparency is lost in the way.
- Expert judgment, possibly influenced by conflict of interest, is a sensitive point for REACH, and its presence in the UA should be limited. However, the PRA offers it an important place.

The choice of the method for risk characterization is not neutral. On the contrary, literature shows that, in chemical risk assessment, the results, and potentially conclusions regarding the risk, are not the same if deterministic or probabilistic risk assessment procedure is chosen (Bruce et al., 2007). Research is needed

for understanding if probabilistic risk assessment might produce results for risk assessment systematically lower or higher than deterministic risk assessment.

3. Uncertainty analysis is recommended in an advanced stage of the CSA, i.e., in the refinement of the risk characterization. In other words, only few substances could be concerned under REACH. However, all the substances will be assessed for hazards, therefore uncertainty in assessing hazards (ex.: in deriving the CMR character or the P, B and T characteristics) could potentially play the most important role.

This may lead to lack of visibility on the type II errors during hazard assessment, i.e., obtaining false negatives in determining the SVHC character of a substance. This is a sensitive issue, as it was repeatedly shown that type II errors are very controversial (i.e., finding an effect of a substance some time after failing to find it, EEA, 2001).

The tiers approach and the provisions for UA use are based on several implicit assumptions:
1. Uncertainty is quantitative;
2. UA is not influenced by expert subjectivity;
3. UA is meant exclusively at improving the technical quality of risk assessment. Indeed, the guide chapter specifies that "*uncertainty analysis can be a useful tool for increasing the robustness, reliability and adequacy of the chemical safety assessment*" (ECHA, 2008b, pp. 10). However, another major reason for analyzing and communicating uncertainty is social, i.e., increasing the public trust in the scientific knowledge produced on environmental risks. We argue that quantitative UA does not adequately answer to this objective.
4. Uncertainty in both exposure and hazard can be represented using a probabilistic approach, which ignores, for example, epistemological uncertainty (lack of knowledge), i.e., uncertainty which cannot be measured through probabilities.

Differentiating among quantitative and qualitative aspects of uncertainty (Table 1) is important for several reasons:
5. The failure to differentiate between quantitative and qualitative natures of uncertainty leads to confusion among methods used for dealing with them. Several qualitative aspects of uncertainty (e.g., related to the choice of the testing method) are inappropriately addressed using quantitative approaches of UA. The scientific literature offers methods for addressing each of them in accordance with its nature: whereas technical uncertainty can be addressed through quantitative methods, methodological and epistemological dimensions need qualitative approaches.
6. The results of Probabilistic Risk Assessment (PRA) are difficult to understand and interpret; if communication of uncertainty is to follow the "progressive disclosure of information" principle, the results of the PRA should be destined to be communicated after those, more receptor-friendly, issued from analysis of qualitative dimensions, to a relatively specialized public.
7. The conclusions of the analysis of each type of uncertainty on its own significantly enriches the conclusions of the global UA, allowing to specify which are the measures needed for addressing each of the uncertainties found. "Producing more knowledge" is not the solution for addressing uncertainty in all situations and mixing quantitative and qualitative uncertainty in a probabilistic approach cannot specify what must be done (collecting data? testing and validating methods? developing knowledge on the functioning of a specific environmental compartment or dose-response pattern?)

5.2. UNCERTAINTY TYPES AND SOURCES

5.2.1. Regulatory-induced uncertainty

Because any regulation must be clear and equally applicable for all those concerned, the framing of the risk assessment in REACH is well established and standardized as much as possible. The side effect of

this willingness for precision is that there is less attention for opportunities of evolution of REACH, according to the advancements in the state of knowledge. One of the purposes of being continuously aware of the framing uncertainty, which we called "regulatory-induced uncertainty", is to remain conscious about the potential failures of the Regulation and of the opportunities offered by the evolution of knowledge.

REACH was not built as the state-of-the-art in chemical risk assessment, but as a compromise between many objectives, some of which are scientific, but some others being economic, social, political… As any compromise, it could offer many opportunities of improvement in the future. One has to stay aware of the fact that the seven-year negotiation process has probably introduced uncertainty sources in the risk assessment process. Taking into account regulatory-induced uncertainty means being aware that further improvements are possible and stay vigilant, knowing that some risks could not be identified by the current regulatory system.

Choice of tonnage as classification criterion

In REACH, regulators have stipulated which substances to test, which tests to submit them to, how to carry out the tests, and which endpoints to analyze. However, the selection of substances and tests is not necessarily more efficient regarding their ability to discover harmful effects of chemicals and the exposure levels at which these effects occur only because they are now part of a regulation (Wandall et al., 2007). Standardized tests represent the result of a compromise between the need for comparability and scientific quality of results, issues of cost-efficiency and feasibility, and socio-economic stakes implicitly or explicitly defended in the work of industry and academia representatives in the committees for test validation.

For example, in REACH, substances manufactured in volumes below 1 t/y/manufacturer need not be registered and tested. Using production volumes for prioritization is based on the hypothesis that high-volume substances are likely to be widely used, thereby increasing the likelihood of exposure. However, Rudén and Hansson, 2006 and Wandall et al., 2007 argue that the supposed correlation between risk and production volume has not been scientifically substantiated, based on three reasons. First, it is not known to which degree production volume predicts exposure, which is influenced by the persistency and the reactivity of a substance. Secondly, substances with low toxicity might be over represented among high-volume substances, and therefore correlation between exposure and production volume does not necessarily means correlation between risk and production volume. These authors suggest that it is possible that many of the most harmful chemicals are only manufactured in lower volumes. Finally, exposure is not necessarily uniformly distributed, and a small number of persons can be exposed to a small volume of high-risk substances (Rudén and Hansson, 2006).

Adaptation of standard requirements

Regarding the standard information requirements under REACH, expert judgment and value-ladenness could play a major role, as the regulation allows, for flexibility concerns, some of them to be adapted, waived or replaced, or new requirements to be proposed. Furthermore, the standard testing regime may also be adapted under certain conditions, and demonstration of control of risk must take into account cost-efficiency considerations (ECHA, 2008a).

Classification and labelling system

The definition of "dangerous" in REACH is established according to the Directives 67/548/EEC and 1999/45/EC. Studies of the accuracy of the classification of substances as dangerous in the framework of the Directive 67/548/EEC showed that about 15% of the substances investigated were underclassified with respect to acute oral toxicity, and about 8% were overclassified (Hansson and Rudén, 2006).

Epistemological uncertainty

Epistemological limitations of the underlying knowledge base for CSA could refer, for example, to lack of consideration given to synergic or antagonistic effects of chemicals or to multicausality (interaction between chemicals and other causes for determining an effect, interaction between degradation products of a substance and other natural or man-made chemicals present in the environment or in the human body, interaction between the different exposure pathways – like working place, consumption and current life, etc.).

REACH does not consider these aspects in its framing of the "chemical risk problem". However, this kind of uncertainty should be somehow considered in order to highlight potential need for research. In other words, providing a possibility for taking into account epistemological uncertainty in REACH could create the conditions for updating regulation for including new scientific findings, on the one hand, and for providing politically and socially-relevant orientation for the risk research, on the other hand.

5.2.2. <u>Source uncertainty</u>

Source uncertainty is uncertainty issued from the selection of the sources (references) used, and among them, of the sources which are considered as being appropriate for use in the assessment process. This can play a major role on the outcomes of risk assessment (Rudén, 2001).

The registrant must assemble all the relevant information on a substance, or information that may be useful to inform on the properties of that substance, which is available to him. This demand targets exhaustiveness but, in some cases, some sources of information could be unavailable for confidentiality reasons. There is no mean for REACH to check if all unpublished information available to manufacturers or importers has been provided.

The ECHA, 2008c chapter addresses information searching strategies, and the evaluation of the completeness and of the quality of the information is addressed in ECHA, 2008d.

<u>Data quality</u> is defined through three properties (ECHA, 2008d, pp. 7, reproduced from Klimisch et al., 1997):
- <u>Adequacy</u>, i.e., the "*usefulness of data for hazard / risk assessment purposes*". This is the criterion referring to the **selection** of sources among all those available. "*Where there is more than one study for each endpoint, the greatest weight is attached to the studies that are <u>the most relevant and reliable</u>*".
- <u>Relevance</u>, i.e., "*the extent to which data and tests are <u>appropriate</u> for a particular hazard identification or risk characterization*"
- <u>Reliability</u>, i.e., which is referring to the "*inherent quality of a test report or publication relating to preferably standardized methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings*".

However, the assessment of all these three properties leaves important room to report author subjectivity.
- Assessment of <u>relevance</u> leaves important place to subjectivity in assigning a meaning to the "appropriateness" of data and tests. Their "adequacy" is not defined through some set of clear criteria allowing assessment of this property.
- <u>Reliability</u> looks relatively easy to assess for data issued from standardized tests, but more difficult for those data for which such standardized tests do not exist or were not used (e.g., in published literature). The scoring system developed by Klimisch et al. (1997) is proposed for describing the level of reliability of the data, but the assessment of the scores involves a high level of subjective appreciation, particularly for data issued from non-standardized tests.

Other tools for addressing data quality include Hill's criteria for evaluation of epidemiological data, ranking of chemicals son their endocrine potential or evaluation of ecologic risk (ECHA, 2008d).

The definition of the "reliability" of studies and data could play a major role in REACH. Indeed, it is probable that many published studies are not done, for example, under GLP. Peer-reviewed journals are preferred, without further indication about the quality of a journal (e.g., impact factor) to be favored in the source selection process. ECHA, 2007 rightly mentions that "*the correct choice of the key study is also important for the CSR (e.g., classification and labeling, PNEC-calculation, etc.).*" (pp. 48) However, the process of selection of the key studies, i.e., of the "most adequate studies", is not precise, leaving place to important influence of expert judgment.

Data completeness is defined in ECHA, 2008d through comparison between the available information and the information required under REACH.

Allowing an important influence of report author judgment in the selection and evaluation of data quality can have major effects in the risk assessment outcomes. Based on the analysis of 29 risk assessments for trichloroethylene, Rudén (2001) found that the data sets utilized by the different risk assessors were surprisingly incomplete and that biased data selection may have influenced some of the their conclusions. Furthermore, risk assessors were shown to often interpret and evaluate one and the same study in different ways and there were also indications of bias in both interpretation and evaluation of primary data. The differences of interpretation can be very significant, as shown by the fact that for 6 of the 19 experiments (27%) considered by Rudén (2001), different risk assessors have interpreted the results both as showing a positive result regarding carcinogenicity and as showing negative results.

The ECHA, 2008d guidelines does not indicate if the registrant has an obligation to report the details his assessment of data quality, or if the guidance is only destined at giving broad indications for helping those registrants willing to assess the quality of the data they use. For the sake of transparency in the CSA and for allowing its informed evaluation by the competent authority, the communication of the details of data quality assessment is important. Summaries are only demanded for key studies (ECHA, 2008d), therefore an open question rests on how the choice of the studies and data, made by the registrant, will be appreciated during the evaluation process.

The Klimisch scoring system has four levels for scoring reliability: "reliable without restrictions", "reliable with restrictions", "not reliable" and "not assignable". Two of these levels, i.e., "reliable with restrictions" and "not reliable" are very close and the choice of one or another seem dependent on expert subjectivity, however their meaning for establishing the adequacy of a study can be very different. The involvement of expert judgment can play a very important role, as it was shown in the literature that the quality of studies and data feeding the risk assessment process can be interpreted very differently by different experts (Rudén, 2001).

In a more advances stage of REACH implementation, it would be interesting to compare the assessments made by different registrants for the same study, in order to understand how the quality criteria are applied.
Therefore, real transparency in data selection would involve a detailed description of the reasons for assigning one or another level of reliability and/or relevance, as much more as both Klimisch et al. (1997) and ECHA, 2008d propose very clear criteria for deciding the "reliability" level for toxicity and ecotoxicity studies. A detailed explanation of the level of reliability assigned to a study, criterion by criterion, would insure comparability between the different assessments, would be easy to make, transparent and easy to communicate. All the criteria should be assessed, in order to avoid selection of those criteria which might be favorable to a preconceived position regarding a study or a dataset (for all the factors which might influence expert judgment, see subsection 5.3.4).
Among the three properties assessed, "reliability" seems the easiest to assess precisely and to communicate, as the meaning of "relevance" is less clear and potentially harder to assess without good

data availability. Descriptions of the assessment of each criterion would correctly address this potentially important source of uncertainty.

Previous research found that, left by their own, risk assessors do not discuss, in most cases, the reasons for their evaluation of the quality of a study. Explicit and comprehensive descriptions of the assessed scientific quality of primary data are rare exceptions and only a few risk assessors have a general policy statement on quality criteria for primary data (Rudén, 2001).

5.2.3. __Methodological uncertainty__

Selection Uncertainty

Wandall et al., 2007 have proposed a description of the "biases" ("sources of lack of quality") in the toxicological and ecotoxicological information produced during the process of regulatory testing. Among them, several are relevant for REACH:
- In the stage of developing and implementing the research protocol, **the choice of species and strains** that are used for testing can be important, because of their different sensitivity to chemicals. Study designs are highly standardized in REACH, but nevertheless the selection of study methodology is left partially open regarding the balance to be made between the choice of the most sensitive species and their relevancy for humans, recommended by ECHA, 2008g (pp. 22).
- When performing the experiment, collecting and recording data, one may refer to what is called as **"experimenter's bias".** Indeed, it was shown that if an investigator is (explicitly or implicitly) expecting a particular result, this may lead to a biased collection and recording of data (Kaptchuk 2003, in Wandall, 2007). This bias cannot be presently identified during the evaluation process in REACH, as long as experimentations follow standardized tests.
- During data and results analysis, the **choice of the statistical method for analyzing the data** and the **interpretation of the results** are much influenced by expert subjectivity. Indeed, depending on the statistical tool chosen, it was shown that the same experiment has been interpreted both as showing and not showing a significant effect (Rudén, 2001).

Besides these sources of uncertainty in mandatory testing, **voluntary testing** could focus on a selection of substances and endpoints for which companies perform such tests. Indeed, more data could be synonymous to limitations in the sale and use of a substance, which is a disadvantage for the company.

Wandall et al., 2007 proposed several solutions for addressing these problems:
- avoid experimenter's bias through use of blinding or use of review by a panel of experts;
- when interpreting the results, and especially those showing no statistically relevant adverse effect in the treated groups, assess the sensitivity of the study, the inclusion of appropriate positive and negative controls, the bioavailability of the test substance and whether it reaches the test organ. As well, comparing how different experts interpret the same results of individual studies;
- a registry in which all studies would have to be registered before being carried out, for addressing underreporting bias;
- study the manner in which companies prioritize substances for voluntary testing.

Assessment of chronic effects

For human health, repeated-dose[13] toxicity studies required are 28-day studies for $10 - 100$ t/y chemicals, and 90-day studies for > 100 t/y.

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[13] "*Repeated dose toxicity refers to general toxic effects that occur after daily dosing with a substance for 28 or 90 days, or major part of the lifespan, in case of chronic exposure. Effects examined in these studies may include changes in morphology, physiology, growth or life span, clinical chemistry or behaviour*" (ECHA, 2008g, pp. 25).

The recent study of Malkiewicz et al., 2009 highlighted the opportunities of improvement of the ECHA guidance regarding the derivation of assessment factors for covering subacute – subchronic, subchronic – chronic and subacute – chronic extrapolations. Indeed, whereas ECHA, 2008b recommends the use of default uncertainty factors for such extrapolations, another chapter of the same guidance, i.e. ECHA, 2008h, allows their modification according to the substance-specific information available.

These authors showed that the choice of endpoints has a considerable impact on the derivation of uncertainty factors for duration, e.g., that choosing mortality as endpoint underestimates the assessment factor needed for reaching a given level of protection for non-lethal points.

Characterization of dose – response relationship

The dose – response relationship is not necessarily linear for all substances. However, all the existing tests are based on the assumption of a linear dose – response relationship[14]. This means that the risk of substances which do not respect this type of relationships could be "lost", i.e., not detected.

Furthermore, the tests to be done on a substance should be adapted to the dose found in organisms, but these are data which are usually hard to find in the literature[14].

Regarding regulatory methodological choices, previous examples show that rules established through regulation can sometimes prove to be inadequate for risk assessment. In some cases, it is possible that the risk assessment procedure established through regulation is not adequate for the properties of the substance whose risk is assessed (see the conclusions section for the case of the effects of imidacloprid on honeybees).

5.2.4. Value-ladenness

Several references are available in Wandall et al, 2007, showing clearly the correlation between **expert expectations** and **institutional affiliation**, on the one hand, and his/her judgment on the quality of a study, on the relevancy of the results or on particular aspects of risk assessment such as the existence of thresholds and the value of animal models to identify human risk – on the other hand. Details on the factors influencing the different appreciation of primary data by different experts are also given by Hansson and Rudén (2006).

One of the sources of expert subjectivity is **conflict of interests**. These are situations occurring when there is a conflict, financial or non-financial[15], between an individual's private or institutional interests and his/her official duties in a position of responsibility or trust (Wandall et al., 2007). Several studies have shown that industry-sponsored research tends to yield pro-industry conclusions, and in some cases they can be attributed to study design factors such as choice of control or dose (Krimsky, 2005, Wandall, 2007). Two major types of conflict of interest have been identified by Claxton, 2007 on a case study basis:
   a) financial (producing results favorable to the funding agent),
   b) professional and philosophical (funding work by scientists for deliberately denigrate scientific results going against one's interests; corrupting science professionals for using his/her professional position for promoting information produced under undisclosed conflicts of interest; delays in publication or imposing confidentiality of results issued from research funded by the industry).

In REACH, many of the steps of the CSA involve decisions based on expert judgment and the responsibility for producing information is with the industry. Therefore, conflicts of interest could potentially play an important role. This aspect is of major importance from the perspective of the

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[14] Personal communication from an ecotoxicologist specialized in testing methods under REACH.
[15] E.g., responsibilities towards family members, mentor, mentee, colleagues, or co-authors

controversial potential of REACH implementation, because conflict of interest is one of the most socially-sensitive sources of lack of quality in a risk assessment process.

Kloprogge et al., 2005 distinguishes four types of value-ladenness:
- socio-political (influence of the political preferences of the analyst on his/her professional judgment),
- **disciplinary** (influence of the discipline on the analyst's judgment),
- **epistemic** (judgment is colored by the approach that the analyst prefers) and
- **practical** (the analyst is forced to make simplifying assumptions due to time constraints).

As well, it was shown (Van der Sluijs et al., 2003, Burgman et al., 2006) that expert judgment can be influenced by many **cognitive factors and psychological mechanisms** people use for reducing the complexity of problems and make them more manageable, like:
- perception and memory (what the expert knsown and what he/she remembers that he/she known),
- framing (a change in the presentation of a choice influences choice behavior, even when the objective characteristics, e.g., probabilities, do not change
- anchoring on values that have been previously suggested, or adjusting to the values first found
- overconfidence
- coherence (future events are considered more likely when they seem coherent)
- representativeness (place more confidence in a single piece of information that is considered representative of a process)
- unstated assumptions
- satisficing (search through a limited number of solution options and to pick from among them)
- availability (tendency to give too much weight to readily available data or recent experience)
- cognitive styles, values, attitudes or motivational factors (distorting judgment for justifying a pre-determined choice), etc.

5.2.5. <u>Validation uncertainty</u>

REACH does not refer to any system for field monitoring system for chemicals risks, in real conditions. However, confrontation between risks and effects really measured in human population or the environment could help at validating and/or adapting the risk assessment strategies in the future.

5.2.6. <u>Communication-related uncertainty</u>

Linguistic uncertainty

Linguistic uncertainty can refer to two phenomena (Levin et al., 2004) that could be encountered in CSR:
- A phrasing indicating that the level of confidence of the report author is below "full certainty" regarding a particular statement, whose meaning is nevertheless clear;
- A propositional content whose effect is to make the meaning of a statement inexact, intentionally or not. This can apply to cases where the conclusion of a particular reasoning allows an interpretation unjustifiably straightforward or, on the contrary, unjustifiably large or even opposite compared to the evidence available. This type can be referred to as "linguistically created uncertainty".

Linguistic uncertainty expresses through textual formulations and can render very flexible the message communicated by a set of evidence, even dependent on the personal communication abilities of the reporting author. Linguistic uncertainty represents both a way of communicating an existing uncertainty, and a tool for creating the impression of uncertainty where in fact there is no "objective" uncertainty.

Levin et al. (2004) highlighted four types of linguistic uncertainty, for which he developed indicators useful for recognizing it in texts describing risk assessments:
- contentual (contained in the way in which the propositional content is expressed),

- epistemic (referring to the degree of belief),
- conditionalising (expressing the dependence of the statement of a situation which is not fully known or understood)
- inferential (contained in the manner in which causal relationships are expressed).

REACH does not contain provisions for addressing this type of uncertainty, which may be however important in terms of impact on the receptors of the message communicated through the CSR or the SDS.

Reporting uncertainty

During the stage of reporting data and results, the **underreporting bias** may consist in incomplete reporting of testing outcomes to authorities, and there is no mean for REACH to check if all unpublished information available to manufacturers or importers has been reported. There could also be a lack of reporting towards the scientific community, the stakeholders and the general public (see also discussion on transparency), for reasons of confidentiality or because toxicology journals are often not interested in results of standardized testing.

Another type of reporting uncertainty can be related to the robustness of studies synthesis, i.e., its preciseness, exhaustiveness and correctness in communicating the main results contained in the extended text.

5.2.7. <u>Procedural uncertainty</u>

Transparency

Rosqvist, 2003 highlights a major aspect of uncertainty related to the social status of the risk assessment process, namely transparency, directly influencing its credibility in the eyes of the general public and the stakeholders.

The correctness and completeness of the risk information produced by the registrants is dependent on the capacity of the competent authorities, scientists and other stakeholders to audit the information (Koch and Ashford, 2005). Furthermore, insuring transparency in the CSA is a fundamental request for the procedural quality of any potentially controversial risk assessment. Transparency has not only a political dimension related to democratic participation, but also makes reference to inter-groups social justice, as consumers should have the right to know and to decide what they are sold to and consume.

Under REACH, citizens will have access to information on chemicals of very high concern in articles only upon request. The response period is set to 45 working days. REACH specifies that "*EU-citizens should have access to information about chemicals to which they may be exposed, in order to allow them to make informed decisions about their use of chemicals. A transparent means of achieving this is to grant them free and easy access to basic data held in the Agency's database, including brief profiles of hazardous properties, labeling requirements and relevant Community legislation including authorized uses and risk management measures*" (Article 117 of the Regulation, Official Journal of the European Union, 2006, pp. 36).

The Regulation also specifies that: "*Available information, including that generated by this Regulation, should be used by the relevant actors in the application and implementation of appropriate Community legislation, for example that covering products, and Community voluntary instruments, such as the eco-labeling scheme*" (Article 14 of the Regulation, Official Journal of the European Union, 2006, pp. 6).

The rules on transparency regarding safety of substances have been defined by the ECHA (ECHA, 2008f). Among others, stakeholders will be invited to send comments, information or studies to the ECHA in several circumstances (for testing proposals, classification and labeling dossiers, identification of SVHC substances, etc.). Only information considered as being non-confidential by the registrants will

be made publicly available, but the ECHA document does not specify rules according to which some information may be considered confidential and other not.

Transparency has an important potential of contributing to the efficiency of REACH. Researchers and stakeholders, working on REACH in their daily professional life, can provide a useful feed-back on the quality of the information provided by the registrants and thus help the Member States Agencies and the ECHA in their work. This argument can be supported through an opposite example, in which a team of researchers who investigated the accuracy of the European classification and labeling system regarding acute oral toxicity found that an important proportion of substances were misclassified, but could not provide an understanding of the reasons for this situation, due to the fact that the Commission did not publish the documentation of its classification decisions (Hansson and Rudén, 2006). This kind of feed-back can prove to be particularly useful for the European Commission, regarding its own work.

Operational uncertainty

Operational uncertainty consists in lack of quality of knowledge due to practical aspects such as time and resource constraints. This type of uncertainty can appear in the phase of knowledge production (e.g., when cost-efficiency of testing is considered during decisions about choice of species and strains to use, about additional testing to propose, etc.).

An example of operational uncertainty relates to the influence of the focus on cost-efficiency on tests made for hazard assessment. For example, ECHA, 2008a recommends balancing cost-efficiency and uncertainty in the results for deriving a final DNEL / PNEC: "*By conducting additional testing, eventually more relevant data on the hazards of the substance may become available. This may lead to a lowering of the assessment factors used for derivation of no-effect-levels (DNELs and/or PNECs) and these then become more precise. However, whether or not the additional test data will lead to a higher no-effect-level depends on the toxicity found by conducting additional tests. Thus, the costs of more testing (in terms of animal lives and money) could be weighed against the likelihood that a higher no-effect-level will be achieved*" (pp. 13).

Evaluation - related uncertainty

Previous studies showed that procedures very similar to that of comitology tend to favor the implicit or explicit expression of arguments lying outside the scope of purely scientific considerations, i.e., more related to socio-economic and political strategies of the Member States concerned. Thus, Rudén, 2003 studied carcinogen risk assessment of the chlorinated solvent trichloroethylene within the European Union existing substances program and the classification and labeling process. She focused on the most active and influential participants of this process, namely, those from the United Kingdom, Germany, and Sweden, and from industry. Her results show that the member state and other experts have different opinions regarding the appropriate classification of trichloroethylene for mutagenicity (no classification or category 3) and carcinogenicity (category 3, 2, or 1), based on arguments outside of the exclusively scientific sphere of the risk assessment.

The degree and influence of expert judgment and subjectivity in evaluating the available results has become obvious during the process of identification of the substances to be first submitted to authorization in 2009. Member States proposed 15 substances, among which ECHA retained only 7. In the same time, a group of European NGOs called ChemSec published an alternative list, containing about 300 substances identified based on the official criteria for authorization established through REACH.

Procedural devices established through regulation can have therefore an important influence on what is considered to be the "quality" of the CSA (and therefore the uncertainty associated to the information contained in it). These devices refer to patterns of expertise, the role of different kinds of expertise in the evaluation process, the influence of socio-economic interests, the composition of expert committees

regarding balance between the representativeness of different interests, competences and Member States, etc.

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6. Discussion and conclusions

REACH has known a controversial development process, whose memory revives from time to time since its adoption. This shows that, despite (or because of) the compromise which has been reached, the reasons for controversy are not ready to be forgotten by the stakeholders involved. Politically, this is an important issue for the successful implementation of REACH.

The uncertainty dimensions highlighted above have a potential to influence the even "raison d'être" of REACH, i.e., obtaining robust and trustful information on the risks of the chemicals actually on the market. Indeed, these dimensions of uncertainty are also those that were often at the heart of previous controversies.

One of the examples we might cite is that of the controversy on the risk of the insecticide Gaucho® (active substance imidacloprid) on honeybees, in France. This case started in 1994 when beekeepers first observed new symptoms in their honeybees during sunflower flow. In 1999 the insecticide has been banned in application of the precautionary principle in sunflower seed-dressing, and in 2004 it has also been banned in maize seed-dressing. Evidence of the risk caused by imidacloprid emerged when the substance's effects on honeybees were first studied in publicly-funded research 1997 - 1998. Political measures were taken in a context of vehement social debate, involving beekeepers, Bayer (the company that produces Gaucho®), researchers, the French Ministry of Agriculture, farmers, the press and representatives of the civil society.

In this controversy, several major categories of uncertainty, which we also addressed above for REACH, have been at the core of the debate:
- Uncertainty in problem framing, i.e., in the assumptions made regarding the absence of exposure of honeybees due to the application of the insecticide in seed-treatment;
- Regulatory-induced methodological uncertainty, associated to the lack of relevance of the regulatory risk assessment for pesticides for the properties of the insecticide assessed;
- Methodological uncertainty associated to the lack of standardized tests for the assessment of sublethal and chronic effects of imidacloprid on honeybees;
- Technical uncertainty associated to the performance of measurement techniques, and especially to the sensitivity of the detection and quantification limits used by the company in its risk assessment of imidacloprid; this strongly influenced the results obtained for NOEC / LOEC and for the measurement of the exposure through pollen and nectar;
- Conflict of interests, associated to the systematic difference between the lack of risk found by Bayer-funded scientists and the existence of a risk found by publicly-funded scientists;
- Linguistic uncertainty, associated to the discursive patterns of Bayer communication on the risk of imidacloprid on honeybees;
- Procedural uncertainty associated to the lack of resources at the Ministry of Agriculture for the appropriate evaluation of the authorization dossier submitted by Bayer for marketing imidacloprid in seed-dressing;
- Epistemological uncertainty on the unusual (non-linear) dose-response pattern of imidacloprid.

Details on this case study can be found in Maxim and van der Sluijs, 2007.

Another example relevant for our argument is the case of the controversy on endocrine disrupters, in which the following types of uncertainty play an important role:
- Epistemological uncertainty, related to the particularities of the potentially non-linear dose-effect pattern and to the synergic effects (indeed, it was shown that cocktail of molecules can have damageable effects on health, whereas each molecule taken in itself has no such effect);
- Conflict of interest- related to the opposition between the results found by industry (e.g., on phthalates) and by publicly-funded research; for example in France, phthalates producers argued

for the absence of effects of phthalates on human health in order to downplay the ban on their use in toys (1999);

- Validation uncertainty – lack of monitoring being used by the chemical industry to argue in the same case of phthalates, that these substances had been used for 40 years without any effect on human health; one of the aspects of this kind of uncertainty relates, in France, with the lack of monitoring of the cases of cancer in the country;
- Methodological uncertainty – related to the confirmation of an effect found following exposure to a substance only if an action mechanism can be highlighted; this type of uncertainty significantly influenced for example, in 2000, the reinsuring conclusions of the International Agency for Research on Cancer (IARC) on the risk of Di(2-ethylhexyl) phthalate (DEHP), contested by other expertise;
- Uncertainty in data selection, e.g., regarding the absence of some existing sources among those used in 2003 by the Scientific committee on Toxicity, Ecotoxicity and the Environment (European Commission) for producing a state of knowledge on endocrine disrupters in Europe;
- Technical uncertainty related to the sensitivity of detection and quantification limits.

These examples (and many others could be given) demonstrate the importance of qualitative dimensions of uncertainty (related not as much on "how much data we have" but on "how was the data obtained" and "how is the data used") in controversies.

In addition to drawing a picture of the lack of knowledge, one of the main objectives of uncertainty analysis under REACH should be to insure the credibility of the information produced. For this, quantitative approaches should be supplemented by qualitative analyses. It is important to isolate these different types of uncertainty, to address them using the appropriate (existing) uncertainty analysis tools and to focus their use and communication towards the public for which they were initially created, i.e., the policy-makers, the general public and the stakeholders.

Finally, we argue that increased transparency could improve the credibility of the information produced under REACH and provide additional helpful feed-back on its quality.

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