WP 2
D2.4.2 Inter-case study analysis
D2.4.3 Identification of issues cutting across case studies

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Table of contents

1 Introduction 6
1.1 Context 6
1.2 WP2 and this report 6
1.3 Methodology 9
1.4 Executive Summary 12
D2.4.3 Identification of issues cutting across multiple case studies 14
2. Complexities and controversies regarding the relevance of the PP 14
2.1 Framing of the PP and innovation 14
2.2 Subjectivity and objectivity in risk assessment 16
2.3 The difficulty of admitting uncertainty 16
2.4 Layers of uncertainty 17
2.5 Aspects of hazards 19
2.6 Weighing of benefits and uncertainties 20
2.7 The difficulty of prevalence and path dependencies 21
2.8 The problem of no established science 22
3. Complexities and controversies with regard to the procedures around the application of the PP 23
3.1 The meaning of applying the PP 23
3.2 Address regrettable substitution 23
3.3 Need for transparency 24
3.4 Organization of knowledge networks 24
3.5 Public involvement 25
3.6 Industry involvement in risk assessment 26
3.7 Cost-benefit analysis and proportionality 26
3.8 Aligning innovation with precaution 27
3.9 Precautionary principle vs principle of prevention 28
3.10 Alternatives to regulation 28
4. Complexities and controversies with regard to the effects of the application of the PP for innovation 29
4.1 Incremental vs radical innovation 29
4.2 Alternative innovation pathways 29
5. Discussion and lessons from case study comparison 30

5.1 Overview of lessons derived from the inter-case study analysis 30
5.2 Discussion of results 34
D2.4.2 Inter-case study analysis 36
6. Annex 36
6.1 RECIPES general overview of research questions according to the methodological framework 36
6.2 Table overview of all 9 case studies 40
7. References 198

List of tables

Table 1: Overview of case studies performed in the RECIPES project 3

Table 2: Overview of lessons in the dimension relevance from intra-case study comparison 31

Table 3: Overview of lessons in the dimension procedures of intra-case study analysis 32

Table 4: Overview of lessons in the dimension effects of intra-case study analysis 34

List of abbreviations

CSS	Chemical Safety for Sustainability
CDSS	Clinical Support Systems
EDCs	Endocrine Disrupting Chemicals
GMO	Genetically Modified Organism
LGMO	Law on Genetically Modified Organisms (Bulgaria)
Neonics	Neonicotinoid insecticides
PP	Precautionary Principle
SPIs	Science Policy Interfaces
SDGs	Sustainable Development Goals
WFD	Water Framework Directive
WP	Work Package

1 Introduction

This document fulfils RECIPES delivery 2.4.2, the inter-case study analysis and delivery 2.4.3, identification of issues cutting across multiple case studies. The criteria for the analysis are presented in delivery 2.2 as the comparative multiple-case design, which is the methodological framework developed in task 2.2. Delivery 2.3 explains the case study selection process which was undertaken to arrive at the nine cases studies that have been carried out in WP2. Delivery 2.4.1 compiles all nine case studies carried out in the RECIPES project.

1.1 Context

This report is part of the EU funded project entitled REconciling sCience, Innovation and Precaution through the Engagement of Stakeholders (RECIPES). The precautionary principle guides decision-makers faced with high risks, scientific uncertainty and public concerns. As a general principle of EU law, it allows decision-makers to act despite scientific uncertainty. The precautionary principle has been criticised for hindering technological innovation, therefore some stakeholders have developed an innovation principle, which requires taking into account the potential impacts of precautionary action on innovation. The RECIPES project aims to reconcile science, innovation and precaution by developing new tools and guidelines, based on co-creation with stakeholders, to ensure that the precautionary principle is applied while still encouraging innovation.

The RECIPES project comprises three research phases. In the framing phase of the project, the RECIPES Consortium has examined the effect and the application of the precautionary principle since 2000 by combining legal analysis, desk research and a narrative literature review, complemented with a media analysis of the public discourse around the principles of precaution and innovation, in order to understand the different stakeholder perspectives. In the analytical phase of the project, an innovative conceptual framework for comparative multiple case study analysis has been developed, in order to perform case-study analyses. This will be combined with scenario building. In the developmental phase of the project, scenario workshops will be combined with a multi-criterion assessment framework to develop and assess the usefulness of the to-be-proposed new tools.
This report contributes to the analytical phase of the project. It comprises the inter-case study analysis and the identification of issues cutting across multiple case studies.

1.2 WP2 and this report

The overall aim of WP2 is to understand and explain the differences in the application or potential application of the precautionary principle in nine different case topics, in a way that reflects the particular context of the case study topic. The

multiple case study component of the RECIPES project is one of the key analytical phases of the project.
Within the scope of the entire RECIPES project, WP2 builds on aspects of WP1, in particular the report which presents the stock taking of the precautionary principle since 2000. In addition, WP2 feeds into WP3, the development of new tools and approaches to the PP in a co-creation approach, as well as ensuing communications in other work packages.
The complete list of WP2's project deliverables and milestones can be seen below.

Deliverables
D 2.1: Literature research on multi-case study analysis
D 2.2: Development of criteria for multi-case study analysis
D 2.3: Selection of case studies
D 2.4.1: Intra-case study analysis
D 2.4.2: Inter-case study analysis
D 2.4.3: Identification of issues cutting across multiple case studies
D 2.5.1: Comparison of case study analysis with results of WP1

Milestones
M 2.1: Formulation of hypotheses on role and interaction of PP/ IP
M 2.2: Methodological framework for comparative multi-case study analysis
M 2.4: Emerging themes and conclusions of individual and cross-case analysis
M 2.5: Developing scenarios of application PP and IP to emerging technologies

This document fulfils delivery 2.4.2 Inter-case study analysis and 2.4.3 Identification of issues cutting across multiple case studies. WP2 tasks 2.1-2.4 encompass the entire case study analysis component of WP2. Task 2.5 concerns the synthesis of the WP2 case study analysis with WP1, and development of scenarios for the future of the precautionary principle and innovation in the EU. Task 2.5 is thus the key linkage between WP2 (and aspects of WP1), and WP3 and the ensuing RECIPES project deliverables. The scenarios developed for task 2.5 will be validated in stakeholder workshops, and will themselves help inform the development of new tools for policy makers in further RECIPES work packages.

The following table shows the nine case studies performed within the RECIPES project.

Table 1: Overview of case studies performed in the RECIPES project

D2.4.1: Intra case study analysis of 9 selected case studies	Authors
1. New gene-editing techniques (gene drives)	Rosanne Edelenbosch, Tijs Sikma, Petra Verhoef; Rathenau Institute
2. Genetically Modified Organisms (GMOs)	Ventseslav Kozarev, Zoya Damianova, Desislava Asenova; Applied Research and Communications Fund
3. Endocrine disrupting chemicals (EDCs)	Afke Groen, Christine Neuhold; Maastricht University
4. Neonicotinoid insecticides (Neonics)	Laura Drivdal, Jeroen P. van der Sluijs; University of Bergen
5. Nanotechnologies	André Gazsó, Anna Pavlicek; Institute of Technology Assessment, Austrian Academy of Sciences
6. Glyphosate	Sabrina Röttger-Wirtz, Maastricht University
7. Financial risks in urban infrastructure planning	Fritz-Julius Grafe, Harald A. Mieg; Humboldt-Universität zu Berlin
8. Artificial Intelligence in Health Care, clinical decision support systems (CDSS)	Tijs Sikma, Rosanne Edelenbosch, Petra Verhoef; Rathenau Institute
9. Microplastics in food products and cosmetics	Miriam Urlings, Maastricht University

D2.2 has detailed the methodological framework for carrying out the RECIPES case studies. Delivery 2.3 has introduced the RECIPES WP2 case studies and explained the case study selection process that was used to select the cases.

D2.4.2 Inter-case study analysis

The methodological framework for the identification of issues cutting across multiple case studies has been detailed in delivery 2.2. Delivery 2.4.1 presents the intra-case study analysis of each case based on the methodological framework. Delivery 2.4.2 compares the nine case studies along the dimensions identified by the methodological framework. The results are presented at the end of this re-

port in table to provide an at a glance overview and to allow for easier navigation between and across case studies.

D2.4.3 Identification of issues cutting across multiple case studies

In D2.4.3 Identification of issues cutting across multiple case studies, the research focuses on the complexities and controversies which cut across the cases. They are identified based on **epistemological challenges in risk governance, namely complexity, uncertainty and ambiguity**. The findings are analysed based on the guiding research questions (overview in appendix 6.1) and the results are discussed along three analytical dimensions.

Relevance: Complexities and controversies with regard to the procedures around the application of the principle (chapter 2)

Procedures: Complexities and controversies with regard to the procedures around the application of the principle (chapter 3)

Effects: Complexities and controversies with regard to the effects of the application of the PP for innovation (chapter 4)

1.3 Methodology

The aim of D.2.4.2 is to understand and compare the individual cases in their specific context. The case study comparison is based on a common conceptual and methodological framework which increases comparability of cases and thus the quality of the intra- and inter-case study analysis. The methodology of WP2 therefore rests on the conceptual framework and the methodological framework.

The conceptual framework addresses several key aspects of the RECIPES project's larger conceptual approach to the precautionary principle, specifically within a risk perspective[1]. Within this risk perspective the key epistemological challenges are complexity, uncertainty and ambiguity (SRA 2018; Renn 2008). These epistemological challenges highlight the limits of our understanding and our ability to communicate effectively about risk and innovation (Renn, Klinke, van Asselt 2011).

The mythological framework serves as a blue print for carrying out the case study research by the case study researchers. The main research goal for the inter-case study comparison is, to better understand the complexities and con-

[1] In the RECIPES project risk is defined as „uncertainty about and severity of the consequences (or outcomes) of an activity with respect to something that humans value" (Aven and Renn 2010).

troversies with regard to the relevance, the procedures and the effects around the application of the PP in practice across the nine case studies. What role do complexity, ambiguity, and especially uncertainty play? Based on the preparatory work in the two framework documents the aim of the case study comparison is to draw lessons from concrete cases in which the precautionary principle was (or could have been) applied in relation to a presumed socio-technological or socio-economic innovation.

The phrases complexities and controversies warrant an explanation. **Complexity** implies that human intuition cannot be relied upon to understand cause and effect (IRGC 2018). Complexity refers to the difficulty of identifying and quantifying causal links between a multitude of potential candidates and specific adverse effects (Renn, Klinke, van Asselt 2011). It includes the interplay of human agency within the context of regulation, innovation, legal decision-making, changing societal values, and vested interests, which result in higher-level complexity than the technological system alone. Many of these variables play a role and are intertwined in cases where the PP is applied. The application of the PP is thus accompanied by a variety of complexities.

Controversies are modes of communicative action centering on themes associated with considerable levels of societal disagreement[2]. Controversies influence the societal discourse on risk. Conflict theory claims that many modern societies are essentially structured by the evolution of conflicts and shifts in the patterns of conflict resolution (Lau 1989; Giegel 1998). Three types of conflicts can be identified that are of relevance in the RECIPES context: conflicts of interest, conflicts of values and conflicts on knowledge (cf. Böschen 2010). Therefore debates and controversies can arise at three levels, 1. within science, 2. at the science-policy interfaces (SPIs), and 3. at the level of public discourse (van Nest et al. 2014).

With regard to the case studies in the RECIPES projects an increasingly multi-layered and diversified socio-political landscape can be observed, in which a multitude of actors, their perceptions and evaluations draw on a diversity of knowledge and evidence claims, belief and value orientations, and political interests in order to influence processes of risk analysis, decision-making and risk management (Renn & Klinke 2013).

Complexities and controversies are first of all a logical symptom of the fact that the application of the PP is accompanied by high stakes, uncertainties and social values at dispute (cf. Funtowicz & Ravetz 1993). Based on the results of the in-

[2] For analytical purposes we follow here a position of „epistemological hierarchicalism" with regard to knowledge claims about risk and uncertainty. Epistemological hierachicalism "posits variations in the quality of knowledge claims along a continuum ranging from those of considerable agreement to those of great disagreement. Knowledge claims, while always short of absolute truth, admit to degrees of approximation to what is true". (Rosa 1998, p. 38)

ter-case study comparison, D2.4.2, on the following complexities and controversies can be identified.

Complexities and controversies

1.) with regard to the relevance of the PP. Insight into the complexities and controversies that play a role in establishing the relevance of the PP in relation to a particular socio-technological or socio-economic innovation.

2. with regard to the procedures concerning the application of the PP in relation to innovation:

2.1. Comprehension of decisions, procedures, measures, legislation etc. that are derived from the application of the PP.

2.2. What procedures and measures are derived from the application of the PP? How are they influenced by other societal/economic/political dynamics?

3. with regard to the effects of the application of the PP for innovation: Did the application of the PP have an effect on the innovation pathway, if so, how?

The following chapters 2-4 present the cross-cutting issues surrounding complexities and controversies of the case studies. Each issue is based on evidence from the inter-case study analysis (D2.4.2) and supplemented with evidence from the intra-case study analysis (D2.4.1). Furthermore, each issue puts forth lessons learnt which will inform task 3.2 "Development of tool and guidelines" D2.4.2 Inter-case study analysis is presented in table form at the end of the document, including an overview of the guiding research questions.

1.4 Executive Summary

The case study comparison has identified several issues of complexities and controversies surrounding the case studies. These issues can be arranged in three subcategories: 1. with regard to the relevance of the PP, 2. focusing on the procedures regarding the application of the PP, and 3. with respect to the effects of the application of the PP for innovation.

Firstly, reoccurring issues induced by complexities and controversies across the cases that played a significant role in the with regard to the relevance of the PP are concerning four main aspects: 1. layers of uncertainty, 2. aspects of hazard, 3. weighing in the benefits and uncertainty of benefits and 4. the difficulty of prevalence and path dependencies.

These main trajectories of complexities and scientific uncertainties indicate that they need to be understood as a correlate of the type of environment in which the technology is introduced. For instance, the unpredictability and complexity of a healthcare system, the many variables and interactions at play in ecosystems (EDCs, glyphosate, nanotechnology, GMOs, gene drives) or the intersection of social systems with financial systems (financial risks in water infrastructure planning) point towards the importance of situational context. A main lesson especially derived from the issue of layers of uncertainty but also derived from other identified issues in the case study comparison, s that there is a need for more integrative risk governance frameworks that connect between different types of uncertainties which can inform risk assessors on the applicability of the PP in the case of accumulated uncertainties.

Secondly, reoccurring issues identified across the cases in the subcategory procedures regarding the application of the PP, can be grouped around four main aspects: 1. framing of the PP and innovation in the discourses, 2. the meaning of the PP and its measures, 3. the organization of knowledge networks, 4. cost benefit analysis and proportionality. Regarding issue 3. organization of knowledge networks the key question was how different knowledge and perspectives about a technology must be assembled to ensure a reasonable application of the PP? The nanotechnology case provides valuable insights for identifying, structuring and evaluating the available information on a certain technology. Therefore another main lesson is to organize transdisciplinary knowledge networks. This requires a trusted platform of deliberation to identify structure and evaluate the available information on the technology from stages of infancy onwards.

Thirdly, when complexities and controversies are analysed with regard to the effects of the application of the PP for innovation in the case study comparison two aspects need to be considered: 1. incremental vs radical regulation/innovation, 2. alternative innovation pathways.

The comparison across cases indicates that the application of the PP has had a positive effect on incremental innovation in many cases. Furthermore, the application of the PP contributed (if it was applied in the case) often to alternative, more responsible innovation pathways, like green chemistry (EDCs), new plant protection technologies and non-chemical alternatives to pest management (neonics), green nanotechnology and safe-by-design approaches in nanotechnologies.

An overview of the lessons from the inter-case study analysis is provided in section 5.1.

D2.4.3 Identification of issues cutting across multiple case studies

2. Complexities and controversies regarding the relevance of the PP

2.1. Framing of the PP and innovation

A reoccurring theme in the cases concerned how the PP and innovation were framed. The term framing refers to differences and conflicts about what major societal actors select as risks and what types of problems they label as risk problems (rather than opportunities or innovation potentials, etc.). Framing in this context encompasses the selection and interpretation of phenomena as relevant risk topics (cf. Renn 2008)[3].

Framing in a narrower sense means that "the initial analysis of a risk problem looking at what the major actors, e.g. governments, companies, the scientific community and the general public, select as risks and what types of problems they label as risk problems". This defines the scope of subsequent work. Therefore framing in this context is linked to problem framing in the Pre-Assessment phase of risk governance. As with the framing part, judgements on acceptability rely on two major inputs: values and evidence. What society is supposed to tolerate or accept can never be derived from looking at the evidence alone. Likewise, evidence is essential if we are to know whether a value has been violated or not (or to what degree). With respect to values and evidence we can distinguish three cases: (1) ambiguity on evidence but not on values (interpretative ambiguity) (2) ambiguity on values but not on evidence (normative ambiguity) and (3) ambiguities on values and evidence (Renn 2008).

In the neonics case the perceived interaction between precaution and innovation seemed to depend a lot on the framing of innovation: 'In a narrow framing of innovation, in this case as innovating new plant protection products, then innovators asked for creating more predictability in the EU legal framework (in this case, espe-

[3] When framing the issue, besides the distinction of what is selected as risk and what is labelled as risk problems the classic distinction between evidence claims and normative claims is relevant because justifying claims for evidence versus values involves different routes of legitimisation and validation, namely, whether a consensus or conflict evolves about what requires consideration as a relevant risk depends on the legitimacy of the selection rule. The acceptance of selection rules rests on two conditions: first, all actors need to agree with the underlying goal; secondly, they need to agree with the implications derived from the present state of knowledge (whether and to what degree the identified hazard impacts the desired goal). Dissent can result from conflicting values as well as conflicting evidence, and, in particular, from the inadequate blending of the two.

cially considering article 21 of regulation 1107/2009[4]), formalizing an impact analysis, and making more time for creating more certainty in risk assessments. (...) If one would opt for a broader definition of innovation, one could see more realistic possibilities for aligning innovation with the PP, more in line with the Integrated Pest Management approach and with Responsible Research and Innovation (RRI)?' (cf. case study neonics, p. 39). With regard to neonics, different perspectives on agriculture played on the background: like idealized images of local farming or idealized images of agricultural industry as a feeder of the world (cf. case study neonics, p.21).

In the case of technologies of which many uncertainties exist it seems to be tempting to search for a familiar frame. Very generally speaking frames are cognitive concepts that provide a structure that can help to understand the unknown on the basis of what one already knows. Risks assessment data is in public and policy discourse for instance interpreted on the basis of these frames. . In some cases very strong frames tended to distort the debate and led to controversy.

The GMO case study emphasised that the controversies span around a 'division [that] is not merely between pro and anti-GMO, but goes deeper in both directions, because it is, in fact, rooted into differences of values. […] Thus, underlying values also affect the perception and definition of safety, as well as on the scope of evidence required to determine such safety' (cf. case study GMO, p. 10.).

In the glyphosate case it is emphasised, 'that in framing the risk analysis process through regulation, political choices are made and that '[g]lyphosate (…) has become a catalyst for testing existing dichotomies' and that 'glyphosate has the potential of re-politicizing the field of science based-law' (cf. case study glyphosate, p. 39).

In the case of CDSS it is important that different patient groups can trust that a CDSS works to each advantage, and for instance does not discriminate against women (cf. case study CDSS, p. 6f).

Lesson from the case study comparison: The importance of understanding each other's meaning of framing and stimulating reflection on different frames, including one's own presuppositions to avoid prejudices and polarization in discussions.

[4] concerning the placing of plant protection products on the market and repealing, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1107&from=EN

2.2 Subjectivity and objectivity in risk assessment

Another reoccurring theme in the intra-case studies are discussions about the extent to which a risk can be seen as something objective or subjective. This too leads to complexity and controversy, as apparent 'objective' assessments may obfuscate private or political interests, while claiming that all risk assessments are subjective tends to undermine the status and legitimacy of risk assessment institutes and scientists.

In the **GMO case**, for instance, 'there is clear divergence between how risks are objectively assessed via scientifically agreed methods and protocols, and what is being referred to as socially constructed risks, or what society perceives as a risk.' (cf. case study GMO, p. 13)

In the **microplastics** case it was however observed that: '(…) we can see that development of scientific knowledge does not happen in a complete vacuum, but is driven by societal attention for a subject.' (cf. case study microplastics, p. 26). Namely, growing societal attention for the issue of (micro)plastic pollution leads to more research efforts into the consequences of this pollution. Simultaneously, these research efforts are also promoted by awarding research funding.

This especially seems to lead to controversies with regard to 'risks' that have a less established status in risk assessment methods, like risks related to human rights, socio-economic risks and ethical dilemmas, because generally beyond scientific uncertainty these are accompanied with more normative and interpretative ambiguity (cf. case studies gene drives, p. 6 f.; CDSS, p. 6-9; financial risks in water infrastructure planning, p. 6-8)

Lesson from the case study comparison: the need for more transparency with regard to the subjective aspects of risk assessment. This implies the need for more inclusive and deliberative assessment methods, without delegitimizing the role of experts and avoiding 'partisan' risk assessments.

2.3 The difficulty of admitting uncertainty

Another complexity in relation to the relevance of the PP has to do with 'admitting' uncertainty. Human knowledge is always incomplete and selective and thus contingent on uncertain assumptions, assertions and predictions.

In the case of the use of **CDSS in healthcare**, there is a need for understanding the broader effects and new risks (datafication, loss of control, lack of human element, division of labor) that such system may have on healthcare professionals and patients. Technology developers however have the tendency and interest to showcase simplicity surrounding their products (cf. case study CDSS, p. 5-8).

In the case of glyphosate the actors involved in the approval procedure emphasized the absence of scientific uncertainty: 'the existence of scientific uncertainty is not recognized. As the hazard and risk assessment performed by EFSA and ECHA concluded that glyphosate is not a carcinogen, from the perspective of these Agencies and the Commission, there is no scientific uncertainty on this question.' (cf. case study glyphosate, p. 35). So complexities and controversy in this case indicate, that other questions than carcinogenicity is at the core of the dispute.

So the complexities and controversies in the cases above exemplify the need to take a broader array of potential consequences into account, in order to develop technology with a fair distribution of risks and benefits.

The PP can only be invoked when scientific uncertainties about particular risks are admitted. This necessitates a culture of openness in scientific and technological practices.

In the case of microplastics there is no uncertainty about microplastics building up in the environment, leading to damage in this environment. However, there are many uncertainties when it comes to human health effects because the effects of microplastics on the body are difficult to measure.

Lesson from the case study comparison: the need for characterization of uncertainty. Need to take a broader array of potential consequences into account, in order to develop technology with a fair distribution of risks and benefits. More open communication about the fallibility of science and the limits of scientific knowledge and technological solutions.

2.4 Layers of uncertainty

The main complexity for the relevance of the PP is the multi-layered aspect of uncertainty, and especially how such layers relate to one another.

1. **Scientific uncertainty** refers to cases in which the technology itself lacked a shared definition (cf. case studies nanotechnology, p. 9; microplastics, p. 12., CDSS p. 12 f.; gene drives, p. 10, neonics p. 15 f; EDCs, p. 11 f.), lack of data, measurement, methods, protocols, measurement devices, unwillingness to admit or examine uncertainty, lack of personnel and funding to research uncertainties). In the case of nanotechnologies, the upcoming debate on embed nanomaterials into a bigger field (as "advanced materials") makes the lack of common definition all the more obvious (cf. case study nanotechnology, p.9).

2. **Uncertainties around particular properties of the technology in question**. These uncertainties are related to inherent properties of the technology, e.g. Artificial Intelligence-systems that can display apparent autonomous behaviour

and the countless possibilities to combine nanoparticles and their physical properties with other nanoparticles or even biological entities on this level.

3. **Uncertainties as a correlate of the type of environment in which the technology is introduced**, e.g. the unpredictability and complexity of a healthcare system, the many variables and interactions at play in ecosystems (cf. case study EDCs, p. 8-10; glyphosate, p. 6-9; nanotechnology, p. 15 f.; GMOs, p. 7-9.; gene drives, p. 6-8.) or the intersection of social systems with financial systems (cf. case study financial risks in water infrastructure planning, p. 6-8). These uncertainties might be a valid characteristic for all so called "Key Enabling Technologies (KETs)"[5], because their main characteristic is their universality regarding the field of application.

4. **Uncertainty as a consequence of the types and multitude of interactions that the technology engages with in various environments**. In the case of nanotechnology, such interactions are multivariate, e.g. nanoparticles can be distributed through the wind, water and the soil. This influences their bioavailability and subsequently their toxicity to different organisms (for instance soil organisms) and the potential exposure and negative health effects on (specific) groups of humans. Another layer of uncertainty stems from inabilities to get clarity with regard to the characterization of the interactions between the technology and its environment. There are for instance debates within the science of toxicology and health sciences with regard to what should be considered toxic (cf. case study nanotechnology, p. 20) or unhealthy.

5. **Uncertainty with regard to knowledge about risk management**. Assumptions are implicitly made with regard to the possibility of reversing the effects of a technology after its introduction. This refers especially to the norm of "irreversibility". The assessment of uncertainty subsequently always seems to make use of knowledge or information about the possibilities of risk management. Such considerations were explicitly made in the gene drives debates, but it seems they were reflected upon in the microplastics and glyphosate debates.

6. **Uncertainty with regard to risk governance** seems (justifiably) to be part of determining unacceptable uncertain risks. In the gene drives case (cf. case study gene drives, p. 26), the difficulty of transboundary governance plays a legitimate argument for delineating the unacceptable uncertain risks with regard to the introduction of gene drives.

[5] Key Enabling Technologies (KETs) – a group of six technologies: micro and nanoelectronics, nanotechnology, industrial biotechnology, advanced materials, photonics, and advanced manufacturing technology. Source: https://knowledge4policy.ec.europa.eu/foresight/topic/accelerating-technological-change-hyperconnectivity/key-enabling-technologies-kets_en

Lesson from the case study comparison: There is a need for more integrative integrative risk governance frameworks[6] that connect between different types of uncertainties, in order to inform risk assessors on the applicability of the PP in the case of accumulated uncertainties.

2.5 Aspects of hazards

The case study analyses often touched upon the question what should be taken into account during risk assessment. This varies between taking into account primarily traditional indicators of risks, like toxicity and carcinogenicity, to also including socioeconomic impacts, impacts for future generations, stable financial structures and human rights. However, multiple, interrelating risks are often the issue and it seems difficult to assess their causal relationships. Artificial Intelligence in Clinical Decision Support Systems (CDSS), for instance, could pose severe risks in relation to human rights and unwanted dependencies in healthcare systems. Endocrine disruptors[7], neonics,[8] microplastics, nanotechnologies[9] and glyphosate[10] are associated with a wide variety of (individual) health and environmental risks of which can be asked to what extent each of them sufficient for invoking the PP.

In the context of financial risks in water infrastructure planning 'planning risks' and 'financial risks' are described as risks that can also have longstanding, irreversible and serious consequences (cf. case study financial risks in water infrastructure planning, p. 12 f.).

The main issue here is that the discussion is not about one clearly defined hazard but a wide combination of (mutually reinforcing) hazards that make the PP relevant. It seems difficult to formalize such considerations into fixed standards or models. It has been criticised that not clarifying such relations sufficiently might lead to an overburdening of the PP. The PP might lose its legitimacy and risks being put away as a political tool. This also indicates the importance of involving different scientific disciplines in the risk assessment process.

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[6] cf. white paper towards and integrative risk governance framework (Renn 2008) or integrating approaches in Food Safety Governance (Renn & Dreyer 2009)

[7] health effects related to obesity, diabetes and cardiovascular diseases; female and male reproductive health; hormone-related cancers in females – including breast cancer – and prostate cancer in males; thyroid health; and neurodevelopment and neuroendocrine systems. But also: linked, inter alia, to the occurrence of dyslexia, IQ loss, ADHD, and autism (cf. case study EDCs, p.6).

[8] autism, schizophrenia and ADHD) and a possible role in Parkinson and Alzheimer's disease (cf. case study neonics p. 8)

[9] Associated amongst others with cardiovascular diseases, asthmatic inflammation malignant mesothelioma, and other types of cancer (cf. case study neonics, p.13).

[10] Glyphosate is estimated to also work as an Endocrine disruptor (cf. case study glyphosate, p.1).

The need for a more integrative risk assessment framework is expressed in the case of microplastics (p. 21), financial risks in water infrastructure planning (p. 11); gene drives (p. 25); CDSS (p. 10).

The nanotechnology case study stood out as a case in which a transdisciplinary approach and the involvement of many stakeholders was part of EU strategies towards nanotechnology from the start (and the National Action Plans that followed): 'It is somewhat interesting to note that the reinvention of physics by creating a new research field has also led to a revitalisation of human and environmental toxicological research and also the increased development and testing of different communication and participation formats.' (cf. case study nanotechnology, p. 13)

The early involvement of other disciplines in the nanotechnology case also seems important to avoid that regulatory and risk assessment science fall behind, as happened in the neonics case: 'Regulatory science and risk assessment frameworks lag systematically behind new scientific insights with huge time delays, as evident in that the Bee Guidance document, drafted in 2013, still not is fully approved and employed in regulatory assessments of new pesticides.' (cf. case study neonics, p. 39)

Lesson from the case study comparison: There is a need for more integrative risks assessment frameworks that involve various scientific disciplines in the risk assessment process.

2.6 Weighing of benefits and uncertainties

Another reoccurring issue is the question of how benefits of the innovation should be taken into account with regard to the relevance of the PP. In some cases there seem to be a felt need to also take into account the (huge) benefits a technological innovation brings, to truly know the 'real' risks of the technology, and the need to invoke the PP.

What stood out in most cases is that it is very common to assess the uncertainty of a risk, but that there seems to be less (scientific) discussion on the uncertainty around the benefits of a technology[11]. This was especially relevant in the cases where the benefits of the innovation in question were less than speculated, or where soon other (more responsible) technologies were able to provide the same

[11] This finding can also be seen in context of to the "Collingridge Dilemma", it states that the further development of a technology faces a double-bind problem: (1) An information problem: impacts cannot be easily predicted until the technology is extensively developed and widely used. And (2) A power problem: control or change is difficult when the technology has become entrenched. This means that it is inherent to new technologies that their development paths are uncertain – it is even to a certain extent necessary to have this uncertainty to develop something new. This also means that at this stage a technology cannot be sufficiently regulated, at least not in a conventional way (Collingridge 1980).

type of benefits. Once a technology has been implemented on a wide scale, such steps are difficult to reverse.

In the neonics-case some studies have not found clear and consistent evidence on yield benefits from the use of neonicotinoids on different crops (cf. case study neonics, p. 10). The benefits of the use of glyphosate may be relativized because the weeds which glyphosate is supposed to kill over time become increasingly resistant to it (cf. case study glyphosate, p. 5). For many applications of CDSS the effectiveness and efficiency is contested (cf. case study CDSS, p. 39). And the effectiveness of gene drives with regard to diseases is also yet uncertain (cf. case study gene drives, p. 6).

The importance of patience for alternative safer (social) solutions to some problems seems to be relevant in almost all the cases that were accompanied by a strong technology push and unrealistic expectations on technological solutions for deeper societal or ecological problems. Alternative innovation pathways towards sustainable pesticides seems to have been hampered because of a strong industry push towards the use of glyphosate, the price and largescale application of which sustainable alternatives cannot compete easily.

Lesson from the case study comparison: There is a need to take alternative (emerging) innovation pathways in the context of risk assessments into account.

2.7 The difficulty of prevalence and path dependencies

The prevalence and societal/environmental entrenchment of a technology seems to be accompanied by a whole set of new questions. Societies develop a dependency on large scale implemented technologies. As for instance a technology like plastics has been firmly accepted in a society, many industries have adopted it in their production-network. The replacement of such a technology subsequently goes against many interests. The widespread use of plastics provides a clear example of this complexity. Plastics are used almost everywhere in it is a big challenge to reverse this. The wide use and prevalence of glyphosate and neonics poses similar problems. Agrochemical industries and some farmers are highly attached and invested in these agrochemicals and therefore wield active resistance against regulation (cf. case study glyphosate, p. 5). The same might occur in the emerging nanotechnology industry where nanomaterials are potentially applicable in diverse products and applications, ranging from electronics and automotive technology to consumer products and environmental technology.

Lesson from the case study comparison: More attention on irreversible consequences of large scale (disruptive) innovations in innovation policy, already in the R&D

phases. In general, more attention needs to be paid to reinforcing factors of risk – additionally to the conventional assessment of risks by impact and probability. These reinforcing factors are – besides of the lack of reversibility – the propagation and diffusion of a damage (in time and space), or, in case of health risks, the change from acute to chronic disease. There seems to be a need for interim risk assessment after introduction of some new technologies.

2.8 The problem of no established science

A complexity is that sometimes there does not exist any established science yet, such as with gene drives and endocrine disruptors. This gives rise to the conundrum that risks can only be really understood when such a technology is (locally) researched: 'in order to reduce the epistemic uncertainty about risks, research activities (field trials) must be undertaken that themselves pose risk' (cf. case study gene drives, p. 25). The problem of the absence of established science is implicitly drawn upon in the case of the use of some CDSS (p. 9 f.) and EDCs (p. 11 f.).

Lesson from the case study comparison: Regular 'emerging technologies' scanning, capacity building and foresight for public policy are important. There is a need to think about 'robust' research policy, for example policy aimed at problem oriented research, which does not necessarily require a specific technology as a starting point.

3. Complexities and controversies with regard to the procedures around the application of the PP

3.1 The meaning of applying the PP

The PP is a legal principle with a very general significance, from which different measures for the application can be inferred, dependent on the context of the question. In some cases the cause of controversy lies in the fact that that different stakeholder struggled with how the PP should be applied. In many of the cases it seems that the stakeholders perceive they encounter an inconsistent or contradictory application of the PP because the different possible measures in applying the PP are not made explicit. A case in point is provided by the gene drives case study. In this case, there is little agreement on how the PP should be applied (cf. case study gene drives, p.23).

Lesson from the case study comparison: There is a need for more clarity on the different possible measures in relation to applying the PP.

3.2 Address regrettable substitution

A lot of cases struggled with a regrettable substitution, the introduction or adoption of chemicals that may not be safer and potentially worse, e.g. the replacement of bisphenol A (BPA) with the substance bisphenol S (BPS), that followed the application of the PP and the substitution of the three banned neonicotinoids by other neonicotinoids (thiacloprid and sulfoxaflor) that were not yet banned, but similarly harmful to pollinators.

'As shown in our case study, even if EDCs are regulated, this can lead to regrettable substitutions, which can be seen as a 'lose-lose scenario': it is costly for the regulator and costly for the company in question' (case study EDC, p. 25). In some cases (cf. case study EDCs, p. 23) this was related to a process-focussed governance – and the shift towards a process of 'one substance – one assessment'.

Lesson from the case study comparison: The PP needs to be applied early on in the process in order to avoid sudden regrettable substitution. Also, there is a need for more integrative risk governance.

3.3 Need for transparency

In some cases the **need for transparency of the risk assessments** during the application of the PP was emphasized. In multiple cases the legitimacy of the industrial studies was questioned, partly due to a lack of transparency on used methods (cf. case study EDCs, p. 26; case study glyphosate, p. 32).

EDCs: 'As shown, in the EU the delay by the Commission to take regulatory decisions concerning EDCs has been the result of lobbying activities, especially by the chemical industry. Here we come back to the dilemma raised at the outset: How to take time, but address the issue in a diligent and thorough manner? This in turn is linked to larger societal issues of transparency and the role of lobbyists: How can the public distinguish between 'regulators taking a slow but diligent approach' and 'regulators being delayed by lobbying activities'? We thus see the need for regulatory transparency' (cf. case study EDCs, p. 26).

The case study on Financial risks in water infrastructure can serve as evidence for the need of transparency, especially the case of London water infrastructure, where a non-transparent financing and ownership structure has been created (cf. case study financial risks, p. 17).

Lesson from the case study comparison: There is an increased need for (regulatory) transparency.

3.4 Organization of knowledge networks

A very fundamental question with regard to the application of the PP was on how different knowledge and perspectives must be assembled to ensure an adequate application of the PP.

In the **neonics** case, the current social organisation of expertise regarding the ban by some neonics, especially regarding the risks that neonics pose to pollinators was questioned (cf. case study neonics, p. 39).

The **nanotechnology** case, however, an exemplar of how to organize knowledge networks. 'An important contribution to identifying, structuring and evaluating the available information on a certain technology when it is in its infancy an independent and neutral actor is necessary to provide a platform of deliberation which is trusted by many if not all concerned parties. In the case of the Austrian nanotechnology debate this has been provided by the Austrian Academy and its project NanoTrust. This holds also true for the German speaking countries: in 2007 the so called "Dialogue of Authorities" (Behördendialog) has been established and is still active. Therefore, appropriate strategies to secure neutrality and independence are absolutely vital because of the threat to lose the necessary variety of potential as-

pects and the possibility to be instrumentalised by other, often funding organisations' (cf. case study nanotechnology, p. 17).

In the **gene drives** case researchers similarly seemed to search for a solution that the technology could offer. Instead it is better to organize knowledge networks around (grand) societal challenges, so that the problem comes first and the development of a specific technology is only viewed as one possible solution (cf. case study gene drives, p. 24).

Lesson from the case study comparison: Transdisciplinary knowledge networks should be organized so that problems addressed in the Global Sustainable Development Goals (SDGs) gain priority and the development of a specific technology is viewed as one possible way to resolve one or several of these issues. This requires a trusted platform of deliberation to identify, structure and evaluate the available information on the technology when in its infancy stage.

3.5 Public involvement

In some cases there seemed to exist disagreement with regard to the extent that the general public should be involved during the application of the PP.

In the GMO-case the outcry of the general public seemed to result into a heightened pressure on the Government and parliament, which led to decisions that seemed to be based on political opportunism (cf. case study GMOs, p. 2).

The **case study of financial risks** in water infrastructure planning in Milan on the other hand showcased an example in which public involvement led to a more balanced and broadly supported decision making: 'As the case studies have shown, open, transparent and egalitarian processes help navigating contemporary multi-risk environments with more success' (cf. case study financial risks in water infrastructure planning, p. 22).

It seems that the organization of public involvement is very important (with a focus on early on deliberation instead of raising unnecessary conflict). In some cases, however, conflict seemed to be justified and functional. In the case of glyphosate, public concerns (partially) led to more research into possible carcinogenicity of the substance.

Lesson from the case study comparison: Generally, deliberative methods and processes are very valuable, but a decision has to be made which questions can be discussed and evaluated and which questions are not included. Deliberative methods should be deployed without obfuscating possible differences in evidence and different reasons for conflicts on interests, values and knowledge.

3.6 Industry involvement in risk assessment

Another controversial issue was the question to which extent industry should be involved in the risk governance process. Arguments in favour of industry involvement concerned the fact that industry often had more means to, for instance, perform quick assessments.

Multiple cases on the other hand showed that the risk assessments of industry actors were more positive about the risks of an innovation than, for instance, EU agencies (cf. case study glyphosate, p. 9-11; microplastics, p. 14; EDCs, p.18 f; neonics, p. 14 f).

In the glyphosate case 'the uncertainty with regard to the glyphosate risk is presented less as a clash of scientific findings but rather a problem of conflicting regulatory scientific choices in the hazard identification/risk assessment stage. (…) 'scientific uncertainty is mostly fuelled by normative and interpretative ambiguity (…) the reliability of industry studies is questioned, and regulatory authorities apply a weight of evidence approach that leads to academic studies being of limited significance to the risk assessment performed, leading to opposing findings concerning the highly contested carcinogenicity of glyphosate' (cf. case study glyphosate, p. 36).

Lesson from the case study comparison: There is a need to clarify role of industries in the risk assessment compared to possible other risk assessors. Also, the decisive role of evidence risk assessment needs to be made explicit. Furthermore, risk assessment needs to reflect constantly on validity, potential bias, and transparency.

3.7 Cost-benefit analysis and proportionality

In most cases a **cost-benefit analysis** has been carried out during the application of the PP and the proportionality of measures was taken into account. There were differences however in what benefits had to be taken into account for whom and how such benefits should be assessed in relation to costs.

In the case of microplastics it is argued: 'Since it is not realistic in the current society to ban all plastic products, yet we need to find a way to deal with potential negative effects, a cost-benefit analysis needs to have a central place in this discussion' (cf. case study microplastics, p. 20)

In the case of gene drives the issue is described as follows: 'cost benefit analyses tend to discount future interests and needs: the focus is mainly on short term benefits, while long term social costs are taken into account to a lesser degree' (cf.

case study p. 12). In this case there was no formal cost benefit analysis, costs and benefits were perceived differently by different stakeholders.

Based in the **neonics** case it should be acknowledged that cost-benefit analysis may come with limitations, as future costs and benefits are difficult to estimate precisely and that such analysis would contain several uncertainties and limitations (cf. case study neonics, p. 31).

Lesson from the case study comparison: There is a need for more transparency concerning the details of cost-benefit analysis, proportionality and acknowledgement of the limits and uncertainties inhibiting cost benefit analysis. This includes short term versus long term costs and benefits. Also, an institutional memory and repository of knowledge needs to be established that fosters mutual learning.

3.8 Aligning innovation with precaution

The only cases in which the innovation principle demonstrably had a role was the case EDC's (case study, p. 24) and neonics (case study, p. 36) The PP did not have an effect on innovation pathways according to the case study researchers.

This does not mean that the benefits of innovation were not taken into account in the cases. The benefits of potential innovations were part of the public and policy discourse in many of the cases.

The case study on water infrastructure planning demonstrates that the implementation of the PP requires innovation in technologies, organization as well as in financing.

Lesson from the case study comparison: Most case studies demonstrate clear examples of technology push in the public discussions as well as in regulatory decisions and in the use of cost-benefit analysis/proportionality and impact assessments. In one case, a lack of technological innovations has been compensated by organizational or financial innovation.

3.9 Precautionary principle vs principle of prevention

In some cases there existed controversy with regard to the question if the precautionary principle or the principle of prevention[12] was more appropriate (cf. case studies microplastics p. 14; neonics p. 2).

Lesson: More analytic clarity is required with regards to what distinguishes the PP from the principle of prevention.

3.10 Alternatives to regulation

Many case studies showcase examples of other ways in which precaution was applied towards technological innovation, besides regulation.

In the scientific-technological environment examples of applying precaution without regulation can be found in:

- The role of peer review in academic journals (cf. case study gene drives, p. 19)
- Research in to technologies that mitigate risks (cf. case study gene drives, p. 19f)
- Raising awareness in the scientific community (cf. case study nanotechnology, p.13; gene drives, p.19)
- The construction of risk assessment frameworks in combination with technology research (cf. case study gene drives, p.20; nanotechnology, p.21))
- The engagement of scientists in public debates as to improve mutual understanding (cf. case study microplastics, p.22)
- The application of safety-by-design (cf. case study nanotechnologies, p.14)

With regard to economic dynamics, the following precautionary strategies can be found in the case studies:

- Pressure from consumers (cf. case study EDCs, p. 25)
- Letters of intent to buy new products, as well as public scrutiny of the behaviour of global brands (cf. case study EDCs, p. 23)

In relation to societal interactions/norms, precaution is enforced through:

- Public pressure from consumer organisations, think tanks and NGOs, as well as from (some political parties in) the European Parliament (cf. case study EDCs, p.25)

[12] In the terminology of risk management actions, the term risk prevention refers to the process of actions to avoid a risk source or to intercept the risk source pathway to the realization of damage with the effect that none of the targets are affected by the risk source (Aven et al 2015).

- The role of mass media and social media (cf. case study microplastics, p. 22)

Some cases (CDSS, p. 22; nanotechnology, p. 11) showcased the advantages of early precautionary thinking and foresight early in the innovation pathway.

Lessons from the case study comparison: There is a need for more integrative risk governance approaches, foresight and stakeholder involvement with regard to risk regulation and innovation policy.

4. Complexities and controversies with regard to the effects of the application of the PP for innovation

4.1 Incremental vs radical innovation

In many cases the application of the PP seemed to foster incremental innovation rather than radical innovation. In some case studies it was argued that the application in some instances could halt radical or disruptive innovation. The application of the PP also often did not lead to 'radical' regulation, even if deemed necessary (as was deemed necessary by some stakeholders for instance in the case of AI and nanotechnology).

In the case of EDCs it was stated that 'locally, incremental innovation is safer and more profitable, given that other industries are not co-investing. However, globally, radical innovation can be seen as more profitable. Here public-private cooperation is required to create the critical mass necessary for radical innovation. In this context we also need more of a debate on the role of regulatory agencies in the context of radical innovation' (cf. case study EDCs, p. 26)

Lessons from the case study comparison: More empirical research is required to test the claim that the PP currently halts important radical innovations in the EU.

4.2 Alternative innovation pathways

The application of the precautionary principle contributed (if it was applied in the case) often to alternative, more responsible innovation pathways, like green chemistry (cf. case study EDCs, p. 27), improvements to the quality of seed treatment formulations, modifications to planting equipment using deflector techniques that reduce emission of dust during sowing of seeds coated with neonics, new plant pro-

tection technologies and non-chemical alternatives to pest management (cf. case study neonics, p.35), green nanotechnology, which recently appears to be embedded into overarching policy concepts like circular economy and the sustainable development goals (SDGs).

As nanomaterials are also chemical substances to a certain extent the discussion also connects to the recent EU strategy on Chemical Safety for Sustainability (CSS)[13]. And safe-by-design approaches (cf. case study nanotechnology, p. 42) as well as different strategies for overcoming infrastructure gaps (cf. case study financial risks in water infrastructure planning, p. 16).

In other cases it has stimulated the use of non-technological solutions, like social innovations in the neonics case study (cf. case study neonics, p.36).

Only in the case of EDC's (cf. case study EDCs, p. 25) did the application of the PP lead to regrettable substitution (though it can be questioned if this was only the effect of the application of the PP).

Lessons from the case study comparison: There is the need to stimulate possibilities for alternative solution pathways for innovations.

5. Discussion and lessons from case study comparison

5.1 Overview of lessons derived from the inter-case study analysis

The main research goal of the inter-case study comparison is to better understand the complexities and controversies around the application of the PP in practice across the nine case studies. What are the complexities, uncertainty, and ambiguities associated with the case studies and how have they been understood by various relevant actors (legal, policy makers, the risk community, NGOs, industry, the public)?

Based on the nine intra-case study analyses, the case study comparison aims to draw lessons from concrete cases in which the precautionary principle was (or could

[13] COM (2020) Communication from the EU Commission: Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, No. No 667, 15.10.2020 https://eur-lex.europa.eu/resource.html?uri=cellar:f815479a-0f01-11eb-bc07-01aa75ed71a1.0003.02/DOC_1&format=PDF

have been) applied in relation to a presumed socio-technological or socio-economic innovation.

The following table below merges all lessons from the intra-case study analysis and provides an overview of the lessons learnt from the case study comparison.

Table 2: Overview of lessons in the dimension relevance from intra-case study comparison

Relevance	
Lesson No.	Issue
1.1	Framing of PP and innovation
The importance of understanding each other's meaning of framing and stimulating reflection on different frames, including one's own presuppositions to avoid prejudices and polarization in discussions.	
1.2	Subjectivity and objectivity in risk assessment
The need for more transparency with regard to the subjective aspects of risk assessment. This implies the need for more inclusive and deliberative assessment methods, without delegitimizing the role of experts and avoiding 'partisan' risk assessments.	
1.3	The problem of admitting uncertainty
The need for characterization of uncertainty. Need to take a broader array of potential consequences into account, in order to develop technology with a fair distribution of risks and benefits. More open communication about the fallibility of science and limits of scientific knowledge and technological solutions.	
1.4	Layers of uncertainty
There is a need for more integrative integrative risk governance frameworks[14] that connect between different types of uncertainties, in order to inform risk assessors on the applicability of the PP in the case of accumulated uncertainties.	
1.5	The many aspects of hazards
More integrative risks assessment frameworks. Involving different scientific disciplines in the risk assessment process	

[14] cf. white paper towards and integrative risk governance framework (Renn 2008) or integrating approaches in Food Safety Governance (Renn & Dreyer 2009)

1.6	Weighing of benefits and uncertainties
There is a need to take alternative (emerging) innovation pathways in the context of risk assessments into account.	
Lesson No.	Issue
1.7	The difficulty of prevalence and dependencies
More attention on irreversible consequences of large scale (disruptive) innovations in innovation policy, already in the R&D phases. In general, more attention needs to be paid to reinforcing factors of risk – additionally to the conventional assessment of risks by impact and probability. These reinforcing factors are – besides of the lack of reversibility – the propagation and diffusion of a damage (in time and space), or, in case of health risks, the change from acute to chronic disease. There seems to be a need for interim risk assessment after introduction of some new technologies.	
1.8	The problem of no established science
Regular 'emerging technologies' scanning, capacity building and foresight for public policy are important. There is a need to think about 'robust' research policy, for example policy aimed at problem oriented research, which does not necessarily require a specific technology as a starting point.	

Table 3: Overview of lessons in the dimension procedures of intra-case study analysis

Procedures	
Lesson No.	Issue
2.1	The meaning of applying the PP
There is a need for more clarity on the different possible measures in relation to applying the PP.	
2.2	Address regrettable substitution
The PP needs to be applied early on in the process in order to avoid sudden regrettable substitution. Also, there is a need for more integrative risk governance.	
2.3	The need for transparency
There is an increased need for (regulatory) transparency.	
2.4	Organization of knowledge networks

Transdisciplinary knowledge networks should be organized so that problems addressed in the Global Sustainable Development Goals (SDGs) gain priority and the development of a specific technology is viewed as one possible way to resolve one or several of these issues. This requires a trusted platform of deliberation to identify, structure and evaluate the available information on the technology when in its infancy stage.	
Lesson No.	**Issue**
2.5	Public involvement
Generally, deliberative methods and processes are very valuable, but a decision has to be made which questions can be discussed and evaluated and which questions are not included. Deliberative methods should be deployed without obfuscating possible differences in evidence and different reasons for conflicts on interests, values and knowledge.	
2.6	Industry involvement
There is a need to clarify role of industries in the risk assessment compared to possible other risk assessors. Also, the decisive role of evidence risk assessment needs to be made explicit. Furthermore, risk assessment needs to reflect constantly on validity, potential bias, and transparency.	
2.7	Cost-benefit analysis and proportionality
There is a need for more transparency concerning the details of cost-benefit analysis, proportionality and acknowledgement of the limits and uncertainties inhibiting cost benefit analysis. This includes short term versus long term costs and benefits. Also, an institutional memory and repository of knowledge needs to be established that fosters mutual learning.	
2.8	Aligning innovation with precaution
Most case studies demonstrate clear examples of technology push in the public discussions as well as in regulatory decisions and in the use of cost-benefit analysis/proportionality and impact assessments. In one case, a lack of technological innovations has been compensated by organizational or financial innovation.	
2.9	Precautionary principle vs principle of prevention
More analytic clarity is required with regards to what distinguishes the PP from the principle of prevention.	
2.10	Alternatives to regulation in precaution
There is a need for more integrative risk governance approaches, foresight and stakeholder involvement with regard to risk regulation and innovation policy.	

Table 4: Overview of lessons in the dimension effects of intra-case study analysis

Effects	
Lesson No.	Issue
3.1	Incremental vs. radical innovation
More empirical research is required to test the claim that the PP currently halts important radical innovations in the EU.	
3.2	Alternative innovation pathways
There is the need to stimulate possibilities for alternative solution pathways for innovations.	

5.2 Discussion of results

The results of the inter-case study analysis indicate that there are three main categories which need to be considered in the forthcoming process of the RECIPES project: chapter 2 issues regarding relevance, chapter 3 regarding procedures and chapter 4 regarding effect. These three dimensions can serve a suitable analytical grid to contribute to an improved alignment of the PP and innovation. Cross-cutting issues that played a significant role in the complexities and controversies with regard to the relevance of the PP are issues concerning four main issues: 1. layers of uncertainty, 2. aspects of hazard, 3. weighing of benefits and uncertainties 4. the difficulty of prevalence and path dependencies. In the second dimension, i.e. complexities and controversies with respect to the procedures regarding the application of the PP, issues relate to four main aspects: 1. the meaning of framing in the discourses, 2. the meaning of the PP and its measures, 3. the organization of knowledge networks, 4. cost benefit analysis and proportionality.

Therefore, there is a need for more integrative risk governance frameworks that connect between different types of uncertainties which can inform risk assessors on the applicability of the PP in the case of accumulated uncertainties. Further a second lesson is that transdisciplinary knowledge networks are required that focus on investigation of societal needs. Technology development should be focussed on answering these needs and requirements. This approach requires

trusted platforms of deliberation to identify, structure and evaluate the available information on the technology, when in its infancy stage.

The analysis of the complexities and controversies indicates that two main reasons for controversies and disputes are located at conflicts between claims of evidence and values (Linkov et al. 2014, Renn 2008) the overarching meta-theme is a need for integration of competing and controversial knowledge claims. This raises the question how different knowledge and evidence claims can be compared, evaluated and assessed in order to feed into scientific policy advice.

The scientific evidence gained in the intra- and inter-case study analysis, obtained through systematic research and evaluated according to established methodology and rules, is essential for understanding complex natural, technological as well as social phenomena and, therefore, for making informed decision. And for the policymaking process and related decisions made by policymakers should be evidence-informed but the scientific advice itself must always be evidence-based (Renn, Bahamian & Capaccioli 2019).

The results of the intra-case study comparison indicate that the compiled knowledge builds on robust scientific evidence (Nowotny 2003; Nowotny, Gibbons & Leydersdorf 2001)[15] which needs to be contextualized e.g. in participatory processes, so that evidence-based knowledge can evolve into evidence-informed collectively binding decisions.

[15] Nowottny et al suggest that scientific knowledge, in other words evidence-based knowledge needs to be contextualized, because it is no longer sufficient, because in more open knowledge environments that are now emerging, knowledge also needs to be 'socially robust', because its validity is no longer determined solely, or predominantly, by narrowly circumscribed scientific communities, but by much wider communities of engagement comprising knowledge producers, disseminators, traders, and users.

6. Annex

6.1 RECIPES general overview of research questions according to the methodological framework

1. Core characteristic of the case	1.1 Time period	1.2 Geographic focus	1.3 Role of the PP in case	1.4 Unique characteristics of the case
2. Innovation assessment	2.1 Why has this product/technology been developed? What problems will it / does it solve?	2.2 Economic, social, environmental benefits	2.3 Are these benefits themselves debatable? What is the evidence/uncertainty discussion?	2.4 What do the different stakeholders say about the benefits?
3. Risk/threat	3.1 What is the overall risk(s) of the topic?	3.2 Describe how different societal groups (individual health, local communities, the local environment, and future generations) are threatened or potentially harmed.	3.3 potential severity / scope of the harm	3.4 extent of (ir)reversibility of deployment
4. Scientific analysis about threat	4.1 What is the state of the research field?	4.2 Which sciences were involved in risk assessment		
5. Epistemological challenges	5.1 Complexity	5.2 Uncertainty	5.3 Ambiguity	
6. Relevance of the PP to the case	6.1 Why is the PP relevant to this case	6.2 Normative underlying arguments		

7. 1 Risk governance **Political/juridical dynamics: context**	7.1.1 What is the legal status of the PP in your case and jurisdictions?	7.1.2 If applicable, describe the discussion of the acceptability/tolerability/intolerability of risk in regulatory decisions.	7.1.3 Has an impact assessment has been made prior to the adoption of precautionary measures?	7.1.4 Optionally, how other regulatory policies (i.e. ISO, EU bodies, standards, voluntary regulations, research policies) have been used in this case.
7.2 Risk governance **Political/juridical dynamics: core components**	7.2.1 How has the threshold of damage been set, and met or not met, in existing legal cases or regulatory decisions?	7.2.2 If the PP has been invoked, have both the cost-effectiveness of the measure, and the proportionality of the measure been considered in existing legal cases or regulatory decisions?	7.2.3 If the PP has been invoked, is the measure reversible?	7.2.4 Has a reversal of the burden of proof been specifically implied or requested in legal or regulatory decisions?
7.3 Risk governance **2nd order dynamics**	7.3.1 The scientific-technological environment	7.3.2 The economic dynamics	7.3.3 Societal interactions/ norms	
8. Reflection on the PP in the literature	8.1 Who have reflected on (and criticized) the present use and application of the precautionary principle	8.2 Any alternative proposals for the application and use of the precautionary principle with regards to the case study topic	8.3 Have stakeholders called for the revision of the PP in the case?	8.4 Important relevant context (like economic forces)
9. Effect of the PP on innovation pathways	9.1 What alternative innovation pathways can or has the PP opened up, if any?	9.2 Other innovation pathways in other geographical regions	9.3 Other types of solutions than innovation?	9.4 Regrettable substitution?

10. Innovation principle	10.1 Which stakeholders invoked IP? Are there plans to invoke it?	10.2 How is the IP positioned? How could it be positioned (if not invoked)?	10.3 How was it juxtaposed to the PP?	10.4 Did the IP have any effects on the innovation pathways?
11. Synthesis	11.1 The role of complexity, ambiguity and uncertainty in understanding your case	11.2 Risk governance of uncertain risks: a. How did the geographical region deal with the risks and what factors play a role? b. How did these representations relate to what we know now?	11.3 The overall tension between PP/ IP: a. The possibility of win-lose, lose-lose, and win-win dynamics between precaution and innovation b. Whether the IP can improve these dynamics, or whether (other) changes would need to be made to the PP to accommodate the issues in your case.	11.4 Recommendations to the case study comparison team, lessons learnt for RECIPES tools and guidelines; discussion of responsible/sustainable innovation and RRI

Case studies in order of appearance in the rows of the table:

Not	Case Study
1	Genes Drives
2	Genetically Modified Organismus (GMO)
3	Endocrine Disrupting Chemicals (EDCs)
4	Neonicotinoid insecticides (neonics)
5	Nanotechnologies
6	Glyphosate
7	Financial risks in water infrastructure planning
8	The use of Artificial Intelligence in healthcare – Computer Decision Support Systems (CDSS)
9	Microplastics in food products and cosmetics

6.2 Table overview of all 9 case studies

NB: In the analysis not all research questions are relevant or could be answered in each case study, therefore some fields in the following table may not be filled out.

The content in the tables are originally taken from the texts in each case study and arranged for analytical reasons following the grid of the research questions (rows) and the case studies one below each other (columns).

1. Core characteristics case	1.1 Time period	1.2 Geographic focus	1.3 How has the PP been applied?	1.4 Unique characteristics / outstanding features of the case
New Gene Editing techniques: gene drives	First proposal theoretical concept for gene drives (1960) – in silico research invertebrates (2020).	EU	Applied to the GMO regulations applicable to gene drives	Case is not about inconclusive evidence, but about a missing field of scientific knowledge about the environmental effects of genetic modification on a population level.

Genetically Modified Organisms (GMOs)	1973 the first example of a GMOs and spurs the development of the field - 2020	Bulgaria	Applied to ban all GMOs and nearly all gene-editing research, but not evidence-/science-based. The LGMO refers directly to the precautionary principle, and explicitly states as its primary objective the need to ensure protection of the human health and the environment from any hazards resulting from the activities it sought to regulate. These are explicitly specified to include any work with GMOs in contained environment, deliberate release of GMOs in the environment, release to the market of GMOs or combination of GMOs as single products or product ingredients, the relocation, transportation, import and export of GMOs, and	GMOs have been considered as synonymous to risk, and are not well perceived in the country (Bulgaria). The attitude among legislators reflects a strong precautionary principle whereby risks are assumed to be highly probable, without cost-benefit consideration.

			further specifies the scope of management and control of these activities.	

Endocrine Disrupting Chemicals		EU	Some EDCs have been banned for certain applications, others not yet	EDCs widely prevalent, but processes to identify EDCs remain contested. Dilemma between societal pressure to regulate and time to gather evidence. Resulted in regulatory stalemate, as well as in regrettable substitutions.
Neonicotinoid insecticides	Neonics invented in the 1980-90, put on the market 1990s, risk discovered in the mid/late 1990s – ongoing, then the PP was invoked in the 2000 – ongoing (in the EU, specifically in 2013 and 2018, court case on-	EU	Some neonics have been banned for certain applications, others not yet	Risk assessment including independent research and stakeholder input. EC regulation allowing a reassessment of approval before approval period ended.

	going).			
Nanotechnologies	1997 First mention of nanotechnology within an EU-level strategic document – 2020 Horizon Europe Framework Programme – 2021-2027	EU, German speaking countries, Austria	1. EUC nanotechnology action plan "Safe and sustainable development of NT" 2. specific legislation in consumer product areas 3. risk governance activities for evaluation of the available knowledge (uncertainty management) 4. guidelines for worker safety 5. safety research programmes 6. establishment of public communication strategies	Umbrella term of very different scientific approaches and disciplines; interesting new features and functionalities; combination of engineering and life science approaches; now incorporated in the field of advanced materials

Glyphosate	2012-2017 (time period of renewal procedure). [Monsanto developed and patented the use of glyphosate to kill weeds in the early 1970s and first brought it to market in 1974, under the Roundup brand name.]	EU	The substance has not been banned (yet), but the regulation which governs the re-assessment process is based on the PP; the fact that the assessment takes place is an application of the PP; the limited length of the authorisation is a form of precaution	Risks became known after long time of use only; Scientific uncertainty in face of multitude of studies; EU institutions do not acknowledge scientific uncertainty;

Financial risks in water infrastructure planning	1989 - 2017	Milan and London	Applied, without attention to cost/proportionality of measure. The relationship between cities and their infrastructure defines how society interacts with the environment, thus emphasizing the importance of the way we govern, maintain and construct urban water infrastructure. The precautionary principle by means of the WFD, thus enacts immense influence over the way we organize our cities. A particular key issue is the Urban Waste Water Treatment Directive, which is one of the 'industry directives' born from the WFD. It has been utilized to sue cities within the European Union that do	It provides a reverse perspective on the precautionary principle, it does not follow the introduction of a new product or technology in tension with the precautionary principle, but it examines the long-term impacts of a precautionary principle regime. Size of the project, 'white elephants', The London case focusses on an individual infrastructure project and shows how financial innovation has shaped the case. The Milan case presents a longer-view perspective that shows how structural changes in the infrastructure

			not conform with the imposed waste water standards	sector have enabled an environment for sustainable financial innovation.
The use of Artificial Intelligence in healthcare (CDSS)	1972 (MYCIN) – March 2020	EU	Not applied. It has been mentioned in relation to the implementation of AI in general	Possible 'emerging' case. Human rights focus

Microplastics in food products and cosmetics	1950: Industrial development led to large scale plastic production – 2020: Final opinions on the restriction proposal by the Risk Assessment Committee and the Socio-Economic Assessment Committee of ECHA	EU	The PP is not yet applied, but the European Commission is working to ban microplastics in cosmetics via the REACH regulation	1. Lack of a definition of microplastics 2. because of limited hazard and risk assessment, it is not possible to determine a maximum threshold for exposure in food at this moment

2. Innovation assessment	**2.1 Why has this product/technology been developed? What problems will it / does it solve?**	**2.2 Economic, social, environmental benefits**	**2.3 Are these benefits themselves debatable? What is the evidence/uncertainty discussion?**	**2.4 What do the different stakeholders say about the benefits?**
New Gene Editing techniques: gene drives	(contribution to) eradication of vector borne disease or invasive pests, increased resilience of spe-	Public health, environment	Very large / ignorance	

	cies.			
Genetically Modified Organisms (GMOs)	Many different GMOs/ benefits Transferring beneficial traits across species to improve herbicide resistance and pesticide tolerance; to increase yield; to improve nutritional values. Insulin producing bacteria or bacteria for oil spill mitigation	Potentially solving food shortages Reducing long-time horizons and limited scalability of conventional breeding Agricultural benefits, economic benefits, nutritional benefits, enhanced food qualities, enabling therapeutics	Especially the broader benefits are debatable	Many of these alleged benefits however are commonly linked to commercial interests, and sometimes to specific corporations hosting and sponsoring the research, marketization and commercialisation of GM crops. This makes it particularly challenging to provide an unbiased and credible assessment of the extent to which benefits can be transferred onto end consumers. 'The authors further claim that NGO reports and

				non-scientifically reviewed publications were found to be more likely to report lower estimates of positive impacts of GM crop benefits than ones published in peer-reviewed journals.‘

Endocrine Disrupting Chemicals	They were originally engineered so as to produce benefits for various industries, consumers, and individuals. As such, EDCs can be found in many products They were originally engineered so as to produce benefits most importantly – but not exclusively – for industry and agriculture, households and consumers, as well as for medical and personal health care. In the area of household products, the most well-known chemicals with endocrine-disrupting properties were originally developed for the plastics industry	In the field of agriculture, pesticides and herbicides have represented "a great benefit for human health", for example by helping to "control agricultural pests […] and plant disease vectors" and by insuring "increased food production [and] a safe and secure food supply"		

	Finally, some chemicals have been purposefully designed to have endo-crine-disrupting properties so as to benefit human health. This particu-larly includes EDCs devel-oped for fe-male heath, such as for birth control and for the treatment of menopause symptoms.			

Neonicotinoid insecticides	The invention of neonicotinoids in the late 1980s and 1990s, are often highlighted as significant technological advancement in pesticide developments, signifying a new era of pest management, with a higher versatility in application methods and a high target specificity	They are promoted for providing a cost-effective in increasing yields, but it is also argued that their targeted use has decreased the use of other pesticides.	Countering this, other studies have not found clear and consistent evidence on yield benefits from the use of neonicotinoids on different crops. Another issue is that due to the widespread use, some species have started developing resistance to some neonics (see Bass et al., 2015 for review of literature on pest resistance to neonicotinoids). Additionally, a decline of pollinators may have huge consequences for yields of crops that depend them	

Nanotechnologies	Because of their high variability and universal use nanotechnologies are among so called key enabling technologies (KET) Nanomaterials and products have already found their way into everyday life, being used in consumer goods, construction, pharmaceuticals and chemicals, healthcare, power generation and information technology	KETs are technologies which are meant to retain the competitiveness of the European industries and capitalise on new markets worldwide.	Nanomaterials are already being used in various commercial consumer products, such as electronics, but still very little is currently known about their production volumes, market distribution and their fate and impact over the value chain and life cycle, because valid information is missing. It is therefore essential to further develop reliable, standardised reference materials, robust analysis and measurement methods as well as a harmonized registration system for all nanomaterials.	

Glyphosate	Glyphosate-based herbicides are used worldwide to remove unwanted weeds not only in agriculture, but also forestry, gardening and use in public parks, and to remove unwanted weeds from railways Especially in combination with GMOs, glyphosate was claimed to have many advantages, the first being that it leads to a reduction of other chemical and mechanical ways of killing weeds, which were said to be more harmful to the environment	Farmers' organisations like the British National Farmers' Union (NFU) stress that glyphosate is very important in agriculture and that a withdrawal of approval would have many negative consequences, including the increased need for tillage leading to a decrease in earthworms, a decrease in soil organic matter and increasing CO2 emission (NFU 2017).	However, the benefits presented in the context of glyphosate may be relativized. The weeds which glyphosate is supposed to kill will, over time, become increasingly resistant to it. In turn this leads to an increase in the use of glyphosate-based pesticides, the return to tillage, and an increase in combining the use of glyphosate-based pesticides with other pesticides	

Financial risks in water infrastructure planning	Access to clean water and sanitation has been recognised as a human right water infrastructure is a key prerequisite for the development of cities			
The use of Artificial Intelligence in healthcare (CDSS)	Faster, easier, cheaper, more accurate, efficient and effective decision-making in healthcare	Public health, personalised medicine, less healthcare costs, general, increase technological competiveness	In many cases effectiveness and efficiency is contested, extra costs for maintenance and education, more long term studies are needed	

Microplastics in food products and cosmetics	Microplastics have not been developed as a solution to one clear issue. Rather, it is a side effect of the growing use of plastic in a wide variety of uses. Microplastics in cosmetics is a cheaper alternative to natural substances for the purpose of exfoliation, scrubbing etc. Microplastics in food is a side-effect from the widespread use of plastics in all kinds of applications. This is often a cheap, light-weight option for packaging materials	The innovation and mass production of plastics has been a great contributor to the growing wealth in the western world. Because plastic is, in comparison to other materials, low costs, low weight and highly resistant to heat and chemicals it is suitable for many applications. For example, in cars and planes, the use of plastic reduces the weight of the vehicle, leading to lower CO2 emission and fuel costs.		

3. Risk/threat	3.1 What is the overall risk(s) of the topic?	3.2 Describe how different societal groups (individual health, local communities, the local environment, and future generations) are threatened or potentially harmed.	3.3 Potential severity and scope of the harm	3.4 The extent of (ir)reversibility of deployment
New Gene Editing techniques: gene drives	Risks for biosafety and biosecurity, moral hazard		Potentially very severe and broad scope	Irreversible

Genetically Modified Organisms (GMOs)	Risks for human health, ecosystems and the environment. Genetic Contamination/Interbreeding Competition with Natural Species Increased Selection Pressure on Target and Nontarget Organisms Ecosystem Impacts Impossibility of Follow-up Horizontal Gene Transfer Adverse Effects on the Health of People or the Environment Unpredictable and Unintended Effects Loss of Management Control Measures			Irreversible

	Long-Term Effects Ethical Concerns			

Endocrine Disrupting Chemicals	There is indeed evidence that exposure to EDCs induces various types of diseases, which are related to any hormonal system in the body. Amongst other threats to human health, there is strong scientific evidence that endocrine disruptors induce negative health effects related to obesity, diabetes and cardiovascular diseases; female and male reproductive health; hormone-related cancers in females – including breast cancer – and prostate cancer in males; thyroid health; and neurodevelopment and neuroendocrine systems. Exposure to EDCs has been linked, inter alia, to the occurrence of dyslexia, IQ loss, ADHD, and autism	Although EDCs can thus be seen as "a risk that concerns us all", they pose risks especially to unborn and young children (Unborn) children and pregnant females are thus most importantly threatened and potentially harmed, as are future generations (WHO, 2012b): changes caused by EDCs at an early stage "underlie disorders that may manifest later in adult life and contribute to 'diseased ageing' with a multitude	Given that EDCs can have serious and irreversible health consequences "throughout life", the WHO has called them a "global threat that needs to be resolved" (WHO, 2012a, p. 27).	Irreversible

		of chronic diseases" (Bergman, Rüegg & Drakvik, 2019, p. 2). Fertile populations, workers exposed to EDCs in their environment, and people with low incomes are also among the societal groups that are most importantly at risk (Di Renzo et al., 2015; WHO, 2012a). the 'cocktail effect'. Finally, the threats that EDCs pose are not limited to human health but have implications for the		

		environ-ment as a whole and the well-being of wildlife		

Neonicotinoid insecticides	Water surveys in more than a dozen countries have documented widespread contamination of surface waters around the world at levels that frequently exceed water quality norms (Giorio et al., 2017). Studies also confirm wide spread environmental contamination by neonics in soil, air, wild plants (including pollen and nectar), agricultural produce, bees, beehives, honey, human urine and effluent of waste water treatment plants (ibid). Neonics are persistent in soil and can accumulate from one planting season to the next and are taken up by non-treated follow-up crops. In both research and in public debate, the main attention has been on the risk that neonics pose to pollinators, especially bees. Pollinator decline is a serious risk because they provide key ecosystem ser-		Very prevalent	Irreversible

	vices as many important agricultural crops depend on them. Additionally, 94% of all flowering wild plants depend on insect pollinators for reproduction (IPBES 2016), and a decrease in insect abundance can in turn have consequences to insect eaters such as birds. There is also a growing amount of research demonstrating risks for other species and ecosystem services. Lastly, risks on the effects of neonics on human health remains poorly understood. While highlighting that more research is needed, the limited literature on this field suggest concerns for neurodevelopmental effects on brain development during prenatal and early life exposure (possibly leading to increased incidence of autism, schizophrenia and ADHD) and a possible role in Parkinson and Alzheimer's disease			

Nano-technol-ogies	Laboratory studies indicate that the dose-response relationship between nanoscale carbon black or titanium dioxide with toxic effects such as oxidative stress, inflammation or genotoxicity correlates with particle size [68][69]. In addition, other physicochemical and functional material parameters such as state of aggregation, density, surface properties, crystallinity, biological impurities as well as solubility rates and surface reactivity have toxicokinetic relevance [70]. Laboratory investigations using the example of pulmonary exposure in mice show that nanoscale titanium dioxide (nano-TiO2) has not caused any DNA damage compared to its larger counterparts, but has led to increased inflammatory reactions [71]. Reduced lung functionality and increased inflammation values were also found in workers exposed to nanoscale carbon	From a toxicological viewpoint a certain risk posed by a substance is connected not only to the adverse effect, but foremost to the exposure of a person or a living being to the respective substance. In the case of nanotechnology, the risk for human health is often identified as occurring at the workplace (including laboratories) where nanomaterials are created or handled. The other group mainly concerned are consumers		

	black (carbon black) [72]. In general, inhalation of ENMs is also associated with cardiovascular diseases, where not only the particle size but also shape has toxicological relevance. However, CNTs not only cause asthmatic inflammation [73], but several publications on bioassays in rats suggest that CNTs have carcinogenic effects as well. Although more recent studies rather address environmental interactions and transformation processes significantly influencing toxic effects (e.g.: particle agglomeration, dissolution), there is still a paucity of information and discrepancies in literature about their environmental impacts. A very important issue which turned up rather late both	because they can come into contact with nanomaterials via nanoproducts.		

	in public and in scientific discourse is the behaviour of nanomaterial-containing products at the end of their life cycle and their effects on waste streams and environmental media			

Glyphosate	In 2013 the NGO Friends of the Earth published a media briefing, in which they pointed to the toxicity of the substance. The briefing, mostly referring to data from Latin America, also cited studies pointing to birth defects, an increased rate of miscarriages and a risk of genotoxicity (leading to genetic mutation and an increased cancer risk). Furthermore, according to other research, it is estimated that glyphosate exposure poses risks to the kidney and the liver (Myers et al 2016). Carcinogenicity Endocrine disruptor First, specific species are harmed by glyphosate and, second, it might endanger the whole ecosystem through its negative effects on biodiversity, which in turn harms many species forming part of the ecosystem.	Many of the case-controlled cancer studies that are used in the IARC assessment were conducted amongst male farmworkers, excluding women from the studies (IARC 2015). Also the EU risk assessment of glyphosate has been criticised for lacking attention to vulnerable groups, for example through not examining the risk of exposure for pregnant women Endocrine disrupting effects differ per gender	Due to the popularity of glyphosate and glyphosate-based herbicides (GBHs), humans are exposed to it in various ways. First of all, obviously the application of a glyphosate based-herbicides exposes humans to it: there is the occupational exposure to glyphosate (farmers, workers in garden and landscape maintenance, forestry workers etc.), but also exposure through household use, as weed killer on private properties (IARC 2015). Furthermore, the continuously increasing use of glyphosate has resulted in the fact that glyphosate and aminomethylphosphonic (AMPA, the product into which glyphosate is metabolised) can be detected in air, water, soil and also food (Benbrook 2016).	

Financial risks in water infrastructure planning	The costs associated with the infrastructure investments needed to comply with the increasing standards are so high, that they present a challenge in themselves to cities. Underfinanced infrastructure leads to lack or degradation of water supply systems which affects water quality Financial risks Planning risks			
The use of Artificial Intelligence in healthcare (CDSS)	Depends on application. Harm to (public) health and violation human rights (privacy, autonomy over body, equality, access to healthcare)	Data-risks: especially women,, racial minorities, lower socio-economic groups, low educated Risks related to a loss of control/lack of human element/ another		In some case this might lead to irreversible consequences that endanger the sustainability of the healthcare system

		division of labour: patients, healthcare profes-sionals and socie-ty as a whole		

Microplastics in food products and cosmetics	Microplastics stay widespread in the environment for long; while leaking added chemicals in the environment. Adverse effects of microplastics in cosmetics consider mostly the environment. The risk of microplastics in food is considered less serious: most particles will be excreted by the body, however specific effects on human health are unknown. A recent review on the human health effects of microplastics mentioned a variety of outcomes potentially being related to microplastic ingestion, including oxidative stress, cytotoxicity, chronic inflammation and increased risk of cancer, neurodegenerative diseases and autoimmune diseases Apart from the potential risks caused by the actual pieces of microplastics, microplastic particles carry other chemical substances on their surface or inside the	(sea) animals, through food Although the scientific base for health risks caused by microplastic exposure in foods is still thin, there is no reason to believe that the exposure or risks are specific for certain groups in society. Microplastic pollution is a widespread problem and the food products that transport microplastics from the environment into the human body are consumed in all layers of society. Alt-	The presence of large amounts of microplastics in the environment has been established conclusively	This combination of being present in large amount and for such a long time makes it an unpredictable and undesirable situation for the environment. Once in the environment, not many options are available to get them removed

	particle	hough no difference in the exposure to microplastics are expected between genders or specific local communities, there is specific concern for future generations		

4. Scientific analysis	4.1 What is the state of the research field?	4.2 Which sciences were involved in risk assessment?		
New Gene Editing techniques: gene drives	Although scientists have been investigating gene drives for decades, the assessment of risks did not seem pertinent because the technology was weak and its development was incremental. However, the scientific breakthrough of CRISPR-Cas9 has quite suddenly made applications possible that were not before, raising immediate question pertaining to safety and ethics more generally Field release with research purposes is at least a few years away and expectations are that a fully evaluated technology to control disease vectors will not be available for another 10 years. This is partly due to the large amount of knowledge necessary to assess the technique's safety and efficacy Some aspects of this knowledge can be obtained by modelling environmental impacts and from experience with similar technologies or application Scientists are also learning from experience with similar technologies or application domains, like situations where GMOs have been detected in wild plant populations due to seed or pollen movement and the control of pest animals			

Genetically Modified Organisms (GMOs)	Industry-funded scientific studies, as well as those authored by molecular biologists, tend to be more likely to express positive attitudes to GM crops and argue against serious inherent risks. Publicly funded scientists, and those trained in ecology, are more likely to purport negative attitudes,	Even scientists within the same disciplinary domain continue arguing, and others have noted inconsistencies in data availability, data interpretation, cases of poor methodological rigour or questionable commercial interests casting doubt on the impartiality of the research results and/or their interpretation. Across disciplinary domains, there is even less agreement.		

Endocrine Disrupting Chemicals	Scientific analysis of the risks posed by endocrine-disrupting chemicals to wildlife, laboratory animals, and humans most importantly includes many "thousands of published studies"	Reports from amongst others WHO, UNEP and the International Labour Organisation, consumer organizations Given the nature of endocrine disruption, the risk assessment of EDCs has been a mostly interdisciplinary endeavour		
Neonicotinoid insecticides	During the 1990s, the first early-warning reports emerged linking neonics bee-colony losses in France, and the PP was applied to ban products containing neonics for certain crops Large amounts of independent peer-reviewed research on the risks of neonics, especially on bees. Many lab studies, but also some field studies. Industry research and industry funded research Independent peer-reviewed research	Mostly natural scientists (including the disciplines chemistry, biology, toxicology, ecology) A few social scientists like economist.		

	EC mandated EFSA reviews			

Nano-technol-ogies	First of all, nanotechnological substances and compounds can be formed from more than 50 different chemical elements, the most common being silicium, titanium, carbon and metal oxides. In the case of carbon the number of possible chemical compounds is almost unlimited The next level consists of the physical behaviour of nanomaterials in itself and their tendency to form aggregates and agglomerates on their own and with components of their environment. Nanomaterials can not only be described by their chemical behavior but also by their physical properties such as surface area, surface charge or catalytic activity. On the next level they will have to be described according to their behaviour in natural environments (water, air, soil) and living beings, which adds to complexity the complexity of this environment. And finally, the universal applicability of nanomaterials in nearly every conceivable product and usage is to be considered. The risk of a nanomaterial is determined by its chemical composition, other physicochemical properties, its interactions with tissues, and potential exposure levels. The schematic general outline for risk assessment of nanomaterials is shown in Figure 5. (EFSA risk assessment scheme)	Because of their probabilistic nature this is valid for all scientific statements, but for emerging technological systems and new scientific developments this inherent uncertainty is absolutely decisive. Moreover, this contributes to their evolutionary flexibility. Regarding advanced materials like engineered nanomaterials one has to add their general propensity to be used for a wide variability of applications. Therefore, talking of uncertainty additional sources of uncertainty have to be considered	Scientifically ambiguous is also the way to define a dose which is one of the central questions on toxicology and still an unsolved question for nanomaterials because their effects are mainly based on surface properties and not on mass. In toxicology a dose can be either the mass/weight of a dissolved substance per volume (concentration/gram per litre) or the molar concentration of a dissolved amount of substance (number of atoms, to be calculated by the specific weight) per volume (molarity, mol per litre) or finally, the particle density or particle concentration per volume (par-	

	Only to give an impression which information needs are considered by the EFSA to be necessary to sufficiently characterize nanomaterials, only the first step of physico-chemical characterization is listed here: 1) specific morphology (e.g. rigid, long tubes or fibres, high aspect ratio nanomaterials, fullerenes, crystal structure, porosity), carrier materials with cores and shells of different biopersistence (e.g. multifunctional nanomaterials); 2) complex transformations (e.g. ageing, changes in surface properties, porosity) or metabolites or de novo formed particles from ionic species 3) altered hydrophobicity/hydrophilicity; 4) persistence/high stability (e.g. in water, fat, or body fluids, lack of dation/dissolution	such as linguistic and terminological vagueness (this is the reason why terminology and metrology represent the first areas of standardisation – so too in nanotechnology). Additional aspects which might enlarge the uncertainties concerning new materials are the lack of data, the lack of measurement methods and protocols, inadequate measurement devices and generally the inability to ask the right research questions. Simultaneously the necessity to regulate	ticle counts per volume). The definition of dose depends very much on the circumstances the material in question will be produced, applied or handled. However, even the concept of toxicology itself can be regarded as scientific ambiguous depending on the determining disciplinary background. The concept can be chemical-driven, morphology-driven or radiation-driven. Although there are still no binding workplace limit values for most fine dusts and dusts from nanomaterials, recommendations for signifi-	

		); 5) increased reactivity compared to equivalent non-nanomaterial (e.g. catalytic, chemical, biological); 6) targeted or controlled release by the nanomaterial; 7) nanomaterials having antimicrobial activity; 8) different or increased mobility of the nanomaterial in vivo compared to the conventional non-nanomaterial, i.e. possibility of increased bioavailability and internal exposure (e.g. transport via macrophages; transport through cell membranes, blood-brain barrier and/or placenta, delivery systems) and mobilisation potential (e.g. infiltration, sorption, complex formation); 9) interac-	the implementation of these new materials and products increases the pressure on decision-makers.	cantly lower threshold values have already been proposed for some nanosubstances. These recommendations vary depending on the responsible authorities even if they concern the same substances	

	tions with biomolecules such as enzymes, DNA, receptors, potential 'Trojan horse' effects on immunotoxicity); 10) bioaccumulation; 11) quantum effects (e.g. altered optical, electronic, magnetic, mechanical or redox properties in nanoscale materials).			

Glyphosate	Glyphosate has been the focus of a large and still growing number of scientific studies. However, since the mid-2000s several animal and epidemiology studies published by non-industry associated scientist seem to call the safety of glyphosate into question Studies by IARC, ECHA and EFSA			
Financial risks in water infrastructure planning	A key aspect of urban water is the highly integrated nature of all these risks and dynamics, which all need to be taken into consideration to achieve urban socio-environmental sustainability	Many disciplines, but primarily economic financial policy studies		
The use of Artificial Intelligence in healthcare (CDSS)	To some degree, clinical trials have been executed on CDSS. In most instances these studies seem to focus on effectivity and economic benefits, and there still exists considerable uncertainty about the long-term effects and the more ambiguous and complex risks (with regard to a loss of control, another division of labour, lack of a human element and data risks).	Analyses have been made in in the field of AI research, computer science, (Bio)-ethics, STS/TA-institutes, Medicine, Health IT, Risk governance, risk assessment, Law and policy studies		

Microplastics in food products and cosmetics	Scientific research, which functions as the basis of the risk assessment process, on the health effects of microplastics is relatively new. In earlier decades, research on (micro)plastics was focussed on environmental effects and the amount of pollution. Since approximately ten years, scientific research has shifted towards potential human health effects. Consequently, not much long-term evidence is available yet and no definitive, scientific answer has been provided with regard to the relation between microplastics exposure via food or cosmetics and harmful effects on human health.	Apart from research at universities, scientific analyses have been written by European institutions to map the potential consequences of microplastic pollution for health and the environment.		

5. Epistemological challenges	**5.1 Complexity**	**5.2 Uncertainty**	**5.3 Ambiguity**	**other**

New Gene Editing techniques: gene drives	Once introduced into the wild, the technology could cause a cascade of population dynamics and evolutionary processes (NASEM, 2016). Not only do gene drives affect the environment, vice versa the environment affects the (impact of) gene drives. A complicated interwoven web of biotic and abiotic factors give rise to a large degree of ecological and evolutionary complexity Importantly, the results may be partly or wholly offset by unintended, aggregate and long-term ecological and economical effects that play out through complex feedback loops Complicating this further is the imagined range of gene drive applications, each with their own impacts. Applications diverge with respect to the types of systems they are built into (i.e. health, agricultural or natural systems), their social contexts (in different regions of the world and in different types of applications) and the values underlying their application (Sandler, 2017).	Gene drives are associated with a large degree of epistemic uncertainty. In the end, models of the application in nature will never perfectly capture ecological, biological and social contexts, especially in regard to long term impacts Empiric tests are impossible Furthermore, implementation of gene drives could also result in 'random' effects, as an ecological system –the wild– behaves in	The literature also shows cases of interpretative ambiguity. Scientists from different research fields have different perspectives on the impact gene drives could have, just like they do in regard to GMOs. Another point of interpretative ambiguity is the extent to which gene drives should be considered 'synthetic biology' – and thus should be regulated as such-, as the modification of genes is limited. In addition, there is ambiguity about whether all CRISPR-Cas9 edited organisms are GMOs.	

		different and complex ways Experts at the Scientific Foresight Unit workshop on gene drives (STOA, 2019) argued that gene drive technology is not a silver bullet and that complete eradication of a species was deemed impossible, as even smallpox has not been completely eradicated. In addition, because it would take many generations for a population to become extinct.	Gene drives also give rise to normative ambiguity People with different value systems, including cultural and religious beliefs, will have different understandings of life, nature, the human relationship and responsibility to nature, and the value of technology and innovation, leading to different perspectives on the moral quality of gene drives as an intervention	

Genetically Modified Organisms (GMOs)	GMOs represent a clear case of complex interdependencies within food supply chains and throughout food systems	There is frequently inherent uncertainty in the final result of the modification. Foreign gene insertion can have different outcomes. Even though the role and function of the gene in the "source" organism may well be understood, the full range of consequences of the transfer are not always known or may not always be adequately predicted.	On the one hand, decision-makers are faced with the lack of confirmed information on, or knowledge of, the subject they need to regulate due to sometimes conflicting evidence that precludes the attainment of undisputed knowledge.	

Endocrine Disrupting Chemicals	First, regulating the risk of endocrine disruptors is complicated by hazard complexity and exposure complexity (Vogel, 2005). Hazard complexity means that it has been highly complicated to disentangle the causal relationship between exposure to EDCs and biological changes and diseases in humans and wildlife. They do not behave as 'usual' toxic substances, but rather behave like hormones In addition, the toxicity and hazard of chemicals is commonly established on a case-by-case basis. Yet EDCs are clearly "being added on top of the endogenous hormonal milieu, such that complex mixtures, dose additivity, and synergism between and among hormones and chemicals are the norm" Whereas hazard complexity thus concerns the measurement of the causal mechanisms of EDCs, exposure complexity concerns the measurement of how humans and wildlife are exposed to EDCs regulating the risk of endocrine disruptors is complicated by the broader system in which EDCs are governed. Clearly, to detect which chem-	These uncertainties can be linked to three main factors: 1. Lack of data; 2. Lack of testing methods; 3.Indeterminacy about effects. Secondly, the delayed effects of endocrine disrupters are uncertain. This is mostly the result of time lags of many years – or even several decades – between exposure during the 'sensitive window' of post-natal development and the development of disease at	There seems to be insufficient knowledge to universally define what constitutes an adverse endocrine effect. There are also no adequate standardised test methods to identify such possible effects	

	icals have endocrine-disrupting properties, scientists have had to abandon the conventional, simplifying assumptions for establishing the toxicity of chemicals. This has led to regulatory complexity. That is, the regulatory system in which EDCs are governed is 'path-dependent' Moreover, different regulations and the different regulatory agencies involved have had different understandings of how best to regulate these chemicals – depending on matters such as their expertise and regulatory framework. Finally, the complexity of endocrine disruptors as a risk also gives rise to important, wider political complexity. This is so because different stakeholders adhere to different positions	a later stage in life (p. 6). And thirdly, the complex mechanisms through which natural hormones and endocrine disruptors may work together to cause a non-monotonic response to doses of EDCs remain uncertain. Given the complexity of EDCs, both in terms of hazard and exposure, some of this uncertainty "probably cannot be resolved"		

Neonicotinoid insecticides	First, there are complexities of the types and applications of neonics. Secondly, and linked to the variety of applications, there is a complexity of residues and possible routes of exposure for non-target species. Third, there is a complexity of species affected. Fourth, there is a complexity of ecological contextual factors that affect the consequences of neonics exposure for different species.	The uncertainty of exposure is related to the lack of knowledge on residues of neonics. It is well known that neonic residues persist and accumulate in both soil and water, nectar and pollen (Goulson et al., 2013), but there is limited knowledge on the exact residues in different areas, as they may vary significantly. Further, there are uncertainties on the consequences of different levels of exposure, especially of lower	The risks that different stakeholders relate to neonics should be seen in light of the two diverging ways of framing plant protection products (PPP) (Bozzini 2017): One way of framing PPPs is to see them as threats to conserving biodiversity and ecosystem services. With this frame, the focus is on how industrial farming and the increased use of pesticides has decreased biodiversity, and the case of DDT is often drawn in as an example of the destructive consequences of PPPs. Another very different way of framing PPPs, is faming them as	

		sub-lethal exposure over time. The largest knowledge gaps seem to be that the long-term toxicity to certain species, such as hoverflies or butterflies and moths has not been investigated. The same holds for soil organisms (beyond earthworms) (van der Sluijs et al., 2015). In addition, there is a high degree of uncertainty around possible 'cocktail effects' of the combination of different pesticides that bees to varying	vital tools in providing food security. With this frame, the historical and ongoing advances in food production that are necessary to ensure sufficient food production for a growing world population is central. Rather, the controversy centers more on the what the problem is, more specifically to what degree neonics really causes pollinator decline, and what kinds of regulations that are necessary. Related to this, there is ambiguity around acceptability of risk and what a "high	

		degrees are exposed to. With the high degree of contextual complexities, there are several uncertainties connected to the methods chosen for measuring the effects of neonics on pollinators.	level of protection" to be achieved by the EU's pesticide regulation 1107/2009 implies for the case of neonics Another source of ambiguity centres around the uncertainties in lab-studies and field studies, which have enabled different policy conclusions to be drawn by different interest groups. Another aspect regards how to judge what constitutes a high quality and trustworthy research, especially regarding reports that are not peer-reviewed and/or are funded by	

			the industry, or NGOs. This ambiguity over evidence is also evident in at a more detailed level, where specific studies are interpreted differently from different stakeholders e.g. the debate on the 'Country-specific Effects of Neonicotinoid Pesticides on Honey Bees and Wild Bees' (Woodcock et al., 2017).	

Nanotechnologies	First of all, nanotechnological substances and compounds can be formed from more than 50 different chemical elements, the most common being silicium, titanium, carbon and metal oxides. In the case of carbon the number of possible chemical compounds is almost unlimited The next level consists of the physical behavior of nanomaterials in itself and their tendency to form aggregates and agglomerates on their own and with components of their environment. Nanomaterials can not only be described by their chemical behavior but also by their physical properties such as surface area, surface charge or catalytic activity. On the next level they will have to be described according to their behavior in natural environments (water, air, soil) and living beings, which adds to complexity the complexity of this environment. And finally, the universal applicability of nanomaterials in nearly every conceivable product and usage is to be considered. The risk of a nanomaterial is determined by its chemical composition, other physicochemical properties, its interactions with tissues, and potential exposure levels. The schematic general outline for risk assessment of nanomaterials is shown in Figure 5.	Because of their probabilistic nature this is valid for all scientific statestatements, but for emerging technological systems and new scientific developments this inherent uncertainty is absolutely decisive. Moreover, this contributes to their evolutionary flexibility. Regarding advanced materials like engineered nanomaterials one has to add their general propensity to be used for a wide variability of applications. Therefore, talking of uncertainty addi-	Scientifically ambiguous is also the way to **define a dose** which is one of the central questions on toxicology and still an unsolved question for nanomaterials because their effects are mainly based on surface properties and not on mass. In toxicology a dose can be either the mass/weight of a dissolved substance per volume (concentration/gram per litre) or the molar concentration of a dissolved amount of substance (number of atoms, to be calculated by the specific weight) per volume (molarity, mol per litre) or finally, the	

	(EFSA risk assessment scheme) Only to give an impression which information needs are considered by the EFSA to be necessary to sufficiently characterize nanomaterials, only the first step of physico-chemical characterization is listed here: 1) specific morphology (e.g. rigid, long tubes or fibres, high aspect ratio nanomaterials, fullerenes, crystal structure, porosity), carrier materials with cores and shells of different biopersistence (e.g. multifunctional nanomaterials); 2) complex transformations (e.g. ageing, changes in surface properties, porosity) or metabolites or de novo formed particles from ionic species 3) altered hydrophobicity/hydrophilicity; 4) persistence/high stability (e.g. in water, fat, or body fluids, lack of degradation/dissolution); 5) increased reactivity compared to equivalent non-nanomaterial (e.g. catalytic, chemical, biological); 6) targeted or controlled release by the nanomaterial; 7) nanomaterials having antimicrobial activity; 8) different or increased mobility of the nanomaterial in vivo compared to the conventional non-nanomaterial, i.e. possibil-	tional sources of uncertainty have to be considered such as **linguistic and terminological vagueness** (this is the reason why terminology and metrology represent the first areas of standardisation – so too in nanotechnology). Additional aspects which might enlarge the uncertainties concerning new materials are the lack of data, the lack of measurement methods and protocols, inadequate measurement devices and	particle density or particle concentration per volume (particle counts per volume). The definition of dose depends very much on the circumstances the material in question will be produced, applied or handled. However, even the concept of toxicology itself can be regarded as scientific ambiguous depending on the determining disciplinary background. The concept can be chemical-driven, morphology-driven or radiation-driven. Although there are still no binding workplace limit	

	ity of increased bioavailability and internal exposure (e.g. transport via macrophages; transport through cell membranes, blood-brain barrier and/or placenta, delivery systems) and mobilisation potential (e.g. infiltration, sorption, complex formation); 9) interactions with biomolecules such as enzymes, DNA, receptors, potential 'Trojan horse' effects on immunotoxicity); 10) bioaccumulation; 11) quantum effects (e.g. altered optical, electronic, magnetic, mechanical or redox properties in nanoscale materials).	generally the inability to ask the right research questions. Simultaneously the necessity to regulate the implementation of these new materials and products increases the pressure on decision-makers.	values for most fine dusts and dusts from nanomaterials, recommendations for **significantly lower threshold values** have already been proposed for some nanosubstances. These recommendations vary depending on the responsible authorities even if they concern the same substances.	

Glyphosate	Generally, pesticide risk assessment is complex as they span over a wide range of products from naturally occurring ones to synthetic chemicals (Bozzini 2017). Moreover, pesticides are used in the whole food production chain from farming to trading, as well as in landscaping and forestry. A large source of complexity in the risk assessment of glyphosate-based pesticides is that next to glyphosate as active **substance they contain other chemicals as well, and this formulation** will be different for the over 750 different products on the market. While the formulation of the different products causes a first level of complexity, this is enhanced through complexities regarding the **accumulation and mixing of pesticides that the current scientific methods and regulatory framework is not able to comprehensively address.** The physicochemical properties, make it very difficult to analyse. Bioavailability is unclear.	Added to the complexities as elaborated in the previous section, is the uncertainty of the ever-evolving scientific methods. Another factor that contributes to the scientific uncertainty with regard to glyphosate relates to the absence of reliable data on the use of glyphosate-based herbicides	Especially regarding the question of carcinogenic risks, ambiguity – difference in interpretation of the scientific data - is a core characteristic of the risk assessment process concerning glyphosate. Next to disputes over the interpretation and methodology of single studies, the different assessment of the scientific evidence regarding carcinogenicity between the IARC on the one hand and the regulatory agencies in the EU on the other hand dominated the public and scientific debate. Thus, the ambiguity in	

			the assessment of glyphosate follows from the **"trade-off** between **regulatory science'** and **'research science'**, that is between the need for standard testing criteria (…) and the need for research designs that are innovative (...).	

Financial risks in water infrastructure planning	In terms of planning risks, complexity increases as decisions set pathways far into the future, increasing uncertainty and introducing new **dependencies**. The group of **financial risks introduces the greatest volatility**, as potential feedback loops and network effects are localized, and local administrations are potentially brought to financial collapse. Here, the **increasing complexity is even advantageous to some actors**, as they can then leverage superior knowledge vis-à-vis other less informed market actors. The literature has not identified tipping points per se, but the network effects of systemic risk in the finance sector as well as the outcomes of lack of transparency and weak competition are well established.	Uncertainty as to the effects of environmental impacts is low. In terms of the planning risks taken on by local administrations, complexity is largely due to scientific uncertainty over future challenges such as climate change, infrastructure vulnerability and economic issues	Not only are solutions dependent on local specificities (existing infrastructure, investment practices, water availability, etc.), but they are also dependent on a critical number of actors agreeing on which path to pursue. The Tideway Tunnel project shows how discrepant visions for the future can yield very different outcomes: environmental advocacy groups were supporting sustainable drainage systems as a solution for overcoming the sewage overflow issue, as opposed to the tunnel project which was favoured by investors	

			and the water operator. Another key aspect of ambiguity is represented in the case of Milan: different interpretations of the facts can only exist if different actors are invited to participate in the process.	

The use of Artificial Intelligence in healthcare (CDSS)	Emergent and self-organizing behaviour, Complexity of the healthcare environment, it interacts and adapts to complex and unpredictable entities: humans (reflexivity), mediation between different standards, inputs and multiple different sets of data, interaction of a CDSS with other (AI) systems (feedback loops), 'good' (and consequently safe) decision making in healthcare consists of many elements, risks are intertwined and their relation is difficult to assess	Apparent autonomy of some AI systems, small variations in the initial conditions of a (learning) AI system (for instance: its core code statements) can have highly divergent results, Epistemic uncertainty can follow from the fact that the design of an AI system or the way it is connected to other IT-systems can be obscure, Healthcare professionals often have to make decisions under uncertainty about events as well as the likelihood	Ambiguity lingers about what AI exactly is and when a CDSS exactly makes use of it. Ambiguity exists to what extent an artificial system supports or replaces the decision-making of healthcare professionals in a CDSS. Ambiguity with regard to responsibility of harm is exacerbated when an algorithm is opaque, and due to the fact, that, especially in software development, components are sometimes 'blindly' borrowed or improved No clear	

		of these events, Data-risks are difficult to predict/assess	consensus exists about how the possible risks surrounding AI should be characterized and ethically framed. Risks are surrounded by difficult ethical questions Normative ambiguity about risks is strengthened because the integration of AI in healthcare systems can be decisive for how the costs and benefits of these systems are distributed.	

Microplastics in food products and cosmetics	Research has indicated that toxicology of microplastic depends largely on the polymeric composition, shape of the plastic particle, the surface area, density of the material and the added chemicals on the plastic particle surface (45). However, large variation exists in the complete group of microplastic with regard to many of these characteristics. Consequently, no general definition exists of what a microplastic is. This size variation does not only lead to complexity when it comes to making and enforcing regulations, but also in adequately comparing evidence coming from academic studies Since not one standardized measurement tool is available, this is a well-know issue that reduces the generalisability of scientific evidence and makes it difficult to compare studies Another factor contributing to the complexity of microplastics is the fact that there is a wide variety in materials.	The important point that needs to be taken into account in understanding the risk is, knowing whether the alleged health outcomes are actually caused by exposure by microplastic, and not other substances. Additionally, uncertainty is caused by an absolute lack of data with regard to the exact hazard and exposure of microplastics (9). This lack of data can be explained by the previously mentioned complicat-	In the risk assessment of microplastics there is some discrepancy in how serious the uncertain human health risks are interpreted in the reports of EFSA and SAPEA. Additionally, there is discussion on different types of bias. Studies reporting positive findings are more likely to be published, regardless of their scientific quality. Especially since not much scientific evidence is present of its exact harmful effects, industry argues that there is	

		ing factors such as no universal definition, large variety in size, materials and added chemicals. Additionally, researchers have argued that a substantial part of the research has been performed with concentrations of microplastics that are unrealistically high.	no reason for all microplastic particles to be banned in the same way On the other hand there are environmental NGO's which have a much lower tolerability to the potential risks caused by microplastic pollution.	

6. Relevance of the PP to the case	**6.1 Why is the PP relevant to this case?**	**6.2 Normative underlying arguments**		

New Gene Editing techniques: gene drives	Gene drives are associated with uncertain systemic risks. Gene drives could give rise to a black swan event	systemic and irreversible risks, the precautionary principle would hold parties involved morally accountable for unintended harm. Second, in such a complex research and –as we shall see- governance context, responsibilities would be shared amongst all parties involved in the value chain of the innovation. Third, we have seen that also with regard to gene drives, **cost benefit analyses tend to discount future interests and needs**: the focus is mainly on short term benefits, while long term social costs are taken into account to a lesser degree. Eliminating		

		particular pests might be beneficial for one generation, while long term ecological effects tend to become visible after a long time. In addition, although benefits might be distributed more equally, the risks of gene drives are less 'non-discriminatory', as a loss of ecosystem resilience would hit those with low socioeconomic status harder. Fourth, the precautionary principle can be argued to give more voice to nature. Fifth, the ambiguity around the interpretation of evidence and the values of nature implies the need to emphasize mutual learning across academic, regulatory and		

		other civil society communities.		

Genetically Modified Organisms (GMOs)	Although risks of GMOs have been identified and studied from multiple perspectives, there are still inherent uncertainties and complexities that preclude a unanimous and categorical judgement on their consequences, particularly when used as food and food ingredients. The scientific uncertainty remains in part because it is not entirely possible to determine the full extent and likelihood of possible harms, especially when the exact source or reason for such potential harm may not be clear.			

Endocrine Disrupting Chemicals	The precautionary principle is of utmost relevance for the governance of EDCs. Relevant actors in this field, such as the WHO and the United Nations Environmental Programme (UNEP), but also non-governmental organisations (NGOs) and the European Parliament (EP), have previously invoked a need to act on the basis of the precautionary principle, with the aim to reduce or curb serious consequences of EDCs for human health and the environment			

Neonicotinoid insecticides	However, a main ground for concern, and for applying the PP, is that pollinator decline (especially of wild bees) is irreversible. As pollinators provide the vital ecosystem service of free pollination of crops, a significant decline of pollinators could have disastrous consequences for food production. Thereby, the seriousness risk for society and environment could justify precautionary action.			

Nano-technolo-gies	Following a Communication regarding a European strategy for nanotechnology [15] stated: "Despite some calls for a moratorium on nanotechnology research, the Commission is convinced that this would be severely counter-productive. Apart from denying society the possible benefits, it may lead to the constitution of "technological paradises", i.e. where research is carried out in zones without regulatory frameworks and is open to possible misuse. Our consequent inability to follow developments and intervene under such circumstances could lead to even worse consequences. The Precautionary Principle, as used up to now, could be applied in the event that realistic and serious risks are			

	identified." The EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) and the Scientific Committee for Consumer Products (SCCP) identifies knowledge gaps and pointed out the need to improve the knowledge base, in particular regarding test methods and risk assessment (hazards and exposure) methods. "An indication is given in the annexed Commission Staff Working Document Where the full extent of a risk is unknown, but concerns are so high that risk management measures are considered necessary, as is currently the case for nanomaterials, measures must be based on the precautionary principle." [20] "Measures			

	adopted under the precautionary principle must be based on general principles of risk management and must therefore inter alia be proportionate, non-discriminatory, consistent, on an examination of benefits and costs of action or lack of action, and on an examination of scientific developments.”			

Glyphosate	Thus, glyphosate represents a case not only of contestation of science, but also of contestation of scientific uncertainty. This also warrants the close analysis of the application of the precautionary principle in the EU risk governance concerning glyphosate as discussed in the following section.			
Financial risks in water infrastructure planning	The key issues of the case relating to the precautionary principle are the environmental and health risks at the onset of the case studies, the complexity related to the planning and financial risks, the uncertainty related to the long timescales at play, as well as the ambiguity resulting from the multitude of actors involved in water issues. The precautionary principle touches upon all of these issues			

	and acts as a driver in multi-risk environment, where it emphasizes certain aspects in lieu of others, thus shaping the overall trajectory of urban water systems in Europe.			
The use of Artificial Intelligence in healthcare (CDSS)	Our analysis in the previous sections seems to indicate that the precautionary principle may be applicable to the use of CDSS, but only in specific circumstances.	Irreversibility, intergenerational equity, Hippocratic oath		

Microplastics in food products and cosmetics	Ideally, when performing a risk assessment, this should combine all information on the hazard and likelihood and conclude in a quantative expression of the risk. Based on this conclusion, an acceptable threshold for the risk can be determined and can function as a basis for policy measures. From interviews with highly placed officials in EFSA and ECHA, we learned that, based on the limited scientific evidence available, and with debated scientific quality, it is not yet possible to set such an acceptable risk level in food. Regarding microplastics in cosmetics, the issue relates mostly to the environmental burden. Because the build-up of microplastics in the environment is undesirable in itself, regardless	Irreversibility, intergenerational, equity		

	of specific harmful consequences on the long term, the restriction of microplastics in cosmetics via the REACH regulation, which has no end data, seems to be more prevention instead of precaution.			

7.1 Risk governance **Political/juridical dynamics**	**7.1.1 What is the legal status of the PP in your case and jurisdictions?**	**7.1.2 If applicable, describe the discussion of the acceptability/tolerability/intolerability of risk in regulatory decisions.**	**7.1.3 Has an impact assessment been made prior to the adoption of precautionary measures?**	**7.1.4 Optionally, also consider how other regulatory policies (i.e. ISO, EU bodies, standards, voluntary**

				regulations, research policies) have been used in this case.
New Gene Editing techniques: gene drives			N/A- no impact assessment have been done	

Genetically Modified Organisms (GMOs)	In Bulgaria the regulatory framework on GMOs is defined mostly in the **Law on Genetically Modified Organisms (LGMO)**.The LGMO refers directly to the precautionary principle[16], and explicitly states as its primary objective the need to ensure protection of the human health and the environment from any hazards resulting from the activities it sought to regulate. As Bulgaria is an EU Member		None	

[16] "prioritising the protection to human health and the environment in the face of probable potential adverse impacts regardless of existing economic interests or the absence of scientific proof.

	State, the regulatory framework is based closely on the relevant EU directives and regulations.			

Endocrine Disrupting Chemicals	As chemical substances that are by far and large synthetic, endocrine disruptors are regulated under EU law. The precautionary principle is detailed in Article 191 of the Treaty on the Functioning on the European Union and may thus be invoked for the risk management of EDCs. In practice, EDCs are regulated under various pieces of EU regulation (see the 'List of EU legal acts under which EDCs are regulated' below). This is the result of	It is crucial to note, however, that the development of scientific criteria for the identification of EDCs under the BPR and the PPPR was severely delayed by the European Commission. Two judgments of the European Court of Justice are important with regard to the standard of proof required to identify a substance as a SVHC based on endocrine-disrupting properties. First, in its ruling on Deza versus ECHA (T-115/15 and C-419/17), the Court considered that the "probability that an endocrine disruptor may have adverse effects on the environment is sufficient" to label a chemical as a SVHC (paragraph 173, emphasis ours). Second, in its ruling on Plastics Europe versus ECHA, the Court confirmed this judgment with regard to identifying a chemical as an endocrine disruptor to human health	Different assessment of the impact of PP regulation of EDCs have provided different conclusions (e.g. between ECHA and EFSA)	

	their use in diverse products that are regulated under different pieces of legislation, including pesticides, food contact materials and cosmetics. Strikingly, "different regulatory approaches exist in different pieces of legislation for substances identified as endocrine disruptors" (European Commission, 2018, p. 9). There is thus no harmonised EU legal framework on EDCs (see e.g. Dang et al., 2016). Second, and in contrast to			

	legislation on the environment, regulation of EDCs relating to the area of health and **food safety is not based on the precautionary principle**. Rather, endocrine disruptors are considered "like other substances that can negatively affect human health". Third, also under REACH, which is part of EU regulation on the internal market, EDCs can be subject to authorisation. Here, chemicals suspected of having endocrine-disrupting			

	properties are subject to a risk assess-ment or socio-economic analysis to establish "whether a threshold (safe lev-el) or non-threshold approach is to be applied			

Neonicotinoid insecticides	In the EU, the PP was applied to regulate neonics in 2013 and 2018. These regulations occurred much due to the Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market, which entered into force in 2011. With the procedures this framework provided, pesticides already approved on the European market could be reassessed if new evidence on risks were found. As the research on risks related to neonics increased,		Different assessments of the impacts of PP regulations of neonics have provided different conclusions	

	especially regarding bees that provide significant ecosystem services, the EC requested the European Food Safety Authority (EFSA) to conduct a risk assessment. In 2013, after receiving EFSA's conclusions, the Commission Implemented Regulation (EU) No 485/2013 - banning outdoor use of imidacloprid, clothianidin and thiamethoxam, which are **three of the six neonics** marketed in Europe in crops attractive to bees			

Nano-technologies	At European level, there are various pieces of legislation that regulate nanomaterials in e.g. consumer products, some of them in general and some of them in specific terms. These regulations are implemented in Austria, but also in the other member states of the European Union, within the framework of existing national legislation. REACH Regulation (EC) No 1907/2006		The Commission recommendation for a code of conduct for responsible nanosciences and nanotechnologies (N&N) research (code of conduct) dates from 2008 [24]. Another important approach to regulate the use of nanomaterials and nanotechnologies is standardisation. The Austrians standardisation committee 052.73 "Nanotechnology" consists of experts from research institutions, engineering and safety authorities. Risk management measures are dependent on the sector-specific preconditions	

			and the concrete context where they are applied. An appropriate risk management regime will tremendously differ by scope, accountabilities and responsibilities. Because of the high variance of nanotechnologies and the fairly universal use of nanomaterials it is therefore not possible to give a one-for-all solution which can be applied to all applications and areas. These juridical documents and directives are complemented by a multitude of pre-legal and quasi-legal provisions, such as standards, registries, guidelines and codes of conduct.	

			Nanotechnology registries for example have been established in several countries within the EU and the EEA (France, Denmark, Belgium, Sweden, Norway) and operate in rather different ways. Another important approach to regulate the use of nanomaterials and nanotechnologies is standardisation. Nanotechnology standards are developed in international committees such as ISO/TC 229 "Nanotechnologies" and the CEN/TC 352 "Nanotechnologies" since more than 10 years. They are actively supported on the national level by the national standardisation authori-	

			ties such as DIN (Germany), BSI (UK), AFNOR (France) or ASI (Austria). At the same time risk management procedures have been developed to effectively regulate the use of nanomaterials and nanotechnological procedures at national and international level.	

Glyphosate	Although in the Treaties the precautionary principle is only mentioned Article 191(2) TFEU on environmental policy, it applies also to other policies especially where they are aimed at the protection of public health and human health, which includes the Pesticides Regulation. Therefore, it is not surprising that also Regulation 1107/2009 refers to the principle.		No impact assessment	
Financial risks in water infrastructure planning		This high prioritization of water quality has led to the overshadowing of other risks: expensive measures introduce new dependencies and open the door	Individual studies without direct mention of PP	

		to financial instability.		
The use of Artificial Intelligence in healthcare (CDSS)	General principle in EU law	-	PP has not been applied	

Microplastics in food products and cosmetics	Thus far, there is no European legislation in place to regulating the existence of microplastics, in cosmetics or in food, on the market on European level. Nevertheless, there are several documents that critically assess the way in which microplastics in food and cosmetics could be regulated. Additionally, some EU member states and other countries, such as the United States, have undertaken action to ban the use of intentionally added microplastics.		No impact assessment of the PP has been performed	One regulation where secondary microplastics might be expected is the regulation on Food Contact Material (Regulation (EC) No 1935/2004). This regulation aims to regulate i.a. "materials that can reasonably be expected to come into contact with food". Although this is a very generic description, the regulation does not once refer to microplastics specifically.

				The European Commission has various committees of scientists and other stakeholders in place to provide advice on the risks surrounding microplastics. The World Health Organisation (WHO) on the other hand does not include it in their list of priority environment and health risks(57)

7.2. Risk governance **Political/juridical dynamics; core components**	7.2.1 How has the threshold of damage been set, and met or not met, in existing legal cases or regulatory decisions?	7.2.2 If the PP has been invoked, have both the cost-effectiveness of the measure, and the proportionality of the measure been considered in existing legal cases or regulatory decisions?	7.2.3 If the PP has been invoked, is the measure reversible?	7.2.4 Has a reversal of the burden of proof been specifically implied or requested in legal or regulatory decisions?
New Gene Editing techniques: gene drives				
Genetically Modified organisms (GMOs)				

Endocrine Disrupting Chemicals	For chemicals suspected of having endocrine-disrupting properties, the relevant regulatory agencies, EFSA and ECHA, have thus evaluated whether there is an acceptable level of exposure – that is, a 'threshold' – for both humans, animals, and the wider environment, or not. Strikingly, given that there is no harmonized EU regulatory framework on EDCs, the threshold of damage can be – and has been – defined differently by different authorities, even in cases in which it concerns the same (potential) endocrine disruptor.	As one of the co-legislators in the EU, the European Parliament has in the past explicitly requested a reversal of the burden of proof on EDCs in the context of the 1999 Community strategy for endocrine disrupters (resolution A5-0197/2000). That is, the responsibility for providing the information necessary to approve a chemical should be with the producer rather than with the national or European authorities. In principle, some regulations that concern chemicals with (potentially) endo-		

	Perhaps the most illustrative court case in this regard is that of Plastics Europe versus ECHA (T-636/17) concerning the chemical bisphenol A (BPA).	crine-disrupting properties indeed specify a reversal of the **burden of proof** Yet also here, the standards for the information that producers have to submit are, however, different in the context of different regulations. Most notably, while the ECJ confirmed the reversal of the burden of proof, it also pointed out that the burden of proof is on the Commission when the Commission reviews a chemical before the end of a temporary approval period.		

Neonicotinoid insecticides				
Nanotechnologies				
Glyphosate		When considering the role of cost effectiveness/ proportionality, as glyphosate has been renewed, no cost-effectiveness assessment of a ban has taken place.	With regard to reversibility of the glyphosate renewal in 2017, one has to refer to the possibility to review any approval under Article 21 of the Pesticide Regulation where this is warranted by new scientific findings and technical knowledge.	In the case of pesticide approvals, the manufacturers are required to provide scientific evidence of the safety of their product. Next to performing own tests, manufacturers are required to also compile peer-reviewed scientific literature for the active substance in question

Financial risks in water infrastructure planning	The primary risk of unmet water quality standards was put to the test in the two legal cases. Secondary risks, resulting from the efforts to achieve solutions to the primary problem to cost and date, are not yet subject to the precautionary principle in the water sector.	The quality and sustainability of the infrastructural solutions themselves have not been part of the legal cases. This is largely due to the long construction and implementation periods. Neither proportionality nor cost-effectiveness were met in the case of London and investor interests prevailed.	Obduracy and path dependencies put in place by large-scale physical structures immensely restrict the reversibility of implemented changes.	The European Commission has brought the first evidence underlying the legal case, the burden of proof has since been reversed, so that both cities were under the obligation to document their improved compliance to the UWWTD. Both cities did so successfully.
The use of Artificial Intelligence in healthcare (CDSS)	PP not applied	PP not applied	PP not applied	PP not applied

Microplastics in food products and cosmetics	Following from the little amount of scientific evidence, the lack of a general definition of microplastics and the lack of standardised measurement tools, no threshold of damage has been established yet.		Precautionary measures will be applied when intentionally added microplastics in cosmetics are taken up in the REACH regulation. Consequences of this measure will be completely on the account of the cosmetics industry. In case, after new scientific evidence comes to light, the precautionary measure would be lifted, it can be relatively easy for industry to switch back to using microplastics.	The producer of cosmetics has the responsibility of showing its products are safe. Once the intentionally added microplastics are added to the REACH regulation, the burden of proof is on cosmetic companies accordingly. In order for a product with intentionally-added microplastics to be approved under REACH, the company has to provide evidence to ECHA showing the safety, for both environment and health, of the product. With regard to secondary microplastics and

				the occurrence of microplastics in foods, such as seafood, it is much more difficult to allocate where the **burden of proof** should be.

7. 3 Risk govern-ance **Other dy-namics**	**7.3.1 The scientific-technological environment**	**7.3.2 The economic dynamics**	**7.3.3 Societal interac-tions/norms**	**7.3.4 Other**

New Gene Editing techniques: gene drives	Scientists seem to be getting increasingly wary of the societal backlash of technological harm, and in academic discussions about regulating gene drives, public trust is considered to be paramount. Scientists are also researching technological ways to mitigate gene drives risks. Peer reviewed journals could also have a role to play in governance. The topic of governing the risks of gene drives research and applications has also received quite some attention in academic research and in other reports-	Interestingly, Mitchell et al (2017) argue that safer, self-limiting gene drives provide a better business model. At the same time, emerging economies represent important potential markets for synthetic biology applications and products. Considering the regulatory gaps in many emerging economies, balancing a precautionary approach with potential economic benefits of gene drives could be challenge (Redford et al, 2019).	As gene editing techniques and possibly gene drives become more accessible and democratized, there is a rapidly expanding international ecosystem of actors (Redford et al, 2019), including scientists from different fields, DIY biohackers, NGO's, policy makers, and actors from industry, some of who are involved in a heated discussion around gene drives. Kahn (2020) notes that the technology was new for many members and delegates at the United Nations Convention. For the layperson it is difficult to make sense of the disparate viewpoints represented in the debate: extreme benefits versus extreme danger, worst versus best case scenario's.	

	this literature itself thus contributing to the governance of gene drives. Researchers are also contributing to new risk assessment frameworks that gene drive developers can use. Finally, as tools associated with synthetic biology are becoming increasingly accessible to private actors, the research field is expanding to include actors who may not have the backing of an established institution			

Genetically Modified organisms (GMOs)				
Endocrine Disrupting Chemicals			There has been considerable public pressure to adopt a more comprehensive precautionary approach to the regulation of endocrine disruptors. This pressure comes both from academia, stakeholders such as consumer organisations, think tanks and NGOs, as well as from (some political parties in) the European Parliament.	
Neonicotinoid insecticides				

Nano-technologies	Safety is nothing of all that. Apart from the eminent influence of empirical data on the development of safe machinery and working processes, safety and sustainability have innovative aspects in themselves and considering safety aspects often lead to new and rather unexpected solutions. Therefore, integrating safety aspects in an early stage of technology development can be regarded as fostering innovation rather than hindering it. For this reason, nanotechnology research has been accompanied by safety and sustainability research from the beginning.	Nanotechnological scientific discoveries do not generally change society directly but they can set the stage for change in a context of evolving economic needs. Nanotechnology is so diverse and complex that its effects will take time to work through the socio-economic systems	Public risk perception: The study showed that the topic of nanotechnology was largely unknown to the population. Nanotechnology has been massively influenced by dialogue. The spectrum ranges from stakeholder dialogues to participatory dialogues and even to informational sessions that are now often described as dialogues. Governments also call for and promote dialogue as the political instrument par excellence for the responsible use of nanotechnology. The action plan on nanotechnology of the European Commission as well as numerous national action plans (e.g., Austria, Germany and Switzerland) suggest activities especially in	

	Unfortunately, the recent research policy tends again to favour strictly disciplinary research and limits the space for activities which seeks to employ genuine interdisciplinary research and development of new technologies. The main goal is the integration of safety aspects in innovation processes as early as possible.		two areas in order to achieve responsible risk management. Firstly, it seeks to intensify research on environmental and health risks (EHS), and secondly, it encourages the establishment of scientifically founded risk communication processes in order to contribute to an informed public debate [137]. The media play an important role in the formation of society's opinion by drawing attention to selected topics and bringing them closer to the public. This has been specifically the case for nanotechnologies. The reporting on nanotechnology in the media in the three German-speaking countries is largely science-centred and at-	

			tracts a generally low level of attention amongst the broad public thanks to its less emphasised placing. Finally, a focus on risks and controversial reporting, a concern raised regularly in expert circles, was not observed in the media. Risk topics played a role in fewer than 20 % of articles, whereas the benefits and opportunities of nanotechnology, on the other hand, were mentioned in 80 % of all articles. Benefits are seen above all for science [140]. + politicians and environmental organizations not often interviewed	

Glyphosate			It should be made clear that the debate surrounding glyphosate is deeply entangled with a bigger societal, political, ecological and economical question on the future of agriculture	
Financial risks in water infrastructure planning		There exists also a dedicated instrument for cooperation between economic regulators to encourage innovation and transfer of knowledge on the European Level called European Water Regulators (WAREG)		As mentioned earlier, the water sector is highly integrated into complex urban systems and is regulated at several levels.
The use of Artificial Intelligence in healthcare (CDSS)				

Microplastics in food products and cosmetics	Apart from performing scientific studies, scientists have also engaged in the public discussion on how to deal with the risks concerning microplastics. Several scientists have expressed the criticism that there is mismatch between the state of affairs in science and how this is presented in the media.	Pressure from consumers	Microplastic pollution has gained much public attention in recent years. To a large extent, this movement has been generated by environmental NGOs, who put pressure on policy makers and industry to reduce the use of microplastics. The growing public attention for the issue of microplastic pollution can be seen in a wider context of public movements. The mass media, including social media, has also taken up a great role in raising public awareness for the potential health effects caused by microplastics	

8. Reflection on the PP in the literature	8.1 Who have reflected on (and criticized) the present use and application of the precautionary principle?	8.2 Any alternative proposals for the application and use of the precautionary principle with regards to the case study topic?	8.3 Have stakeholders called for the revision of the PP in the case?	Important relevant context (like economic forces)

New Gene Editing techniques: gene drives	No disagreement on application. There is however disagreement on how the principle should be applied: what do uncertain and potentially irreversible risks of gene drives mean in terms of regulatory measures?	In the NASEM report, it is argued that existing systems to govern biotechnology are adequate in the first phase of contained use of gene drives, but that a precautionary approach might be useful for their experimental release. The IUCN 2019 report concludes that their report should feed into decision making on gene drives that takes place on a case-by case basis, considering the full range of appropriate stakeholders, operating with free access to all information, and informed by the framework of the precautionary principle.		

		The ENSSER report (2019) is very critical of claims that the precautionary principle slows innovation, arguing that objections come down to a misalignment of the technological pathways developed under it with corporate and private interests. General moratorium is proposed by some		

Geneticall-y Modified Organisms (GMOs)	All the experts we interviewed for this case study recognised the importance of the precautionary principle as a cornerstone in the GMO regulations, and no one criticised the principle as such. However, they all agreed that the problem is how the principle is being used politically. "state of perversion, not a state of precaution", because even though contained use is not banned, field experiments are impossible, which in turn makes it impossible for scientists to validate the results of their work and establish the safety of any GMO they developed. As a consequence, Bulgaria can import particular GM seeds from other countries, for which all risk assessments have been carried out, and use them as	The review of the debates on the LGMO in Section 4 suggest of a variant of the precautionary principle that could be characterised as a strong precautionary principle. It is generally understood in opposition to cost-benefit approaches, ignoring the highest expected utility at the expense of adopting explicitly cautious approach to risk management. This is precisely the approach followed by several cohorts of parliamentarians since at least 2003.		

	feed, but Bulgarian scientists cannot develop their own.			

Endocrine Disrupting Chemicals	See previous table on social dynamics	No, but; In view of the "dilemma" concerning the regulation of EDCs, in the long term he – amongst other recommendations – calls for open support to the EU regulatory agencies from "neutral, evidence-based and trusted third parties such as senior academics". To him, such alliances may help to rebuild public trust in "science-based policy making"		

Neonicotinoid insecticides	Industry stakeholders have criticised the use of the PP to restrict neonics. The critiques are related to different aspects of proportionality; adapting different restrictions to more proportionate to the different uses of neonics, and that the process of applying the PP should include an impact analysis NGOs and some independent researchers have criticised that the PP was applied too late and for too few types of insecticides.		Industry stakeholders have called for a revision of ECs application of the PP to ban three neonics, through filing court cases against the EC. Answering the question: 8.3 Have stakeholders called for the revision of the PP in the case?	

Nano-technolo-gies				
Glypho-sate	The use of the precautionary principle in the approval proce-dure of glypho-sate and the pes-ticides frame-work in general have been ex-tensively reflect-ed on and criti-cised	Not only the risk assess-ment process was criticized for a lack of transparen-cy, but also the risk management process was deemed to lack trans-parency		
Financial risks in water in-frastruc-ture plan-ning	Even though the precautionary principle lies at the very founda-tion of regulating urban water, it is rarely reflected upon.			
The use of Artificial Intelli-gence in healthcare (CDSS)	PP not applied. Reflections on possible applica-tions have been made by scholars	yes	Yes (?)	

Microplastics in food products and cosmetics	In general, the precautionary principle is seen as useful to deal with microplastics	This criticism is specifically coming from the Italian cosmetics industry. They are a large producer of products containing intentionally added microplastics. They argue that limiting the use of microplastics as proposed in the REACH regulation is too cautious, by not making any distinction between different types of microplastics. On the other hand, environmental NGOs argue that the precautionary principle is not applied strict enough and see loopholes for industry in the proposed ban for intentionally added microplastics in cosmetics via REACH	Not mentioned	

9. Effect of the PP on innovation pathways	9.1 What alternative innovation pathways can or has the PP opened up, if any?	9.2 Other innovation pathways in other geographical regions	9.3 Other types of solutions than innovation?	9.4 Regrettable substitution?
New Gene Editing techniques: gene drives	Gene drive developers are building in precaution with self-limiting gene drives.			
Genetically Modified Organisms (GMOs)	Precaution prohibits all GMO-related innovation. In the Bulgarian case, the *de facto* ban on GMOs did not lead to the pursuit of an alternative innovation path	Not mentioned	Not mentioned	Not mentioned

Endocrine Disrupting Chemicals	More precaution could lead to radical innovation (green chemistry)		From this perspective, hence, "innovation must be driven by focusing on the demand side" rather than by legislation, which "takes too long" (Jones, 2013). Possible pathways to create such 'demand' for innovation are the development of letters of intent to buy new products that are free of EDCs, as well as public scrutiny of the behaviour of global brands (ibidem). Political initiatives and policy steps towards the development of a circular or bio-based economy can be seen as another important 'push' for innovation on the front of substituting EDCs.	There is some evidence that bans on the use of particular EDCs have led to so-called 'regrettable substitutions': the introduction or adoption of chemicals that may not be safer and potentially worse. It can be argued that such substitution is facilitated by the case-by-case approach of current EU regulations that govern endocrine disruptors. That is, a chemical that is highly similar to a previously banned chemical is not automatically also banned The regulation of cer-

			Indeed, NGOs and think tanks, as well as political parties on the left/green spectrum of the political debate have brought up so-called 'sustainable innovation' as an alternative to the current approach	tain EDCs can thus lead to a domino effect, in which there are new complexities, uncertainties and ambiguities about the hazards and risks of regrettable substitutes.

Neonicotinoid insecticides	Firstly, history has shown that innovations of new pesticides do appear under restrictions, because new crop protection practices (including new pesticides) are often created as a consequence of other practices being banned. Secondly, Milner and Boyd (2017) mention that, when not too abruptly, the withdrawal of pesticides can incentivise innovations, not only of new types of pesticides but also of innovations around cultivation methods. This opens up for a broader perspective on innovation, not only seeing innovation as developing new types of plant protection products. Regarding the application of		Lastly, the IPM framework also includes the possibility of 'social innovations'.	

	neonics, some mitigative innovations have taken place for reducing the emissions of neonics. Particularly, there has been improvements of technical means of treatment recipe, improvements to the quality of seed treatment formulations, and modifications to planting equipment using deflector techniques that reduce emission of dust during sowing of seeds coated with neonics Another innovation pathway is to look towards the development of new plant protection technologies that could be promising for having the benefits of plant protection with less collateral damage to the environment and human health include nanopesticides			

	However, there are also innovations of non-chemical alternatives to neonics for pest management.			

Nano-technologies	green engineering/green nanotechnology; Safe-by-design approaches are heavily discussed			
Glyphosate	debate surrounding the glyphosate re-approval has been a catalyst for rethinking pesticide use and farming in general - will lead to innovation			
Financial risks in water infrastructure planning	The case shows how the PP contains an innovation dimension The two cities utilized different strategies for overcoming their specific infrastructure gaps. Both of these strategies resulted in specific innovation pathways			This balancing of risks in a multi-risk environment is one of the key challenges to the precautionary principle in the infrastructure sector, where the regulation of one aspect can lead to the introduction of regrettable substitutions

				elsewhere.
The use of Artificial Intelli-gence in healthcare (CDSS)	The PP has not been applied, but precaution has led to more responsible and human-centric AI (for example safe-by-design, explainable AI)			No

Microplastics in food products and cosmetics	because the upcoming ban for microplastics in cosmetics via REACH, industry is working on innovation in cosmetics. For microplastics in food, no innovation is seen. Prohibiting the use of these primary microplastics is therefore relatively easy, yet can be very expensive for industry. Although the benefits of microplastics in terms of product characteristics are real, alternatives are available. For example, natural, degradable particles or fibres like coffee, sugar or salt can be used as replacement to synthetic polymers. The European Commission recognises that the plastic industry is a big driver for European economy.	Regulation on microplastics in amongst others the USA, with the Microbead Free Water Act, the USA was the first country in the world to ban all intentionally added microplastics in cosmetic products.		

	Improving its sustainability will bring forward new business opportunities and accordingly create new jobs.			

10. Innovation principle	10.1 Which stakeholders invoked IP? Are there plans to invoked it?	10.2 How is the IP positioned? How could it be positioned (if not invoked)?	10.3 How was it juxtaposed to the PP?	10.4 Did the IP have any effects on the innovation pathways?
New Gene Editing techniques: gene drives		The IP has not been referred to		
Genetically Modified Organisms (GMOs)	-	There is no evidence of the innovation principle being applied, or even considered at any stage of the evolution of the GMO legislation. However, It is not difficult to ascertain that the restrictive GMO legislation, strongly focused on risk avoidance, pays little to no consideration to innovation, particularly when it comes to	-	-

		biotechnolo-gy use in agriculture.		

Endocrine Disrupting Chemicals	Some stakeholders in the discussion about EDCs, mostly from the chemicals industry, have invoked an 'innovation principle' so as to prevent further regulatory bans on EDCs. Stakeholders who have advocated this include the UK-based Chemical Industries Association (CIA), the Brussels-based European Chemical Industry Council (Cefic), and the European Risk Forum (ERF), but not the pan-European association of plastics manufacturers, PlasticsEurope.	Mentioned that PP regulation of EDCs (e.g. of phthalates) would hinder innovation. Notably, the UK-based Chemical Industries Association has argued that "there is a danger […] that innovation be hindered where benefits of new technologies and solutions cannot be considered alongside potential risks, an example being a cancer treatment drug that uses the mechanism of endocrine disruption to kill cancer cells	It is also notable that in its influential 2015 document setting out the 'innovation principle', the ERF explicitly mentions examples of chemicals that were regulated given (uncertain) evidence about endocrine-disrupting activity. Discussing public attitudes towards risks, ERF brings up EU regulation of endocrine-disrupting neonicotinoid insecticides. It argues that this is an example of a regulation that is not based on scientific risk assessment and established toxicological models. For ERF, such "systemic short-term risk aversion" and "inappropriate and disproportionate" use of the precautionary principle unnecessarily amplifies public concerns (ERF, 2015, p. 15).	-

Neonicotinoid insecticides	In this case, we have only found one direct mention of the 'Innovation Principle' directly in relation to neonics. In an article in the Agrochemical magazine 'Outlooks on Pest Management, Robin Blake (a Senior Consultant for Compliance Services International (CSI), chair of the Agrisciences committee for the Society of Chemical Industry and Associate Editor for the journal Pest Management Science), argue that the application of the PP in the case of neonics is at odds with the desire to innovate and the "Innovation principle" – whenever policy or regulatory decisions are under consideration the impact on innovation as a driver for jobs and	Mentioned that the PP regulation of neonics reduces companies desire to innovate	He further goes on to argue that the PP and IP should be complementary, recognizing the need to protect society and the environment while also protecting the EU's ability to innovate (Blake, 2018). In this paper, it is however not clear exactly how the PP and IP should be balanced, but there seem to be a focus on economic impact assessments. This raises a fundamental problem, namely that economic impact assessment belongs to the domain of the prevention principle where costs and risks can be quantified. The Precautionary Principle is introduced for uncertain risks, where one cannot weigh fundamentally unknown costs to fundamentally unknown benefits	

	growth should be assessed and addressed.			
Nanotech-nologies		Has not been men-tioned ex-plicitly but foster-ing innova-tion plays a central role in NT-research	On the national level the innova-tive potential of these new group of materials has been always tightly linked to safety consider-ations.	

Glyphosate	This study has not found evidence that the innovation principle has been invoked formally in the context of the debate surrounding glyphosate.	Not been referred to explicitly		
Financial risks in water infrastructure planning	-	The innovation principle has not been explicitly addressed in either case. In the case of London, however, the prioritization of a solution driven by financial innovation shows that the innovation principle was applied here. The cases however make an interesting argument for the innovation dimension already being contained within the pre-		

		cautionary principle. As stated before, this case study differs in the regard that it does not have the introduction of a new technology or product as its subject, but that it inspects the consequences of the ongoing employ of the precautionary principle as a guiding principle in the water sector.		

The use of Artificial Intelligence in healthcare (CDSS)	The Information Technology and Innovation Foundation (ITIF) has advised that the innovation principle instead of the precautionary principle should be applied by policy makers when AI is concerned. The European Commission has also connected the innovation principle with AI in a communication on AI in 2018 The Centre for European Policy Studies also mentions AI in its 'study supporting the interim evaluation of the innovation principle'	The ITIF relate the innovation principle to the conviction that '(…) because the overwhelming majority of technological innovations benefit society and pose modest and not irreversible risks, government's role should be to pave the way for widespread innovation while building guardrails, where necessary, to limit harms.'	The Information Technology and Innovation Foundation juxtaposed the PP to the IP: , They juxtapose the innovation principle to the precautionary principle: 'While some people advocate for an almost completely hands-off approach to regulating new technologies, those who recognize that there is a legitimate role for government take two distinct approaches toward action: the precautionary principle and the innovation principle.'	No

Microplastics in food products and cosmetics	As mentioned in paragraph 3.5, Italian cosmetic producers mentioned that the role of industry is not represented sufficiently in the current proposal to limit the use of microplastics via REACH. Implicitly here a link is made with the innovation principle, by saying that the industry perspective should be weighted in setting boundaries for specific microplastics. However, in official documents this view is not discussed.	The IP is not mentioned		

11. Synthesis	**11.1 The role of complexity, ambiguity and uncertainty in understanding your case**	**11.2 Risk governance of uncertain risks:** **How did the geographical region deal with the risks and what factors played a role?** **How did these representations relate to what we know now?**	**11.3 The overall tension between PP/ IP:** **The possibility of win-lose, lose-lose, and win-win dynamics between precaution and innovation** **Whether the IP can improve these dynamics, or whether (other) changes would need to be made to the PP to accommodate the issues in your case.**	**11.4 Recommendations to the cross-case comparison team**

New Gene Editing techniques: gene drives				A precautionary approach can benefit both science and society. The PP does not mean all/nothing- but should be introduced early in tech development, provide guidance to developers & involve broad stakeholder perspective. Political debate should start from realistic representation of both benefits and risks. A heated debate on gene drives technology shows disparate viewpoints on the technology's risks and how to govern them: extreme benefits versus extreme danger, worst versus best case scenario's and a global moratorium versus slight adaptations of current risk as-

				sessment frameworks. Second, gene drives bring with it an interesting conundrum: in order to reduce the epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. Transboundary risk is difficult for involving stakeholders

Genetically Modified Organisms (GMOs)				GMOs have been considered as synonymous to risk, and are not well perceived in the country. The attitude among legislators reflects a strong precautionary principle whereby risks are assumed to be highly probable, without cost-benefit consideration. The case also demonstrates how scientific uncertainty can translate into legislative uncertainty, due to different interpretations and perceptions of the scope, severity and impact of risks. Thus a very relevant question for GMO research in Bulgaria is whether there will be sufficiently motivated (young)

				scientists, who would build further the national knowledge base on GMOs, who would be capable of advising – impartially and objectively - regulators and authorities in the future should this become necessary. The innovation principle can hardly provide or be a solution in this case. As the authors of the case study, we consider this to be a specific example of how precautionary thinking can in fact have a wider scope that a normative interpretation of the precautionary principle/approach.

Endocrine Disrupting Chemcials			As shown in our case study, even if ECDs are regulated, this can lead to regrettable substitutions, which can be seen as a 'lose-lose scenario': it is costly for the regulator and costly for the company in question	Need for regulatory transparency and harmonised EU legal framework, perhaps including a horizontal definition of EDCs. This dilemma is very much apparent in what has been coined a **"regulatory stalemate"** that the EU is currently facing when it comes to "the risk assessment required under the precautionary principle" (Garnett, van Calster & Reins, 2018, p. 12). It is the nature of the system – or the 'path dependency' of the EU criteria for the regulation of risks – that makes quick action on the basis of invoking a precautionary principle impossible. Closely linked to this observation is the

				fact that **reversing the burden of proof is often practically unfeasible and very costly**, when the precautionary principle is playing 'catch-up'

Neonicotinoid insecticides	Throughout this case, it is evident that complexity and scientific uncertainty is at the heart of the controversies around the application of PP to regulate neonics		In this case, the balancing of PP and IP seem to depend a lot on the framing of innovation. If innovation is defined narrowly, in this case as innovating new plant production products, then balancing the PP with innovation concerns creating more predictability in the EU legal framework (in this case, especially considering article 21 of regulation 1107/2009), formalizing an impact analysis, and making more time for creating more certainty in risk assessments. Perhaps the issue on impact assessment could be considered when balancing the PP and IP. However, it raises the question 'what kind of	Risk assessment guidelines need to be updated as innovations develop, and independent research should be included in risk assessment process Key promises of the neonic innovation included: carefully targeted, high specificity. Both proved to be wrong. Regulatory science and risk assessment frameworks lag systematically behind new scientific insights with huge time delays, as evident in that the Bee Guidance document, drafted in 2013, still not is fully approved and employed in regulatory assessments of new pesti-

			impact and for whom'?. If one opts for a broader definition of innovation, one could see more realistic possibilities for balancing the PP and the IP, more in line with the Integrated Pest Management approach and with Responsible Research and Innovation (RRI)?	cides. - There are major epistemic controversies on **weight of evidence**

Nano-technologies	Lack of data and/or measuring procedures contribute to statistical uncertainties, the formation of new borders of the research field lead to terminological and linguistic vagueness, and new results of various and very different research projects are object of cognitive discourse and ambiguous interpretation. For all these reasons an appropriate regulation of emerging technologies is not that much risk management than the management of uncertainty depending both on the quality of the available information and of the willingness of people with very diverging interests	Science, especially Technology Assessment, is able to make an important contribution to identifying, structuring and evaluating the available information on a certain technology when it is in its infancy. An independent and neutral actor is necessary to provide a platform of deliberation which is trusted by many if not all concerned parties. In the case of the nanotechnology debate during the last decade scientific actors have been central organisers of inter- and transdisciplinary risk and uncertainty assessment procedures.		safety and sustainability measures have to be integrated in F&E at a very early stage. They have to be integrated in research programmes more tightly - this needs to be associated by appropriate communication processes between R&D and safety research; safety research regarding new technologies has to be independent; continuity of the communication processes is decisive - these are long-term processes highly dependent on trust and confidence; risk evaluation of new technologies is mainly uncertainty analysis and depends on proper processes for structuring

Glypho-sate		What is re-markable about the risk govern-ance on EU level is that the existence of scientific uncertainty is not recog-nized	What is clear is that the glyphosate controversy, together with the debate surrounding other pesti-cides such as neonics, has reinvigorated the public and political pres-sure to re-think the use of pesticides in European agriculture. In this regard, the precau-tionary prin-ciple has been a catalyst for innovation.	PP in risk management should be more trans-parent; re-think role of independent scientist and the insights their studies can offer

Financial risks in water infrastructure planning	Scientific uncertainty is defined by increasing complexity across the three risk groups. The financial risk group becomes even further complicated by the fact that certain actors profit from this complexity and instrumentalize it to their own ends. This emphasizes the critical role of ambiguity in the sector, as costs and impacts are spread across society for extended periods of time, the consensus process itself is critical for successful project developments.	If we compare the different approaches to risk governance of these specific infrastructure projects in London and Milan, we see the innovation principle at work in London, but RRI in Milan.	It details the innovation dimension inherent in the precautionary principle The first occurrence of innovation is within the financial sector, where the precautionary principle creates a need that could not be met by existing strategies and tools, which thus encourages the development of new solutions. The second area of innovation is within the development of the infrastructural solutions themselves. The Tideway Tunnel project is filled with technological innovations that make the construction of a tunnel under a river	PP needs to consider multi-risk environments As the cases have shown, transparency is a fundamental issue for achieving balanced solutions which take the multi-risk environment and long timescales into consideration. These uncertainties become further complicated by the fact that decision making processes are always defined by those actors who end up at the table. Their particular evaluation of significant timescales, complex interrelations of risks and eventual personal benefits have significant impact on whether solutions will be achieved proportionally and in a cost-

			across the breadth of city possible.	effective manner

The use of Artificial Intelligence in healthcare (CDSS)	The risks are all characterized by a high degree of uncertainty: both with regard to their precise effects and with regard to their probability First of all, this uncertainty is highly dependent on the specific technological properties of a CDSS Secondly, the use of CDSS is characterized by uncertain risks due to the nature of the environment in which it is implemented. A third cause for the uncertainty around the risks of CDSS is the variability in the nature of the risks, which makes them difficult	First of all, precaution towards the limits and risks of CDSS was already voiced early on by a variety of researchers in the field of AI. Secondly, precautionary thinking about the specific design of CDSS also seems to have been present early on. Thirdly, EU risk governance around CDSS seems to have emerged in the context of a strong economic incentives. Fourthly, the risks of CDSS have been embedded in a complex web of EU legislation.	The precautionary principle seems to be potentially applicable to CDSS, but only on a strict case by case basis. In extreme cases the risks of implementing a CDSS meet the criteria of the threshold of damage (public health and human rights). The innovation principle does not seem to be particularly relevant in this case. Careful considerations about the uncertainties and requirements of CDSS in the vulnerable domain of healthcare, logically seem to have the upper hand over the benefits of innovation in terms of jobs and economic growth or the	There are similarities between the nature of challenges faced in the area of the data protection laws and environmental laws. Many of the most serious risks of CDSS are related to the violation of human rights. Many of the risks of CDSS are new 'types' of risks. CDSS, and AI systems in general, are (generally) geographically closed off systems. It should however be noted that a disruption of a healthcare system by a CDSS can also have additional effects on societies as a whole.

	to assess	To reduce complexity and legal uncertainty, the European Commission has recently undertaken a variety of initiatives that are more specifically aimed at AI and the risks of AI (in healthcare).	health benefits that CDSS may offer in the long run. Especially because many of the risks surrounding CDSS are about the question if the automation of decision making is desirable and beneficial in the first place.	This case is primarily about risks that ultimately come down to 'interaction' between humans. CDSS are made by humans, for humans, used by humans, on humans.

Microplastics in food products and cosmetics	Looking at the different components of the precautionary principle, the risk characteristics of scientific uncertainty, complexity and ambiguity seem to be met. Looking at the legal practice, actually applying and enforcing the precautionary principle seems to be complicated, especially with regard to microplastics in food. Namely, there is no general definition of the concept 'microplastics'. Much variation in microplastic substances and a lack of valid and credible measurement tools to determine the amount of microplastics in food and cosmetics, complicate the perfor-		Plastic is inself an innovation that has brought many positive sides as well, because of its low weight and long durability. Precautionary actions to reduce the amount of microplastics in food should deal with the amount of plastics in general, e.g. in packaging materials. Via plastic pollution in the ocean, these microplastic particles end up in food products, such as sea food. However, replacing plastic in packaging by other materials, such as glass containers or paper bags, bring other negative side effects, such as high weight and short shelf-life. The downsides of these alternatives should	Definition of microplastic and appropriate measurement tools are needed in order to put regulation in place and check for compliance. Potential implementation of the PP (for microplastics in cosmetics) already promotes innovation towards more sustainable solutions. In applying the precautionary principle it is therefore important to focus not only on the 'better safe than sorry principle', but also take into account substitution strategies, cost-benefit analyses and life-cycle assessments. This trade-off between plastics and other materials should be performed at different levels, in order

	mance of scientific research and assessment of risks.		be weighted in taking strong precautionary actions. Also innovations in the direction of biodegradable microplastics (to be used also in cosmetics) are not undeniably positive, since uncertainty exist on how they degrade in the environment.	to act responsibly with regard to the social, economical, environmental and human perspective.

7. References

Aven, T., and O. Renn (2010). Risk Management. Risk Management and Governance. 121–158. Berlin: Springer Science+Business Media.

Aven, T., Ben-Haim, Y., Andersen, H. B., Cox, T., Droguett, E. L., Greenberg, M., & Zio, E. (2015). SRA glossary. *The Society For Risk Analysis*, 1-16. https://www.sra.org/wp-content/uploads/2020/04/SRA-Glossary-FINAL.pdf.

Böschen, S. (2010). Reflexive Wissenspolitik: die Bewältigung von (Nicht-) Wissenskonflikten als institutionenpolitische Herausforderung. In Umwelt-und Technikkonflikte (pp. 104-122). VS Verlag für Sozialwissenschaften.

Collingridge, D. (1980): The Social Control of Technology. New York: St. Martin's Press; London: Pinter.

COM (2020) Communication from the EU Commission: Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, No. No 667, 15.10.2020. https://eur-lex.europa.eu/resource.html?uri=cellar:f815479a-0f01-11eb-bc07-01aa75ed71a1.0003.02/DOC_1&format=PDF

Dreyer, M., & Renn, O. (2009). *Food safety governance*. Berlin: Springer.

Funtowicz, S. O., & Ravetz, J. R. (1993). Science for the post-normal age. Futures, 25(7), 739-755.

Giegel, H.-J. (1998): Gesellschaftstheorie und Konfliktsoziologie. In: ders. (Hrsg.): Konflikt in modernen Gesellschaften. Frankfurt am Main: Suhrkamp, S. 9-28.

IRGC (2018). Guidelines for the Governance of Systemic Risks. Lausanne: International Risk Governance Center (IRGC).

Linkov, I., Anklam, E., Collier, Z. A., DiMase, D., & Renn, O. (2014). Risk-based standards: integrating top–down and bottom–up approaches. Environment Systems and Decisions, 34(1), 134-137.

Lau, C. (1989): Risikodiskurse. Gesellschaftliche Auseinandersetzungen um die Definition von Risiken. In: Soziale Welt 40, S. 418-436.

Nowotny, H. (2003). Re-thinking science: From reliable knowledge to socially robust knowledge. Entangled Histories and Negotiated Universals, 14-31.

Nowotny, H., Scott, P., Gibbons, M., & Leydesdorff, L. (2001). Books-Re-Thinking Science: Knowledge and the Public in an Age of Uncertainty. Science and Public Policy, 28(6), 484-486.

Rosa, E. A. (1998). Metatheoretical foundations for post-normal risk. Journal of Risk Research, 1(1), 15–44. https://doi.org/10.1080/136698798377303

Renn, O., Baghramian, M., & Capaccioli, M. (2019). Making sense of Science for policy under conditions of complexity and uncertainty. SAPEA.

Renn, O., Klinke, A., & van Asselt, M. (2011). Risk governance: Coping with complexity, uncertainty and ambiguity—A synopsis. AMBIO, 40(2), 231– 246.

Renn, O. (2008). White paper on risk governance: Toward an integrative framework. In Global risk governance (pp. 3-73). Springer, Dordrecht.

Vos, E. & de Smedt, K., (2020). 'Taking stock as a basis for the effect of the precautionary principle since 2000', RECIPES WP 1 Report ,available via: https://recipes-project.eu/sites/default/files/2020-03/Report%20Taking%20stock%20as%20a%20basis%20for%20the%20effect%20of%20the%20precautionary%20principle%20since%202000.pdf, last accessed: 02.12.2020.

van Asselt, M. B. A., & Vos, E. (2012). EU Risk Regulation and the Uncertainty Challenge. In S. Roeser, R. Hillerbrand, P. Sandin, & M. Peterson (Eds.), Handbook of Risk Theory. Springer Netherlands. http://www.springerlink.com/index/10.1007/978-94-007-1433-5

Van Enst, W. I., Driessen, P. P., & Runhaar, H. A. (2014). Towards productive science-policy interfaces: a research agenda. Journal of Environmental Assessment Policy and Management, 16(01), 1450007.