D2.4.1 Intra case study analysis

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1 Introduction

This document fulfils RECIPES delivery 2.4.1, the intra-case study analysis. 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.

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 will examine 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, to understand the different stakeholder perspectives. In the analytical phase of the project, an innovative conceptual framework for comparative multiple case study analysis will be 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 compiles all nine case studies carried out in the RECIPES project.

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 2.4.1: Intra-case study analysis. WP2 tasks 1-4 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 nice 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.

In the following sections the nine case studies are provided.

New gene-editing techniques: a focus on CRISPR-Cas9 gene drives

Rosanne Edelenbosch

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Abstract

The main research aim of this RECIPES case study is to understand the complexities and controversies around the possible application of the precautionary principle to CRISPR-cas9 based gene drives. The study focuses on the risk governance of gene drives at the EU level, while taking into account the broader international context.

Synthetic gene drives could be used to spread artificially modified genes through wild populations faster. The development of this technology has taken flight since the 2012 discovery of CRISPR-cas9, a new tool capable of engineering the genomes of diverse species. Gene drives promise to enable the suppression or even elimination of a population, or to make a population more resilient. So far, CRISPR-cas9 based gene drives laboratory research has been done in yeast, fruit flies and three different mosquito species.

Gene drives are increasingly becoming important areas of public health and biosecurity research. They are aimed at the improvement of human health through the elimination of vector borne-disease, for conservation purposes through the elimination of invasive species or gain of function of the species under threat, and for agriculture, through the elimination of pests and weeds. The main promise of a gene drive is that it would spread itself, but at the same time, release into the environment can also give rise to systemic risks. In addition, gene drives could have economic and social effects that are beneficial in the short term, but fail to take into account more fundamental issues like poverty or climate change.

Experience with current methods of risk assessment offers little knowledge about the release of a gene drive into the environment. In order to reduce epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. This translates into great challenges for the regulation of gene drives that are further exacerbated by the technology being able to spread beyond regulatory borders.

The EU works under the Convention on Biological Diversity (CBD) and the Cartagena Protocol on Biosafety, that allow for some, well-regulated risks in gene drives research. Currently in the EU, CRISPR-cas9 and gene drives are within the scope of GMO regulations. GMO developers have to apply for authorization under the Deliberate Release Directive. This application process has not resulted in authorization for cultivating GMOs in the EU since 1998.

In 2018, the European Food Safety Authority (EFSA) was mandated by the European Commission to identify potential risks in terms of impact on human and animal health and the environment that gene drive modified organisms could pose and to look for potential novel hazards of gene drive modified organisms. They have concluded that the risk assessment approach for gene drives can build on the existing comparative risk assessment paradigm for GMOs, but that some aspects, including the effect on a population level of the inheritance of the selfish genetic element and the large step to open field-testing, require further consideration or updated guidance.

The possible risks associated with gene drives have also been governed in ways other than laws and regulations. As gene editing techniques become more accessible and democratized, there is a rapidly expanding international ecosystem of actors involved in a heated discussion around this technology. Scientists are taking it upon themselves to fill the regulatory gap by designing soft rules for application, engaging with the public, and also developing technological ways to reduce the risks of field testing.

The findings of this study suggest that a precautionary approach does not need to block innovation. All stakeholders involved seem to agree that a precautionary approach to gene drives is necessary, including the scientists developing gene drives. However, there

is less agreement on what this approach would entail. Some argue that if applied in an earlier research phase, precaution could lead to other innovation pathways that depart from the underlying causes of the problem. Others see a solution in building precaution into gene drives that are safe by design. In both approaches, the engagement of a broad group of stakeholders in early research phases is crucial. Risk governance should not only focus on mitigating risk, but also on the promotion of research opportunities with aims and in contexts that justify the use of particular types of gene drives and have a responsible business model- while keeping in mind alternative ways of approaching the problem that gene drives aim to solve. This is not something that gene drive scientists can do alone.

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List of abbreviations

CA	Consortium Agreement
CBD	Convention on Biological Diversity
CC	Consortium Committee
DARPA	Defence Advanced Research Projects Agency
DOA	Description of Action
EFSA	European Food Safety Authority
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GA	Grant Agreement
GMA	Genetically Modified Animal
GMO	Genetically Modified Organism
LMO	Living Modified Organism
PCG	Project Coordination Group
PO	Project Office
RIVM	Dutch National Institute for Health and the Environment
WP	Work Package

1 Introduction

1.1 Introduction

Usually, a genetic change in one plant or animal takes a long time to spread through a population. That is because the gene is inherited by only half the offspring (Ledford 2015). Gene drives promise to facilitate the spread of artificially modified genes through entire populations (Frieß et al, 2019). This way, populations in the wild could be suppressed or replaced by a genetically modified one. Gene drives are present in nature, and using CRISPR-cas9, a new genetic modification technique, they can also be created synthetically. Gene drives promise to contribute to public health, the conservation of nature and agriculture. So far, CRISPR gene drives laboratory research has been done in yeast, fruit flies and three different mosquito species (Raban et al, 2020).

The past years have however witnessed a heated debate about the application of gene drives. For the layperson –and this includes many regulators– 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.

Gene drives promise to promote public health by eradicating populations of organisms that transmit infectious pathogens between humans (vectors), such as mosquitos transmitting dengue or malaria. For the conservation of species, gene drives can be used to either eliminate threats (for instance, invasive pests) or to adjust the threatened population. Potential benefits of using gene drives compared to other technologies are its potentially rapid effect targeted to a specific population, and the ability to reach remote areas that are difficult to access.

However, the capability of gene drives to spread and invade, which is necessary to genetically engineer wild populations of animals and plants, can also be considered its greatest risk. A lack of spatio-temporal control could potentially affect whole species and/or associated ecosystems (Cotter et al, 2020). The uncertainty about these risks is substantial, and the interaction between gene drives and the environment requires an entirely new field of knowledge. Problematically, the field trials necessary to learn more about these risks are themselves not without risk. Caution is therefore warranted in taking the (research) steps necessary for implementation.

In 2019, calls for a global moratorium at the United Nation Convention of Biological Diversity were dismissed, although precautionary steps were taken in requiring a step-by-step, case-by-case risk assessment of gene drives research. There are layers of uncertainty, complexity and ambiguity present in both the scientific evidence and the governance of risks associated with gene drives. This makes this technology an interesting case for learning about the complexities and controversies around the application of the precautionary principle- the main aim of RECIPES WP2.

The study focuses on the risk governance of gene drives at the EU level. As gene drives are a technology that can cross regulatory boundaries, the broader international context was also taken into account. The research was conducted through a literature review, and results were validated during three interviews with gene drive experts

1.2 Key timeline

Political	*Legal*	*Science/risk assessment*	*Public debate*	*Other*

Year	Event	Relevance to case study
1960	Craig, Hickey and VandeHey publish 'An Inherited Male-Producing Factor in Aedes aegypti' in *Science.*	First proposal theoretical concept for gene drives.
2001	The EU Directive 2009/41/EC on the contained use of genetically modified micro-organisms becomes effective.	This Directive explicitly takes the precautionary principle into account and sets out a step-by-step approach for introduction of a GMO into the environment.
2003	Burt publishes 'Site-specific selfish genes as tools for the control and genetic engineering of natural populations' *in Proceedings of the Royal Society.*	First proposal to synthetically engineer gene drive using homing endonucleases.
2003	The Cartagena Protocol on Biosafety to the Convention on Biological Diversity becomes effective.	The Biosafety Protocol makes clear that products from new technologies must be based on the precautionary principle.
2009	The EU Directive 2009/41/EC on the contained use of genetically modified micro-organisms becomes effective.	The Contained Use Directive establishes that risks to human health and the environment of the contained use of a new GMO must assessed before research commences.
2012	Jinek et al publish 'A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity' in *Science*.	First proof of principle that CRISPR-cas9 can be used to perform genome editing.
2014	Oye et al publish 'Regulating Gene Drives' in *Science*.	First CRISPR-cas9 gene drive reported.
2015	Liang, P. et al publish 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes' in *Protein Cell.*	First successful applications of CRISPR Cas9 in humans.
2016	At the Conference of the Parties of the Convention for Biological Diversity, environmental activist organizations call for a global moratorium on field research.	A global moratorium would invoke a strong interpretation of the precautionary principle (this call was rejected).
2018	The European Commission gives the European Food Safety Authority (EFSA) a mandate to determine whether the existing guidelines for risk assessment are adequate and sufficient for gene drive modified organisms.	First time the EU considers gene drives as a new genetic technique that warrants a potentially specific approach.
2019	Again, at the Conference of the Parties of the Convention for Biological Diversity, environmental activist organizations call for a global moratorium on field research.	A global moratorium would invoke a strong interpretation of the precautionary principle.

2019	See above. A global moratorium is rejected, and the Convention allows some, well-regulated risk in gene drives research.	This is a "weak" interpretation of precautionary principle.	t h e
2020	The EFSA publishes 'The 'Evaluation of the adequacy dives for the molecular characterization and comparative environmental risk assessment of although genetically modified insects with consideration. synthetically engineered gene drives'. What this means in practice remains yet uncle ar.	The EFSA concludes that the existing EFSA guidelines for assessment approach for gene build on the existing assessment paradigm for GMOs, some aspects need specific	r i s k c a n r i s k

2 Gene Drives

Essentially, a gene drive is a genetic element that allows a trait to be inherited more frequently than normally seen in Mendelian inheritance. In other words, they cause more offspring to have the driven genetic trait than individuals in the parent population, allowing "one to affect many" (Esvelt, 2017).

The idea of 'driving' a particular gene through a population is not new. In 1950, Hermann Muller, who was awarded a Nobel Prize for his work on radiation-induced genetic mutations, received a letter from entomologist Edward Knipling asking him whether genetically sterilized pest insects could be used to eradicate damaging species. This led to the rearing and release of hundreds of millions of irradiated insects to successfully eradicate screwworm, a major cattle pest in the US. In order to broaden the reach of this technology, researchers continued to think about means by which genetic traits could spread through a population even though they decreased the insect's fitness (Brossard 2019). This idea would however take several decades to be put into practice. A theoretical concept for gene drives was proposed in 1960 by Craig, Hickey and VandeHey (1960) and Hastings (1994) suggested to use so called "selfish genes" for that purpose. In 2003, Burt introduced the possibility of using naturally occurring selfish 'homing endonucleases', a genetic element that copies itself onto the competing allele. This made gene drive research possible, but because this enzyme is sequence-specific, it remained a challenge to target specific sequences of DNA of interest (Champer, 2016). It was only after *CRISPR-Cas9* (see box 1) was discovered that the technology for creating gene drives became more effective.

Box 1: Synthetic biology, CRISPR-cas9 and genetic engineering

Synthetic biology is a multidisciplinary field of science that seeks to develop innovative approaches for engineering new biological systems or re-designing existing ones for useful purposes. Recent advancements in this field have provided broadly applicable tools capable of engineering the genomes of diverse species, the most promising of which is CRISPR-cas9 (Champer 2016).

The acronym CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. These are particular patterns in the DNA code that were discovered in bacteria in 1987. It took until 2007 before its function was understood: it is part of a natural defense mechanism of bacteria against viruses, together with the so-called Cas9 enzyme (CRISPR-associated protein-9 nuclease) that can cut the double helix of DNA. So-called guidance RNA tells the Cas9 enzyme in which precise location in the DNA it should cut.

Inspired on this mechanism a precision genome editing tool named CRISPR Cas9 was developed in 2012 (proof of concept) and first successfully applied on mouse and human cells in the lab in 2013 (Ledford 2015).

CRISPR Cas9 has become a very popular tool for genetic engineering of its many benefits. First, it is applicable to all species. Second, it is cheap and fast: what was a 4-year PhD project with the previous genome editing tools you can now do in a few days. Third, it is precise: it can recognize sequences of as little as 20 base pairs and can edit single base-pairs. Fourth, it is supported by widely accessible online tools to design and order the target sequence and to online-order the matching guidance-RNA for the target. Fifth, it is easy to use: BSc level biology lab skills are enough and the required basic lab-equipment can be ordered online by all, making the technology accessible and suitable for amongst others DIY/garage biologists (Ledford 2015).

CRISPR is a genome editor that differs from conventional genetic engineering used in most genetically modified organisms (GMO's). Conventional genetic engineering is based on recombinant DNA, which involves either the combining of DNA from different genomes or the insertion of foreign DNA into a genome.

In gene drives, the CRISPR mechanism -essentially molecular scissors that cut DNA at specific locations and delete or replace sections- is inserted into the reproductive cells of the organisms, together with the new, 'driven' gene. This allows a mutation made by CRISPR on one chromosome to copy itself to its partner in every generation, so that nearly all offspring will inherit the change (Ledford, 2015). As a result, with each generation, the driven gene will be present in a larger part of the population. Gene drives can be used to supress or even eliminate a population when they decrease fitness, induce sterilization, or lead to death before propagation. Gene drives that increase fitness can be used to make a population more resilient.

Gene drives are becoming increasingly important areas of public health and biosecurity research. They have attracted significant investment, with the Gates Foundation pledging US$75 million and the Defence Advanced Research Projects Agency (DARPA) awarding US$65 million (Faunce et al, 2018).

However, despite having a history of half a century, gene drives research is still in an early stage. Although it has been hypothesised that gene drives could be developed for most species that reproduce sexually (Faunce et al, 2018), engineered gene drive systems for vertebrates are currently only theoretical. Technology development for application to invertebrates is further developed, both in-silico (mathematical modelling on computers) and in the laboratory (Redford et al, 2019). In March 2015 the first successful CRISPR gene drive application in the lab was reported (Gantz and Bier, 2015).

Potential applications

All the benefits that will be described below are hypothetical, as the gene drive has yet to leave the lab. The benefits of gene drives would differ per application. There are gene drive approaches aimed at the improvement of human health, for conservation purposes, agriculture and for the advancement of scientific knowledge (Redford et al, 2019). In some applications benefits would be multifold: a reduction of the use of pesticides in vector control or agriculture would also better the environment.

The main focus of gene drives research encountered in the literature is human malaria. Malaria has led to an estimated 435.000 deaths worldwide in 2017 (WHO, 2018). Travel, trade and climate change could bring these infections to new regions (Mitchell et al, 2017). Infected persons require long periods of treatment and recovery, and can suffer

life-long losses of capacity and productivity (WHO, 2018). Target Malaria[1], a large, non-profit research consortium, is researching the reduction of the mosquito population with the aid of genetically modified mosquitoes, preferably with a trait that will manifest itself in the mosquito population through a gene drive. This could be done by spreading infertility amongst female mosquitoes, or by eliminating the trait that makes it possible to find blood.

Endemic diseases and parasites impose large burdens on tropical and sub-tropical regions. Using gene drives to eliminate or greatly reduce the malaria mosquito and other vectors that transmit endemic diseases and parasites would therefore have indirect economic and demographic effects and could increase wellbeing. Resources available to fight these diseases would become available for other purposes (STOA, 2019).

Another example of vector control is the theoretical plan to release genetically modified mice in Martha's Vineyard, an island on the East coast of the US, to battle Lyme's disease. Because mice are the primary host of the ticks that carry Lyme's disease, their elimination would lead to the reduction of this disease (Elvin, 2017).

Gene drives could potentially also be used for conservation. When natural barriers that isolate natural populations break down, invasive species can cause great damage to the functioning of ecosystems, infrastructure and agriculture.[2] For example, invasive rodents are threatening endemic bird populations in New Zealand. When gene drives are used to eliminate invasive species, this would reduce the need for current control techniques, which include chemical and physical management (Redford et al, 2019).

Gene drives could also possibly contribute to conservation by genetically adapting the population under threat. This is referred to as 'genetic rescue' and examples are improving species resilience/resistance to climate change or disease, or their viability by increasing genetic diversity (Redford et al, 2019).

Last but not least, gene drives could provide agricultural benefits. Researchers are pursuing applications that enable controlling a number of economically significant agricultural pests like Lepidopteran insects and spotted wing Drosophila (Brown, 2017). They could also be used in weeds to eliminate any developed resistance to herbicides. This is a contested application as this would benefit the planet less than the corporation selling the herbicides (Kahn, 2020).

What is the innovation of synthetic gene drives?

The main promise of gene drives is that they would spread themselves, making it possible to manipulate populations in the wild and to reach areas difficult to access. Gene drives could thus benefit people's health in remote communities or eliminate invasive pests in large conservation areas. An additional advantage of gene drive vector control methods could be that once released in a particular area, all people living in that area will receive equal benefit. Furthermore, when gene drives for specific organisms have already been developed, they can be used to respond relatively rapidly and precisely to pests or disease (Redford et al, 2019). For example, in New Zealand, the invasive rodents would otherwise keep returning, as they arrive with ships on a regular basis.

In order to further understand which innovation gene drives bring, we compare them to specific other technologies and alternative measures. In the literature, a comparison is often made between CRISPR-Cas9 gene drives and genetic modification, especially when organisms are modified on a population level. Some researchers consider gene drives to be a special class of genetic modification with a potentially high technological power and range (Frieß et al, 2019). However, the application of gene drives is limited to organisms

1 See https://targetmalaria.org/ . This organisation is primarily funded by the Bill & Melinda Gates Foundation and the Open Philanthropy Project.

2 See https://www.theatlantic.com/science/archive/2017/11/new-zealand-predator-free-2050-rats-gene-drive-ruh-roh/546011/

that reproduce sexually and have short generation spans. Therefore, they cannot be used to synthesize or modify bacteria and viruses (as they reproduce asexually), and would not be effective on humans (as they have a long life span) (NASEM, 2016).

As shown in the other RECIPES case on GMOs (Kozarev, 2020), GMOs have been widely criticized for negatively influencing the availability of genetic and knowledge resources and ecological sustainability. Currently, most GMOs are applied in the agricultural sector (Mitchell and Bartsch, 2020). However, due to their nature, gene drives in agriculture would serve a different purpose. While genetic modification is used to enhance crops, gene drives would be used to change the pests threatening those crops. Gene drives are less applicable to crops and livestock: crops are kept under human control as new seed is planted each season and livestock have a relatively long life cycle.

In recent years, GMOs have been used for vector management. For example, a number of field tests have been carried out in Brazil and Panama, among others, with genetically modified (GM) mosquitoes of the species Aedes aegypti. This mosquito species is responsible for transmitting the Zika virus, yellow fever and dengue, among others. The company Oxitec changed the male mosquitoes' DNA in a way that they live for only four days and their offspring never develops beyond the larval stage. When these males are released in nature in large quantities, they compete with the natural population, and the mosquito population decreases. Oxitec has published positive results[3], although a report by Gene Watch strongly doubts the effectiveness of this method (2018). However, this approach would require the release of millions of genetically modified insects –a problem that would be solved by using gene drives.

For some proposed applications of gene-drive modified organisms there are other existing strategies to address the issue (NASEM, 2016). Alternatives for gene drives are for example mosquito nets, bug repellents, vaccination, the use of pesticides but also the conventional breeding or genetic modification of disease resistant crops. Gene drives are mostly being thought of a technology that can be used in addition to other measures: for malaria, mosquito nets and DDT would still remain in use. They are also seen as 'last mile' interventions: the final stages of an elimination or eradication programme, when disease is still circulating, although at much reduced levels (Redford et al, 2019).

3 Risks and scientific uncertainties

3.1 Risk/threat

Stirling (2008) describes the conventional science-based understanding of risk as the combination of what may happen – the hazards, possibilities, outcomes – with the likelihood that it might happen.[4] But this raises the question: what constitutes a hazard? It is not possible to consider risk without also taking into account cultural values (Shrader-Frechette, 1991) because 'what is at stake' will be considered differently by different actors. In the following section, we describe risks from this broad point of view.

Potential consequences of gene drives

New genetic engineering techniques can produce unexpected and unpredictable effects in the resultant organisms. In contrast to other genetic modification technologies, gene drives are designed to spread, invade and persist in the environment (Frieß et al, 2019). Their way of operating therefore make gene drives difficult to contain and these unexpected/unpredictable effects can be irreversible (Redford et al, 2019). We describe two elements of the technology's risk profile separately: the integration of the gene drive

3 See https://www.oxitec.com/en/public-health

4 See WP2's Conceptual Framework, pp 22.

construct into the genome in the laboratory (contained use), and the release of the resulting modified organism in the environment.

The contained application of gene drives brings with it biosafety and biosecurity risks. These include accidents or the possibility of deliberate misuse. Gene drives cannot be used for asexually reproducing viruses or bacteria with pandemic potential, but their propensity to spread beyond control could pose a major risk to the environment (NASEM, 2016).

Ultimately, release into the environment is an essential part of gene drives, if the technology is to be used for the modification of wild populations. This brings with it systemic risks that are mainly ecological risks but also concern our public health. The magnitude of these risks will differ by species and by nature of the change (Esvelt, 2017). Both the short- and long-term consequences of genetically engineered populations on the functioning of ecosystems and biodiversity are difficult to predict and could include impairment of ecosystem resilience.

When gene drives are used in the adaptation of species, there is a risk for adverse effects involving non-target impacts: the enzyme used for the gene drive may increase mutations in organisms it is applied for (STOA, 2019). Recent studies have shown that CRISPR Cas9 is not as precise as is sometimes proclaimed. Off-target mutations occur – and they do so more frequently in higher organisms (Fu et al, 2013)– because the bespoke guidance-RNA (see Box. 1) that tells Cas9 in which precise place it should cut (the target site) will also fit to off-target sites where duplicates of that code-sequence in the DNA are stored. There, it can have unintended effects. But unintended effects on target also occur: Kosicki et al (2018) reported that the natural repair mechanism of cells after double-strand breaks induced by CRISPR–Cas9 can lead to large deletions and complex rearrangements at the targeted sites in the DNA, with possible pathogenic consequences.

Gene flow, the transmission of genes from one species into the gene pool of another species (Cotter et al, 2020), is also possible. It has been observed in the Anopheles mosquito complex, a set of closely related species, some of which transmit the malaria parasite, but never between other species (STOA, 2019).

Where synthetic biology is used to alter the fundamental niche of a species, it could potentially alter the ecological and evolutionary trajectories for that species, with potentially adverse long-term consequences. For example, when an adaptation to climate change is engineered, and climate change is eventually reversed, the organism would be mal-adapted (Redford et al, 2019).

Releasing gene drives into the environment also brings with it a potential health risk. For example, other disease-spreading species could gain momentum if the mosquito species that spread malaria are supressed (STOA, 2019).

Wide accessibility and malicious intent

As described above in Box 1, CRISPR-Cas9 is a relatively accessible technology in terms of cost and skill required. In theory, this makes it possible for a single researcher to alter ecosystems (Esvelt, 2017). For example, a team of students competing at iGEM (a yearly student competition in synthethic biology) attempted to build gene drives. Although they did not succeed, this does show that the necessary tools are available (Redford et al, 2019). This amount of technological power in the hands of anyone capable of harnessing CRISPR technology is not without risks, even if thoroughly regulated.

Another risk difficult to regulate is the deliberately malicious use (dual use) of gene drives. In the past, insects have been used for biological warfare[5] (Lockwood, 2008). Just like mosquitos can be made unfit for carrying malaria, they can conceivably be designed to carry and spread an extra lethal cargo using gene drives (Gurwitz, 2014). Similarly, research into gene drive strategies for crop protection could also be used for agro-terrorism (Kupferschmidt, 2018).

Secondary effects and moral hazard

The economic and social effects of this technology are not straightforward. Crop technologies can be profitable at the individual farm level and for early adopters, but used on a large scale they can also decrease prices and reduce farm income because larger supplies lead to lower prices (Mitchell et al,2018). This could also be true for vectored diseases: the technology could directly increase individual welfare, but may have more mixed aggregate effects. For example, with regard to malaria, the technology distracts from underlying conditions of poverty, inequality and lack of education that create human vulnerability to mosquitos in developing countries (Braverman, 2017). The development of technology aimed to correct symptoms of more fundamental socio-political problems result in a type of 'moral hazard', and some consider gene drives a technological fix that may distract from dealing with the system failures that cause public health and conservation issues in the first place (Redford et al, 2019).

What is more, gene drives are likely to continue the growing dependency on technologies, as we have already witnessed in modern agriculture. For instance, to keep populations of malaria mosquitos low, periodic releases of gene drive mosquitoes might be required (STOA, 2019). What if a disease is removed from the environment, only to return when local immunity is reduced (EFSA, 2020)?

With regard to conservation, the possibility of applying gene drives enable a vision in which traditional habitat and species protection can be replaced by technology that makes species and habitats resilient to new stresses (Redford et al, 2019). But the patenting of this technology would result in increasing dependence on biotech corporations for the preservation of ecosystems. This is a concern because these systems fulfil essential public services like food, clean air, water control, pest control, waste decomposition, medicinal resources, recreational services, resources for local economies etc. If the unintended effect of gene drives is the loss of ecosystem resilience, this hits those with low socioeconomic status harder and in this sense discriminatory. However, because these effects are indirect, they frequently are not taken into account in cost-benefit or risk analyses.

3.2 Scientific analysis

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 (Kahn, 2020). As discussed previously, the risk profile of gene drives consists of two elements which are researched (and governed) differently: the integration of the gene drive construct into the genome, and the release of the resulting modified organism.

Traditionally, biosafety focuses on work within laboratory spaces and transport between laboratories and the containment of agents that should never leave the laboratory. The key criterion for determining the risk of work in biological laboratories is the risk of harm

[5] Regulated by the United Nations Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, see https://www.un.org/disarmament/wmd/bio/

to human health (Lunshof, 2017). However, scenarios using models of yeast, mice and fruit flies developed by the Dutch National Institute for Public Health and the Environment (RIVM) show that the escape of a gene drive organism would especially have unpredictable consequences for the environment. Moreover, a gene drive can spread rapidly and permanently in a population, and may also cross national borders (Van der Vlught et al, 2017). The experience with the current method of risk assessment offers little knowledge about these aspects.

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 (Redford et al, 2019).

Some aspects of this knowledge can be obtained by modelling environmental impacts and from experience with similar technologies or application domains (2020). Computational models have recently been used to model the potential spread and persistence of engineered gene drive organisms without actually releasing them into the environment. To feed the models, behavioural and demographic data and a good understanding of the mating system and of gene flow between target and non-target species is necessary (Mitchell and Bartsch, 2020). However, the assessment of hazards still lacks adequate criteria, methods and models (Frieß et al, 2019).

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 (Mitchell and Bartch, 2020). Oxitec has already paved the path for genetic work on mosquitoes through its introduction of sterile male mosquito populations that are periodically released (Braverman, 2017).

The European Food Safety Agency (EFSA) has recently (17 feb 2020) released a draft opinion of the Scientific Panel,[6] assessing the adequacy of current guidelines for the environmental risk assessment (ERA) of genetically modified animals (GMAs) for gene drive modified disease-spreading mosquitoes and agricultural insect pests, and the potential for novel hazards/risks associated with deliberate release. This assessment was done based on the scientific literature and consultations with stakeholders. It takes into account ecology and population dynamics and experience from existing vector/pest control strategies.[7] According to the draft report, the following aspects require further consideration or updated guidance: gene drives in insects not intended for food/feed uses, the effect on a population level of the inheritance of the selfish genetic element, the large step to open field-testing, and the definition of case-specific information required to support risk assessment.

3.3 Scientific uncertainty

3.3.1 Complexity

According to Frieß et al (2019), the technology of synthetic gene drives constitutes a tipping point in the development of genetic engineering, due to their inherent capability to spread and invade. 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, the environment also affects the gene drives. A complicated interwoven web of biotic and abiotic factors give rise to a large degree of ecological and evolutionary complexity (Frieß et al, 2019). Even with the most sophisticated computer models and risk assessment systems, the result of introduction

6 See http://www.efsa.europa.eu/en/consultations/call/public-consultation-gmo-panel-scientific-opinion-evaluation.

7 See https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2501

into the wild is difficult to predict (NASEM, 2016). 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 (Mitchell et al, 2018).

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).

3.3.2 Uncertainty

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. In addition, more research data is required to determine if the modelled spread causes actual harm.

To challenge model predictions and solidify scientific understanding, experimental evidence is necessary (Redford et al, 2019). This is problematic, as inherent risks of the technology cannot be analysed without release into the environment, where control over the technology has to be given up, to some extent. There is no safe space (Guttinger, 2019). There is also no consensus on what type of (geographically isolated) field sites may be best for trialling genetic biocontrol (Redford et al, 2019). So in order to reduce epistemic uncertainty, research activities must be undertaken that themselves pose some risk (Redford et al, 2019). This trade-off between reducing uncertainty and avoiding risk will challenge the decision making process (Mitchell and Bartsch, 2020).

Furthermore, implementation of gene drives could also result in 'random' effects, as an ecological system –the wild– behaves in different and complex ways (variability uncertainty). Frieß et al (2019) argue that gene drives could have great spatio-temporal consequences, as they can be self-sustaining for multiple generations and potentially undergo mutational changes over time. The CRISPR/Cas9-gene drive technology could also fail, with unknown environmental effects. This means that the non-knowledge (known- and unknown unknowns) about the possible consequences of gene drives is high, reaching "from enormous scientific uncertainties to vast ignorance" (Frieß et al, 2019, p. 22). Taking into account possible malicious intent or an unstable international legal order further augments these uncertainties.

However, not all researchers agree there is uncertainty about risks that are potentially large. 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. According to Kevin Esvelt (2017), a prominent researcher in the gene drives field, it is not easy to make changes to a system evolved to optimize reproduction –a gene drive would cause a fitness burden. He argues that "ecosystems are not so fragile that an accidental release from a laboratory would cause problems. It would take careful engineering to build a gene drive that can't be blocked by a natural DNA sequence variation" (genetic resistance). In addition, because it would take many generations for a population to become extinct, there would be enough time to block this process, for example by immunizing populations to the gene drive with a secondary gene drive.

3.3.3 Ambiguity

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 GMO's (Hilbeck et al, 2020). Some reviews, like a meta-analysis by Frankham (2015), show that genetic rescue has increased the fitness of populations. Others argue that genetic rescue could create unforeseen problems and overlooks

underlying problems that threaten species (Redford et al, 2019). Mitchell (2018) argues that this also holds true for economic effects: policy makers and researchers often focus on the direct effects, while applications could also generate unintended negative social impacts in the long term. We would argue that in such a complex field of study, it is not feasible for one person to have a complete overview and deep insight into the factors at play. For example, Braverman (2017) mentions that the gene drives scientists she interviewed were under-educated in all matters ecology related.

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. It has for instance been argued that an organism in which a gene has been knocked-out with CRISPR Cas9 is not a GMO according to several of the present legal and scientific definitions of GMOs (see e.g. Dankel, 2017).

Gene drives also give rise to normative ambiguity. Normative questions we encountered in the literature are for instance: is it a morally right to "remake nature" through biological engineering? (Lunshof, 2017). Is it right to alter living organisms and the environment, to change relationships between humans and non-humans, and between humans and their environment? (Sandler 2017). Which kind of evolution is worth more: biological evolution or the cultural, technological kind (Sandler, 2017)? Should changes made through the means of synthetic biology be judged differently from changes that occur spontaneously, by "natural" causes? (Lunshof, 2018).

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. Kuiken (2017) describes in more detail two perspectives at the different extremes of the spectrum: ecocentrists and technocentrists.

Many conservationists have an ecocentrist view: everything in the biosphere is interdependent, intrinsically valuable, and sacred. This perspective can lead to opposition of the concept of 'genetic rescue' due to concerns for the integrity or "naturalness" of species. In addition, there are concerns that such interventions are a "slippery slope". At what point should we bring a halt to genetic modification? Many conservationists tend to be conservative and risk-averse (Redford et al, 2019). They face a difficult dilemma: the conservation of species threatened by climate change increasingly requires new approaches that are in tension with commitment to preserving historical continuity and human-independent ecological processes (Sandler, 2018).

In contrast, the techno-centric view aims to disrupt current conservation models and harness innovation to improve efforts to end human induced extinction. Gene drive pioneer Kevin Esvelt for example, describes nature as "red in tooth and claw". According to him, existence in nature is unmitigated pain and suffering, and wilderness is a/immoral and tinkering with nature is not only a right but also a duty (Braverman, 2017).

The ethical dimensions of the use of CRISPR metaphors such as "editing the genetic code", "Cas9 scissor protein" and "CRISPR may soon become as reliable as a text editor" have been questioned too (Maben 2016): is it responsible to use such metaphors? According to Nordgren (2001) metaphors should not go beyond what is scientifically established at the time, while the example above does. Pauwels (2013) argues that describing genetic systems as though they are electrical ones (whereby genes are switched on and off with deterministic outcomes) works to a degree, but unlike switching on a light, the activation of a particular gene depends on numerous parameters and the genome is a complex system where other genes can take over the functions previously

performed by a knocked- down gene. Blasimme et al (2015) warn that the currently skewed metaphors can silence the negative aspects of technology.

3.4 Relevance of the PP to the case

The precautionary principle is relevant to this case because there is a lack of scientific certainty with regard to serious risks. This technology is intended to achieve permanent genetic changes to the make-up of wild populations of animals and plants, and could potentially cause disruption to ecological and food production systems (NASEM 2016). There is scientific uncertainty about both the potential *hazard* of gene drives, the damage they could do, and the likelihood that this hazard would occur. Perhaps these risks are even unknowable, as experimental research on the effect of deliberate release of gene drive organisms into the wild presents a great challenge. Gene drives could also potentially give rise to what Nassim Taleb, in his strong interpretation of the precautionary principle (See the RECIPES D1.1 Stocktacking report), calls a 'black swan' (2007): unforeseen and unforeseeable events of extreme consequence. Clearly, this technology warrants a precautionary approach.

Arguments underlying the use of the precautionary principle (see RECIPES D1.1. Stocktaking report) relevant to this case are the following. First, considering the potential serious, 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.

4 Risk governance and the precautionary principle

4.1 Political/juridical dynamics

This section starts with a short description of the international regulatory context relevant to EU governance of gene drives. Next, we provide an overview of the EU regulations for GMOs, currently also in place for gene drives. Recently, the European Food and Safety Authority (EFSA) has published a draft report about the environmental risk assessment (ERA) of gene drives applications, which we discuss in some detail. Finally, we discuss the governance of gene drives in The Netherlands.

International context with regard to the Precautionary principle

The EU works under the Convention on Biological Diversity (CBD) and the Cartagena Protocol on Biosafety. The CBD has been ratified by all UN member states, with the exception of the United States. The precautionary principle is formulated in its preamble: "Where there is a threat of significant reduction or loss of biological diversity, lack of full

scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat."

Under the CBD, GMOs are covered by the Cartagena Protocol on Biosafety. It is ratified by 171 Parties, but in 2018, only 53% had fully enacted the necessary regulatory systems and developed appropriate enforcement bodies to meet the protocol's requirements (Faunce et al, 2018). Countries such as the United States, Canada and Argentina are not Parties to the Protocol but do have their own national laws on risk assessment and management in the context of biosafety (Redford et al, 2019).

The Cartagena Protocol aims to protect biodiversity and human health and sets international rules to ensure the safe handling and transportation of GMOs, which are referred to as living modified organisms (LMOs). The Cartagena Protocol requires Parties to "establish and maintain appropriate mechanisms, measures and strategies to regulate, manage and control risks" connected with the use, handling and transboundary movement of LMOs, including "possible adverse effects of LMOs on the conservation and sustainable use of biological diversity" [Arts. 15, 16]. Where LMOs are intended for introduction into the environment, the decision to allow import must be based on a risk assessment and apply precaution [Arts. 7, 10(6), 15]. As discussed on page 11, it is ambiguous whether or not engineered gene drive would fall under the definitions of Living Modified Organisms (or GMOs), that are subject to the risk assessment requirements of the Cartagena Protocol. Deliberations are ongoing (Redford et al, 2019).

In 2019, the Convention held the fourteenth Conference of the Parties in Sham el Sheik, Egypt. This resulted in a "weak" interpretation of the precautionary principle (see the RECIPES D1.1. Stocktaking report) that has allowed for some, well-regulated risk in gene drives research (Redford et al, 2019). In short, depending on a case-by-case risk assessment, decisions will be made on risk management measures and involvement of local communities. Phrasings are used like "guidance may be useful" and "consultation might be warranted" and "as/where appropriate". The full text of this decision is available in Appendix 1.

EU GMO regulations

CRISPR-cas9-based gene drives are a relatively new technology, and its regulation is based on the regulation of existing technologies. Currently in the EU, all new synthetic biology techniques involving transgenesis and non-physical, non-chemical mutagenesis are within the scope of GMO regulations, including CRISPR-Cas9 and gene drives.

GMO's are essentially regulated by two directives, which both take into account the precautionary principle (Mitchell and Bartsch, 2020):

• Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (the Contained Use Directive)[8];

• Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the Deliberate Release into the Environment of Genetically Modified Organisms (the Deliberate Release Directive)[9].

The EU applies what is considered a 'process approach', meaning the way in which the technology is developed is the main trigger for oversight. Therefore, the definition of GMOs is broader, as an organism "in which the genetic material has been altered in a

8 The Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms is available at https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32009L0041 (Accessed on 13/4/20).

9 The directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms is available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0018 (Accessed on 13/4/20).

way that does not occur naturally by mating and/or natural recombination" (2001/18/ EC Art. 2(2)). Because all genetic modification is monitored and reviewed at the point of research, there is less risk to the community. Process-based regulatory models, however, are facing challenges because cutting-edge applications of CRISPR/Cas9 do not match up with existing process definitions- the technology is developing faster than regulation can keep up with.

The Contained Use Directive establishes that risks to human health and the environment of the contained use of a new GMO must assessed before research commences. Risk assessment is carried out on a case by case basis. This assessment results in the assignment of a risk category, with class 1 activities having no or negligible risk, and class 4 activities having high risk. The class determines the kind of safety measures appropriate for the purposes of the activity so that there is no risk to human health and the environment.

The Deliberate Release Directive sets out a step-by-step approach for introduction of a GMO into the environment, including an ERA and monitoring and surveillance. The application process starts with the applicants submitting his application to the national authority, who then forwards this to the European Food Safety Authority (EFSA). EFSA needs to finish its overall opinion within six months, but time is stopped for the periods that EFSA requests additional information from the applicant. Once EFSA has delivered its scientific opinion, the European Commission formulates a draft decision on how to manage any potential risks highlighted by EFSA and whether or not to grant EU-wide permission to import or cultivate that GMO (STC, 2015). Member states must then, by a qualified majority, approve any release based on the scientific evidence. If member states fail to reach a decision, the application then passes to the European Commission which can approve or deny the application based on the scientific opinion of EFSA (Post Notes, 2010).

Even if a genetically modified plant is authorized for the EU market, member states have powers to "opt out" and close areas and even the whole country to its release (Winter, 2016). In addition, other laws may prevent the release of GMOs for specified areas. In Germany for example, farmers have agreed to declare regions GMO-free (Redford et al, 2019).

Risk assessment under the Deliberate Release Directive does not consider costs, while risk management (monitoring and surveillance) can consider regulatory costs and other concerns, depending on the wording of the applicable law (Winter, 2016). The evaluation of impacts on human health and the environment include (1) general surveillance for unanticipated adverse effects and (2) case-specific monitoring**.** General surveillance is not based on specific indicators, and it can be unclear which aspects should be considered (interview 2). Indicators can differ per member state. In The Netherlands for example, there are specific 'Habitat guidelines' that provide monitoring recommendations. Case specific monitoring checks for effects identified beforehand in the ERA.

The precautionary principle on the EU's regulatory approach to GMOs is visible in the language used in the current legislation. The Deliberate Release Directive states that "the precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it."(8)[10]. The Deliberate Release Directive also takes into account ethical issues broader than safety. Socioeconomic advantages and disadvantages of each category of GMOs authorized need to be considered in a report to be issued every 3 years by the EU Commission (Mitchell and Bartsch, 2020).

Environmental risk assessment of gene drives

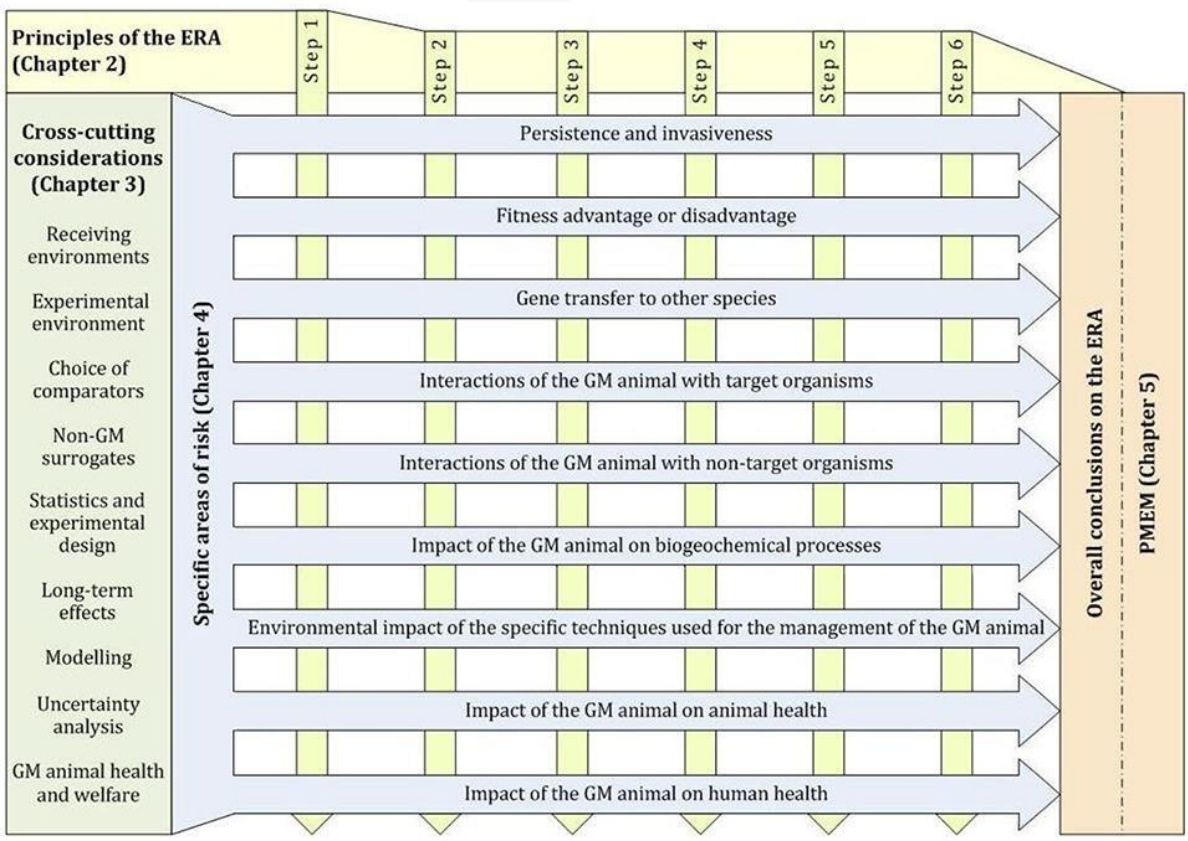
10 See https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0018

The ERA required by the EU Directive on deliberate release into the environment of genetically modified organisms is defined as "the evaluation of risks to human health and the environment, whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose (…)" (EU Directive 2001/18/EC, arts. 2(8), 4(2)). The principles for the ERA of GMO's are described in Annex II of the Directive on Deliberate Release. Here, reference is made to the precautionary principle as underlying a number of general principles that should be followed when performing the ERA:

"- identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations;
- the ERA should be carried out in a scientifically sound and transparent manner based on available scientific and technical data;
- the ERA should be carried out on a case by case basis, meaning that the required information may vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment, taking into account, i.a., GMOs already in the environment;
- if new information on the GMO and its effects on human health or the environment becomes available, the ERA may need to be readdressed (…)"

An important characteristic of this assessment is the familiarity approach, described as a "comparison of the characteristics of the GMO(s) with those of the non- modified organism under corresponding conditions of the release or use". This helps identify potential adverse effects arising specifically from the genetic modification (Redford et al, 2019). Details of this approach in the ERA of genetically modified animals are shown in figure 1.

Figure 1: Structure of the EFSA Guidance document on ERA of GM animals (source: EFSA, 2013)



Evaluation is done of the potential consequences of each adverse effect if it occurs (hazard) and of the likelihood of the occurrence. An estimation of the risk to human health or the environment posed by each identified characteristic of the GMO should be made as far as possible, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences. When risks that require management are identified, a risk management strategy is defined. The interpretation and implementation of these stipulations however remain highly controversial. As mentioned in the Ambiguity section, EFSA and other scientific groups have made different interpretations of the evidence and come to contrasting conclusions about possible risks.

To date, the EU has granted approval for the import of over 40 genetically modified (GM) food and feed varieties. However, since 1998, every attempt to reach an EU decision on cultivation a GM crop has resulted in an inconclusive vote amongst member states, with no qualified majority for or against the proposed authorisation. According to the UK Science and Technology Committee (2015), a result of this is that "several applications for GMO cultivation have become 'stuck' in the regulatory system for many years while others have been withdrawn." Only one GM crop is currently authorised for cultivation in the EU: a variety of insect-resistant Bt maize, which was approved in 1998, before the current regulations were in place (STC, 2015).

To summarize, the release of GMO's into environment/market is not forbidden per definition in the EU. However, as part of a precautionary approach, the developer of a GMO has to apply for authorization under the Deliberate Release Directive. This application process, which includes extensive research on biosafety, takes many years and can cost the developer millions of euros. At the same time, one GMO authorisation could open the way for substantial changes in agricultural production methods and pesticide use across the EU. This is relevant to the assessment of the cost effectiveness and proportionality of measures taken with regard to GMOs in account of the precautionary principle. However, with regard to gene drives, no such assessment can be made yet, as there has been no application for the authorization of deliberate release of gene drive organisms.

For activities involving organisms with a gene drive under contained use, The RIVM has developed a new, adapted risk assessment method. As there is much discussion on how to even conduct a risk assessment in relation to uncontained use there is no risk assessment framework for deliberate release in place anywhere in the EU (interview 2). The EFSA is in the process of determining whether additional guidance is required with respect to the specific challenges gene drives bring, as we will describe in the next section.

EFSA guidance for risk assessment of gene drives

GMO regulations are accompanied by different guidance documents which detail how to compile GMO applications dossiers and what type of scientific data and other information must be included. This includes guidance on how to conduct risk assessments for specific types of GMO's.

In June 2018, the European Commission gave the EFSA a mandate to "identify potential risks in terms of impact on human and animal health and the environment that gene drive modified organisms could pose"; to "identify potential novel hazards of gene drive modified organisms"; and to "determine whether the existing guidelines for risk assessment are adequate and sufficient for gene drive modified organisms" (CEO, 2019) EFSA was not requested to develop new guidelines for the ERA of gene drive modified organisms and thus the current guidance on the ERA of GM plants and animals are still valid.

EFSA accepted the mandate in August 2018 and created a Genes Drives working group at the end of the year. This GMO Panel Scientific Opinion focuses on gene drive modified

insects, as they are perceived to be the most likely cases for deliberate release into the environment at present. It has recently (17 Feb 2020) released a draft opinion for public consultation[11], and the report is due to be finalized around the time of writing.

The preliminary version of the report (2020) makes explicit reference to the Convention of Biological Diversity and the Cartagena Protocol on Biosafety. The precautionary principle is only mentioned in an appendix describing the comments raised at EFSA's stakeholder workshop "Problem formulation for the ERA of gene drive modified insects". The text reads as follows (p.6 of Appendix A):

"j. The precautionary principle does not provide sufficiently definite guidance on how to balance potential risks of GDMIs for deliberate release into the environment with the protection of the environment. Some participants considered that the deployment of gene drive strategies in insects can be compatible with the precautionary principle, as it states that "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation'". However, since GDMIs designed for self-sustaining vector/pest control can have effects that may be unlimited in space and time, without an obvious way of containing or reversing environmental impacts, some other participants argued that the application of the precautionary principle would preclude the deliberate release of GDMIs."

The EFSA concludes that the risk assessment approach for gene dives can build on the existing comparative risk assessment paradigm for GMOs. In the case of gene drive modified insects, this is specially the EFSA Guidance on the ERA of genetically modified animals, which applies to insects.

According to EFSA (2020), the following aspects require further consideration or updated guidance: gene drives in insects not intended for food/feed uses, the effect on a population level of the inheritance of the selfish genetic element, the large step to open field-testing, and the definition of case-specific information required to support risk assessment.

4.1.1 Other regulations

Regulating risks across regional boundaries

The international regulatory context is especially important in relation to gene drives as this technology has the potential to cross regulatory boundaries. No nation has regulations in place for gene drives and no case of release of an organism with a gene drive has been recorded (Brossard, 2019). However, the technology clearly creates new regulatory interdependencies and raise questions related to coverage and implementation of existing frameworks for managing transboundary movement of GMOs and addressing transboundary harm (Redford et al, 2019).

With regard to GMO's, national regulatory regimes take different approaches. Where the EU, together with other countries like Brazil, India, China, Bolivia, Australia, Burkina Faso and New Zealand take a process approach, others, like The United States, Argentina, Canada, the Philippines and Bangladesh, have product-based approaches: oversight is triggered by characteristics of products considered to pose a risk, no matter by what processes the product was generated (Redford et al, 2019).

The EU's approach to GMO regulation is frequently contrasted with the US, where many GM products are approved and cultivated on a large scale. These include herbicide

11 The 'Evaluation of existing EFSA guidelines for the adequacy for the molecular characterization and environmental risk assessment of genetically modified insects with synthetically engineered gene drives is available at: http://www.efsa.europa.eu/en/consultations/call/public-consultation-gmo-panel-scientific-opinion-evaluation

tolerant and insect resistant corn, cotton and soybeans, blight resistant potatoes and ringspot virus resistant papaya (Johnson and O'Connor, 2015).

Causes for the regulatory divergence are understood to be multicausal and decisions made in the respective systems are highly resistant to change (Pollack and Shaffer, 2009). In the US, there is no specific regulation to GMOs in place, there is no central GE testing authority, there are no labelling obligation for GMO products, and decisions are depoliticized in the sense that they are made by independent regulatory agencies, with States having no direct influence. Most importantly –considering the focus of RECIPES -, the US government frames their approach to the risk management of innovation as 'sound science based', rather than 'precautionary principle based' (Bühl et al, 2016).

Even if the US eventually chooses a different regulatory path for gene drives than it does for GMOs, other countries like China or in Africa could take the lead in gene drives research and application (STOA, 2019). The High-Level African Union Panel on Emerging Technologies has assessed that CRISPR-Cas9 gene drive for malaria elimination presents realistic options for achieving high-impact and large-scale malaria control and elimination (NEPAD, 2018). However, there is evidence of gaps in legal frameworks and capacity for regulatory oversight in many developing countries (Redford et al, 2019).

A lack of international standards for gene drives means that researchers can shift jurisdiction to sidestep tougher regulatory requirements. An example of this is the company Oxitec, who conducted field trials in Brazil and Argentina after experiencing regulatory delays in the US (Faunce et al, 2018). Several recent reports looking at engineered gene drive for malaria control have raised the importance of regional approaches (James et al, 2018), or coordination and communication between neighbouring countries (NASEM, 2016). However, it could also be important to establish minimum requirements at a global level (Faunce, 2018).

Other normative systems that apply to the governance of GMO's in the EU

The IUCN report (2019) shows how the possibilities of new genetic modification engage with our normative systems in a broad way: legal, customary and industry systems, at the international, regional, national and subnational levels are put under pressure not only concerning risk assessment and management, but also with respect to liability for harm, intellectual property and ownership, and the sharing of benefits. Relevant international frameworks include:

- **The Nagoya Protocol.** In 2017 the Secretariat of the CBD commissioned a report examining the impacts of digital sequence information as it relates to the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity (Wynberg and Laird, 2018). An Ad Hoc Technical Expert Group was also established to provide recommendations for member states on those impacts and a draft decision was submitted with vast disagreements (CBD/SBSTTA/22/ CRP.10, 2018). These deliberations continue.
- **The convention on International Trade in Endangered Species of Wild Fauna and Flora** (CITES). CITES has engaged in a discussion on the question of synthetic products that are indistinguishable from products from listed specimens and the status of modified organisms and products under the convention [Decisions 17.89 to 17.91, 2016; SC69 Doc. 35, 2017].
- **International Law**: A basic principle of international law is that states have sovereignty over natural resources in their territory as well as responsibility for activities within their jurisdiction or control that cause damage to the environment of other states or areas beyond the limits of national jurisdiction [Stockholm Declaration 1972, Principle 21]. States also have responsibility for transboundary harm. There is an international customary rule that a state must prevent and

provide compensation for damage wrongfully caused from its territory to other states [ICJ Pulp Mills 2010]. In addition to the "ex post" liability approach, the principle of state responsibility for transboundary harm implicates an "ex ante" approach in the form of a responsibility to conduct environmental impact assessments where there is potential for significant transboundary adverse impact [ICJ Pulp Mills 2010; UNCLOS art. 206]. Depending on scope, this could apply in cases where synthetic biology or engineered gene drives cross boundaries (Redford et al, 2019).

4.2 Other governance dynamics

So far, governance of gene drives in the EU is only partly done through laws and regulation. As the technology is only just emerging, formal risk governance structures for the specific innovation that gene drives bring have not yet been put in place. The EFSA has come forward with recommendations for the guidance of risk assessment of gene drives, but these recommendations have not yet been implemented. This means there is a regulatory gap. However, there are also other modalities that can govern risk, as we shall see in the next sections.

Scientific-technological environment

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. Braverman (2017) argues that in the absence of regulation, the implementation of social responsibility has been left solely to scientists, who she describes as 'scientist-regulator hybrids'. Scientists have for example represented public interest in applying for patents to protect the public from dangerous private interests. Gene drives researcher Kevin Esvelt has also written an article (2017) about the 'rules' scientists should follow in gene drives research- summarized as "be humble and start local".

Scientists are also researching technological ways to mitigate gene drives risks. Besides strictly regulated containment in the laboratory, biological containment mechanisms could render global gene drives local (Hurlburt, 2017). Scientists are for example thinking about the development of a daisy chain drive, in which the elements that the gene drive needs to copy itself are split up, so that the drive would vanish over a few generations (Esvelt, 2017). It could also be possible to develop secondary reversal drives or overwriting drives ('rescue gene drives') to make populations immune to another drive (Esvelt et al, 2014). Finally, if the targeted species is eradicated, it is possible to reintroduce it from lab populations (STOA, 2019). Not everyone agrees on the desirability and feasibility of these solutions, as they themselves not without risk, and all of them remain unproven (Frieß et al, 2019).

Hurlburt (2017) challenges containment strategies in the lab as a means of governing risk, warning against the idea of "preparing technology for the world" and the competence and authority claimed by synthetic biologists to govern their own creations. He argues that governance becomes matter of technical expertise and that risk is constructed in a narrowly technical way, governable within the laboratory. From this perspective, risk is solvable by technical but not by social means, constructing legal and political institutions as highly limited in their ability to manage risk without inhibiting beneficial technological innovation.

Peer reviewed journals could also have a role to play in governance (Lunshof, 2018). For example, in 2011 research into the airborne transmissibility of a strain of influenza among ferrets and the consequences for transmissibility among humans triggered a worldwide debate on gain-of-function research. Upon initial submission of two manuscripts, both Nature and Science initially declined publication due to biosecurity concerns. Dissemination of information about the methods was seen as posing high risk by itself (Lunshof, 2018).

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- this literature itself thus contributing to the governance of gene drives. The technology poses a number of challenges for regulation that researchers are bringing to light. Engineered gene drives may fall into an area of regulatory ambiguity, uncertainty or even overlap – it may not be clear how they fit into existing governance frameworks (Redford et al, 2019).

Researchers are also contributing to new risk assessment frameworks that gene drive developers can use. Lunshof et al (2017) have developed an adaptive approach to risk assessment of contained use. They argue that the necessary minimum for safe research with gene drive technology requires a thorough biosafety risk assessment to be in place before the research commences, at least 2 stringent (molecular, ecologic, reproductive, or barrier type) confinement strategies, and that organisms carrying gene drive systems should not to be distributed to other laboratories until formal biosafety procedures have been established. Kuzma (2019) has made the case for a Procedurally Robust Risk Assessment Framework (PRRAF) for the deliberate release of gene drive organisms,

based on existing frameworks for use in conditions of high uncertainty that go beyond the traditional linear and technical quantification of risk. With the PPRAF framework, the risk assessment conducted by the FDA of Oxitec's genetically modified mosquito was assessed to have several shortcomings. Most importantly, it did not take into the account the severity of adverse effects.

In addition to the regulatory question, the potential of intended or unintended transboundary movement raises challenges for stakeholder engagement, to ensure that public consultation can be carried out at the appropriate level. Important questions raised in academic literature is which publics are relevant to a learning process about gene drives, and what their 'say' is. Will scientists endorse decisions made with public input? (Braverman, 2017) Should the public include non-humans? Who can speak for Nature and/or future generations?

In the literature on Responsible Research and Innovation (RRI), similar lines of questioning have been developed, an example of which is given in Figure 2 below. The goal of RRI is to better align research with societal needs. The clear link to the precautionary principle is that stakeholder engagement is a way of dealing with the ambiguity of uncertain risks. However, it goes beyond the scope of this case study to go deeply into RRI as a mode of governance, as it is not specific to gene drives. It should be mentioned that the Journal of Responsible Research and Innovation has published a special issue on gene drives[12].

Figure 2: Lines of questioning on responsible innovation (Stilgoe et al 2013)

Product questions	Process questions	Purpose questions
How will the risks and benefits be distributed?	How should standards be drawn up and applied?	Why are researchers doing it?
What other impacts can we anticipate?	How should risks and benefits be defined and measured?	Are these motivations transparent and in the public interest?
How might these change in the future?	Who is in control?	Who will benefit?
What don't we know about?	Who is taking part?	What are they going to gain?
What might we never know about?	Who will take responsibility if things go wrong?	What are the alternatives?
	How do we know we are right?	

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. As DIY biology becomes more accessible to users not associated with a particular institution, this may raise challenges for enforcement of biosafety and environmental regulations against actors with bad intent. While the

12 Available at: https://www.tandfonline.com/toc/tjri20/5/sup1?nav=tocList

community's own regulations may support safe practices among well intentioned operators, informal or illegal operators with bad intent may be difficult to identify and hold liable (Garrett, 2013). However, there are still limits on the capability of community laboratories to create organisms that would cause significant environmental damage, and to date there has been no evidence of attempts or intent to do so (Lentzos, 2016).

Economic dynamics

Interestingly, Mitchell et al (2017) argue that safer, self-limiting gene drives provide a better business model. With a self-sustaining gene drive, the initial release would need to generate the entire required economic return. In addition, the potential market for such gene drives would be quite small as there are not so many diseases or pests, and so little or no private investment would occur unless the individual contracts are of very high value. Possibly, the financial consequences of the potential risks involved also provide a barrier to companies. As a consequence, Mitchell et al expect that this type of problem may be targeted by public agencies or non-profits, or public–private partnerships. In contrast, releases of gene drives with spatial or temporal limits could attract more investments, generate more income, and further expand gene drive applications. The authors (2017) even go so far as to say that private companies will likely strategically lobby for high regulatory or safety thresholds based on various types of self-limitation or containment, not only to ensure a commercial gene drive market, but also as a deterrent to competition.

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).

During the STOA workshop in 2019, participants argued that much depends on patent holder behaviour in the context of humanitarian applications of gene drives. In the case of Target Malaria, all research is published, which means that the novelty criterion for patents is not fulfilled. Target Malaria has one patent for gene drive in its entirety in order to protect the technology and avoid any attempts to patent applications of it for commercial instead of humanitarian use.

It is also necessary to mention here that the majority of synthetic biology funding in the US comes from DARPA, the defense advanced research projects agency (60% in 2014) (Kuiken, 2018). Military use of gene drives and the role of DARPA should be discussed internationally and in bio and chemical weapons treaties more broadly (Kuiken, 2018).

Societal interactions/norms

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.

Different international environmental organisations have articulated grave concerns over the potential adverse impacts of gene drives on the environment and agricultural systems. The Corporate European Observatory question the independence of the European Food Safety Authority (EFSA) experts tasked to assess gene drives' potential risks (CEO, 2019). During the past United Nations Convention on Biological Diversity in Egypt, critics have called for a moratorium on field trials and some laboratory research (Cotter et al, 2020).

In an article in the New Yorker, journalist Jennifer Kahn provides an interesting account of this convention: "a coalition of activist groups compared gene drives to the atomic bomb and accused researchers of using malaria as a Trojan horse to cover up the

development of agricultural gene drives for corporate profit". One of her interviewees from the ETC group, an international organization for eco-justice, argues that a high, disruptive, level of activism is necessary because from the beginning, the discussion has been framed around best-case scenarios in healthcare and conservation, with little discussion on how this technology will be developed with regard to applications in agriculture, the food system and by the military.

In return, scientists working with the Gates Foundation that fund Target Malaria, accuse activists of trying to hijack the meeting and argued that activists' claims were non-scientific. But there is also evidence that the Gates foundation has paid a PR firm called Emerging Ag to recruit a covert coalition of academics to manipulate the UN decision-making process[13].

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. The UN rejected the moratorium, but did agree to a weaker type of precautionary approach, as described in section 4.1.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

In our literature research, we have not encountered any debate on whether the precautionary principle is applicable to gene drives- everyone seems to agree that application of the principle is in order. The 2016 National Academies of Sciences, Engineering, and Medicine (NASEM), the 2019 International Union for Conservation of Nature (IUCN), and the 2019 European Network of Scientists for Social and Environmental Responsibility (ENSSER) reports on gene drives all discuss the precautionary principle at length. 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 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. In relation to gene drives, they conclude that

"….in terms of the science and current knowledge, we cannot see how to make the release of gene drive organisms safe, or even how to perform an adequate and robust risk assessment that would cover all the points we have raised and that we regard as essential to safeguard biodiversity as well as human health. For the present, the strict application of the Precautionary Principle might be our best guide in terms of this new and potent technology." (p. 132)

13 See https://www.independentsciencenews.org/news/gates-foundation-hired-pr-firm-to-manipulate-un-over-gene-drives/

They advocate that such an approach should commence at the very start of technology development, when first considering a GDO as a possible response to a stated problem. It requires a move away from evaluation of the attributes of a single technology, towards addressing a much broader range of options available for mitigating or solving the problem that is addressed, with a broad group of stakeholders.

Some, like The Civil Society Working Group on Gene Drives, call for a moratorium. They believe that "no case can be made for proceeding with gene drive experiments or developments at this time. Moreover, in our view, recent proposals to move ahead with real world gene drive trials are reckless and irresponsible […]."[14]

Others claim that a moratorium could cripple the field and block potentially beneficial advances. Bartsch (2017) for example laments how NGO's have used the PP to delay the application of gene drives: "Concerned non-governmental organizations are fully responsible for delaying the application of technologies that can be helpful, and I have hope that there is sufficient conscience for courageous solutions and innovative visions that are not poorly driven by fear".

According to Lunshof (2018), precaution is a valuable concept but cannot be applied in a broad manner to synthetic biology and other emerging technologies. In her view, the precautionary principle in decision making about risks can be effective only if applied to a concrete technology or research project: evaluation on a case-by-case basis is an absolute requirement (Lunshof, 2018).

5.2 Effect of the PP on innovation pathways

As there is no specific regulation in place for gene drives, it cannot be argued that the precautionary principle has 'opened up' new innovation pathways. It is too early to say whether a "weak" interpretation of the precautionary principle that we recognize in the Convention of Biological Diversity and the recent EFSA gene drives report (Redford et al, 2020) will lead to the exploration of other research pathways, with funding delegated to for example alternative malaria research.

Clearly, leading gene drives researchers are imbued by the necessity of precaution, which they interpret from a technocratic perspective. As mentioned in section 4.2, researchers are integrating a precautionary approach into their technological design: self-limiting drives or reversal drives that could undo the unintended consequences of intentionally released gene drives could provide room for field research- although this can never be *without* risks. It would be difficult for gene drive researchers to consider (technological) alternatives, as gene drives researchers are limited to their particular expertise, and it would not match their interests.

5.3 Innovation principle

With regard to GMO's more broadly, discussions about the innovation 'principle' are quite prominent, but these fall out of scope of this case study. We have found no reference to the innovation principle with regard to gene drives in official documents. It is therefore difficult to assess what such a principle would mean for the development and direction of this technology. Sandler (2018) argues that in light of precaution, promising applications of gene drive technology are those where the threat is local. Perhaps the applications of self-limiting gene drives in relatively contained environments could be in line with an innovation friendly legislative culture that also takes into account the precautionary principle –but these are not the great promises of gene drives -like the eradication of malaria- that have brought in the most funding.

14 See http://www.synbiowatch.org/2016/08/reckless-driving/?lores

6 Synthesis

The CRISPR-cas9 gene drive technology facilitates the spread of artificially modified genes through wild populations of a species of plant or animal. The capability of this technology to spread into the wild is argued to have great potential benefits, like combatting the malaria mosquito. At the same time, the resulting lack of control is considered the technology's greatest risk. 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 assessment frameworks.

As argued in section 3.4, most of the arguments underlying the use of the precautionary principle described in the RECIPES D1.1. Stocktaking Report are relevant to this case. Considering the potential serious, systemic and irreversible risks, the precautionary principle would hold parties involved morally accountable for unintended harm. Furthermore, in such a complex research and governance context, responsibilities would be shared amongst all parties involved in the value chain of the innovation. 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. Moreover, 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. The precautionary principle can also be argued to give more voice to nature. Finally, 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.

The following lessons can be learned from this case study about the complexities and controversies around the application of the precautionary principle:

First, this case is not about inconclusive evidence, but about a missing field of scientific knowledge: the field that combines the risks of genetic modification with evolutionary dynamics. Gene drives have not been tested outside of the laboratory, and inside of the laboratory the technology cannot be tested fully, as the integration of the gene drive construct into the genome is only part of the equation. For most other technologies studied as part of the RECIPES project, the relations between the technology and the damage to health or environment are difficult to measure because of complexity. However, in the case of gene drives, there is no (direct) evidence of harm, as there has been no field release.

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. It could be possible to test gene drives in an isolated location, but that would also make the test less applicable to most envisaged real life applications. This would mean that most promising cases for gene drives are those where the threat is local and relatively contained, not the further reaching conservation cases or vector-control cases. The question is whether field tests for the second type of case, necessary to better understand their risks, would ever be justified in light of the precautionary principle.

Third, even when field tests for these cases are assessed to be justified, the complexity of the risks of gene drives also mean that they have an unknowable quality. A complex system of biotic and abiotic factors give rise to a large degree of ecological and evolutionary complexity. Gene drives are a technology with high power: they can be self-sustaining for multiple generations and potentially undergo mutational changes over time. In this sense, gene drives can give rise to unforeseen and unforeseeable events of extreme consequence. Even if field trials would not provide evidence of any harm

because the likelihood of hazardous events occurring is very small, it still can be argued that the precautionary principle is in order. A stronger interpretation of the precautionary principle would therefore also effectively stop any gene drives research outside of the laboratory.

Fourth, just like the risks of gene drives are uncertain, complex and ambiguous, so are the benefits. During the STOA workshop (2019) is was argued by one of the experts that perhaps it would be unethical *not* to make use of gene drive in order to diminish/eradicate malaria. However, it is not certain that the technology will work, and if it does, it is not certain it will work the way scientists want it to, both directly and indirectly. The other RECIPES technologies will also be accompanied by promises that are uncertain, but as described above, gene drives have not been tested in practice at all.

Fifth, the governance of this technology also shows particular complexities/ uncertainties/ ambiguities. The current regulation of gene drives in the EU is based on existing regulation for GMOs. The EFSA recently concluded that the risk assessment of gene drives can build on the existing guidance for the risk assessment for genetically modified animals, although the effect on a population level and the large step to open field-testing need further consideration. It could however be argued that these two aspects are what define synthetic gene drives as a technology, and that they are the exact reason why they are such a challenging technology to regulate. Risk assessment of GMO's are based on a familiarity approach, meaning that the characteristics of GMO's are compared to non-modified organisms under corresponding conditions of the release or use. However, with regard to gene drives, it is unclear what corresponding conditions of release or use would be. For the regulation of gene drives, a clear understanding and analysis of the novelty of gene drives compared to existing technologies seems very important, but difficult to achieve in practice, considering the complexity of the knowledge field.

Sixth, the potential to cross regulatory boundaries sets this case apart. As of yet, no nation has regulations in place for gene drives and no case of release of an organism with a gene drive has been recorded. However, the future could change this, with or without the precautionary principle being followed. In the past twenty years we have seen that current EU regulations have led to a de facto moratorium on GMOs in Europe, but in other countries this has not been the case, resulting in trade tensions between Europe and the US. It could be argued that in order to have control over the direction of this technology, the EU needs gene drive research to take place in Europe.

Seventh, the potential of intended or unintended transboundary movement also raises challenges for stakeholder engagement. Learning from the history of GMOs, in the governance of gene drives attention needs to be paid to public perceptions and how they differ culturally. Especially in the context of uncertain risks, these perceptions need to be taken into account when making decisions about a technology.

So, what can this case teach us about how to deal with possible tensions between innovation and precaution? We have seen that precaution is deemed to be in the interest of both scientists and society. For gene drive scientists, societal trust is paramount, and they are taking it upon themselves to fill the regulatory gap by designing soft rules for application, engaging with the public, and also developing technological ways to reduce the risks of field testing. A safer, self-limiting gene drive also brings with it a better business model for gene drive developers, not only because they are innovating more responsibly, but also because they can sell more of their innovation. In the case of gene drives, we would argue that so far, innovation and precaution have not been in competition. Rather, the precautionary approach taken up by gene drive scientists has led to new research questions and technological approaches to risk mitigation.

Others question whether technology that is 'safe by design' is safe enough. Who will be responsible of the impact of the overall use of the technology? What would be the limit?

If the incentive is to sell as much of it as possible, the overall impact might be huge, even though at risk assessment level it might look acceptable.

In any case, this means that scientists should be guided in this process more, research funding systems should allow for moving to alternative research pathways, and regulators could come into the scene earlier. Risk assessment on a case by case basis takes place when the thought and effort has already been put into the proposed research/application by scientists. We need to develop ways in which policy makers, together with representatives from science and society, can identify conditions for responsible research: modes of actions, aims and contexts that justify gene drives research and also have a responsible business model. However, it should also be financially possible to move away from research that has already been invested in. Only under these conditions, innovations can be developed to fit societal needs.

This also means that the use of gene drives needs to be put into perspective. Claims of large scale potential benefits, used by gene drives researchers and regulators alike, obscure the discussion. These claims are just as uncertain as the risks, fully disregard a precautionary approach, and can lead to societal backlash. If we want to further an innovation-friendly research culture in the EU, it is important to start small, with a realistic representation of the aims of a technology.

7 Conclusion

Gene drives research is accompanied with a large degree of uncertainty, complexity and ambiguity on different levels. This 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. In order reduce the epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. The complexity of the risks of gene drives also mean that they could give rise to unforeseen and unforeseeable events of extreme consequence. This all translates into great challenges for the regulation of gene drives, which are further exacerbated by the technology being able to spread beyond regulatory borders.

All stakeholders involved seem to agree that a precautionary approach to gene drives is necessary, including the scientists developing gene drives. However, there is less agreement on what a precautionary approach would entail in practice, whether this means the precautionary principle should be 'invoked'- and to which consequence. While gene drives scientists are theorizing about building precaution into their innovation, polarized discussions between stakeholder groups have focussed on how to assess potential risks. This points to a disconnect between the implementation of the precautionary principle and the development of innovation that is safe and in line with stakeholder interests.

The findings of this study show that a precautionary approach can lead to more responsible innovation when precaution and the interests of a broad group of stakeholders, including nature and future generations, are taken into account from the very start of the innovation process. Regulation, policy and funding structures should stimulate policy makers, researchers and stakeholders to together find appropriate solutions to problems at hand. A precautionary approach to risk could warrant the active promotion of (alternative) research opportunities, paying attention to responsible business models. The furthering of an innovation-friendly research culture in the EU furthermore requires a realistic representation of innovation goals that account for such a precautionary approach.

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9 Appendix 1

Decision 14/19 of the Convention on Biological Diversity[15]

The Conference of the Parties:

"9. Recognizes that, as there could be potential adverse effects arising from organisms containing engineered gene drives, before these organisms are considered for release into the environment, research and analysis are needed, and specific guidance may be useful, to support case by case risk assessment"

"10. Notes the conclusions of the Ad Hoc Technical Expert Group on Synthetic Biology that, given the current uncertainties regarding engineered gene drives, the free, prior and informed consent of indigenous peoples and local communities might be warranted when considering the possible release of organisms containing engineered gene drives that may impact their traditional knowledge, innovation, practices, livelihood and use of land and water;

"11. Calls upon Parties and other Governments, taking into account the current uncertainties regarding engineered gene drives, to apply a precautionary approach in accordance with the objectives (14/19) and also calls upon Parties and other Governments to only consider introducing organisms containing engineered gene drives into the environment, including for experimental releases and research and development purposes, when:

(a) Scientifically sound case--by--case risk assessments have been carried out;

(b) Risk management measures are in place to avoid or minimize potential adverse effects, as appropriate;

(c) Where appropriate, the "prior and informed consent", the "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities is sought or obtained, where applicable in accordance with national circumstances and legislation"."

[15] See https://www.cbd.int/conferences/2018/cop-14/documents for the full report.

Genetically Modified Organisms and the Precautionary Principle

Insights from Bulgarian Parliamentary Debates since 2003

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Abstract

Genetically modified organisms (GMOs) are the product of advanced biotechnology and are non-naturally occurring plants, animals and microorganisms whose genomes have been altered intentionally and artificially. The modification is typically achieved by inserting a gene from another, often unrelated, organism into the DNA of the host, with the intention of introducing a new trait. Despite their numerous applications, commonly GMOs are most frequently associated with crops and foods.

This case study looks into the evolution of the Bulgarian regulatory context around GMOs and the ensuing policy discourse, with the intention to investigate and demonstrate the relevance of the precautionary principle and its integration within legislative and broader debates in the country. It recounts the legislative experience in the adoption of the Law on Genetically Modified Organisms (LGMO), and on key amendments in the period 2003-2017.

While derived from EU law, the Bulgarian LGMO is considered to be rather conservative and restrictive, and is discussed in this study as an example of a strong precautionary principle - adopting explicitly cautious approach to risk management. 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. It concludes with a short discussion of the repercussions on innovation, narratives on which were entirely absent from the Bulgarian parliamentary debate on the LGMO.

Table of Contents

List of abbreviations

HGT	Horizontal transfer of recombinant genes
GA	Grant Agreement
GM	Genetic modification
GMO	Genetically modified organism
LGMO	[Bulgarian] Law on the genetically modified organism

1 Introduction

1.1 Introduction

The advances in biotechnology and the ever increasing knowledge in the fields of genomics over the last quarter of the 20th century have enabled the emergence of science-based industries with allegedly huge transformational and innovation potential. Genetically modified organisms (GMOs) have gained public attention at the end of the 20th century[1] and have since been the subject of controversies and disagreements – both within the community of scientists and experts, among politicians, and within the general public. The scope of these disagreements has typically remained focused on three main concerns: the effect that GM-derived foods have on human health; the impact that GM crops have on the environment and biodiversity; and the overall socio-economic impacts of GM-focused agriculture.[1]

The "term" GMO is widely and popularly understood to refer to any plants, animals and micro-organisms whose genomes have been altered through biotechnology resulting in a non-naturally occurring species. In the EU, they are subject to strict regulation with a common regulatory framework, supplemented by a range of national solutions in the different member states that build upon, extend or restrict the EU regulations. To the general public, however, GMOs are commonly associated with certain foods and crops, while other applications, such as drug-producing bacteria, farm animals, soil bacteria or even more novel approaches such as plant-derived vaccination[2], are largely unknown.

This case study looks into the evolution of the Bulgarian regulatory context around GMOs and the ensuing policy discourse, with the intention to investigate and demonstrate the relevance of the precautionary principle and its integration within legislative and broader debates in the country. It recounts the legislative experience in the adoption of the Law on Genetically Modified Organisms (LGMO), and on key amendments in the period 2003-2017. It attempts to explain how legislative decisions are influenced, or not, by arguments of precaution and science, and how very often these arguments were challenged by a great degree of uncertainty and socially constructed perception of risks. The study does not offer any assessment or normative conclusions regarding the alleged or potential benefits, harms, safety or threats of GMOs or related technologies.

The case starts by presenting some general aspects that are not country specific, around GMOs and establishes the main issues that make this a contentious subject. Therefore, the intention of the authors is to make the case study interesting to a broader audience, while using the specificity of the Bulgarian experience to contribute to the wider understanding of the GMO debate.

In Bulgaria the regulatory framework on GMOs is defined mostly in the Law on Genetically Modified Organisms (LGMO). It was submitted to the Parliament in July 2003, and was enacted into law almost two full years later – in March 2005, entering into effect on June 1st 2005. Effectively, parliamentary debates on this initial draft took around a year, with 6 months passing from the draft's submission to the first plenary debate on February 12th 2004.[3]

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[1] Jennings, R.C. (2015). "Conflicting Values in the GM Food Crop Debate", *Journal of Clinical Research and Bioethics,* vol.6(5)

[2] Phillips, T. (2008). "Genetically modified organisms (GMOs): Transgenic crops and recombinant DNA technology". In *Nature Education,* vol.1(1).

[3] Details of the debate can be seen in Bulgarian language at https://parliament.bg/bg/plenaryst/ns/1/ID/1278.

Since its initial adoption the LGMO has been amended 17 times, the last time in 2017, or about once every year on average. The most significant changes were made in 2010 when amendments or additions were made to more than 220 of the law's articles. Between 2011 and 2016, in comparison, less than a total of 30 changes have been made, with most of them editorial, reflecting changes in names of different regulatory bodies concerned. The amendment adopted in 2017 (last one at the time of writing this case) introduced further 70 changes, with most providing greater detail on various administrative procedures.[4] Thus, the most significant overhaul of the LGMO was done in 2010, which also coincided with heightened public attention to the law itself, lengthy debates in parliamentary committees and in the plenary, as well as by a spike in the number of media publications on the topic.[5] As Bulgaria is an EU Member State, the regulatory framework is based closely on the relevant EU directives and regulations.

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

In early 2010 the national GMO debate suddenly expanded to the general public, as the proposed amendments were effectively ending some of the restrictions on GMOs and would allow the deliberate release of GMOs into the environment. This triggered serious public outcry, resulting in heightened pressure on the Government and the Parliament. MPs from the governing party proposed a draft for a resolution to ban any GMO-related activities, contained use, deliberate release within Bulgarian territory – at the very same time as the Government had proposed amendments to the LGMO. Following a series of public protests heated parliamentary debate, and heightened media attention, the final redaction of the proposed amendments to the LGMO effectively made it impossible for any GMO release into the environment, including field trials, and imposed stricter regulation and control on contained use, as well as stricter risk management procedures.

To prepare this case study, the authors have reviewed scientific articles, popular (science) blogs and web sources, a number of EU policy regulations, several Bulgarian laws that provide the regulatory framework on GMOs, transcripts of debates in plenary and in parliamentary standing committees, particularly in the period 2003-2005 when the law was first adopted, and in early 2010 when the largest and most significant changes were introduced. Several interviews with scientists (plant biologists, molecular biologists and geneticists) from Bulgaria and France were carried out to help frame the scope of the case and improve our own understanding of the scientific discourse on GMOs. Unfortunately, several scientists and former Members of Parliament, all of whom had taken part in the legislative debates on the LGMO since 2003, either declined or did not respond to our invitations for an interview, so their insights could not be included. Therefore, the case takes into account only their official positions at the time, as recorded in parliamentary transcripts.

[4] Numbers are based counting the number of changes per each amendment to the law, as reported in the digital version of the LGMO available at https://www.lex.bg/laws/ldoc/2135501153.

[5] That spike is clearly visible through a simple browsing through and counting media publications containing references to GMOs in the title, and is further evidenced through Google Trends analysis, indicating peak popularity of the search term "GMO" (in Bulgarian) of 100 (the maximum score, indicating the most popular search term over a given period) for February 2010, as shown at https://trends.google.com/trends/explore?date=all&geo=BG&q=%D0%93%D0%9C%D0%9E.

The case attempts to demonstrate the relevance of the precautionary principle to GMOs, with a particular reference to their use as food and feed, which is where the majority of current controversies are. We chose to look more closely at the Bulgarian regulatory experience as a specific example of how GMO regulations are being impacted by precautionary reasoning, public sentiments, and compatibility requirements with the EU regulatory framework.

1.2 Key timeline

The following table presents a summary of relevant developments that contributed to the development of the regulatory framework and the overall perception of GMOs. As it is not possible to include all relevant historic milestones, a priority for inclusion was given to events and facts referred to in the case study.

Political	***Science/risk assessment***	***Public debate***

Year	Event	Relevance to case study
1973	Scientists Herbert Boyer and Stanley Cohen develop a method to transfer a gene from one strain of bacteria into another	This achievement is considered the first example of a GMOs and spurs the development of the field
1987	First time genetic modification is used in crops for food	This opens up the discussions on risks to human health and gives rise to controversies within society
1992	The UN adopts the Rio Declaration of Environment and Development	The declaration provides the classic definition of a precautionary approach that later gives shape to the legal Precautionary Principle used by the European Commission
2000	The Bulgarian Parliament ratifies the Cartagena Protocol on Biosafety to the Convention of Biological Diversity	The protocol is a key international agreement which aims to ensure the safe handling, transport and use of living modified organisms resulting from modern biotechnology (including GMOs) that may have adverse effects on biological diversity, taking also into account risks to human health. The Cartagena Protocol recognises that biological diversity can be faced with risks from GMOs. It embodies the Precautionary Principle to allow signatory states to take protective measures against possible threats and damages from GM foods and crops.
2003	The Cartagena Protocol on Biosafety enters into force The draft of the first Bulgarian Law on Genetically Modified Organisms is submitted to the Parliament	The LGMO is the principle legislative document regulating GMOs, specifically contained use, deliberate release, release to the market, risk assessment and control procedures. It refers to the Precautionary Principle.
2005	The Bulgarian LGMO enters into force.	Bulgaria has a dedicated law regulating contained use, deliberate release to the environment and release to the market of GMOs, which embodies the precautionary principle and provides measures to ensure safety, risk assessment and management, as well as administrative sanctions.
2010	Public protests and heightened media attention to GMOs, in response to proposed amendments to the LGMO Most significant amendments adopted to the LGMO	The beginning of 2010 saw the most significant changes to the LGMO, but due to public pressure, the Law remained restrictive, effectively banning experiments in the field, deliberate release and release to the market of GMOs.

2 Potential benefits

Discussing benefits – real or claimed – of GMOs is still a subject of controversy and disagreement. This study does not make an attempt to advocate for, to endorse, or in any other way to argue for the value of any claimed benefits. That would require a different method, or at least a far broader scope. Any of the benefits claimed by the authors cited are perhaps the subject of denial from others, but here benefits are listed from an exploratory perspective – to provide the reader with the list of the typical beneficits associated to GMOs.

Genetically modified organisms are "plants, animals or microorganisms in which the genetic material (DNA) has been altered in a way that does not occur naturally by mating and/or natural recombination".[6] A major premise behind GMOs is that through the underlying techniques used to produce them it has become possible to change certain plants and organisms and have them obtain a new trait or property – resistance to disease, insects, weather impacts, tolerance to particular herbicides, improving nutritional values or yields.[7] In principle, a GMO is the product of the so-called recombinant DNA, which enables the transfer of genes from one organism to another, including from an unrelated one.[8] Hence, GMOs are also seen as products that "do not occur naturally by mating and/or natural recombination."[9] Other authors additionally emphasise that GMOs are necessarily the product of biotechnological modification.[10] The first successful genetically modified organism is attributed to scientists Herbert Boyer and Stanley Cohen in 1973, who developed a method allowing them to transfer a gene from one strain of bacteria into another, making the latter resistant to antibiotics.[11] This was followed by several other successful applications of the technology in the delivery of commercially viable products with clear and undisputed benefits (such as insulin producing bacteria or bacteria for oil spill mitigation). It also sparked ongoing debate within and outside science on the potential ramifications and consequences on human health, ecosystems and the environment. Most subjected to controversy was the use of genetic modification in crops and food, once the latter became a reality in the late 1980s.

GM technology enables the transfer of (useful) characteristics among unrelated species, by taking genetic material from one species and transferring it to the genome of another, resulting, in theory, in an allegedly improved product. Each organism (and particularly plants and crops) is modified for a different purpose – herbicide tolerance, insect resistance, altered nutritional value being the most typical. Thus, benefits of GMOs (and in many cases – also the risks) can as well be viewed on a micro-level – down to the specific organism and desired trait.

On a more general level, Zhang et al (2016)[8] outline three key reasons why GMOs have received so much attention and why the technology is often being seen as an opportunity for innovation. These arguments have been the cornerstone of GMO proponents, and are

[6] Definition by the World Health Organisation, available at https://www.who.int/foodsafety/areas_work/food-technology/faq-genetically-modified-food/en/.

[7] See https://ec.europa.eu/food/plant/gmo_en.

[8] Zhang, C., Wohlhueter, R. & Zhang, H. (2016). "Genetically modified foods: A critical review of their promise and problems". In *Food Science and Human Wellness*, vol. 5(3), pp.116-123.

[9] Food and Agriculture Organization of the United Nations (2016). http://wwwfaoorg/docrep/005/y2772e/y2772e04htm

[10] See for example Oliver, M. J. (2014). "Why we need GMO crops in agriculture", In *Missouri medicine*, vol. 111(6).

[11] Rangel, G. (2015). "From Corgis to Corn: A Brief Look at the Long History of GMO Technology". In *Science in the News.* Harvard University. Available at http://sitn.hms.harvard.edu/flash/2015/from-corgis-to-corn-a-brief-look-at-the-long-history-of-gmo-technology/.

widely accepted as truthful and legitimate narratives by GMO scientists and commercial producers.

The first such reason is the rapid growth of the global human population, with expectations for growth surpassing 2 billion more people by 2050. Population growth is seen as the direct cause for the growth in undernourished people and is the source for concern regarding future food security and supply. This is seen as an acute challenge for developing countries where malnourishment is a chronic problem. This argument in particular has come under criticism, however, since for the period that GMOs have been in existence, little has changed globally to solve food shortages.[12] On the other hand, a particular kind of modified rice – the so-called *Golden Rice* – is frequently provided as an example (though not without dispute) how GMOs might improve nutritious values – by enhancing rice to produce vitamin A, which is of critical shortage in diets across countries in Africa and South-East Asia.[13]

A second reason to give rise to GMOs, as outlined by Zhang (2016), is the decrease in arable land globally. According to the FAO, it is expected that by 2050, the amount of arable land available for food production will dwindle down by 25% compared to today.[14] This poses a very serious challenge that further compounds the effect of the population increase and potential food shortages, and requires innovative ways to ensure food production can still satisfy global demand. The goal would be to attain greater yield by unit of land, which would require either changes in agricultural practices – such as increased use of fertilisers and water, or genetic modifications to enable higher yields, or both. Either scenario entails further challenges – i.e. continuing urbanisation, increasing demand for biofuels, soil erosion and pollution, climate change and water scarcities.

The third reason has to do with the long-time horizons and limited scalability of conventional breeding, if it is to be relied upon for the expression of certain desired property or trait. Selecting such traits requires years-long process of identifying and selecting the best progeny, and even more years to confirm the new trait and have it commercially available. Biologically, however, such strategies depend on the availability of rich genetic variety, and this is frequently found to be decreasing, turning the attention to other technological solutions – such as utilising chemicals or radiation to induce genetic mutations. None of these, however, have any guarantee to deliver the desired outcome, but depend mostly on random chance, which increases the uncertainty of the outcomes. GMOs on the other hand, are the product of an allegedly more precise and more targeted intervention – down to a particular gene responsible for the desired trait. The technology thus supposedly eliminates the reliance on chance, but the time needed from the lab to the market typically is also considerable and takes several years in order to perform all required assessments of safety and environmental impacts.

The above reasons are frequently used to demonstrate the comparative attractiveness, and alleged economic viability of resorting to biotechnology in order to (comparatively quickly) develop new traits and characteristics of food plants. Thus it is more common to argue for the benefits of GMOs in terms of adding opportunity – to reduce costs in agriculture, to increase the nutritional value of certain crops, to help conserve national habitats, to eliminate or at least put under control plant disease. Many of these alleged benefits however are commonly linked to commercial interests, and sometimes to specific corporations hosting and sponsoring the research, marketisation and

[12] _____(2012). "Are Genetically Altered Foods the Answer to World Hunger?". In *Earth Island Journal*. Published online at https://www.earthisland.org/journal/index.php/magazine/entry/are_genetically_altered_foods_the_answer_to_world_hunger/.

[13] Jamil, Kaiser (no date). "Biotechnology – A Solution to Hunger?". In *UN Chronicle.* Published online at https://www.un.org/en/chronicle/article/biotechnology-solution-hunger.

[14] Alexandratos, N. & Bruinsma, J. (2012). World agriculture towards 2030/2050: the 2012 revision.

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. Following is a brief attempt to group the most commonly cited (macro) *benefits* in the body of literature reviewed by the authors of the case. These alleged benefits are not undisputed either, clearly exemplifying the scope of disagreement underlying the GMO narratives.

- *Agricultural benefits.* It is estimated that since the adoption of GM technology in agriculture, globally GMO crops have accounted for additional "138 million tons of soybeans, 274 million tons of corn, 21.7 million tons of cotton lint, and 8 million tons of canola."[15] Without the added yields of the GMO crops, authors argue, between 11% and 23% more arable land would have been needed to produce an equivalent amount. As crops are frequently modified to become resistant to weather influences or tolerant to herbicides and pesticides, however, GMOs result in changing agronomic practices – alleged reductions in quantities used or a preference towards a particular brand, novel chemicals used as herbicides and pesticides, with consequences to the surrounding ecosystems.
- *Economic benefits.* Increased yields of production result in increased income for the producing farms. According to some authors, 42% of the income gain was due to the increased yield resulting from genetic modification and resistance to pests and weeds, while the decreased costs of production due to reduced usage of pesticides and herbicides accounted for the other 58%.[15,16]
- *Nutritional benefits*. Certain genetic modifications enable the enriching of certain nutrients or substances with proven therapeutic effects or highly regarded health value, such as vitamins or unsaturated fatty acids. Other examples include alterations in the aminoacid composition of proteins or the content of carbohydrates, or changes in enzyme presence.[17]
- *Enhanced food qualities*. Certain modifications have aimed at improving the appearance of the products or to delay ripening (i.e. in tomatoes) in order to allow longer shelf life. There are further examples where genetic modification has been carried out on animal species, such as salmon, to accelerate growth by modifying the production of growth hormones or increase body mass. It is argued that such fish would significantly reduce the negative pressure from overfishing in wild populations.[18]
- *Enabling therapeutics*. There is ongoing research into altering specific plants (rice, soybeans, maize and potatoes) so that they can produce specific antigens as vaccine to certain diseases.[19]

A differently targeted look into benefits of GMOs carried out by Klümper and Qaim (2014)[20] further argues for agronomic and economic benefits, but highlights that impacts vary both by trait and by region, with yields from GM crops being higher in developing

[15] Brookes, G. & Barfoot, P. (2014). "Economic impact of GM crops: the global income and production effects 1996–2012". In *GM crops & food*, vol. 5(1), pp. 65-75.

[16] James, C. (2013). Global Status of Commercialized Biotech/GM Crops: 2013. *ISAAA Brief No. 46*.

[17] Kramkowska, M., Grzelak, T. & Czyzewska, K. (2013). "Benefits and risks associated with genetically modified food products". In *Annals of Agricultural and Environmental Medicine*, vol. 20(3).

[18] Chandler, S. & Dunwell, J. M. (2008). "Gene flow, risk assessment and the environmental release of transgenic plants". In *Critical reviews in plant sciences*, vol. 27(1), pp. 25-49.

[19] Abeysundara, A.T., Aponso, M. & De Silva, G.O. (2017). "A review on edible vaccines: A novel approach to oral immunization as a replacement of conventional vaccines". In *International Journal of Food Science and Nutrition*, vol. 2(4).

[20] Klümper, W. & Qaim, M. (2014). "A meta-analysis of the impacts of genetically modified crops". In *PloS one*, vol. 9(11).

countries that in developed ones. 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. These differences are found to be evidence of the continuing disagreement (although without delving into the causes thereof) on the positive effects of GM crops.

3 Scientific uncertainty about risks

3.1 Risk/threat

If benefits of GMOs, particularly crops and food, are contested, so are their risks. Even though a genetic modification is deliberately introduced in the host organism to enable the transfer of a beneficial trait from the origin species, it also poses a risk, whose scope may not be immediately clear. The consequences of the transfer may not be known and may not be predictable.[21]

A detailed and thorough summary of risks and threats of GMOs are provided by Prakash et al (2011), and is displayed as Table 1 below:[29]

Table 1: Summary of risks of GMO and their impacts (source Prakash et al, 2011)

Risk	Impact
Genetic Contamination/Interbreeding	Introduced GMOs may interbreed with the wild-type or sexually compatible relatives. The novel trait may disappear in wild types unless it confers a selective advantage to the recipient. However, tolerance abilities of wild types may also develop, thus altering the native species' ecological relationship and behaviour.
Competition with Natural Species	Faster growth of GMOs can enable them to have a competitive advantage over the native organisms. This may allow them to become invasive, to spread into new habitats, and cause ecological and economic damage.
Increased Selection Pressure on Target and Nontarget Organisms	Pressure may increase on target and nontarget species to adapt to the introduced changes as if to a geological change or a natural selection pressure causing them to evolve distinct resistant populations.
Ecosystem Impacts	The effects of changes in a single species may extend well beyond the ecosystem. Single impacts are always joined by the risk of ecosystem damage and destruction.

[21] Ellstrand, N. C., Prentice, H. C., & Hancock, J. F. (1999). "Gene flow and introgression from domesticated plants into their wild relatives". In *Annual review of Ecology and Systematics*, vol. 30(1), pp. 539-563.

Risk	Impact
Impossibility of Follow-up	*Once the GMOs have been introduced into the environment and some problems arise, it is impossible to eliminate them. Many of these risks are identical to those incurred with regards to the introduction of naturally or conventionally bred species. But still this does not suggest that GMOs are safe or beneficial, nor that they should be less scrutinised.*
Horizontal Transfer of Recombinant Genes (HGT) to Other Microorganisms	HGT is the acquisition of foreign genes (via transformation, transduction, and conjugation) by organisms in a variety of environmental situations. It occurs especially in response to changing environments and provides organisms, especially prokaryotes, with access to genes other than those that can be inherited. HGT of an introduced gene from a GMO may confer a novel trait in another organism, which could be a source of potential harm to the health of people or the environment. For example, the transfer of antibiotic resistance genes to a pathogen has the potential to compromise human or animal therapy. HGT has been observed for many different bacteria, for many genes, and in many different environments. It would therefore be a mistake to suppose that recombinant genes would not spread to other bacteria, unless precautions are taken. Recent evidence from the HGT technology confirms that transgenic DNA in GM crops and products can spread by being taken up directly by viruses and bacteria as well as plant and animals cells.
Adverse Effects on the Health of People or the Environment	These include enhanced pathogenicity, emergence of a new disease, pest or weed, increased disease burden if the recipient organism is a pathogenic microorganism or virus, increased weed or pest burden if the recipient organism is a plant or invertebrate, and adverse effects on species, communities, or ecosystems.
Unpredictable and Unintended Effects	HGT may transfer the introduced genes from a GMO to potential pests or pathogens and many yet to be identified organisms. This may alter the ecological niche or ecological potential of the recipient organism and even bring about unexpected changes in structure or function. Furthermore, the gene transferred may insert at variable sites of the recipient gene, not only introducing a novel gene but also disrupting an endogenous gene, causing unpredictable and unintended effects.
Loss of Management Control Measures	Regulatory approvals for field trials of GMOs often require measures to limit and control the release in space and time. With the spread of the introduced gene(s) to another species by HGT, a new GMO is created. This new GMO may give rise to adverse effects which are not controlled by management measures imposed by the original license or permit.

Risk	Impact
Long-Term Effects	Sometimes the impact of HGT may be more severe in the long term. Even under relatively strong selection pressure, it may take thousands of generations for a recipient organism to become the dominant form in the population. In addition, other factors such as timing of appropriate biotic or abiotic environmental conditions and additional changes in the recipient organism could delay adverse effects.
Ethical Concerns	Various ethical issues associated with HGT from GMOs have been raised including perceived threats to the integrity and intrinsic value of the organisms involved, to the concept of natural order and integrity of species, and to the integrity of the ecosystems in which the genetically modified organism occurs.

3.2 Scientific analysis

Although GMOs are understood as products of novel biotechnology and have received wider public attention over the past 30 to 40 years, attempting the promotion of certain desirable traits has been practiced for thousands of years through artificial selection and selective breeding, which involves careful selection of parental organisms exhibiting those traits and breeding them to propagate these traits in subsequent generations.[22] Genetic modification through biotechnology became possible after decades of research into genetics in the 20th century, but the real breakthrough came in 1973 when scientists Boyer and Cohen successfully engineered the first transgenic organism. That gave rise to GMO research, to commercialisation of the technology and its products, as well as to a fast growth of industrial agriculture, especially in North America.

But not all scientist share a positive narrative of GMOs' safety. Safety is understood not just in terms of food safety and human health, but also in terms of environmental safety and sustainability. The state of doubt is further reiterated by observations that scientific conclusions are strongly correlated to the source of funding, as well as by the disciplinary training of the authors. [23] 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, ares more likely to purport negative attitudes, emphasising the involved uncertainties and ignorance. The result, as aptly summarised by Hilbeck et al (2015), is this:

> *"[T] he the totality of scientific research outcomes in the f ield of GM crop safety is nuanced; complex; often contradictory or inconclusive; confounded by researchers' choices, a ssumptions, and funding sources; and, in general, has raised more questions than it has currently answered."*

Even though the scientific methods and procedures underpinning genetic modification are well understood by scientists, regardless of their own attitudes and conviction, GMOs are

[22] Raman, R. (2018). "The impact of genetically modified (GM) crops in modern agriculture: A review". In *Biotechnology in Agriculture and the Food Chain*, vol. 8(4), pp. 195-208.

[23] Hilbeck, A., Binimelis, R., Defarge, N. et al. (2015). "No scientific consensus on GMO safety". In *Environmental Sciences Europe,* vol. 27(4).

still not unanimously accepted by the general public across the globe. Both disagreements in science, as well as public distrust, prompted the development of regulations to ensure safety and proper awareness of risks and impacts – especially when it comes to GM foods. Since at least the 2000s serious concerns have been raised about potential irreversible impacts of GMOs when released into the environment.[24] A lot of research has been carried out into both the risks and the benefits of GMO, and numerous safety narratives are in circulation. Thus, even after decades of experience, GMOs are still a source of controversy – not just in science, but also among consumers and the general public. The fact that different jurisdictions favour different approaches to regulatory oversight as a response to differences in the perception of risk and threat, is a further proof that the controversy affects policy making as well.

In addition to the above, the perceptions of risks also differ across countries and cultures. For example, in a meta-review of more than 70 articles, Frewer et al (2013) demonstrate that people in the EU tend to see more and greater risks than people in the EU and in Asia, but at the same time ethical and moral objections tend to be higher in the US than in the EU. This is also reflected in the different regulatory approaches to GMO on both sides of the Atlantic.

Another line of research looks into not only in the controversies themselves, but rather into the scale of polarisation that underlies these controversies.[25] The division is not merely between pro and anti-GMO, but goes deeper in both directions, because it is, in fact, rooted into differences of values. In the words of Biddle (2018), conclusions put forward in the GMO debate are not always based on evidence, so he argues that the "debate includes much space for rational disagreement—that the evidence alone might not settle the question of whether one should be supportive or critical of a particular GM crop, or even how we should characterize the risks of that crop." Thus, underlying values also affect the perception and definition of *safety*, as well as on the scope of evidence required to determine such safety.

GMOs provide a clear case of scientific uncertainty, regardless of their (relatively) long history of use. Despite a large body of research into their risks, there is still little to no consensus across scientific disciplines on their safety, nor within policy communities, and even less among the general public. 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. Thus, although as a technology, genetic modification is already considered mature and well understood, it is the use of GM products that is considered to pose the most serious concerns or even threats, typically on a product-by-product basis. Differences in regulatory approaches – i.e. between the EU and the US, but also among EU member states, only add to the complexity, as the different approaches to regulating GMOs are frequently rooted in the consideration and interpretation of scientific evidence. These discrepancies are additionally fuelled by strong public opinion in some jurisdictions, which are not based on science, but seek to actively refute even well-established evidence, contributing to a heightened and at times heated public debates, where science does not participate on an equal footing.

The extent of the controversies in the GMO narratives also translate into the perception of which risks are relevant within the GMO discourse. Most typically, the risks in question when it comes to GM food are those to health and safety, which some authors consider

[24] Wolfenbarger, L. & Phifer, P. (2000). "The Ecological Risks and Benefits of Genetically Engineered Plants". In *Science,* vol. 290(5499), pp.2088-2093.

[25] Biddle, J. B. (2018). "Antiscience Zealotry"? Values, Epistemic Risk, and the GMO Debate". In *Philosophy of Science*, vol. 85(3), pp. 360-379.

to be the only relevant risks of GMOs.[26] Saletan (2015), for example, argues against the inclusion of socio-economic risks in the debate on GMO since they are not a product of the technology itself, nor are they specific to the processes of genetic engineering. To the extent that socio-economic risks would be considered as probabilities of harm, then such harm would not and cannot be causally linked to the underlying technology since there is nothing inherent in it that increases the probability of that harm. To this, Biddle (2018) responds that it would, however, be completely legitimate to assess a given technology on its intended use. Therefore, as long as the intended uses for which a GMO is designed raise the probability of harm, there is no need to search for causality. Therefore, socio-economic implications can legitimately be considered an integrative part of the risk narrative. Hence, how regulatory frameworks consider the range of risks and weigh their importance is to a great extent a reflection on (public) values.

3.3 Scientific uncertainty, complexity and ambiguity

GMO debates produce their own narratives out of uncertainty and do not help with either advancing or accepting scientific evidence, which further contributes to continuing uncertainty within science itself. In part, this can be attributed to the fast development of the underlying technology that is not adequately matched by objective science communication efforts, leading to the continuous "recycling" of arguments without proper scientific reference or rooting. On the other hand, there is commercial push in some jurisdictions to bring GMO products to the market, and partly due to how knowledge of risk is developed through scientific research. In the latter case, there have been multiple instances when current studies refute prior ones as they employ, for example, different and more rigorous methodologies that add up to the understandings of risks and impacts.[27]

GMOs represent a clear case of complex interdependencies within food supply chains and throughout food systems owing to the fact that once released into the environment, modified crops tend to have an impact not just in the way they were originally designed – i.e. increased yields, herbicide tolerance or insect resistance, but also exhibit a number of spill-over effects (externalities), some of which more obvious than others.

Genetic modifications involve the deliberate transfer of genes from one organism to another, often an unrelated one, with the most common, and most popularly contested, targets being plants used for food. Even though the technological process itself might be well-developed and understood (at least in terms of process), there is frequently inherent uncertainty in the final result of the modification. Gene insertion can have different outcomes. Thus, 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.[21] The rearrangement of genetic sequences may impact functional operation, cause genetic instability or interference, and ultimately increase the likelihood of unforeseen negative outcomes or risks.[28]

Scientific uncertainty translates easily into public misunderstanding and into regulatory uncertainty, and the Bulgarian experience with GMO regulatory developments since at least 2003 is a clear example of that. Legislators' decisions aim to regulate the technology, but science and their understanding thereof is not the only component in

[26] Saletan, W. (2015). "Unhealthy Fixation: The war against genetically modified organisms is full of fearmongering, errors, and fraud. Labeling them will not make you safer." In *Slate.* Available online at https://www.slate.com/articles/health_and_science/science/2015/07/are_gmos_safe_yes_the_case_against_them_is_full_of_fraud_lies_and_errors.html?via=gdpr-consent

[27] Kvakkestad V, Gillund F, Kjolberg KA, Vatn A. (2007). "Scientists perspectives on the deliberate release of GM crops." In *Environmental Values*, vol. 16(1), pp. 79–104.

[28] Dennis, C. (2002). "The brave new world of RNA". In *Nature*, vol.418, pp. 122-124.

regulatory decision-making. Besides taking account of the range of possible risks, the conditions that make them more likely, and designing a framework that controls and mitigates those risks, legislators are often pressured by public and private interests, stretching the span of their accountability.

Uncertainty has at least two complementary dimensions, when it comes to regulatory decision-making on GMOs (although it is not exclusively specific to GMOs). 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. On the other hand – decisions still need to be made, and when that is done on the basis of incomplete or missing information, this leads to uncertainty, especially with regards to the future implications.[29]

It is highly unlikely that there will ever be the same level of understanding of GM technology, processes, risks and benefits between scientists, on the one hand, and consumers, or the general public, on the other. Hayes et al. (2004) argue that the balance of expertise will always be skewed towards the side of the GMO proponents, which are often the companies developing the GMOs and the scientists behind them.[30] This creates a significant challenge to establishing a strong and independent scientific base and to building public understanding and awareness, and results in continuous perpetuation of ambiguity among scientists, policy-makers and society at large.

The Bulgarian experience with the legislation of GMOs provides a strong example to the above. A significant part of the national debate on GMOs, particularly GMO foods, as seen in the transcripts of deliberations in the parliamentary committees and in the plenary, rests on an implicit assumption of GMOs as a significant source of risk to human health and the environment. Regardless of how exhaustive such concerns are, and the degree to which scientific evidence is available and comprehensible, they have strong impacts on policy-making and regulatory developments on national and international level. The Bulgarian legislative debates on GMOs are a vivid example of this since implicit harm from GMOs is put forward in parliamentary deliberations as the core of deliberation. The majority of the narratives used are rarely based on scientific proof or disproof. Instead statements are often found to assign blame to the opponent of being negligent of the risks. That is largely the situation across the EU too, particularly with regards to the import and cultivation of GM crops[31], and some authors have even raised a concern that the EU has been experiencing an increasingly politicised perception of risk, which in turn might increase the risk that consumers would, in the end, consume unsafe products.[32]

Furthermore, in the case of GMOs 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 and how society perceives as a risk.[32] This can be observed in the national debates on the LGMO, as it has had significant impact on how *risk* is being framed and interpreted for regulatory purposes. It represents an evolution in the understanding of risk – not as the product of just hazard and exposure to it, but also to include a third component – termed by Sandman (1994)

[29] Prakash, D., Verma, S., Bhatija, R. & Tiwary, B.N. (2011). "Risks and Precautions of Genetically Modified Organisms". In *ISRN Ecology,* vol. 2011

[30] Hayes, K. R., Gregg, P. C., Gupta, V. V. S. R. et al. (2004). "Identifying hazards in complex ecological systems. Part 3: Hierarchical Holographic Model for herbicide tolerant oilseed rape". In *Environmental Biosafety Research*, vol.3(2), pp. 109-128.

[31] Devos, Y., Reheul, D., De Waele, D., & Van Speybroeck, L. (2006). "The interplay between societal concerns and the regulatory frame on GM crops in the European Union". In *Environmental Biosafety Research*, vol. 5(3), pp. 127-149.

[32] Smyth, S. J., & Phillips, P. W. (2014). "Risk, regulation and biotechnology: the case of GM crops". In *GM crops & food*, vol. 5(3), pp. 170–177.

outrage, which refers to the public's response to and perception of risk.[33] In Sandman's (1994) terminology, hazard and outrage "refer, respectively, to technical and nontechnical (a composite of such factors as control, fairness, familiarity, trust, dread and responsiveness) seriousness of a risk." Smyth and Phillips (2014) refer to outrage as the consumers' and citizens' response to risk, and propose that a sound risk analysis framework should take into account the hazard identification and characterization, exposure assessment, and outrage. The added significance of the *outrage* factor is in that it expands on the scientifically derived measure or risk. From such a perspective, then one could more easily understand how public pressure, albeit entirely unscientific, can influence the legislators' assumption on the likelihood and severity of potential risks, and their use of precaution in defining measures for mitigation, control and avoidance.

From a social science perspective, anti-GMO sentiments appear to be intuitively appealing to the majority of people for quite some time.[31] Most people without a scientific background or training in biotechnology appear to perceive DNA as a product's identity, so they refuse to accept transgenic plants (i.e. fish DNA inserted into a tomato) as having an "identity" of their own, but rather think of them as the confluence of the "identities" of the original species.[34] With years of data from locations where GMOs were cultivates, others further conclude that there is little evidence of increased yield of GMO crops compared to non-GMOs counterparts, coupled with evidence of increased use and concentrations of pesticides.[35] Thus concerns are validly being raised not only on the safety aspects of GMOs themselves, but also on systemic risks resulting from GMO use.

Another line of argument is linked to the fact that GMOs, when used as food and feed, come from and benefit high-tech agricultural industry, and are thus a constituent part of business processes (with little attention to the science itself). On the one hand, this means that GMOs are part of energy intensive (due to scale) agricultural production, which is perceived as a threat to sustainability objectives and is also resource intensive. On the other hand, GMOs enable higher usage of pesticides (as they are intentionally modified to make them resistant to specific pesticides), thus causing potential additional harm to the soil, other plants and animals in the ecosystem, and the environment in general.[36]

3.4 Relevance of the PP to the case

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.

The precautionary principle, at least with regards to biosafety, was first put forward in the United Nation's Rio Declaration on Environment and Development from 1992[37]. It

[33] Sandman P. (1994). "Mass media and environmental risk: Seven principles.". In *Risk*, vol. 5, pp. 251-60.

[34] Gelman S.A., Rhodes M. (2012) "Two-thousand years of stasis: how psychological essentialism impedes evolutionary understanding". In: Rosengren K.S. (2012). *Evolution Challenges. Integrating Research and Practice in Teaching and Learning about Evolution*. Oxford University Press, pp. 3-21.

[35] See for example reporting on https://www.nytimes.com/2016/10/30/business/gmo-promise-falls-short.html.

[36] Odum, Mary (2015). "Arguments against GMOs". Published online at http://prosperouswaydown.com/arguments-gmos/.

[37] Full text of the Declaration is available at https://sustainabledevelopment.un.org/content/documents/1709riodeclarationeng.pdf

grained further significance and through the international Cartagena Protocol on Biosafety to the Convention of Biological Diversity.[38]

The pursuit of technological regulation through law has always been a response to the recognition of existing or possible risks to human health, as well as to the environment, and GMOs provide a suitable example. The science behind the technology of gene modification outpaces significantly the science necessary to identify and quantify the associated risks, resulting in a distinct "lag" and in a period when the true scope of risks – especially to human health - remains unproven or simply unknown.[39] Therefore, regulations that are at least partially premised on insufficient and evolving knowledge of their subject, should recognise this state of scientific ignorance (scientists do not know what they do not know) and follow a precautionary approach. Otherwise scientific ignorance may easily translate into legislative ignorance whereby decision-makers fail to recognise the likelihood of unknown risks and unanticipated consequence.

In the EU, the precautionary principle is a basic tenet in Directive 2001/18/EC, and in the Bulgarian regulatory context – a foundational framing for the LGMO. The Principle is explicitly mentioned at its very beginning. The LGMO provides a short definition of the precautionary principle as "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."[40] The LGMO requires that the Ministry of Environment and Waters maintains a registry of all sites where there contained use of GMOs is authorised (i.e. research labs). Such sites require prior authorisation to begin their work, and interested parties are required to submit a detailed application, which includes a thorough risk assessment, identification of any potential adverse effects on the environment and human health, an assessment of the likelihood of such effects, and an impact assessment. Before contained use is authorised, the applicant is asked to provide an Emergency Response Plan, which is subject to review and update. These plans, and updates thereof, should be provided to the public by the applicant. The final authorisation decision is made by the Minister. The Ministry is further expected to organise public hearings before granting authorisation for the deliberate release of a GMO in the environment. The Ministry's regulatory oversight is further supported by a Scientific Committee, which advises the Minister on each application for authorisation. However, protocols or transcripts from the deliberations of this Committee are not publicly available. Records of Committee meetings' agendas and decisions made are available as a list, but only until 2015, without any clarity for the lack of more recent data. At the same time, the most current data on the website of the Ministry reveal there are currently five locations (research labs) where contained use is authorised, but not a single authorisation for either specific research on any GMO or deliberate release, has been granted (since at least 2010).[41]

The realisation of the precautionary principle through legislative and regulatory texts reflects normative[42] and value-driven assumptions underpinning the principle itself. To this end, the differences in the scope of regulatory measures put forward in the relevant legal texts reflect differences in the interpretation of the precautionary principle, particularly in regards to the scope of discretion allowed in managing risks due to

[38] The Protocol was agreed upon in 2000, and entered into force in the signatory states in 2003. See https://bch.cbd.int/protocol for details.

[39] Van Tassel, K. (2009). "Genetically Modified Plants Used for Food, Risk Assessment and Uncertainty Principles: Does the Transition from Ignorance to Indeterminacy Trigger the Need for Post-market Surveillance?". In *Boston University Journal of Science and Technology Law*, vol.15.

[40] Law on genetically modified organisms, art. 1(2). In force since June 2003. Last amended in June 2017. Available in the Bulgarian language at https://www.lex.bg/laws/ldoc/2135501153.

[41] Data available at https://www.moew.government.bg/bg/priroda/gmo/registri-gmo/.

[42] Vos, E. & De Smedt, K. (2020). Taking stock as a basis for the effect of the precautionary principle since 2000. RECIPES Project Deliverable WP1.

scientific uncertainty (or the apparent lack of scientific certainty). Some authors, however, argue that legal texts, particularly on GMOs, that rest on interpretations of the precautionary principle can become quickly outdated due to the rapid advances in science (i.e. gene editing), as well as the accumulation of newer evidence.[43]

4 Risk governance and the precautionary principle

Risk assessment is a common regulatory tool typically used in the decision-making process, for example – for a proposed commercial release of a GMO into the environment or for GMOs in contained use.[44] Risk assessments are mandated by law, and are meant to ensure the study into possible adverse effects of GMOs on human health and the environment, to details on contained use of GMOs, the probability that an adverse effect does occur, and the severity of the impact should that does happen.

In the EU, risk assessment on GMOs is based on a case-by-case approach, whereby separate risk assessment procedures are carried out for each product or trait as long as there is sufficient scientific information and experience. Risk assessment guidelines are most detailed by the European Food Safety Authority. The regulatory framework has been criticised by some scientists as being "increasingly static up to a point that it has become too cumbersome to cope with technological and scientific developments."[45]

In the EU risk assessment and product approval were decoupled with the establishment of EFSA.[32] EFSA carries out risk assessments based on science-based protocols and procedures, but it does not make the decision – it only provides a report to the European Commission, which has the final say on product approval. Member States can also conduct their own risk assessment, which is then shared with EFSA for an opinion. Typically, EFSA can carry out two types of risk assessments under the same Regulation 1829/2003.[46] One is for the cultivation of GMOs and the other is for GMOs when proposed for use as food and feed. As new scientific information becomes available, it is possible that the concerned Member State can adopt new emergency measures based on the newly identified risk.

The EU has adopted its own legal framework that defines the regulatory scope on GMOs. On the Union level, as well as in Member States, regulatory oversight is process-based – it is the technology of genetic engineering around which regulations are designed.[47] The following directives and regulations are the main pieces of legislation[48]:

- Directive **2001/18/EC** on the deliberate release of GMOs into the environment. This directive establishes in legal terms that genetically engineered crops are fundamentally different to crops improved by any other type of breeding technology. It is further based on the

[43] Davidson, J. & Ammann, K. (2017). "New GMO regulations for old: Determining a new future for EU crop biotechnology". In GM Crops & Food: Biotechnology in Agriculture and the Food Chain, vol. 8(1), pp. 13-34.

[44] Hill, R.A. (2005). "Conceptualizing risk assessment methodology for genetically modified organisms". In *Environmental Biosafety Research*, vol. 4(2), pp. 67–70.

[45] Erikson, D., Custers, R., Björnberg, K.E. & al. (2020, forthcoming). "Options to Reform the European Union Legislation on GMOs: Risk Governance". In *Trends in Biotechnology,* vol. 38(4), pp. 349-351.

[46] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. Accessible at https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32003R1829.

[47] Zetterberg, C. & Björnberg, K.E. (2017). "Time for a New EU Regulatory Framework for GM Crops?". In *Journal of Agricultural and Environmental Ethics,* vol.30, pp. 325-347.

[48] See https://ec.europa.eu/food/plant/gmo/legislation_en.

precautionary principle seen as a set of general principles of risk management, including: proportionality between the chosen level of protection and the measures taken; nondiscrimination in the application of the measures; consistency of the measures with measures already executed in similar circumstances; cost-benefit analysis of action or inaction; revisiting of the measures upon new scientific developments.[49]

- Directive (EU) **2015/412** amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory
- Regulation (EC) **1829/2003** on genetically modified food and feed
- Regulation (EC) **1830/2003** concerning the traceability and labelling of GMOs and the traceability of food and feed products produced from GMOs
- Directive **2009/41/EC** on contained use of genetically modified micro-organisms
- Regulation (EC) **1946/2003** on transboundary movements of GMOs.

Several Bulgarian laws contain regulations addressing GMOs:

- **Law on genetically modified organisms**, in effect since 2005. It transposes Directives 2001/18/EC and 2009/41/EC of the EU into the national legal system, and regulates: 1. the contained use of GMOs; 2. the release of the GMOs in the environment; 3. the placing on the market of GMOs or combination of them as products or ingredient of products; 4. the transfer of GMOs; 5. the import, export and transit of GMOs; 6. the control over the activities under items 1-5. The Law explicitly refers to the precautionary principle as its foundation.
- **Law on foodstuffs**, in effect since 1999. It contains specific provisions addressing GMOs in food, including packaging, labelling and consumer awareness.
- **Law on veterinary practice**, in effect since 2006. Includes administrative regulations addressing release to the market of GM feed for animal feeding.
- **Law on feed**, in effect since 2006. This law treats GMOs when in use as animal feed. It regulates the transportation, marketing, labelling and use of GM feed. It is focused on feed in general, not specifically on GM feed. The law contains substantial number of direct references to Regulation (EC) 1829/2003.

Until 2005 Bulgaria did not have a dedicated law to regulate any aspect of development, experimentation, transportation, release of GMOs. There was a government decree in effect, whose sole focus was on the deliberate release of GM plants obtained through recombinant DNA (so-called transgenic plants). As a regulatory instrument, it was regarded as highly inefficient, not least because MPs could recognise the rapid development of the science and technology behind genetic modification, as well as the ensuing complexity, especially when the draft of the LGMO was submitted to the Parliament in 2003 and the debates started, many of the MPs saw the LGMO as a significant and needed upgrade to the regulatory framework.

A review of the parliamentary debates on the Bulgarian LGMO (and by reference of several other debates where GMOs appear as subject) suggests that the Bulgarian regulators have not been engaged with detailed (public) discussions on the actual risks from GMOs. GMOs were perceived as inherently risky, but risk was seen more as an expression of generally persisting (scientific) uncertainty ("we don't know what could go wrong"). The legislators routinely referred to the EU frameworks and relevant directives as foundational in the definition of risks and risk management procedures. In much of the debates, the attention was on strict monitoring and control as a form of prevention rather than on risk mitigation. The LGMO, which is the principal legal text on GMO regulation, has a detailed section on risk management, and provides for a regime of

[49] Aerni, P. (2019). "Politicizing the Precautionary Principle: why disregarding facts should not pass for farsightedness". In *Frontiers in plant science*, vol. 10.

authorisation and close monitoring for every single GMO and every single site (lab or planting location). Over time, there have been more references to notions of socially constructed risks (referring to public perceptions and mainstream narratives, not necessarily in line with science) to a much larger extent than to scientific evidence or uncertainty of risks. This, to a degree, precluded wider public discussions on understanding the risks, communicating effectively among stakeholders on the scientific evidence of threats, and instead focused the legislative attention on the management and containment of risks seen from a restrictive lens. Moreover, despite the frequently cited concern for ensuring the viability of particular economic sectors (such as bioagriculture), no economic analyses were quoted or provided. Thus it is impossible to infer from the available transcripts of there had been any cost-benefit analysis to inform and support the line of argument that presents GMOs as an economic threat.

The initial adoption of the LGMO took a little over a year between the time the draft was submitted to the Parliament and the time it was enacted into law. The LGMO entered into force on June 1st 2005. Before that date, Bulgaria had no dedicated law, only a government decree with a sole focus on the deliberate release of GM plants obtained through recombinant DNA technology. No regulation was in existence on contained use of GMOs.

The draft LGMO was introduced to the plenary by the then-Minister of the Environment and Waters on February 12th 2004.[50] The minister explained that the law was necessary for two main reasons: "[1] to ensure complete legal regulation of GMO-related activities and [2] to respond to the commitments made by the Government during the negotiations for accession to the European Union."[51] The draft preparation was prepared by a mixed group of experts from relevant ministries, scientists and civil society organisations, under the coordination of the Ministry of the Environment.

A key point in the debate in 2004 concerns the possibility to use the LGMO as an opportunity to promote a policy approach that is unique to Bulgaria, while also complying with the EU directives. One of the MPs openly advocates for that stating the distinct difference in the regulatory approaches used by the United States (key role for the market and multinational companies) and by the EU (key role for governance institutions). While arguing for the necessity of the law, he asked: "Can Bulgaria choose a third kind of policy? One that prohibits the agricultural production of GMOs?", and further promotes stricter control procedures. The key supporting argument used was that GMOs represent a threat to Bulgarian bioagricultural sector, and the LGMO should ensure the restriction of multinational GM seed producers and will thus protect organic and conventional farming – a strategically important sector for the Bulgarian economy.

Another MP, a scientist himself, and at the time a member of the parliamentary opposition, also stated the LGMO is a necessity, and was the only one to refer directly to the precautionary principle as the underlying foundation for this act. He was also the only person to refer to scientific uncertainty as sufficient motive for the adoption of the law, referring to the possibility for cross-contamination of non-targeted species with genetically modified material. His presentation of genetic modification as a technology, however, was framed entirely on notions of risk and threats, with a range of examples of what could go wrong – unexpected production of toxins or allergens threating consumer health; possibility for intentional abuse of GM techniques for bioterrorism; even the theoretical possibility that an GM plant could "breath in" enormous amounts of nitrogen from the atmosphere, thus changing the chemical composition of breathable air causing environmental havoc. He further reiterated the same arguments for the threats to typical products of Bulgarian agriculture, calling for the introduction of market analysis prior to

[50] Transcript of the plenary session is available in the Bulgarian language at https://parliament.bg/bg/plenaryst/ns/1/ID/1278.

[51] Bulgaria acceded to the EU on January 1st 2007. The adoption of the LGMO was part of the years-long process of negotiation and legislation transposing required from candidates.

the deliberate release of any GMO. Other MPs, within the same flow of reasoning, directly objected to any deliberate release of any GMO, and called upon strict regulation of international trade and transportation of GMO crops, emphasising environmental risks and threats to biodiversity. One MP insisted, referring indirectly to the precautionary principle, that the LGMO should explicitly distinguish between products that are researched and developed in a lab, and those that are released to the environment and to the market for food or food ingredients.

The final set of arguments to this first draft proposal directly concerned issues of risk management, stricter regulation and control over contained use, as well as on the lack of clarity of how the different institutions tasked with monitoring and control were going to collaborate and coordinate their actions. Nevertheless, the draft was voted positively (so-called first reading) by a majority in the Parliament, which opened up an opportunity for the MPs to propose specific amendments before each text of the law was to be individually voted by the plenary (so-called second reading). Despite some criticism, the MPs agreed the law was long overdue and was in fact necessary in order to ensure that GMOs, including research, release and marketing, were all closely monitored and strictly regulated.

Despite occasional direct references to the precautionary principle, MPs called for additional precaution due to possible risk to particular economic sectors and higher opportunity costs. This kept the discussion focused not on scientific uncertainty, but rather on risks to the economy, which were, however, not substantiated by any (publicly available or referred to) economic impact analysis.

At the very beginning of 2010, a major revision to the LGMO was proposed, which spurred additional public attention, and even a number of citizen protests across major towns, including several in front of the Parliament building. In the month of February 2010, the term GMO was the most searched for in Bulgaria on Google, according to Google Trends. At no other time since 2004 up until the time of writing of this case study, has that term been so popular. That sudden spike in wider public interest on the matter had an impact on framing the debate in the parliament, which, in parallel with discussing the proposed amendment to the LGMO itself, submitted a draft for a decision to ban deliberate release and cultivation on Bulgarian soil of any GMO. For more than a month, the discussion on both drafts was proceeding in parallel, reinforcing the discourse on risk and uncertainty. A number of media at the time ran interviews with scientists, in an effort to balance the debate. Not surprisingly, none of the interviewed scientists would share the perception of inevitability of risks that was so openly put forward by most parliamentarians. One remarked with a subtle irony that "[Measures that are effectively] blocking [our] research work actually limit the capacity and ability of Bulgarian scientists to properly identify potential risks of releasing GMOs to the environment, which is a key part of GMO science."[52]

The most detailed and heated debate on the LGMO happened at the beginning of 2010 when a large number of significant amendments were proposed by the Government. The major argument in support of the proposal, however, was to harmonise the LGMO with the then-current EU directives due to identified inconsistencies and a warning received from the European Commission. Unlike in 2005, when the majority of MPs expressed their support for the adoption of such a law, in 2010 the proposed amendments were met with far greater controversy. The key reason for that was that some of the amendments appeared to allow the release of GMOs in the environment, effectively easing the restrictions adopted in 2005.

[52] Excerpt from an interview with Prof. Rositsa Buchvarova, Director of the AgroBioInstitute at the Academy of Agricultural Sciences. Published on January 28th 2010 at https://www.dnevnik.bg/biznes/2010/01/28/849542_uchenite_vurnaha_ni_s_20_godini_nazad_s_pulnata_zabrana/#comments-wrapper.

To many MPs that was an unacceptable regression, mostly because, if passed, that would pose a significant threat to the continuing growth of organic agriculture, which is what Bulgaria considered to be a strategic economic advantage. Several organic farmers had provided motivated objections too, arguing that conventional and organic agriculture were both incompatible with GMO-based agriculture as there could not be an effective barrier for the uncontrolled proliferation of genetic material across both adjacent and remote fields. A representative of an association of organic farmers, who was invited to the introductory discussions on the draft in the responsible Standing Committee, even asserted that "Interfering with the laws of nature is dangerous and unpredictable, because GMOs cannot develop natively in the nature."

Only one MP, a scientist, expressed concerns while referring to the precautionary principle. He considered the proposed amendments a significant step back from precaution and explained some of the risks from incontrollable crossing of genetic material to non-targeted organisms – insects, bacteria, and possibly humans, citing possible toxicity, development of antibiotic resistance and irreversible mutations to human gut bacteria. He called for greater precaution, but not solely on grounds of scientific uncertainty. Instead, he asserted, there would be a significant threat to the successful market release of Bulgarian agricultural products, if they were seen as "contaminated by GMOs" by domestic and EU consumers. Other MPs, whose statements followed in the plenary, further motivated their concerns with the amendment not so much with uncertainty and risks to the environment and human health, but with economic uncertainty and the risk of losing even potential market shares of agricultural production. Another MP echoed this concern and further stated that GMOs present a serious risk of disruption of the well-functioning and competitive market of Bulgarian agricultural goods. "On so many levels, adopting this amendment would be a crime to the environment", she concluded.

The debates continued in the relevant standing committees, and took place over a period of a few months. At the same time, the proposed amendment rapidly drew public attention, and caused an outcry among various societal groups – not only environmentalists, but also among less organised groups of consumers. Several spontaneous protests took place in the country, including in front of the Parliamentary building, prompting MPs from the governing party to propose a complete ban (moratorium) on any release to the environment or use of GMOs as food. Thus, while the Parliament was engaged in debates on amendments to the LGMO, a few MPs from the governing coalition proposed a draft for a Decree that would ban any GMO-relevant work or release for a period of five year. Debates on both drafts took place virtually at the same time, which prompted some criticism from opposition MPs on the questionable legislative practice of hurrying up to adopt an amendment to the law while discussing a 5-year-long ban on any of its provisions in regards to GMOs. Throughout these debates, it became rather clear that there is a strong assumption of damage, without any reference to scientific proof, but with a clear motivation to respond to the expectations to an already agitated public.[53] The public outcry was a major reason behind a turning point in the discussion on the LGMO itself, leading to the implementation of greater restrictions (refuting the Government's proposal) through the law itself, and withdrawing the draft of the banning decree, which became obsolete before it was even discussed in any of the standing committees.

As part of the discussions on the LGMO, which took more than two months, one of the debated topics concerned directly the re-assessment of risk when new information becomes available to anyone working with GMOs under containment. The precautionary thinking among some of the MPs resulted in proposing an amendment that changed the original provision in the law from "when new scientific information becomes available" to

[53] Part of the debate took place in the Parliamentary Committee on Agriculture and Forests on February 17th 2010. Complete transcript is available in the Bulgarian language at https://parliament.bg/bg/parliamentarycommittees/members/230/steno/ID/1561.

"when new scientific *or other* information becomes available".[54] The amendment was proposed by the Ministry of the Environment and Waters, and spurred a short debate in the Parliamentary Committee on the Environment and Waters during the second reading.[55] The argument focused on the scope and determinability of what "other information" was which "other information" would be considered legitimate in triggering a response. The Deputy Minister of Environment and Waters, who was explaining the Ministry's proposal, clearly explained that it is not necessary that only scientific information should be used as a trigger, and insisted that any kind of information should be monitored and acted upon, because "anyone who has been granted authorisation to work [with GMOs] under containment, is obliged to monitor everything. In a situation when there is so much public attention, we ought to demand that anyone with an authorisation for contained use should monitor, in addition to their own generated information, everything that is going on in the public space, as well as in the scientific literature." The Chairwoman of the Committee further emphasised that this would include "media information" as well.

This was not agreed upon immediately by the Committee's members. One objected that such a requirement would make reporting and acting upon new information unworkable, but also openly stated he did not object to the proposed change. All of the Committee's Members voted unanimously in favour of adding "other information". Later in the plenary, there was no further debate on that proposal, and it was adopted into the law and has not been changed since.

In March 2010, when the debates on the LGMO had finished, the topic of GMO re-emerged[56] in the discussions on proposed amendments to the Law on Food, where GMO-relevant risks were again highly contested. The debate took place in several of the standing committees, and was mostly focused on issues of food safety resulting from GMO-containing foods and how they were being sold to consumers. It touched upon improving public awareness on GMO content in food products by requiring specific labelling of GMO-containing products in cases when GMO content was above a EU-wide pre-set threshold of 0,9%. A particular concern with regards to food safety was expressed about imported foods for children. The author of the amendment argued: "I am confident that if Bulgarian companies produce GMO-free foods for children, this would be successfully realised not only on the Bulgarian market, but also in the EU. All people everywhere at the moment prefer GMO-free foods."

The quotation is not randomly chosen. This kind of reasoning was presented as a major motivation behind the proposed changes, and it was not questioned by anyone. Besides being an illustration of cross-party consensus that closely reflects dominant public sentiment, at least at the given moment, it is also an illustration of the persisting "fear" of GMOs. That fear, much more than any relevant and valid scientific arguments, gave shape to the precautionary thinking of the lawmakers. Such precaution was additionally informed and encouraged, in a way, by the dominant public sentiments of widespread negativity to anything genetically modified.

Throughout the following years, no major changes have been proposed to the LGMO, which had become particularly restrictive, much like in the majority of other EU Member States. But in debates on various other laws, the topic of GMOs would resurface as an illustration of and in relation to added risks to human health in particular, and would sometimes even be used to ascribe guilt to MPs and political opponents for failing to

[54] Art. 39(1) of the LGMO.

[55] Transcripts of relevant discussions within the Parliamentary Committee of Environment and Waters are available in the Bulgarian language at https://www.parliament.bg/bg/archive/7/3/234/steno/ID/1554.

[56] Transcripts of relevant discussions within the Parliamentary Committee on Legal Affairs are available in the Bulgarian language at https://parliament.bg/bg/parliamentarycommittees/members/226/steno/ID/1608.

oppose GMOs. For example, during a debate in the Plenary in January 2014, an MP from the then-ruling coalition used a number of negatively phrased references to the LGMO, and to several MPs who he claimed did not oppose GMOs during the debates in 2010, as "worthy of shame". In January 2015, the then-Minister of Environment and Water, in a statement to the plenary during debates[57] on the ratification of the Transatlantic Trade and Investment Partnership (TTIP), presented the Government's requirements for the negotiations, one of which is "keeping the ban on GMOs". In January 2020, during discussions[58] on the ratification of the EU-Canada Comprehensive Economic and Trade Agreement (CETA), an MP opposing to the ratification spoke of GMOs as one of the risks of the Agreement, arguing "[it] will enable the silent entry of GMOs to the Bulgarian market and foods" – a claim, ultimately denied in official statements by several Standing Committees, but which did not receive any verification within the Parliament and went largely unnoticed. Another MP, from an opposition party, presented seven groups of arguments against CETA, one of them being GMOs, thus adding to the discourse of negativity around GMOs.

Certainly, none of the above represents an issue about or due to the precautionary principle as such. Nevertheless, these examples illustrate how it is not just the precautionary principle that shapes legal framings and legislators' thinking on GMOs, and possibly on other issues marked by scientific uncertainty and public doubt.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

The precautionary principle has been made foundational to GMO legislation thanks to the Cartagena Protocol on Biosafety to the Convention of Biological Diversity, which is a key international instrument in the GMO regulation and which has informed EU and national regulatory approaches, especially those in the EU.[59] It enables science-informed political decisions, based on identification of risks, acknowledgement of scientific uncertainty, and even safeguarding against ignorance[60], and is considered "the most robust and extensive international legal regime for regulating biotechnology."[59] It make possible the greater control of governments over inquiry into GMO content of food imports, and allows them discretion in deciding whether or not such imports would be allowed if they deem the available scientific knowledge to be insufficient to make a proper risk assessment. Thus governments retain a high degree of agency in limiting the proliferation of GMOs.

The Cartagena Protocol was ratified by the Bulgarian Parliament in October 2000 and entered into force in September 2003, and currently more than 170 countries are signatories on the protocol. A notable exception are the United States, which follow a different regime concerning GMOs (in comparison to the EU, in particular), based on patent law and intellectual property rights. In addition to being products of science, GMOs under such a regime "come to be seen as patentable, ownable, and sellable commodities. [This regime] sets into motion the field of biotechnology as an industry of great potential profit."[59]

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[57] Transcripts of the relevant discussion within the Plenary is available in the Bulgarian language at https://wap.parliament.bg/bg/plenaryst/ns/51/ID/5334.

[58] Transcript of the relevant plenary discussion is available in the Bulgarian language at https://parliament.bg/bg/plenaryst/ns/51/ID/9629?fbclid=IwAR0oivrER30EXJnvu2ZobX2VRkzLzlOWQJ27hSxXYwkCIcpEmrWkT7wxe-E.

[59] Carroll, M. (2016). "The new agrarian double movement: hegemony and resistance in the GMO food economy". In *Review of International Political Economy*, vol. 23(1), pp.1-28.

[60] Myhr, A.I. (2007). "The precautionary principle in GMO regulations", in Traavik, T. and Lim, L.C. (Eds), Biosafety First, chapter 29. Taapir Academic Press, Trondheim, pp. 457-67.

The Bulgarian parliamentary debates on the LGMO, as well as references to GMOs on several other occasions during discussion on unrelated laws, provide an interesting example of how precautionary thinking can shape legislative approaches based, to a large extent, on adopting a wider interpretation of risk as a socially constructed reality. This interpretation appears to disregard actual probabilities, and instead rests on the assumption that risk (of GMOs) is unavoidable, and should therefore be prevented.

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*. One of them was rather critical, stating that the current state of (GMO) affairs in Bulgaria is a "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 feed, but Bulgarian scientists cannot develop their own.

Another said that there has been an overwhelming "lack of convincing evidence" that GMOs (crops) have caused any negative impact on human health, and that some benefits far outweigh publicly feared, but sometimes not even proven, risks – at least those popularly perceived as likely. All of them seemed quite certain that to the extent that risks do exist, there are also ones that the general public does not see and is unaware of them. As an example of such a threat, one of the experts (a retired professor in molecular biology) explained of a case when clearing land to make space for fields of genetically modified soybeans has led to the aggregation of rodent populations that feed on the soybeans and proliferate the newly planted fields. These rodents however are known carriers of Hanta viruses potentially causing severe illness in humans. Thus there is a serious risk of contamination when the seeds are transferred to other locations through global export and import. In this expert's opinion, the risk assessment procedures in place may not in fact be adequate to address such a risk appropriately, but it is real and exists, and the lack of wider awareness or recognition does not make it any less likely.

Notwithstanding opinions of scientists on the limitations enforced by the precautionary framing of the GMO legislation, it is important to consider if there is another viable alternative to how the LGMO could address the management of uncertainty.[47] The precautionary principle thus remains a particularly useful framing in ensuring that legal certainty does not in turn enforce greater scientific uncertainty.

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.[61] This is precisely the approach followed by several cohorts of parliamentarians since at least 2003.

5.2 Effect of the PP on innovation pathways

Bulgaria shares a lot in common with other EU countries when it comes to the scope of regulatory restrictions on GMOs – not just because as a Member State it has to follow many of the same rules. The precautionary principle is strongly rooted in the EU regulatory framework, and is also foundational to the Bulgarian LGMO. In the Bulgarian case, the *de facto* ban on GMOs did not lead to the pursuit of a clear alternative

[61] Koplin, J., Gyngell, C. & Savulescu, J. (2020). "Germline gene editing and the precautionary principle". In *Bioethics,* vol. 34(1), pp. 49-59.

innovation path. None of the GMO-centred debates were found to contain any references to future developments in biotechnology, nor did they demonstrate much of a concern on the development of biotechnology as a sector of the Bulgarian economy with a potential high added value. In general, positive framings of innovation were missing from the debate. Notably, even scientists along the course of GMO legislation's development over the years, did not target the precautionary underpinnings of the legal texts, but framed their critique thereof as being disproportionate to the risks involved.

5.3 Innovation principle

In the Bulgarian context, the dominant arguments have been overwhelmingly against GMOs, so virtually no discussion has been put forward on the potential – real or alleged – benefits of GMOs – not even in terms of advancing national scientific research. All stakeholders, including policy and decision-makers, have used arguments mostly addressed to the public, to assure "Bulgaria will stay free of GMOs", while at the same time also referring to the requirements of the European Union as the key reason to enact the necessary regulations. Essentially, the debate was more closely focused on how not to allow any release of GMOs in the environment, how to limit GMO content in food, and how to ensure proper controlling and that the broadest restrictive measures are in fact in place.

The Innovation Principle is defined by the European Commission as "a tool to help achieve EU policy objectives by ensuring that legislation is designed in a way that creates the best possible conditions for innovation to flourish [, and is meant to] ensure that all new EU policy or regulations support innovation and that the regulatory framework in Europe is innovation-friendly."[62] 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 biotechnology use in agriculture.

In Bulgaria the Innovation Principle has not been formally or informally invoked, especially in the form of legislation, particularly since it is relatively new. As a concept, it has slowly been gaining traction among EU policy makers since 2013, and was officially introduced by the European Commission in 2017 before becoming an official part of DG Research's Work Programme 2018.[63] Thus, the LGMO debates, which were very few and very short since the major revision in 2010, and was last amended in 2017, could have hardly been influenced by any notion of the innovation principle. On the other hand, the theme of innovation has not been part of the two-decade-long Bulgarian debate affecting the LGMO. Instead, all the arguments against GMOs rested on notions of precaution and pre-emptive measures against an imminent threat. This has resulted in a restrictive regulatory framework on GMOs, without engaging parliamentarians in debates of alternative routes for innovation development.

The experts we interviewed (all of whom scientists with practical experience in biotechnology and agronomics) on the subject were cautiously optimistic about GMOs, which opened up a different perspective on the relevance of innovation (though not on the Innovation principle, which they did not acknowledge in the same way they were aware of the precautionary principle). One of them, himself a trained plant biologist, said that the highly restrictive LGMO in Bulgaria serves to calm a concerned public, while complying with the EU regulatory requirements, and that the entire philosophy of the restrictions is based on the assumption of imminent threat – though not only to human health and the environment, but frequently also to "traditional" Bulgarian plants, with roses and tobacco being the most sensitive topics.

[62] Definition available at https://ec.europa.eu/info/research-and-innovation/law-and-regulations/innovation-friendly-legislation_en.

[63] European Commission (2018). *DG RTD Management Plan 2018.* Available at https://ec.europa.eu/info/sites/info/files/management-plan-rtd-2018_en.pdf

> *" Innovation was nowhere in this debate. The restrictive regulatory framework essentially means absence of motivation (coupled with lack of investment and institutional support) for research, and therefore – for innovation. Even trained scientists have to make a choice – whether to apply their skills in a different field, or to move to a different country where they can continue with their research ."*

Despite the absence of innovation as a focus of discussion in the debates on the LGMO, an interesting opinion emerged from one of the interviewees, who considered the GMO field at the moment as "closed for innovation". Rather, he turned to the novel field of synthetic biology and to the latest advances in biotechnology, such as gene editing[64], as possible pathways for biotechnology innovation:

> *" With 30 years of history of development and research into their risks, GMOs are actually quite safe. The knowledge on the methods and their application is solid, and some applications represent not just novelty but actual benefits to society. Addressing remaining concerns on their safety is but a matter of time. The attention for innovation is no longer on GMOs though – it is on gene editing, which evolves really rapidly, and regulations still play catch - up in much of the world."*

However, in July 2018, the European Court of Justice already ruled[65] that organisms generated by mutagenesis, including targeted mutagenesis through CRISPR-Cas and other genome editing tools should be considered GMOs and should therefore be subjected to the same regulations. That decisions has met a mixed reaction, with the division of opinion matching that developed over time towards GMOs. Media reporting (in the EU) in particularly has been found to be biased and often one-sided, and journalists accused of providing biased and unbalanced accounts ignoring the breadth of different positions.[66] The division of opinion among environmentalist groups and the affected industry has also been rather clear and polarised – no less than on the "traditional" GMO debate.[67] Therefore, it still remains to be seen whether, at least in the EU, novel gene editing techniques will change the dynamics of the precaution versus innovation debate, and how this might reflect future regulatory developments.

6 Synthesis

Bulgarian legislation follows closely that of the EU, and has explicitly included the precautionary principle in the national LGMO. Like the majority of EU Member States, Bulgaria has been quite conservative in its regulatory approach to GMOs, effectively banning all GMOs in food products (but not in feed), as well as any planting of GMO crops. The history of the public debate, and in particular – the legislative debate, has demonstrated an approach to precaution, which is not rooted into scientific arguments, however, but rather is based on the implicit assumption of harm. There is also a strong

[64] A key difference between GM technology and gene editing is that the former always involves the transfer of genes from one organism to another, while the latter involves direct manipulation of the genome of the target organism, is more precise, and takes significantly less time.

[65] European Court of Justice Case C-528/16. Summary of the ruling is available at http://curia.europa.eu/juris/document/document.jsf?text=&docid=207002&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=5986525.

[66] Gelinsky, E. & Hilbeck, Angelika (2018). "European Court of Justice ruling regarding new genetic engineering methods scientifically justified: a commentary on the biased reporting about the recent ruling". In *Environmental Sciences Europe*, vol. 30(1).

[67] A summary example of the reactions of different stakeholder groups can be seen at https://uk.reuters.com/article/us-eu-court-gmo/top-eu-court-gmo-rules-cover-plant-gene-editing-technique-idUKKBN1KF15L.

public sentiment against any GMO use. Thus, despite the inherent complexity of the subject, regulatory actions seem to prefer to not address complexity, but rather ensure GMOs are virtually impossible. That reflect also on how risk is being perceived – not as a possibility, but as a certainty, and therefore the legislation is as restrictive as possible, while also being compatible with the EU legislative framework.

This leaves little, if any, space for a discourse on innovation. In fact, GMOs are hardly even considered as innovative. As the experts we interviewed emphasised, even laboratory use is made impossible, and so are any experiments in the field, thus effectively stifling any applied research and making any further innovation highly unlikely. On the other hand, science is fast moving forward already, and attention is being shifted to new generation of gene editing techniques, such as CRISPR-Cas9 that until very recently did not fall into the scope of GMO regulations, and are a source of different controversies. 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. There is a very real threat that in a few years, such expertise would be impossible to find. However, such a presumably negative scenario has not been a part of parliamentary debates, so remains without regulatory legitimation.

On the surface, it seems that indeed too much precaution has led to no innovation, at least with respect to GMO research. It remains however debatable to what extent this situation is in fact a direct result of the precautionary principle as the foundational framework of the LGMO. The precautionary principle is an interface between science and policy, where controversy, risk and uncertainty are formally recognised and institutionalised, and science is key. The application of the principle depends on scientific processes and protocols that have taken long time to perfect. But the Bulgarian case demonstrates something different – the debate on GMOs was not a debate *exclusively* on aspects of, or being informed by scientific arguments (in terms of uncertainty, ambiguity and complexity), not on the limitations of the scientific method, not on the economic and systemic complexities and externalities, but was instead highly politicised and value-driven. In short - it was more focused on political outcomes that on the rationale of precaution or innovation. Not one opinion over more than a decade of debate has been rooted into scientific evidence, findings, or understandings without connecting these to underlying values and attitudes. Instead, it was everything else, resulting in legislative provisions that equate scientific evidence of threat to any other source of information. That is certainly not an example of (principled) precautionary thinking, but one may well argue it is a responsive (rather than a responsible) approach, whereby the opinions of lawmakers resonate with the aspirations of the general public rather than with prior experience with GMO cultivation.

The innovation principle can hardly provide or be a solution in this case. If the legislation is made less restrictive (it has been before 2003), it is questionable to what extent that would result in more (domestic) innovation. There will certainly be implications for the market of foods – crops for human consumption, as well as foods containing GMOs, as well as implications for national agronomic practices and agriculture. Such a scenario, however, has not been debated, even hypothetically. Instead, there has been remarkable consensus among political parties over the years that GMOs are harmful to human health and the environment, which exhausts the scope of the GMO debate.

7 Conclusion

Bulgarian society thus far remains conservative and seems to share a preference towards being overly cautious – a sentiment that is echoed consistently by politicians and

legislators since 2003. Societal consensus on the risks and benefits of GMOs is hardly ever going to be accomplished given the long history of development and use of GMOs across food supply chains, as well as that of regulatory oversight and procedural detailing. There are too many sources of divisions and the complexities are not likely to be resolved. At the same time, science and technology continue their evolution and new regulatory challenges are already present.

This case focused on the Bulgarian regulatory context in order to exemplify how the perception of GMO risks is being influenced by strong normative assumptions about imminent threat, and how the part of science within at least the parliamentary debate can be easily trumped by non-scientific, but just as legitimate, arguments. 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.

The Bulgarian LGMO in itself is hardly unique within the EU, the majority of whose Member States have very similar restrictive legislation. But the political debate, and the influence of public and stakeholder pressures at key points of the debate, are uniquely illustrative of the complexity of the societal dynamics with respect to understanding, accepting, controlling and, we dare say – taming – through legislation, a subject defined by uncertainty and distrust. Furthermore, the debates are also illustrative of how easily the lack of scientific certainty translates into legal uncertainty.

To that end, it might be a subject to further inquiry about the true effects and unintended consequences of a restrictive GMO regulation.

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Endocrine disruptors

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Abstract

Endocrine disrupting chemicals (EDCs) are at the centre stage of a scientific and regulatory controversy. Given the complexities, ambiguities and particularly the uncertainties surrounding the hazards of EDCs, the precautionary principle is of utmost relevance to the case. Even the definition of EDCs remains much contested, as do the scientific processes and methods through which to identify them. On the one hand, there is considerable societal pressure to regulate ECDs 'now'. On the other hand, this quick regulation is often impossible as the limited evidence available does not suffice in the context of traditional EU scientific risk assessment. This results in 'paralysis' and several controversies surrounding EDCs, such as regarding bisphenol A and a long delay by the European Commission to formulate scientific criteria for identifying endocrine disruptors. Bans on the use of particular EDCs have also led to so-called 'regrettable substitutions'. In turn, green chemistry can be regarded as one important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs.

Contents

List of abbreviations

BPA	Bisphenol A
BPS	Bisphenol S
BPR	Biocidal Products Regulation
Cefic	European Chemical Industry Council
CeHoS	Danish Centre on Endocrine Disruptors
CEO	Corporate Europe Observatory
CIA	Chemical Industries Association
DEHP	Di(2-ethylhexyl)phthalate (mainly used in plastics)
DES	Diethylstilbestrol (medical drug)
DG	Directorate General
DNEL	Derived no-effect level
ECHA	European Chemicals Agency
ECJ	European Court of Justice
ED	Endocrine disruptor
EDC	Endocrine disrupting chemical
EEA	European Environment Agency
EEB	European Environmental Bureau
EFSA	European Food Safety Authority
EP	European Parliament
ERF	European Risk Forum
EU	European Union
IPCP	International Panel on Chemical Pollution
IPCS	International Programme on Chemical Safety
NGO	Non-governmental organisation
OECD	Organisation for Economic Cooperation and Development
PNEC	Predicted no-effect concentration

PP	Precautionary principle
PPPR	Plant Protection Products Regulation
PVC	Polyvinylchloride
REACH	Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SVHC	Substance of very high concern
UNEP	United Nations Environmental Programme
US	United States
WECF	Women Engage for a Common Future
WHO	World Health Organisation

1 Introduction

1.1 Introduction

Endocrine disruptors, also called endocrine disrupting chemicals (EDCs), are at the centre stage of a scientific and regulatory controversy. Chemicals shown to have endocrine disrupting effects have mostly been man-made. 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.

Yet there is a link between such widely used chemicals and disorders within the endocrine (hormonal) system. For example, EDCs are seen to be a cause for chronic diseases, including infertility, obesity, diabetes, hormone related cancers, and cardiovascular disease (WHO, 2012a, p. 22-26). And because EDCs can be found in many products that people use or consume on a daily basis – including paint, food packaging, toys, clothing, cosmetics, and medicines – they can be the cause of serious harm for human health. The most widespread and commonly known EDCs are "bisphenol A, phthalates, pesticides, persistent organic pollutants such as polychlorinated biphenyls, polybrominated diethyl ethers, and dioxins" (Gore et al., 2015).

Although EDCs can thus be seen as "a risk that concerns us all", they pose risks especially to unborn and young children (BEUC, 2016, p. 3). Moreover, the threats that EDCs pose are not limited to human health. Existing evidence indicates that exposure to EDCs also has a negative impact on wildlife health trends (WHO, 2012a, p. 11).

The health risks both for humans and wildlife associated with EDCs became increasingly clear over the course of the 1990s (see e.g. WHO, 2002). Various authorities, including the World Health Organisation (WHO) and the European Commission, subsequently issued studies investigating the potential harm caused by EDCs (e.g. EEA, 2012; WHO, 2012a). But problematically, even the very definition of EDCs remains very much contested, as do the scientific processes through which to identify them. To define which chemicals or substances are in fact to be considered as EDCs is key, however, because this has important implications for how they are regulated.

Indeed, the growing scientific evidence on the negative effects of EDCs for health and for the environment caused debate about the identification and regulation of EDCs within the European Union (EU). From 2014 to 2017, in particular, there has been controversy surrounding the Commission's delay to set out scientific criteria for the determination of endocrine disrupting properties. Despite the subsequent establishment of criteria for the identification of EDCs in several – but not all – EU legislative areas, there are ongoing concerns about the suitability of the EU's regulatory framework on EDCs. Such concerns include the absence of a horizontal definition of EDCs, which is a definition that cuts across various matters and subject areas, and more recent evidence that the "health risks associated with EDC *mixtures* are underestimated" (Bergman et al., 2019, p. 3).

> *This case study aims to better understand the complexities surrounding the application of the precautionary principle in the case of the governance of EDCs, as well as the controversies surrounding calls for innovation in this field.*

Against this background, this case study aims to better understand the complexities surrounding the application of the precautionary principle in the case of the governance of EDCs, as well as the controversies surrounding innovation in this field. Because the governance of the risks posed by EDCs most importantly takes place at the level of the EU institutions in Europe, the study focuses on decisions and regulations within the EU,

starting with the first debates of the 1990s. While the case study focuses mostly on the – proven as well as potential – health risks of these chemicals, it also considers the governance of EDCs in the context of the risks to the wider environment and wildlife. This is because the latter risks have likewise received substantial attention in academic research, and in public, political and legal discussions.

More specifically, the case study examines 1) the origin of endocrine disruptors, 2) the risks and scientific controversy surrounding endocrine disruptors, 3) the political and legal dynamics concerning the application of the precautionary principle, and last but not least 4) to what extent there has been a tension between precaution and innovation.

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. Most importantly, these stakeholders see a lack of data to lead to great uncertainties about the degree and extent of risks arising from EDCs. Many of these uncertainties arise from the complexities surrounding both the hazard of and exposure to EDCs, given that "endocrine-disrupting action breaks all the rules and assumptions that have guided toxicology through the era of modern chemical regulation" (Vogel, 2005).

Within the EU, the regulatory framework has been set up in such a way that regulation and the assessment of individual endocrine disruptors takes place within the context of various regulations. In the area of health and food safety, EDCs are regulated within the Cosmetics Regulation (1223/2009) and Food Contact Materials Regulation (10/2011). And within the area of the internal market, EDCs are regulated within the REACH regulation (1907/2006). In the area of environment, EDCs are regulated within the Plant Protection Products Regulation (PPPR) (1107/2009) and the Biocidal Products Regulation (BPR) (528/2012). Crucially, and also problematically, these pieces of legislation contain different regulatory approaches to EDCs (European Commission, 2018, p. 9).

There have been major controversies surrounding the development of these regulations. A main issue in this context is the process through which the European Commission has set scientific criteria for the identification of EDCs subsequent to these regulations. From a legal perspective, a milestone in this respect has been the 2015 judgment of the European Court of Justice (ECJ) in a case that Sweden brought against the Commission (T-521/14). The Court ruled that the Commission had failed to fulfil its obligations under the Biocidal Products Regulation. This was seen to be the case as the Commission had failed to adopt a delegated act[1] to set out the necessary scientific criteria for authorization. At the same time, stakeholders from industry have brought several cases against ECHA to the ECJ concerning the establishment of lists of substances subject to authorization.

Finally, when it comes to innovation pathways, 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. The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS). In turn, green chemistry may be regarded as an important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs. Nevertheless, scientists working within this field do still encounter the complexities and uncertainties in establishing the potential endocrine-disrupting activity

[1] Delegated acts are legally binding acts that enable the Commission to supplement or amend non-essential parts of EU legislative acts, for example, in order to define detailed measures (https://ec.europa.eu/info/law/law-making-process/types-eu-law_en)

of substitute chemicals. At the same time, 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.

1.2 Key timeline

The timeline below lists key events regarding the debate and regulation of endocrine disrupting chemicals. It focuses mainly on the EU institutions, and most importantly the European Commission, but also includes key international scientific reports and influential NGO activity.

In view of the timeline below, it is important to highlight that the case study focuses on the three main different regulatory approaches to EDCs that exist in the EU legal framework. These are

1. the Plant Protection Products Regulation (PPPR) and the Biocidal Products Regulation (BPR), which mostly concern pesticides;
2. the regulations on Food Contact materials and Cosmetics – which are not mentioned in the timeline below as their provisions do not explicitly contain regulations on endocrine disruptors;
3. the REACH regulation regarding production and use of chemical substances within the EU internal market.

Political	***Legal***	***Science/risk assessment***	***Public debate***	***Other***

Year	***Event***	***Relevance to case study***
Around 1960	*Publications by Roy Hertz (1958) and Rachel Carson (1962)*	*First publications on the harm that chemicals can cause to ecosystems and human health. Set off a range of studies on reproductive health of wildlife in the 1960s*
Early 1970s	*Medical tragedies surrounding the drug diethylstilbestrol (DES)*	*First widespread evidence of adverse health effects of EDCs that only emerge after many years (in this case, vaginal cancer in young females after puberty)*
1990s	*Wingspread I conference in the US (1991) and Weybrdige conference in the EU (1996)*	*First international conferences on endocrine disruptors. Wingspread I was "a key turning point" and coined the term 'endocrine disruption' (Schug et al., 2016, p. 836)*
1998	*European Parliament resolution on endocrine-disrupting chemicals*	*Calls for "strict compliance with the precautionary principle" in establishing a regulatory framework on EDCs*
1999	*European Commission strategy for endocrine disrupters*	*First strategy of the Commission on endocrine disruptors, emphasizes the importance of the precautionary principle*

2002	*WHO report "Global Assessment of the State-of-the-Science of Endocrine Disruptors"*	*Finds "weak evidence" for adverse health effects of EDCs, but stresses need for more research*
2006	*"REACH" Regulation*	*Allows identification as industrial chemicals with endocrine disrupting potential*
2009	*Cosmetics Regulation*	*Requests Commission to review Regulation with regard to EDCs by January 2015*
2009	*Plant Protection Products Regulation (PPPR)*	*Requests Commission to present scientific criteria for determining EDCs by December 2013*
2012	*Biocidal Products Regulation (BPR)*	*Requests Commission to present scientific criteria for determining EDCs by December 2013*
2012	*WHO report "State of the Science of Endocrine Disrupting Chemicals—2012"*	*Finds that EDCs are a "global threat" to human health and that there is a severe lack of data on identifying EDCs*
2013	*Scientific opinion of the European Food Safety Authority (EFSA) on the hazard assessment of EDCs*	*Concludes that EDCs do not need to be regulated based on a hazard approach but can be regulated by means of risk assessment*
2013	*European Commission decision for an impact assessment of regulation on EDCs*	*Delayed the establishment of scientific criteria for the identification of EDCs*
2015	*ECJ judgment European Commission failed to act regarding scientific criteria to identify EDCs*	*Case brought by Sweden concerning the overdue deadline for setting scientific criteria in the Biocidal Products Regulation*
2015	*Corporate Europe Observatory report "A Toxic Affair"*	*A vital document in the debate. It reports on lobbying activity by the chemical industry, which led to the European Commission to* ***not*** *take any regulatory action on EDCs.*
2017	*Regulation amending the Biocidal Products Regulation*	*Sets out scientific criteria for the identification of EDCs*
2018	*Regulation amending the Plant Protection Products Regulation*	*Sets out scientific criteria for the identification of EDCs*
2018	*European Commission communication "Towards a comprehensive European Union framework on endocrine disruptors"*	*Concludes there are different approaches to endocrine disruptors within the EU legal framework. Launches "fitness check" of EU legislation on endocrine disruptors*
2019	*European Parliament resolution on Commission communication*	*Considers the current EU framework for*

	about EDCs	*regulating EDCs to be inadequate*
2019	*European Commission consultation on EDCs*	*Launch of a consultation with both public and stakeholders*
2019	*EDC-MixRisk report and policy recommendations (Bergman et al., 2019; Bergman, Rüegg & Drakvik, 2019)*	*Finds that existing regulations for chemicals systematically underestimate the health risks of EDCs*

2 Use of chemicals with endocrine disrupting properties

Chemicals with (potentially) endocrine-disrupting properties are mostly man-made. They were originally engineered so as to produce benefits for various industries, consumers, and individuals. As such, EDCs can be found in many products. This most importantly, but not exclusively, includes products for industry and agriculture, for households and consumers, as well as for medical and personal health care.

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" (Mnif et al., 2011). Yet industry has engineered various pesticides and herbicides that were later shown to have endocrine-disrupting effects, also on human beings. The pesticide DDT, for instance, was widely used until the 1960s to control insects. Amongst other issues, it has been related to an early onset of puberty and menopause in humans, as well as to "critical effects in pregnant and nursing" females (Schug et al., 2016, p. 841). DDT has been banned in the EU since the 1980s but remains present in the environment until today (European Commission, 2003). In turn, the herbicide Atrazine, about which there is evidence that it for example causes abnormal female cycles, has been banned in the EU but remains widely used in the US (see Sass & Colangelo, 2006).

In the area of household products, the most well-known chemicals with endocrine-disrupting properties were originally developed for the plastics industry. These, for instance, include bisphenol A (BPA) and phthalates. BPA is very widely used to make plastic products shatter resistant, colourless, and light weight. It is, for instance, used for various medical devices and for food packaging. Given its widespread use, BPA has been at the centre stage of scientific and public controversies, as the chemical has been related to cancers, changes in metabolism, and neurobehavioral issues such as attention deficit disorders – amongst other health effects (Schug et al., 2016, p. 840). In turn, phthalates such as DEHP (Di(2-ethylhexyl)phthalate) are used to increase the flexibility of plastics. This is useful for products such as toys, wires and cables, and building materials. Phthalates are also widely used in cosmetic products, like perfumes (see e.g. Al-Saleh & Elkhatib, 2016). Researchers have, however, linked phthalates to a wide variety of negative health effects, including also changes in metabolism and neurobehavioral issues, as well as male fertility issues (Schug et al., 2016, p. 840; Westervelt, 2015). The use of BPA and of various types of phthalates has been restricted within the EU.

Finally, some chemicals have been purposefully designed to have endocrine-disrupting properties so as to benefit human health. This particularly includes EDCs developed for female heath, such as for birth control and for the treatment of menopause symptoms. Most birth-control pills, for example, include the EDC 17β-ethinylestradiol (EE2). EE2, however, has been shown to cause serious ecological issues as it ends up in water

through urine and sewage. It causes harm to wildlife, as it is, for example, capable of "feminizing male fish" (Schug et al., 2016, p. 841).

> *" Even purposefully engineered chemicals aimed at benefiting humans can also harbor potential for harm" (Schug et al., 2016 , p. 841).*

As Schug et al. write, then, these examples about the design and use of chemicals show that "even purposefully engineered chemicals aimed at benefiting humans can also harbor potential for harm" (2016, p. 841) – both for human health and for wildlife.

3 Risks and scientific uncertainties

3.1 Risk/threat

3.1.1 Potential risks

On the basis of a number of 'state of the art' reviews by The Endocrine Society, UNEP and the WHO, and the European Commission (see section 3), the current section describes the threats that EDCs pose to different societal groups, as well as to wildlife and the environment. 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).

The scientific evidence on the risks posed by the endocrine disrupting properties of widely used chemical substances has significantly increased since the 1990s, and even more so since the early 2000s. In its influential report on EDCs of 2002, the WHO defines an endocrine disrupting chemical – also referred to as endocrine disruptor (ED) – as a substance that "alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" (WHO, 2002, p. 1). Hence, in simple terms, EDCs are chemicals that interfere with the hormonal system and can thereby negatively affect the health of both humans and animals.

> *In simple terms, EDCs are chemicals that interfere with the hormonal system and can thereby negatively affect the health of both humans and animals.*

Hormonal – or endocrine – systems control various important processes in the body, ranging from early embryonic development and organ formation, to "most tissue and organ functions" in adults (WHO, 2012a, p. 4). EDCs "act like hormones", and can mimic or block natural hormones (ibid., p. 6). As such, they interfere with the normal action of hormones. The most widespread and commonly known chemicals that have broad endocrine-disrupting properties are "bisphenol A, phthalates, pesticides, persistent organic pollutants such as polychlorinated biphenyls, polybrominated diethyl ethers, and dioxins" (Gore et al., 2015, p. 593). These and other EDCs can alter the function of hormones to the extent that they induce diseases, even at – and in some cases also particularly at – very low levels of exposure and concentration (Gore et al., 2013, p. 3958). The latter has also been called the 'low-dose effects' of EDCs.

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 (Gore et al., 2015; WHO, 2012a). With regard to the latter health effects, exposure to EDCs has been linked, *inter alia*, to the occurrence of dyslexia, IQ loss, ADHD, and autism (Bergman et al., 2019; Bergman, Rüegg & Drakvik, 2019; WHO, 2012a, p. 9).

Exposure to endocrine disruptors occurs on daily basis, as EDCs can, for example, be found in plastics, paint, toys, clothing, cosmetics and pesticides, and even in dust released from indoor sources. It is therefore clear that EDCs are a risk that concerns all consumers (BEUC, 2016, p. 3). Crucially, however, there is scientific consensus that the *timing* of exposure is critical. That is, the "most sensitive window of exposure" is during important moments of tissue development, and the effect of EDCs can be irreversible during these periods (WHO, 2012a, p. 6). This includes most importantly prenatal development, and the development of young children, but also of young adults (European Commission, 2018, p. 2; WHO, 2012a). (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 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).

Additionally, there is increasing evidence that combined exposure to different (potential) EDCs provides leads to greater threats to human health, especially for children (Bergman et al., 2019). Endocrine disruptors working "together to produce additive effects" has also been called the 'mixture effect' or 'cocktail effect' (European Commission, 2018, p. 2; see further below).

Finally, the threats that EDCs pose are not limited to human health but have implications for the environment as a whole and the well-being of wildlife. Existing evidence indicates that "exposure to endocrine disrupting contaminants plays a significant role in wildlife health trends", and that there is a relation between exposure to EDCs of wildlife and population decline (WHO, 2012a, p. 11; see also EEA, 2012). This has been shown to be the case for "molluscs, crustacea, fish, reptiles, birds and mammals" (DG Environment, 2019a).

3.2 Scientific analysis

Scientific analysis of the risks posed by endocrine-disrupting chemicals to wildlife, laboratory animals, and humans most importantly includes many "thousands of published studies" (Gore et al., 2013). There are also several major scientific research projects on EDCs that are ongoing or have just been completed. Although there were earlier signs for a link between chemicals and health problems (see the 'Key timeline' in part 1 of this report), most of scientific evidence originates from the decades after the 1990s (European Parliament, 2019, p. 2-3). In Europe, a first international meeting on endocrine disruptors took place in Weybridge, in 1996. It was sponsored by the European Commission and resulted in the publication of a future research agenda in the so-called 'Weybridge Report' (DG Environment, 2019b).

Publications on the risk of EDCs have subsequently been reviewed in a number of influential reports (see also European Parliament, 2019, p. 4-7). The first of these was the 2002 report "*Global Assessment of the State-of-Science of Endocrine Disruptors*" from the International Programme on Chemical Safety (IPCS) – a programme jointly set up by the WHO, UNEP and the International Labour Organisation (WHO, 2002). It was a response to the recommendation of the 1997 Intergovernmental Forum on Chemical Safety. Most importantly, the document systematically assessed existing literature on the effects of EDCs for human health and wildlife. It most importantly concluded that there

was still insufficient data to draw conclusions about the threats posed by EDCs (WHO, 2002).

The follow-up to the 2002 WHO report, entitled "*State of Science of Endocrine Disrupting Chemicals*" was published in 2012. It provided an "assessment of the strength of the evidence supporting the hypothesis that chemicals with endocrine activity are a causal factor in the manifestation of specific conditions" (WHO, 2012a, p. 1). It identified such evidence for several threats to human and wildlife health, but also identified a major lack of data and testing of chemicals suspected to have endocrine disrupting properties.

The publication of the 2012 report of the WHO was preceded by a few other scientific reviews, including the "*Scientific Statement*" of the Endocrine Society (Diamanti-Kandarakis et al., 2009), the "*State of the Art Assessment of Endocrine Disrupters*" from the EU Directorate-General (DG) for the Environment (Kortenkamp et al., 2011), and "*The Weybridge+15 (1996–2011) report*" of the European Environment Agency (EEA) (EEA, 2012).

The EU has also funded several research projects on endocrine disruptors. Most recent projects include the Innovative Training Network "*PROTECTED*" on detecting EDCs that are not synthetic, and the Horizon 2020 projects "*EDCMixRisk*", on the health effects of combined or additive exposure to EDCS, "*EndocRine Guideline Optimalisation*", on the tools for hazard assessment of EDCs and "*FREIA"* on female reproductive toxicity of EDCs (see below under section 2.3.1.5 regarding the latter project). Another relevant Horizon 2020 project is *ERGO*, "which aims to improve hazard assessment of EDCs (…) by breaking down the wall that currently exists between the different research fields that investigate adverse effects of EDCs" (ERGO, project overview). ERGO and FREIA are part of the larger EURION project, "*European Cluster to improve Identification of Endocrine Disruptors*".

Additionally, important reviews on identifying, regulating and testing EDCs have been published by UNEP and the Organisation for Economic Cooperation and Development (OECD). The UN's International Panel on Chemical Pollution (IPCP) has published a series of three reports to provide an overview of 1) initiatives of various stakeholders to identify (potential) EDCs; 2) the environmental exposure and effects of EDCs; and 3) regulatory frameworks and policy initiatives on EDCs (UNEP 2017a; 2017b; 2017c). The OECD published a first "*Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption*" in 2012, and a second, updated, version in 2018 (OECD, 2012; 2018).

Finally, various national consumer agencies have engaged in researching the presence of chemicals with endocrine-disrupting properties in products that people use on a daily basis (see e.g. BEUC, 2016; 2019).

3.3 Scientific uncertainty

3.1.2 Complexity

The risk properties of endocrine disruptors are highly complex. Complexity in this context refers to "the difficulty of identifying and quantifying causal links between a multitude of potential candidates and specific adverse effects" (RECIPES conceptual framework). To understand such complexity for EDCs, it is helpful to distinguish between four forms of complexity, two of which are related to the biological and environmental system in question, and two of which are related to the wider regulatory and political system under which EDCs are governed. It is important to note that the intrinsic complexity of human physiology and of the hormonal system also adds to the complexities of researching EDCs.

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. Most importantly, this is because "endocrine-disrupting action breaks all the rules and assumptions that have guided toxicology through the era of modern chemical regulation" (Vogel, 2005). This is primarily the result of two characteristics of the health hazard of EDCs, namely low-dose and mixture effects.

> *" Endocrine- disrupting action breaks all the rules and assumptions that have guided toxicology through the era of modern chemical regulation" (Vogel, 2005).*

To start with, standard toxicology assumes that increasing exposure to a substance leads to increased effect – a simplifying assumption that has been coined the "monotonic-dose relationship" (Vogel, 2005). EDCs, however, behave differently. That is, they do not behave as 'usual' toxic substances, but rather behave like hormones. And therefore, "like hormones, EDCs exhibit complex dose-response curves, and they can act at extremely low concentrations" (Gore et al., 2015, p. 594). This is known as 'non-monotonic dose-response curves'. For example, the relation between exposure to and the health hazard of some EDCs takes the form of an inverted U-curve, in which higher levels of exposure are associated with a lower health hazard (Vogel, 2005). As a result, one cannot extrapolate the effects (or lack of effects) at the high doses to the low doses, which is the common assumption in toxicology testing. Such non-linearity is a key aspect of complexity.

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" (Gore et al., 2015, p. 594). Thus, the effect of a particular EDC has to be considered in terms of its addition to a 'mixture' of chemicals and hormones, rather than in isolation. The EDC-MixRisk project, for example, concludes that prenatal exposure to various EDCs simultaneously is related to health and developmental effects to an extent that is much greater than was previously estimated on the basis of case-by-case assessment (Bergman et al., 2019). This is likewise an example of non-linearity. Here, the effect of multiple hazards is larger than the sum of its parts, because of interaction.

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. In brief, exposure complexity refers to the situation that it has been difficult to determine the levels at which both humans and the wider environment are actually exposed to EDCs. Determining such exposure levels becomes all the more significant given that exposure to EDCs at a low dose and during a specific moment in time "can be just as or more dangerous" than exposure at a high dose for a longer period of time (Vogel, 2005). Because the endocrine system very much changes over time, the effect of an EDC can be different at different moments in the development of an individual – either being evident at birth or leading to diseases at a later stage in life (Gore et al., 2015).

In this context, it is crucial to understand that "endocrine disruptors are everywhere" (van Kessel, 2019). Yet the level of exposure to EDCs depends on human and wildlife behaviour, for example on the ways in which people encounter, interact with or use products that contain EDCs (Vogel, 2005; see also Di Renzo et al., 2015).

Second, besides the complexities related to the biological and environmental system, regulating the risk of endocrine disruptors is complicated by the broader system in which EDCs are governed. Clearly, to detect which chemicals 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' (RECIPES conceptual framework; see also below under 2.4.2). At its very basis, the system is developed around conventional testing schemes, which were designed for the identification of hazards in chemicals other than endocrine-disrupting properties. Given the hazard and exposure complexities just described, these schemes "have serious deficiencies in estimating EDCs' likely impact on human health and wildlife" (EEA, 2012, p. 19). The development of alternative procedures for testing EDCs has been very costly both in terms of time and resources (EEA, 2012, p.19-20; Vogel, 2005).

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 (European Commission, 2018; see further below).

Finally, the complexity of endocrine disruptors as a risk also gives rise to important, wider *political complexity*. This is so as different stakeholders adhere to different positions; a trend which we do not only see within the EU (see section 4 of this report), but also beyond. One major political complexity concerns international trade agreements. To facilitate free trade, international actors seek to "flatten out" regulatory differences, as such differences may constitute trade barriers (Horel, 2015, p. 4). Given that EDCs are used in many products that are globally exchanged, there is external pressure – most importantly from the US – to change or influence the basis on which the EU acts with regard to EDCs (see Horel, 2015).

3.1.3 Uncertainty

Uncertainty refers to a "lack of knowledge about the outcomes or likelihoods, or both, of an event or process" (RECIPES conceptual framework). There are several scientific uncertainties about substances with endocrine-disrupting properties, and some of this uncertainty is likely to remain also over time. These uncertainties can be linked to three main factors:

1. Lack of data;
2. Lack of testing methods;
3. Indeterminacy about effects.

Firstly, uncertainty about endocrine disruptors is the result of practical limitations in combination with the hazard complexity of EDCs. This combination leads to a large *lack of data* about the identification, the degree and the extent of risks arising from EDCs. Notably, in its 2012 report, the WHO writes that about 800 chemicals are known or suspected to be endocrine disruptors, but that "only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms" (2012a, p. 2). More urgently, "the vast majority of chemicals in current commercial use have not been tested at all" for endocrine-disrupting properties (ibidem). Around the turn of the century, for example, the US Environmental Protection Agency (EPA) estimated that there are 87,000 chemicals that can potentially be endocrine disrupting (Vogel, 2005; see EPA, 2000, p. 8).

> *" The vast majority of chemicals in current commercial use have not been tested at all" for endocrine- disrupting properties (WHO, 2012 a, p. 2).*

Secondly, tests for the endocrine-disrupting properties of chemicals are highly time-consuming and as such there is still a great lack of *testing methods*. For example, testing schemes are still in the process of being developed and revised (compare e.g. OECD, 2012; 2018); the hazard complexities of EDCs can only really be understood through multi-generational studies (EEA, 2012, p. 19); and scientists question if current test methods are sufficiently sensitive to screen for EDCs (Hass et al., 2019, p. 8). Thus, given large practical limitations and hazard complexity, uncertainty about EDCs in the form of a lack of data is likely to persist into the future.

Thirdly, scientific uncertainty about EDCs also arises from *indeterminacy,* that is, scientific uncertainty of the effects of EDCs. It is incredibly difficult to determine the precise causal chains through which EDCs act on the hormonal system of both humans and wildlife. A report of the Danish Centre on Endocrine Disrupters (CeHos) identifies three such major uncertainties when it comes to the effects of EDCs (Hass et al., 2019, p. 5). Firstly, it is "uncertain whether or not there is a threshold for effects of EDs", regardless of the mode of action of the particular EDC (p. 6). Such thresholds cannot be experimentally proven, as the notion of a threshold is an assumption based on current biological and toxicological knowledge.

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 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. This uncertainty is particularly significant for understanding endocrine active drugs against hormone-related cancers, including breast cancer (p. 10).

Given the complexity of EDCs, both in terms of hazard and exposure, some of this uncertainty "probably cannot be resolved" (Vogel, 2005).

3.1.4 Ambiguity

From an analysis of the governance of EDCs in the US context, Vogel (2005) finds that the risk property of ambiguity is "the single greatest limitation to the use of endocrine disruption science in policy". Ambiguity refers to the fact that there are "different legitimate viewpoints from which to evaluate whether there are or could be adverse effects and whether these risks are tolerable or even acceptable" (Renn, Klinke & van Asselt, 2011, p. 240). Scientific experts have indeed been deeply divided about the (potential) adverse health effects of EDCs (see e.g. Zoeller et al., 2014; see also below).

That is, the definition of endocrine disruptors put forward in the 2002 WHO report has become widely accepted (see section 3.1.1). Yet adhering to this definition implies two things. First, that it is possible to make a clear distinction between adverse effects of endocrine disruption and normal physiological modulations of the endocrine system. And second, that adverse health effects are caused by a chemical's hormonal activity. However, and as discussed above, currently 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. This means that adversity, and thus the identification of EDCs, would have to rely on weight-of-evidence approaches; relying on expert judgment and done on a case-by-case basis.

> *On the one hand, the definition of endocrine disruptors put forward in the 2002 WHO report has become widely accepted. On the other*

hand, " the practical application of this definition is surrounded by controversy" (Clahsen et al., 2019 , p. 65).

As Clahsen et al. (2019) note, this "practical application" of the WHO definition "is surrounded by controversy" (Clahsen et al., 2019, p. 65). Ambiguities surrounding endocrine disruptors most importantly relate to the complexities of the risk. They include, among others, disagreements about the specific evidence that is required, particularly in view of identifying causal links between endocrine-disrupting properties and adverse health effects. They also include differences of opinion about the evaluation of results from studies performed outside of living organisms; and the question of threshold effects (Clahsen et al., 2019, p. 65).

Such debates about EDCs are too technical to describe in detail here. For the purpose of the present case study, however, it is valuable to consider the work of Clahsen et al. (2019) on the structure of the argumentation put forward by different experts on EDCs. Their analysis concerned the discussion between Lamb et al. (2014) and Bergman et al. (2015) about various aspects of the science on EDC, with a view to the merits of the 2012 WHO report. They concluded that, out of five differences in starting points between the two sides, only one pertains to an ambiguity concerning the interpretation of data (*interpretive ambiguity*).

The authors explained remaining differences of opinion about establishing causality and about the function of a state of the science report most importantly by divergent ethical and normative assumptions (*normative ambiguity*). Finally, the authors argued that differences pertaining to evaluating the weight of different pieces of evidence reflect a mix of interpretive and normative ambiguity. In turn, differences in the perception of the functioning of the endocrine system – for instance as a "resilient" or as a "vulnerable" system – were primarily cultural (Clahsen et al., 2019, p. 71-77).

In the context of these disagreements, it is important to note that Bergman et al. are the authors of the WHO State of the Science review and that the critique of Lamb et al. received funding from various North American and European chemistry and crop protection councils. A similar debate took place about the merits of the *State of the Art Assessment of Endocrine Disruptors* commission by DG Environment (Kortenkamp et al., 2011), namely between Rhomberg et al. (2012) and Kortenkamp et al. (2012). Also here, it is important to note that Kortenkamp et al. are the authors of the original report and that the critique of Rhomberg et al. received funding from the American Chemistry Council.

4 Risk governance and the precautionary principle

4.1 General framework for risk governance

4.1.1 Interdisciplinary risk estimation

Given the nature of endocrine disruption, the risk assessment of EDCs has been a mostly interdisciplinary endeavour. This is not least because the way in which EDCs act seems to run counter to many of the old assumptions of toxicology, for instance concerning the existence of a threshold of damage. Amongst other disciplines, the risk estimation has involved "reproductive biology, endocrinology, medicine, genetics, behaviour, development biology, and toxicology" (Gore et al., 2013, p. 3958). Leading institutes and

science communities in the field of research on EDCs, such as the Danish Centre on Endocrine Disruptors (CeHos), The Endocrine Society, and Horizon2020 EDC MixRisk project, also work on an interdisciplinary basis.

Some experts have nevertheless challenged the interdisciplinary approach to risk assessment of EDCs. In a 2013 editorial on the decision of the European Commission to develop a regulatory framework on EDCs, various international toxicologists and pharmacologists advocate a 'classical' toxicological approach to the assessment of EDCs. They, for example, contend that "an assessment of a substance should be based on data obtained from toxicity testing on this specific substance and derived information on potency" (Dietrich et al., 2013, p. 2112). Other experts, including those from The Endocrine Society, have responded with reference to the complex nature of EDCs and argued that "we need the fields of toxicology, endocrinology and other stakeholders to work together to address these issues" (Gore et al., 2013, p. 3958).

When it comes to actual scientific practices to assess the risks of EDCs within the regulatory framework of the EU, two major bottlenecks stand out.

Given mixture- effects of EDCs, the single substance risk assessment paradigm potentially severely underestimates risks of endocrine disruption.

First, and as the EDC-MixRisk project has concluded, "although it is clear that real life exposure entails mixtures of chemicals, risk assessment is performed by a compound-by-compound approach" (Bergman, Rüegg & Drakvik, 2019, p. 2; see also EEA, 2012, p. 19-20; Gore et al., 2015). Testing EDCs on a substance-by-substance basis results from the "single substance risk assessment paradigm", which adopts the assumption that substances are released in an original, unspoiled environment (ibidem). Yet EDCs "enter into the environment or a human body" in which other EDCs are already present (ibidem). Given mixture-effects of EDCs, which is however not a challenge specific to EDCs, the single substance risk assessment paradigm potentially severely underestimates risks of endocrine disruption.

Second, and relatedly, "international testing schemes were not designed for EDCs" and have serious shortcomings in estimating adverse effects for both humans, wildlife, and the environment (EEA, 2012, p. 19). The OECD, as well as other organisations, have developed various guideline documents for testing and evaluating EDCs (see also section 2.2.1). Yet tests remain highly costly, time-consuming, and detrimental to animal welfare, so that the EEA has concluded that it is "unsustainable to subject every suspect chemical to such exhaustive testing" (ibid., p. 20).

4.1.2 Risk characterization and risk evaluation

At the level of the EU, the key actors involved in the decision process regarding whether the risk of endocrine disruptors are acceptable, tolerable, or intolerable are most essentially the legislative institutions of the European Parliament and the Council. Indeed, the European Court of Justice writes in its judgment on Du Pont de Nemours that "the responsibility for determining the level of risk which is deemed unacceptable for society lies […] with the institutions responsible for the *political choice* of determining an appropriate level of protection for society" (case T-31/07, paragraph 145, emphasis ours).

This implies that there are two levels of governance in the EU when it comes to risk characterization and risk evaluation:

1. Legislative level, which includes the Council of the EU and the EP;

2. Level of competent authorities, which encompasses EU agencies.

It is thus subsequently up to ECHA and EFSA, as the competent authorities on EDCs, to make an assessment about "the level of risk deemed unacceptable for society [for] each individual case" (paragraph 147; see further below under 2.3.1.4).

As discussed in the sections above, however, it has been very difficult and time-consuming to characterise the risks that EDCs pose, given the very complex nature of these chemicals and the resulting uncertainty about their adverse health effects. The EU criteria for assessing the level of the risks of chemicals in general have, however, been science based. This means that they draw on a 'weight of evidence' approach. Given the complexity of endocrine disruptors, a report of the Dutch National Institute for Public Health and the Environment, for example, mentions that the "data requirements in the current legislation [do] not supply enough information" for identifying EDCs (Dang et al., 2016, p. 3).

Crucially, therefore, the discussion about endocrine disruptors has not just concerned the question of whether the risk that EDCs pose is acceptable, but more importantly also the question of whether it is acceptable to postpone the (further) development of a "risk assessment and regulatory framework for dealing with incomplete knowledge about EDCs" (EEA, 2012, p. 20). Several parties and stakeholders in the debate have deemed this unacceptable. Apart from scientists (e.g. EEA, 2012), these include NGOs and consumer organisations (see e.g. BEUC 2016), as well as the European Parliament.

4.1.3 Risk management

At the stage of making legislation on endocrine disruptors, it is thus up to the co-legislators of the European Parliament and the Council to take decisions. Notably, the European Parliament has explicitly emphasized the precautionary principle in several of its resolutions on endocrine disruptors. Its 2013 "*resolution on the protection of public health from endocrine disrupters*" is most notable in this regard. In this resolution, the EP "call[ed] on the Commission to revise its EU strategy on endocrine disrupters so that it delivers effective protection of human health by placing greater emphasis on the precautionary principle, while observing the proportionality principle, to work towards reducing human exposure to endocrine disrupters where necessary" (European Parliament, 2013, paragraph 17, emphasis ours).

At the stage of risk assessment and management of (potential) EDCs, it is usually the European Commission that is most importantly tasked with the formulation of the scientific criteria for the identification of EDCs, and that has to take the final decisions on risk assessment and management. EU agencies ECHA and EFSA have a very important 'advisory' role by producing so-called 'opinions' about the risk. The roles of the European Commission and the EU agencies, however, depend on the specific piece of legislation (see further below).

The stage of risk assessment involves the various committees of the two agencies. These are the Committee for Risk Assessment and the Committee for Socio-Economic Analysis of ECHA, and the Scientific Panels and Scientific Committee of EFSA. At EFSA, the scientific committees mostly only deal with the risk assessment and leave all considerations in relation to the precautionary principle up to risk managers. At ECHA, the strict division of roles between risk assessors and risk managers is less clear. These differences reflect the different traditions in these two agencies, namely, to regulate based on a risk approach or on a hazard approach (see further below).

Finally, at the stage of disputes, the ECJ is involved in making judgments about the (correct) application of the precautionary principle (see further below).

4.2 Legal and regulatory framework

4.2.1 Legal and regulatory history

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 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).

There is no harmonised EU legal framework on EDCs.

First, the regulation of EDCs relating to the environment, which is established in the Biocidal Products Regulation (BPR) and Plant Protection Products Regulation (PPPR), is explicitly "underpinned by the precautionary principle" (Article 1(4) of Regulation 1107/2009 and Article 1(1) of Regulation 528/2012). Thus, for the BPR and PPPR, a substance that has been identified as an EDCs is "as a general rule […] banned on the basis of hazard". There are only limited possibilities for derogation – that is, deviating from the rules for a limited period – in view of risks or socio-economic issues (Dang et al., 2016, p. 11). In developing these pieces of legislation, the EP and the Council considered that there is ongoing scientific uncertainty regarding the assessment of EDCs (European Commission, 2018, p. 9).

The European Court of Justice has also established the applicability of the precautionary principle in this area. In its judgment on Du Pont Nemours, the Court established that the precautionary principle must be applied in the authorisation of chemicals and assessment of approval criteria under the Plant Protection Products regulation (T-31/07, paragraphs 133, 152-153). Previously, in its judgment on Gowan, the ECJ considered that the existence of differing scientific opinions provides sufficient ground for uncertainty to apply the precautionary principle (C-77/09, paragraphs 76-79).

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. These criteria had been due by December 2013. In the case of Sweden against the Commission, the ECJ ruled that the impact assessment proposed by the European Commission proposed was unnecessary (see further below, under section 2.5). In an unprecedented judgment, the Court ultimately concluded that the Commission had failed to act in accordance with EU law by failing to adopt, in time, the necessary delegated acts to establish scientific criteria on EDCs (T-521/14).

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" (European Commission, 2018, p. 9). Different authorities can, however, still prohibit the use of chemicals that have – or are suspected to have – endocrine disrupting properties on a case by case basis. At the level of the EU, this has, for example, been the case for the substance of bisphenol A (see the table below). Some national authorities, such as in Denmark, had already previously banned bisphenol A from specific products.

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 assessment or socio-economic analysis to establish "whether a threshold (safe level) or non-threshold approach is to be applied" (Dang et al., 2016, p. 11). Yet the essential element in comparison with the BPR and the PPPR is that there is no general legislative ban for EDC. Under REACH (1907/2006), EDCs are mentioned in Article 57(f) and thereby subject to the authorization procedure for a so-called 'substance of very high concern' (SVHC) under article 59. If the criteria of Article 57 (f) are fulfilled, the (potential) EDC can be put first on the candidate list and then in Annex XIV containing substances of very high concern. Only then, the EDC is subject to the authorisation requirement.

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. It considered that findings about the hazard of chemical "should be based on the 'possible' undesirable effects of that substance, not the 'probable' effects". The Court also considered the risk properties of ambiguity and uncertainty. That is, it found that "negative or merely inconclusive epidemiological studies cannot invalidate positive studies in animals", given that there are uncertainties in such studies (T-636/17).

Importantly, these judgments demonstrate that the ECJ in fact interprets Article 57 (f) in line with the precautionary principle, despite the wording of the article being rather strict in terms of establishing the threshold of damage (see further below).

List of EU legal acts under which EDCs are regulated

Regulations relating to the environment
Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC
Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products
Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council
Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties

Regulations relating to health and food safety
Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC
Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food

Commission Implementing Regulation (EU) No 321/2011 of 1 April 2011 amending Regulation (EU) No 10/2011 as regards the restriction of use of Bisphenol A in plastic infant feeding bottles Text with EEA relevance
Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products
Commission Regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials

Regulations relating to the internal market
Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

List of key European Court judgments on EDCs

Case	Parties	Subject	Details
T-31/07	Du Pont de Nemours (France) and Others v Commission	Agriculture and Fisheries - Plant health legislation Environment	Action against restrictions on the use of flusilazole under Directive 91/414. ECJ dismissed action.
C-77/09	Gowan Comércio Internacional e Serviços	Agriculture and Fisheries - Plant health legislation	Action against restrictions on the use of fenarimol under Directive 2006/134/EC. ECJ dismissed action.
T-521/14	Sweden v Commission	Failure to act	Action against failure to adopt delegated acts specifying scientific criteria for identifying EDCs under Article 5(3) of Regulation (EU) No 528/2012. ECJ adjudged action.
T-115/15	Deza v ECHA	Environment Public Health	Application seeking annulment of ECHA decision to identify DEHP as a substance with endocrine-disrupting properties under Article 57(f) of REACH. ECJ dismissed action.
T-108/17	ClientEarth v Commission	Research and technological development	Application seeking annulment of a Commission letter rejecting a request for internal review of the authorization of DEHP under REACH. ECJ dismissed action (that is, the Commission was correct in rejecting the internal review request).
T-125/17	BASF Grenzach v ECHA	Research and technological development	Action for the partial annulment of an ECHA decision dismissing an appeal against a decision requesting further

			information about Triclosan and fixing a deadline for presenting that information. ECJ dismissed action.
C-	Deza v ECHA	Environment	Appeal to the ECJ's judgment in T-115/15.

Case	Parties	Subject	Details
419/17		Public health Research and technological development	The ECJ dismissed appeal.
T-636/17	PlasticsEurope v ECHA	Research and technological development	Application seeking annulment of ECHA decision to identify bisphenol A as a substance with endocrine-disrupting properties under Article 57(f) of REACH. The ECJ dismissed action.
T-207/18	PlasticsEurope v ECHA	Environment Public health	Application seeking annulment of ECHA decision to identify bisphenol A as a substance of very high concern based on Article 57(f) of REACH. Judgment pending.
T-640/19	Sasol Germany and Others v ECHA	Research and technological development	Application seeking annulment of ECHA decision to include 4-tert-butylphenol (PTBP) as a substance of very high concern in Annex XIV of REACH. Judgment pending.

4.2.2 Threshold of damage

The EU regulations that govern endocrine disruptors require an evaluation of whether there is an acceptable level of exposure to EDCs – that is, a 'threshold' – or not (see below under section 2.4.1). The REACH regulation, for example, stipulates that a chemical safety report "requires a quantification of the risk to human health, unless it is not possible to determine a derived no-effect level (DNEL) and a predicted no-effect concentration (PNEC) (ECJ, case T-108/17). 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.

At the same time, from the scientific analysis of and scientific uncertainty about endocrine disruptors, it follows that the way in which EDCs act "undermines the traditional risk assessment paradigm of a threshold dose below which a chemical fails to produce effects" (EEA, 2012, p. 18-19). This is most importantly the result of the issues of the mixture and low-dose effects discussed above (see also Gore et al., 2015). A large degree of uncertainty also remains about the hazard of EDCs.

Against this background of regulatory practices and requirements, on the one hand, and scientific complexities and uncertainties about EDCs, on the other, there has been debate about the 'threshold of damage'. Industry has, for example, challenged the level of exposure of various EDCs that would require or justify regulatory measures, also in legal cases at the ECJ (see the table above). 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.

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). Plastics Europe sought the annulment of an ECHA decision to include BPA on the candidate list for substances of very high concern. It referred to opinions of EFSA. Indeed, for bisphenol A, there are safe levels for use in EU legislation on food contact materials and on chemicals in toys (T-

636/17). In this respect, EFSA has issued an opinion on a "Tolerable Daily Intake" of bisphenol of 4 µg/kg body weight (EFSA, 2015).

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.

ECHA, however, has nevertheless listed bisphenol A as a substance of very high concern in the candidate list for authorisation under the REACH regulation. This means that it can be considered as a non-threshold substance, which means that it is dangerous at any level. The agency most importantly considered that it was too difficult to establish a safe threshold. Amongst other reasons, this was due to uncertainties about the dose-response relationship; studies that showed effects at doses lower than previous starting points used for deriving a no-effect level; and changing levels of sensitivity depending on the window of exposure. The European Court found that specific limits being established in the context of some legislation does not preclude different conclusions in the context of other legislation, given the existence of overall uncertainties about safe thresholds (case T-636/17).

4.2.3 Reversal of burden of proof

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) endocrine-disrupting properties indeed specify a reversal of the burden of proof. The Plant Protection Products Regulation states that "an application for the approval of an active substance or for an amendment to the conditions of an approval shall be submitted by the producer of the active substance […] together with a summary and a complete dossier". Such a dossier should include summaries and tests of all data requirements that the Commission has set out for the chemical (1107/2009, article 7). The BPR likewise requires an authorisation, so that one could argue that the regulation has reversed the burden of proof: to get an authorisation, certain information and proof needs to be provided.

Yet also here, the standards for the information that producers have to submit are, however, different in the context of different regulations (e.g. compare 528/2012, articles 6, 7 and 8; 1907/2006; 10/2011, article 16). It has also been argued that in practice, even when standards for information that producers need to supply are comparatively high, "poor information provided […] in the registration dossiers shifts the burden" to complete risk assessment information 'back' to national authorities and EU agency committees (EEB, 2017).

In the context of regulation 1107/2009 on plant protection products, the ECJ has made some relevant judgments regarding the precautionary principle and the burden of proof. 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. The Court explained that this is also the case if the Commission invokes the precautionary principle for such a review. Nonetheless, the Court establishes that "the Commission discharges the burden of proof" if the Commission establishes that the initial approval criteria are "invalidated by subsequent regulatory or technical developments". Since the PP can be one basis for the withdrawal or amendment of approval, the Commission "need do no more than provide […] solid and convincing evidence which, while not resolving scientific uncertainty, may reasonably raise doubts as to" whether the substance satisfies the criteria (see cases T-429/13 and T-451/13).

The REACH regulation is different from the PPPR and the BPR. Here, the regulation itself does not establish the authorisation requirement. Only in case the Commission has added a substance to Annex XIV, the authorisation requirement applies. Therefore, first, the Commission has to proof that criteria of Article 57(f) are met. One could therefore argue that the burden of proof is not reversed by the regulation itself, but may be reversed in case the Commission adds an endocrine disruptor to first the candidate list and then Annex XIV.

4.3 Gender considerations and the risk governance framework

For both females and males, endocrine disruptors have been linked to the presence of hormone-related cancers and infertility (see section 3 on the on the threat posed by EDCs). There was "a major international review of environmental influences on male health" already in the 1990s, after Scandinavian research showed a relation between environmental exposures and falling sperm counts (Schug et al., 2016, p. 836). Yet it is also clear that female and male bodies are affected by endocrine disruptors in different ways, given their different hormonal systems. Two further considerations are important to mention concerning gender differences in knowledge about and exposure to EDCs.

First, and "in contrast to male infertility, there is surprisingly limited knowledge on the mechanisms by which EDCs can impair female reproduction and test methods to address this" (FREIA, female reproductive health). One of the underlying problems is that it is more difficult to assess how EDCs affect the quality of egg cells other than in terms of their sheer number, particularly in comparison to sperm cells – not least because the retrieval procedure is more invasive. Moreover, disturbance of the embryonic development of the female reproductive system can lead to infertility only at a much later stage, for instance at the age of thirty (van Kessel, 2019). Current test protocols are especially ill-suited to pick up the effects of such early exposure (FREIA, improving test methods). Apart from infertility, EDCs can or may also be linked to endometriosis, polycystic ovary syndrome, premature ovarian insufficiency or failure, irregular menstrual cycles and ovarian cysts (FREIA, female reproductive health).

> *" In contrast to male infertility, there is surprisingly limited knowledge on the mechanisms by which EDCs can impair female reproduction* (FREIA, female reproductive health) *"*

Second, precautionary or preventive measures against the adverse health effects of EDCs by far and large concern females, as exposure during pregnancy can harm both the embryonic and later development of a child. This is why pregnant females are often mentioned as being "vulnerable" to EDCs (e.g. Wemos, 2018). The extent to which government organisations provide information about the potential hazards of endocrine disruptors during pregnancy varies, however, between member states. Some member states, such as Denmark, provide extensive information about how to prevent exposure to (potentially) harmful chemicals during pregnancy (Danish Ministry of the Environment, n.d.). Other member states, such as the Netherlands, do not (van Kessel, 2019; Wemos, 2018).

Indeed, there seems to be inadequate access to information about what are the effects of EDCs for pregnant women across EU member states. On a more positive note, one can point to several initiatives - such as 'Gender and chemicals' Initiative, the EDC-Free Europe Initiative or the FREIA project. All these try to raise attention for the effects of the exposure of EDCs for women, children and the unborn.

It is not entirely clear in how far EU risk governance of endocrine disruptors is sensitive to such gender differences. The lack of proper tests for establishing the health hazards of EDCs is seen as a key problem when it comes to female reproductive health (FREIA,

improving test methods). The latest Communication on the development of a new EU framework on endocrine disruptors mentions that "the Commission will encourage Member States *which deem it necessary* to develop specific information and educational campaigns" on EDCs (European Commission, 2018, p. 11, emphasis ours). All in all, it seems that the EU's current, evidence-based, risk management approach to endocrine disruptors can be deficient particularly for protecting the health of females and for ensuring adequate access to information about exposure to EDCs during pregnancy across EU member states.

On a more positive note, the NGO 'Women Engage for a Common Future' (WECF) has started the 'Gender and Chemicals' Initiative. It is one attempt to raise more awareness for the adverse effects of chemicals in general – and EDCs in particular – for women's health. Here women's priorities for stronger waste and chemical policies are disseminated through TV and social media, for example (see WECF, n.d.). The EDC-Free Europe Initiative also tries to raise attention for the effects of the exposure of EDCs for women, children, and the unborn (see EDC-Free Europe, n.d.).

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

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. To them, the issue of endocrine disruptors is a pressing and major societal risk, of which regulation through the traditional science-based EU regulatory framework would take too long. However, there are differences between those who advocate a scientific and a "non-scientific use of the precautionary principle" (Lofstedt, 2014, p. 155).

In advocating more precaution, academics from various disciplines often make reference to the uncertainties surrounding both the hazard and exposure to endocrine disruptors (see above under section 3.1.3) (e.g. EEA, 2012; Gochfeld, 2003; Klinke & Renn, 2001; Tijani et al., 2016). Influentially, also the Endocrine Society has invoked the precautionary principle. In its first Statement, for example, the Society considered that "in the absence of direct information regarding cause and effect, the precautionary principle is critical to en- hancing reproductive and endocrine health" (Diamanti-Kandarakis et al., 2009, p. 326).

In its second Statement, it further elaborated on the application of this principle. Importantly, it considers that inferences about adverse human health effects drawn from studies that show that a chemical interferes with hormones that "are essential for normal development" are often considered to be precautionary (Gore et al., 2015, p. 601). Yet even though such inferences about adverse effects may not fully characterise the adverse effect, they are still *science-based*. The Society advocates more precaution not just given the uncertainties surrounding EDCs and their potential long-term and chronic effects, but also noting that "it simply is not reasonable to assume a chemical is safe until proven otherwise" – as exemplified by the introduction of regrettable solutions (p. 602; see further below).

Given the tension or "dilemma" between a perceived need for precaution and time-consuming frameworks for risk regulation (Munck af Rosenschöld, Honkela & Hukkinen, 2014), there have been several public controversies over particular chemicals with (suspected) endocrine disrupting properties. The most well-known controversy is that of bisphenol A (BPA). That is, whereas there are many hundreds of studies of BPA, there

are still two sides to the debate of whether the evidence is sufficiently strong and conclusive to ban BPA – most importantly from food packaging and other consumer products. The combination of public pressure and the scientific "division in opinion has resulted in different countries' regulatory agencies deciding on different risk-management strategies for BPA" (Siva, 2012).

This is also the case within the EU, in which Denmark was the first BPA from food containers for young children in April 2010. Other EU member states followed suit, including Belgium, Sweden, and France – the latter banning BPA from all food contact materials (European Parliament, 2018). Commission Directive 2011/8 on plastic feeding bottles did invoke the precautionary principle to prohibit use of BPA. Yet in 2015, EFSA nevertheless established that there is "no health concern for […] dietary exposure" and "low health concern from aggregated exposure". It hence identified a tolerable daily intake for BPA (EFSA, 2015).

The EFSA opinion was heavily criticized by various stakeholders in the public debate, who want to ban BPA also from other products than baby bottles by invoking the (non-scientific use of the) precautionary principle. Other organizations want to embed the precautionary principle more comprehensively in the system of risk governance. The European Consumer Organization BEUC, for example, finds that the "precautionary principle should therefore be enshrined in the legal text of the FCM Regulation as the basis for risk identification, assessment, and management" (2019, p. 8; see also WEMOS, 2018).

Indeed, in this context, Lofstedt (2014) has criticised the way in which the precautionary principle is currently applied by and in the European Union – drawing on the regulation of EDCs as an example of poor use of the precautionary principle. He, for example, notes that the 2013 EFSA opinion on the hazard assessment of EDCs did not mention the 2002 Commission Communication on the precautionary principle. Yet neither did the European Parliament's resolution on the EFSA opinion that did invoke the precautionary principle contain an explanation of what the implementation of the PP would actually entail. 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" (2014, p. 155).

5.2 Effect of the PP on innovation pathways

We did not find evidence that potential benefits of innovation were taken into account in applications of the precautionary principle in regulatory decisions on EDCs. Rather, bans on the use of particular EDCs have in the past led to 'regrettable substitutions' – that is, 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. Rather, it has to go through the time-consuming process of risk assessment and risk management separately (van Kessel, 2019). Financially, there is thus an incentive for industry to develop substitutes that are similar to those chemicals that have been regulated – even when the hazard of these substitutes to humans, animals and the environment are uncertain (see e.g. Camboni, 2017, p. 76-78).

The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS). BPA can be found in a great many products that people use on a daily basis, such as baby and water bottles, food storage boxes, and sales receipts. After scientists discovered the adverse health effects of BPA – and particularly after regulatory restrictions on BPA and societal pressure in the 2010s – the plastics industry sought an alternative to BPA. Manufacturers even started to sell products with a

'BPA-free' guarantee. Yet to produce such BPA-free products, the industry "turned primarily" to BPS, which is "a structural analogue of BPA (Žalmanová et al., 2016, p. 440). BPS has been shown to have endocrine-disrupting properties highly similar to BPA (Žalmanová et al., 2016), as have other varieties of bisphenol that became more commonly used as substitute chemical (for an overview, see CHEMTrust, 2018, p. 12).

The regulation of certain 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. At the same time, it has also been argued that the presence of certain exceptions regarding the use of EDCs, which, for example, exist for medical devices, has been a disincentive for the development of alternatives. This, for example, was said to concern the presence of phthalates in blood bags. 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).

Green chemistry seems to be one important innovation pathway towards developing chemicals that are non-regrettable substitutions for identified or suspected EDCs. Whereas reducing the risk of chemicals has conventionally been focused on reducing or avoiding *exposure*, green chemistry is based on avoiding *hazard* in the first place (e.g. Khetan, 2014; Schug et al., 2013). Moreover, the current approach to regulating (potential) endocrine disrupting substances has been on a case-by-case basis, while green chemistry advocates a re-thinking of the sector approach. In journals such as *Green Chemistry*, scientists have reported on the absence of endocrine activity of bio-based alternatives for EDCs. This, for example, included chemicals like 2,5-FDA which can substitute the commonly used industrial polyesters phthalates, such as in re-useable water bottles and textile fibres (e.g. van Vugt-Lussenburg et al., 2020).

Scientists working within the area of green chemistry, however, also encounter the complexities and uncertainties in establishing potential endocrine-disrupting activity of substitute chemicals, as these are inherent to the current state of science on EDCs. To forestall this, it has been proposed that chemists and toxicologists in Green chemistry work more closely together on endocrine disruption (Schug et al., 2013).

Green chemistry seems to be one important innovation pathway towards developing chemicals that are non- regrettable substitutions for identified or suspected EDCs.

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 (e.g. BEUC, 2018, p. 5-6; RIVM, biobased materials). This includes the European Green Deal, which recalls the need to establish a "ensure a toxic-free environment" (European Commission, 2019, p. 14). The European Green Deal does not, however, mention the precautionary principle as a tool towards stimulating green or sustainable innovation. Rather, the Commission highlights the importance of "simplifying and strengthening the legal framework", including a "move towards a process of 'one substance – one assessment'" (ibid., p. 14). In this context it is noteworthy that stakeholders and NGOs have called for a chemicals strategy as part of the European Green Deal in 2019. Here, the Commission is reminded of her commitment to manage the risks arising from EDCs and as such to deliver on the EU strategy to address ECDs, which is 20 years old (see e.g. EEB, 2019).

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 (e.g. IEEP, 2019). These organisations, for example, contend

that applying the precautionary principle to all EDCs can "boost eco-innovation in finding sustainable and safer substitutes" (IEEP, 2019).

Also here, however, there are numerous complexities linked to innovation pathways when it comes to the circular economy. Clearly, one of the "greatest obstacles" to a circular economy is that of "'legacy substances'". These are substances that remain in the environment, as older products contain(ed) chemicals that were restricted or banned at a later stage only (BEUC, 2017, p. 4). For example, the phasing out of the phthalate DEHP would take about 15 years, while the phasing out of BPA would take about 30 years (EEA, 2017, p. 10). Some have therefore also invoked the precautionary principle on the basis of the argument that the EU needs to avoid such legacy, toxic substances in the move towards a circular economy (BEUC, 2017; 2018).

5.3 Innovation principle

Some stakeholders in the discussion about EDCs, mostly from the chemicals industry, have invoked an 'innovation principle'. Their idea is that an innovation principle would "require[e] to take into account the potential impacts of precautionary action on innovation" and "protect Europe's ability to innovate and to compete with other countries" (see RECIPES conceptual framework). 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.

There are a few explicit communications that link the innovation principle to the topic of chemicals suspected or proven to have endocrine-disrupting properties. Interestingly, these communications draw on examples of the regulation of chemicals with (potential) endocrine disrupting properties to argue in favour of an innovation principle.

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" (CIA, 2019, emphasis ours). CIA goes on to signal a dilemma between precaution and innovation, and to argue that "this dilemma can not be solved by the precautionary principle alone, but should be addressed by application of both principles, alongside each other, in a complimentary sense" (CIA, 2019).

As one example of a "hampering" regulation showing the necessity for an innovation principle, CIA brings up the labelling of the phthalate DEHP as a substance of very high concern under the REACH regulation. It argues that this labelling resulted in the closing down of a recycling plant for the plastic polyvinylchloride (PVC) that had obtained authorisation to recycle PVC containing DEHP. This was because "customers no longer wanted to buy PVC containing an SVHC" in part due to the "loss of the 'green' credentials of the recyclate". For CIA, this "unfortunate and unintended consequence" would have been prevented by including the innovation principle in EU legislation.

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).

6 Synthesis

Endocrine Disrupting Chemicals (EDCs) are a 'textbook case' for the complexities surrounding the application of the precautionary principle as they:

- Are **widely prevalent** and can be found in products we use every day – reaching from shampoo to medication. The potential hazards stemming from EDCs are thus not limited in scope. Health risks both for humans and wildlife associated with EDCs became increasingly apparent during the 1990s. A number of authorities, reaching from the World Health Organisation to the European Commission, commissioned studies to investigate the potential harm caused by EDCs.

- Yet problematically, even the very **definition** of EDCs remains very much contested, as do the scientific processes and methods through which to identify them. While this an issue not limited to EDCs (see e.g. the RECIPES case studies of Urlings on microplastics, or Gaszo and Pavlicek on nanotechnologies), to define which chemicals or substances are in fact to be considered as EDCs is key. This in turn has important implications for how they are regulated.

- This then gives rise to a **dilemma** with the regulation of ECDs as Munck af Rosenschöld, Honkela and Hukkinen (2014) point out. On the one hand, there is considerable societal pressure to regulate ECDs 'now'. This quick regulation is, on the other hand, impossible as there is not enough quantitative evidence for the risk that prevails. To come up with such evidence is time intensive, which leads to postponing regulation and only "increases the societal pressure to regulate now" (p. 29-30).

- 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. Several of the controversies surrounding EDCs, such as on bisphenol A and on the Commission's delay to formulate scientific criteria for identifying endocrine disruptors, are illustrative of this "paralysis" (Munck af Rosenschöld et al. 2014). This is also linked to the fact that there is always a 'need for more research'. Science, by its nature, searches for the remaining uncertainties, which then overemphasizes the amount of uncertainty.

- 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'; is lagging behind. If one needs to test for a very large number of potential EDCs this could bring the entire chemical industry to a halt. Moreover, reversing the burden of proof is also often ineffective. In practice, even when standards for information that producers need to supply are comparatively high, poor information is provided in the registration dossiers, which in turn can shift the burden to complete risk assessment information 'back' to national authorities and EU agencies (EEB, 2017).

- 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. This could be avoided by way of more coordination. Closely linked is the fact that case-by-case regulation creates incremental innovation, while far-reaching regulatory approaches – by way of joining forces with industry – can lead to radical innovation. It comes as no surprise that companies are hesitant to embrace radical innovation such as Green chemistry. At the global level we thus see a

coordination problem: 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. Could they play an active role in creating incentives for radical innovation and reward respective initiatives?

- Overall, **time** available is of the essence for a thorough regulation of ECDs. As pointed out above, the precautionary principle calls for quick action, which is difficult to address due to the lack of clarity on *how* to regulate. Taking decisions too quickly can on the one hand lead to sub-optimal solutions. Yet taking a slow regulatory approach can cause delays. 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**. Processes and the inclusion of different interests and views have to be apparent to stakeholders and the interested public.

7 Conclusion

Endocrine disruptors are at the centre of a scientific and regulatory debate since several decades. Following debates and the 1991 Wingspread conference on EDCs in the United States, the EU did try to be 'ahead of the game' by compiling scientific evidence on EDCs already in the 1990s. The 1996 meeting in Weybridge, which was sponsored by the European Commission, brought together experts from the WHO, the OECD, and Ministries and Institutes and Ministries of the Member States. Here, a considerable degree of consensus was noted between the "various assessments and reports on the **need to take urgent action** to address the uncertainties and gaps in our knowledge and the potential dangers to human and wildlife populations from endocrine disrupting chemicals" (Bergman et al., 1997, p. 103). Moreover, a definition of what can be seen as an EDC was provided.

The fact that this issue of regulating EDCs was on the EU's radar rather early, could lead one to expect a high level of regulation and a coherent approach. The opposite is the case, however. EDCs can be seen to have sparked **institutional controversy**. As mentioned above, the development of scientific criteria for the identification of EDCs under specific regulations in the environmental domain was severely delayed by the European Commission. A Member State (Sweden) then took the Commission to Court in 2014. Here, the ECJ ruled in a landmark case that the Commission had failed to act in accordance with EU law.

The European Court of Justice has also established the applicability of the precautionary principle in this area. Accordingly, the Court established that the precautionary principle must be applied when authorising chemicals and assessing approval criteria. The European Parliament has also explicitly emphasized the **precautionary principle** in several of its resolutions on endocrine disruptors. For instance, in a 2013 resolution the EP called on the Commission to put greater emphasis on the precautionary principle in order to reducing human exposure to endocrine disrupters where necessary.

This, however, did not change the **regulatory approach** of the EU regulatory authorities towards EDCs substantially, nor did this impact on its use and application of the

precautionary principle. The Commission can be seen as not to act systematically on the basis of the precautionary principle in the context of EDCs. Most notably, a 'horizontal definition' of EDCs is missing and the Commission's formulation of standards of proof are seen to be unattainable in practice. Moreover, "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.

One key problem for establishing the health hazards of (potential) EDCs is the **absence of proper tests**. This is seen as a major issue especially when it comes to **female reproductive health.** Overall, it seems that the EU's current, evidence-based, risk management approach to endocrine disruptors can be deficient particularly for protecting the health of women.

The question is to be raised of how to **move forward** given that the risk properties of endocrine disruptors are not only highly complex, but that endocrine-disrupting action is seen to go against all the rules and assumptions that toxicology builds on. Bans on the use of particular EDCs have actually led to so-called 'regrettable substitutions': that is, the introduction or adoption of chemicals that may not be safer and potentially worse. The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS).

In this context, **green chemistry** can be regarded as one important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs. Green chemistry is based on avoiding *hazard* in the first place. Note that scientists working within this field, however, also encounter the complexities and uncertainties in establishing the potential endocrine-disrupting activity of substitute chemicals. To overcome this dilemma, it has been proposed that chemists and toxicologists in Green chemistry join forces. It remains to be seen whether this will lead to the much sought for breakthrough in a highly complex domain characterised by high uncertainty and unpredictability.

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Neonicotinoid insecticides

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Abstract

This case will focus on neonicotinoid insecticides (in short: neonics), and how the Precautionary Principle has been applied, and contested, in the regulation of these insecticides. In the context of increasing pest resistance to established Plant Protection Products, the industry argued that the invention of neonicotinoids signified a new and innovative era of pest management. However, some years after the introduction of neonics on the European market in the 1990s and 2000s, monitoring assessments and studies started to connect the use of neonics to large-scale bee deaths. Thus, the Precautionary Principle (PP) was applied to restrict neonics in some European countries. As studies and risk assessments accumulated, the PP was also relevant when the European Commission (EC) banned three neonics (imidacloprid, thiametoxam, clothianidin) in 2013 and again in 2018. The reasoning for taking precautionary measures was the seriousness of the possible irreversible damaging effects of neonics on important ecosystem services such as pollinating insects. The EC ban of the three neonics caused much controversy, and three agrochemical companies filed court cases against the ban.

In this case, we will outline scientific uncertainties and ambiguities regarding the effects of neonics on pollinators (but also other species), in addition to the diverging perceptions of the role of the PP that became particularly evident in the court case proceedings. Further, we will discuss how innovation and precaution may interact. We find that a narrow framing of innovation and scientific certainty seem to conflate the PP and the Prevention Principle. However, with a broader framing of innovation, one could find possibilities for balancing precautionary regulations of neonics with innovations that are more line with an Integrated Pest Management approach.

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List of abbreviations

EC	European Commission
EFSA	European Food Safety Authority
EP	European Parliament
IPM	Integrated Pest Management
PP	Precautionary Principle
PPP	Plant Protection Products
TSFP	Task Force on Systemic Pesticides

1 Introduction

1.1 Introduction

In Europe, hundreds of different pesticides are allowed in farming. These are used to control fungi (fungicides), weeds (herbicides) and plague insects (insecticides) that may harm the crop. In this case we will focus on neonicotinoid insecticides (in short: neonics) and the relevance of the Precautionary Principle in the regulations of these insecticides due to the risk they pose for the environment and pollinating insects in particular.

Neonics were introduced on the European market in the early 1990s, and they are by now one of the most widely used group of insecticides in the world. In the context of increasing pest resistance to established Plant Protection Products, the invention of neonicotinoids signified a new era of pest management, with a higher versatility in application methods and a high target specificity[1] (Jeschke and Nauen, 2008). As systemic pesticides, they work differently than other pesticides by that they are taken up by the plant sap and translocated to all parts of the plant to provide long-term protection. Neonics are therefore promoted for providing cost-effective, highly targeted and long-lasting protection of crops against pests such as sucking insects, some chewing insects, insects that transfer plant viruses. In 2012, EFSA reviewed the scale of use in Europe and found that more than 200 different plant protection products with the neonics imidacloprid, thiametoxam, clothianidin, thiacloprid or acetamiprid were authorized in Europe for more than 1000 different applications, in a very wide range of crops, fruit trees, tree nurseries, ornamental plants and grass-fields such as golf courses (for complete overview, see table 1-3 in EFSA, 2012c).

In the late 1990s and the 2000s, early warnings started to emerge on that these systemic insecticides posed a risk to pollinators, which first was seen by beekeepers in their honeybees. The use of seeds coated with neonics was linked incidents of large amounts of bee deaths and honeybee colony collapses in several European countries. This led to an increasing amount of research on the un-intended effects of neonics on the environment, particularly on insects which provide significant ecosystem services such as pollination of crops. It was found that neonics not only protects the plant to potential plague insects, but also harms a wide range of non-target organisms such as bees and other pollinators, soil invertebrates such as earthworms, aquatic insects such as dragon flies, mayflies and damselflies and some species of birds (Pisa et al., 2017). However, there are large knowledge gaps and scientific uncertainties regarding residues of neonics in e.g. soil and water, routes of exposure for different species, and the sub-lethal effects of neonics on different species in complex ecosystems. However, the possible irreversible damaging effects on important ecosystem services such as pollinating insects, has led to precautionary action and world-wide controversy in science and society on whether a complete phase-out of neonics is justified.

In the EU, the PP was relevant in the regulation of 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[2]. With the procedures provided by this framework, 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, especially regarding bees who 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. The restrictions were reinforced in 2018 when the

[1] Note that the specificity here only means that it is highly toxic to insects and much less toxic to vertebrates such as mammals and birds, but is it not specific to plague insects versus non-target, beneficial, invertebrates such as bees, butterflies and earthworms.

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32009R1107

Commission implemented Regulations 2018/783, 2018/784 and 2018/785)[3], which limited the marketing authorisations for Plant Protection Products containing imidacloprid, clothianidin and thiamethoxam.

These regulations created much controversy. The agrochemical companies Bayer Crop Science, Syngenta and BASF, supported by industry/seed associations and different European farmers unions, filed court cases against the regulation in 2013. Their complains included that PP was wrongfully applied as the risk assessment was inconclusive, and that the principle of proportionality was neglected due to a lack of a formal economic impact assessment. Further, industry stakeholders have argued that the ban on neonics has negative consequences for innovation in the crop-protection sector in Europe, because industry will be more reluctant to invest when there is less regulative predictability when procedures can change approvals during their period of validity. Beekeepers associations, environmental NGOs and independent researchers on the other hand, have argued that all neonics should be completely banned, and that innovation should focus more on alternative means of crop protection and reduction of pesticide use (in line with the aims of reducing pesticide use as promoted in directive 2009/128/EC).

The main aim of this case is to provide insights into complexities and controversies around the application of the precautionary principle in the case of neonicotinoids in the EU, with attention to tensions between precaution and innovation. In order to provide these insights, we have reviewed academic articles and reports, stakeholder reports and press statements, and court case documents. Following the timeline of the case, we will the outline the innovative aspects of neonics, while part 3 will outline the risks, particularly focusing on scientific uncertainty in assessing the risks related to neonics. Thereafter, part 4 will outline the processes around regulating neonics and highlight controversies around the bans imposed in the EU 2013 and 2018. The last two parts will focus on how this case relates to and challenges the innovation/PP juxtaposition.

1.2 Key timeline

The timeline below[4] presents key innovation and marketing events, political events or decisions, implementations of legal frameworks or court cases, the most crucial scientific findings and risk assessments, and selected public debates. The different categories of actions are visualised by different colours.

Political	*Legal / regulative*	*Science/risk assessment*	*Public debate*	*Market/Innovation/other*
Year	**Event**			**Relevance to case study**
1985-1994	Bayer CropScience patented thiacloprid and imidacloprid as the first commercial neonicotinoids. Following this, thiamethoxam was patented in 1992, acyclic nitenpyram in 1988, acetamiprid in 1989, clothianidin in 1989, and dinotefuran in 1994 (Tomizawa and Casida, 2005: 248).			Innovations and patenting of neonics.
1991-2002	Bayer CropScience introduced imidacloprid to the market in EU member states in 1991. The following years other neonics entered the market, including Thiamethoxam by Syngenta in 1998, Thiacloprid by Bayer in 2000, and Clothianidin by Takeda/Bayer in 2002.			Different neonics introduced on the market, starting the era of neonicotinoid insecticides at a time when many pest insects had developed resistance to other pesticides like organophosphates (Simon-Delso et al., 2015).
1991	Implementation of Council Directive 91/414/EEC that provided an authorisation procedure for plant protection products in the EU			This was the first harmonised authorisation procedure for plant protection products in the European Union.
1993	The Maastricht Treaty came into force.			The treaty states that community policy on the environment shall aim at a high level of protection, and that it shall be based on the **precautionary**

[3] Official Journal of the European Union L132, (30 May 2018) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2018:132:FULL&from=DA

[4] An extended version of this timeline can be acquired by contacting the authors of this case.

		principle (Article 130r. 2)
1994 France	Bee-colony losses were reported by French beekeepers in areas near fields sown with neonic-coated seeds (Gaucho®), and evidence of the risk caused by imidacloprid emerged in independent research *(*Maxim & Sluijs 2007, 2013).	Early warnings indicating that neonics posed risks for bees.
1999, France	A two-year ban on the use of Gaucho in sunflower seed dressing was implemented and renewed in 2001 and in 2004 for 3 years (Maxim and Sluijs, 2007: 3-4).	The first precautionary based regulation in an EU member state.
2000, March-May	Beekeepers in Northern Italy started reporting events of bee mortality and colony weakening in spring, associated with maize sowing (Mutinelli et al., 2009)	Early warnings on risks of neonics to bees.
2002, Feb. 21	The European Food Safety Authority **(EFSA)** was established by the EU under the General Food Law – Regulation 178/2002, following a series of food crises in the late 1990s.	EFSA was to provide scientific advice on risks associated with the food chain. EFSA was mandated to carry out EU peer review of active substances used in plant protection in 2003.
2003	French Scientific and Technical Committee for the Multifactor Study of the Honeybee Colonies Decline publishes a scientific assessment report, concluding that seed-dressing sunflower and maize posed serious risks to honeybee colonies via larvae feeding, pollen consumption by nurses, nectar ingestion by foragers, and honey consumption by honeybees (CTS, 2003)	The by that time most comprehensive risk assessment the risks of neonics to bees, based on the analysis of 338 publication.
2004	The French Minister of Agriculture temporarily bans Gaucho® (containing imidacloprid) in maize seed-dressing.	The first PP based restrictions on neonics implemented in a European country.
2008	Serious bee-colony losses were reported in many European countries. Linking the incidents to use of neonics, national authorities restricted neonics in Italy, Germany, Slovenia.	Precautionary based regulations in several EU countries.
2009 Oct.	**Implementation of Regulation (EC) No 1107/2009** of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. The regulation enters into force in 2011, June 14.	Article 1, p 4 states that the Regulation is underpinned by the **precautionary principle.** This regulation marked a significant change in regulative policy on pesticides (from risk to hazard based) and in the procedures for risk regulation (Bozzini, 2017: 58).
2011, March 18	Due to concerns expressed European Parliament members and beekeeper associations on appropriateness of the risk assessment scheme of the European and Mediterranean Plant Protection Organisation (EPPO), the EC asks EFSA to review this scheme. Particularly, chronic risks to bees, exposure to low doses, exposure through guttation and the cumulative risk assessment were to be reassessed (EFSA, 2012a)	This process resulted in a new draft guidance scheme for risk assessments of plant protection products on bees (EFSA. 2013e). Popularly called 'EFSAs Bee Guidance Document', this risk assessment scheme received much controversy as it was applied in EFSAs risk assessments in 2018.
2012	3 Scientific articles were published in peer-reviewed journals suggesting that field-realistic levels of the neonicotinoids imidacloprid (Whitehorn et al., 2012), thiamethoxam (Henry et al., 2012) and clothianidin (Schneider et al., 2012) significantly affected bee colony stability and survival of honeybees and bumblebees.	These studies gained much attention and were regarded as new knowledge on the risks of neonics to risks to bees. This enabled the EC to follow up on **Article 21 of Regulation (EC) No 1107/2009** stating that approval of active substances should be reviewed in light of new scientific knowledge.
2012, April 25	The EC requests **EFSA** to provide conclusions as regards the risk to bees for the uses of thiamethoxam, clothianidin, and imidacloprid (EFSA, 2013a)	Thereby a thorough and controversial risk assessment processes was initiated.
2013, Jan 16	**EFSA** present to the EC their risk assessments of clothianidin, imidacloprid and thiamethoxam (EFSA, 2013b, 2013c, 2013d). For some uses, a high acute risk for honeybees was found (e.g. from exposure via dust drift of the sowing of maize and cereal seeds coated with clothianidin, imidacloprid, thiamethoxam). It was also noted that due to shortcomings of data and a lack of a finalised risk assessment guidance document, uncertainty remained.	On this basis, the EC proposed to implement **Regulation 485/2013** – on the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances.
2013, May 24	After two rounds of inconclusive voting by the Member States, the EC decided to implement **Regulation (EU) No 485/2013 - banning outdoor use of 3 of the 6 neonicotinoids** that are marketed in Europe in crops attractive to bees. Uses in greenhouses, of treatment of some	The first regulations of neonics were implemented in the EU.

	crops after flowering and of winter cereals were excepted.	
2013, July 4	EFSA publishes the **Bee Guidance Document** (EFSA 2013e). This document was intended at providing guidance for the review of plant protection products (PPPs) and their active substances under Regulation (EC) 1107/2009.	This document created much controversy on the risk assessment process.
2013, August	**Bayer** Crop Science and **Syngenta Crop Protection** – file legal cases against the EC (**Cases T-429/13 and T-451/13** seeking to annul the Commission's Implementing Regulation (EU) **No 485/2013.**	Many of the claims contested the application of the PP for restricting neonics.
2015, Jan.	The **Task Force on Systemic Pesticides (TFSP)** (group of independent scientists convened by the International Union for Conservation of Nature, IUCN) produced a comprehensive scientific assessment of the ecological effects of neonicotinoids, based on a synthesis of over 800 published peer-reviewed including industry-sponsored ones.	TSFP concluded that the levels of pollution with neonicotinoids are likely to have a wide range of negative biological and ecological impacts (van der Sluijs et al., 2015). Regulatory agencies were recommended to consider applying the principles of prevention and precaution to further tighten regulations on neonicotinoids.
2015, Feb. 11	As foreseen in recital 16 of Implementing Regulation (EU) No 485/2013, the Commission initiated a review of new scientific information on 11 February 2015 by mandating **EFSA** to organise an open call for data (EFSA 2015d).	The open call enabled all interested parties to contribute.
2015 April	European Academies Science Advisory Council (EASAC) publishes an influential report " Ecosystem services, agriculture and neonicotinoids" (EASAC, 2015).	The report concluded that the widespread prophylactic use of neonicotinoids has severe negative effects on non-target organisms that provide ecosystem services.
2017	The Bee Coalition was created as a platform for NGOs to join forces and resources at EU level for the protection of bees and pollinators.	Their aim is to make EU decision-makers to completely ban all neonicotinoids, and that the Member states approve the Bee Guidance document.
2017, June	Two papers published in *Science* (Woodcock et al., 2017 and Tsvetkov et al., 2017) received much public attention. The Woodcock study was the largest field study of neonics effects on bees ever conducted, and was sponsored by Bayer and Syngenta	Especially, the study in Woodcock et al., (2017), which was assumed to increase the knowledge on field realistic effects of neonics, was highly debated and received very different interpretations.
2017, Oct.	A worldwide survey of neonicotinoids in honey, found at least one of five tested neonic compounds in 75% of all samples (Mitchel et al., 2017).	This study gained much attention in media as it increased the knowledge on residues of neonics.
2018, Feb.	EFSA presents to the EC its updated risk assessments of clothianidin, imidacloprid and thiamethoxam	For all the outdoor uses of these substances, there was at least one aspect of the assessment indicating a high risk to bees. (EFSA, 2018e).
2018 May 29	The EC implements Regulations (EU) 2018/783, 2018/784 and 2018/785, extending the ban on imidacloprid, clothianidin and thiamethoxam.	The bans on 3 neonics in the EU were continued and reinforced.
2018, May 17	Judgment of the General Court of 17 May 2018 on the Cases T-429/13 (Bayer CropScience AG and Others) and T-451/13 (Syngenta Crop Protection AG). The Court dismissed entirety the actions brought by Bayer and Syngenta in relation to the neonicotinoids clothianidin, thiamethoxam and imidacloprid.	In the judgment, the EC was supported, and it was underlined that the PP was not beached.
2018 July	Appeal /Case C-499/18 P): Bayer CropScience AG against the judgment of the General Court (First Chamber, Extended Composition) in Case T-429/13	The allegations were similar, also disputing the PP, in addition to promoting more regulatory certainty for innovators.
2018, Dec. 18	The European Parliament publishes the report on the Union's authorisation procedure for pesticides (European Parliament 2018/2153(INI). It highlights flaws in the authorisation practice and the effectiveness of Regulation (EC) 1107/2009, and calls for changes in the pesticide approval procedure.	The report calls on the Commission and the Member States in their role as risk managers to duly **apply the precautionary principle**, and highlights that the widespread and prophylactic use of plant protection products is of concern.
2019, 23.10	MEPs block member states' move to weaken bee protection from pesticides (EP Press release, 2019)	Member States opposed the full implementation of EFSAs Bee Guidance document

2020 Jan 13	EC decided not to renew the approval of thiacloprid, following scientific advice by EFSA that the substance presents health and environmental concerns.	This is the 4th out of 5 neonics that first were approved for use in the EU, but that later were restricted since 2013.[5]

2 Neonicotinoids - Innovation and potential benefit

The invention of neonicotinoids in the late 1980s and 1990s, is often highlighted as a 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[6] (Jeschke and Nauen, 2008). They are the newest of the five major classes of insecticides (the others are chlorinated hydrocarbons, organophosphorus compounds, methylcarbamates, and pyrethroids), and by 2011 it was estimated that they make up one-fourth of the world's insecticide market (Tomizawa and Casida, 2011). The most widely used Neonics include the active substances Imidacloprid, Clothianidin and Thiacloprid (by Bayer Crop Science), Thiamethoxam (by Syngenta) and Acetamiprid (by Aventis Crop Science). As systemic insecticides, they work differently than contact pesticides which make the surface of plants toxic to plague organisms. Instead, they are they are taken up by the plant sap and translocated to all parts of the plant to provide long-term protection from piercing-sucking insects (Tomizawa and Casida, 2005).
The importance of innovating new Plant Protection Products (PPP) is often highlighted in the context of food security and the increasing weed and pest resistance to well established PPP (Bozzini, 2017). Most of the neonics were introduced on the EU marked between 1991-2002, at a time when many pest insects had developed resistance to other pesticides like organophosphates (Simon-Delso et al., 2015).

Since their introduction to the market, neonics have become the most widely used group of insecticides in the world. They are promoted for providing a cost-effective for increasing yields, but it is also argued that their targeted use has decreased the use of other pesticides. As summed up in the industry magazine European Seed, "they have dramatically changed farming in Europe and reduced risks for farmers, both because they have improved pest control and have decreased additional chemical applications".[7] Reports and studies have identified such benefits of the use of neonics (e.g., North et al., 2016; Hurley and Mitchell, 2017) and it has been argued that restrictions on neonic has had negative consequences for crops and farmers (HFFA, 2018; Budge et al., 2015; Dewar, 2017; Kathage et al., 2018). Budge et al., (2015) found that farmers who use neonicotinoid seed coatings reduce the number of subsequent applications of foliar insecticide sprays and may derive an economic return. Summing up the negative consequences of implementing restrictions on neonics the UK, Dewar (2017:1308) lists that it increased applications of alternative insecticides, increased evolvement of resistance in target pests, increased level of damage caused by flea beetles, led to a decrease in yield at harvest, a decrease in the area of oilseed rape grown – which has the knock-on effect on the area of flowering crops available to foraging bees in the spring when flowering plants in general are scarce in the UK landscape.
Countering this, other studies have not found clear and consistent evidence on yield benefits from the use of neonicotinoids on different crops (Hladik et al., 2018; Furlan et al., 2017; Milosavljevic et al., 2019; Lundin et al., 2020). For example, it is found that neonic seed treatments offered little yield benefit for soybean production (Seagraves and Lundgren, 2012; EPA, 2015) and for wheat crops (Macfadyen et al., 2014). For oilseed rape, a recent field study found that neonic seed treatments were only economically justified in one year out of three (Lundin et al., 2020). A review of the precautionary regulation of neonics in Italy in 2008 found the average annual maize production per

[5] https://ec.europa.eu/commission/presscorner/detail/en/mex_20_38
[6] Note that the specificity here only means that it is highly toxic to insects and much less toxic to vertebrates such as mammals and birds, but is it not specific to plague insects versus non-target, beneficial, invertebrates such as bees, butterflies and earthworms.
[7] https://european-seed.com/2017/12/impact-ban-neonicotinoids/

hectare remained unchanged after the regulation was implemented (Sgolastra et al., 2017). Another issue is that due to the widespread use of neonics, 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 on them (Van der Sluijs and Vaage, 2016; Furlan et al., 2017). In sum, there are many uncertainties on the relationship between the use of neonics and yield benefits of different crops, which also may be impacted by unpredictable changes in the density and developments of both pollinating and pest insects.

3 Risks and scientific uncertainty

3.1 Risk/threat

The risk discussed in relation to neonics are mostly environmental, as the residues in the environment are found to be high and diverse. 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. It has been found that although the technique of coating seeds with neonics is designed to be taken up into the target crop plant, only 1.6–20% of the active ingredient is absorbed, with the majority remaining in the soil from where it leaks to the surface water and groundwater (Wood and Goulson 2017). Wild trees (most of which are flowering plants that are visited by pollinators) in or around agricultural fields and along polluted surface water also take up neonics and have become contaminated. Soil and foliar runoff are the most common pathways for neonic contamination of surface and groundwater (Wood and Goulson, 2017).

Risks for bees and pollination ecosystem services
In both research and in public debate, the main attention has been on the risks that neonics pose to pollinators, especially bees. Since the early warnings in the 1990s, evidence has been mounting that the large scale use of these chemicals play a key role in colony collapses and are an important driver of the pollinator decline observed over the past decades (Van der Sluijs et al., 2013; 2015; EASAC, 2015; Rundlöf et al., 2015). As a direct consequence of its systemic action, unintendedly the pollen and nectar of treated crops and of wild flowers in or around the fields with treated crops also contain traces of the nerve poison in non-deadly, yet harmful concentrations. Subsequently, not only plague insects are exposed but also beneficial insects such as bees, butterflies and other pollinators get exposed to low doses as they forage. Neonics are over 7 000 times more toxic to honeybees than the insecticide DDT (Simon-Delso et al., 2015). Prolonged exposure to very low doses is ultimately fatal for insects. This is because neonics have the rare property that the duration of the exposure amplifies its toxicity (Tennekes, 2010). Further, so-called sublethal doses disturb navigation and flight behaviour of bees, causing bees to get lost, and weakening the entire colony (Van der Sluijs et al., 2013). Thereby, the large-scale prophylactic use (application of pesticides to all seeds even when there are no signs of pests) of neonics, in combination with their high toxicity, has transformed the agrochemical landscape for pollinators (Van der Sluijs et al., 2013). Recent studies have shown that neonics are the dominant factor driving the increase in toxicity for insects of farmland (Goulson et al., 2018) as is illustrated for UK farmland in figure 1. However, it should be noted that the widespread use of neonics is only one of multiple stressors that are related to pollinator decline. It is the combination of parasites, pesticides, and low availability of floral resources in present day landscapes and lack off

suitable nesting places that together produce the present pollinator declines (Goulson et al., 2015). At present, there is substantial uncertainty, complexity, ambiguity and disagreement around which factors are more important and how these factors relate to each other. This will be explained in more detail in section 3.2.

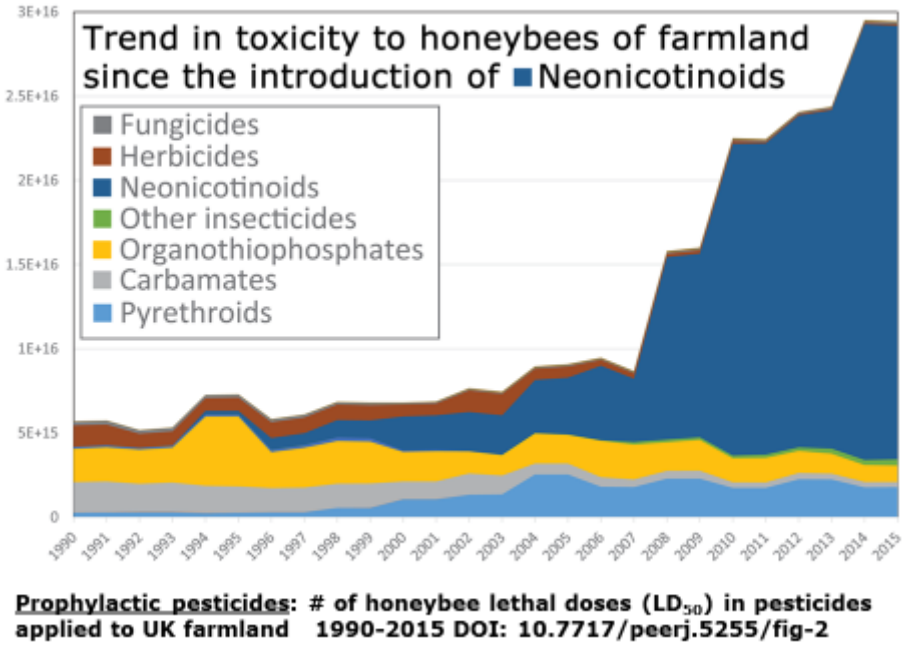

Figure 1: Toxicity to honeybees of farmlands in the UK (Goulson et al., 2018: 4)

Pollinator decline is a serious risk because they provide key ecosystem services 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 for insect eaters such as birds. There is a concern that a tipping point will be reached, where pollinator decline cannot be reversed, despite their seemingly robust structure (Potts et al., 2010: 347). Viewed as essential ecosystem services in food production, pollinator decline can threaten both global and local food security and can destabilize ecosystems that form our life support system (van der Sluijs and Vaage, 2016). It is often referred to that the United Nations Food and Agriculture Organisation (FAO) have estimated that 84% of the 264 crop species in Europe are dependent on pollinators[8]

Risks for other species and ecosystem services

There is also a growing amount of research demonstrating risks for other species and ecosystem services. The findings from the "World Wide Integrated Assessment of the Impacts of Systemic Insecticides on Biodiversity and Ecosystem Services" in 2017, summarized in figure 2, show that at the present scale of world-wide use, the impacts of neonics on insect pollinators and on terrestrial and aquatic insects, cascade into impacts on population level and communities levels and put key ecosystem services at risk.

[8] http://www.fao.org/news/story/en/item/384726/icode/

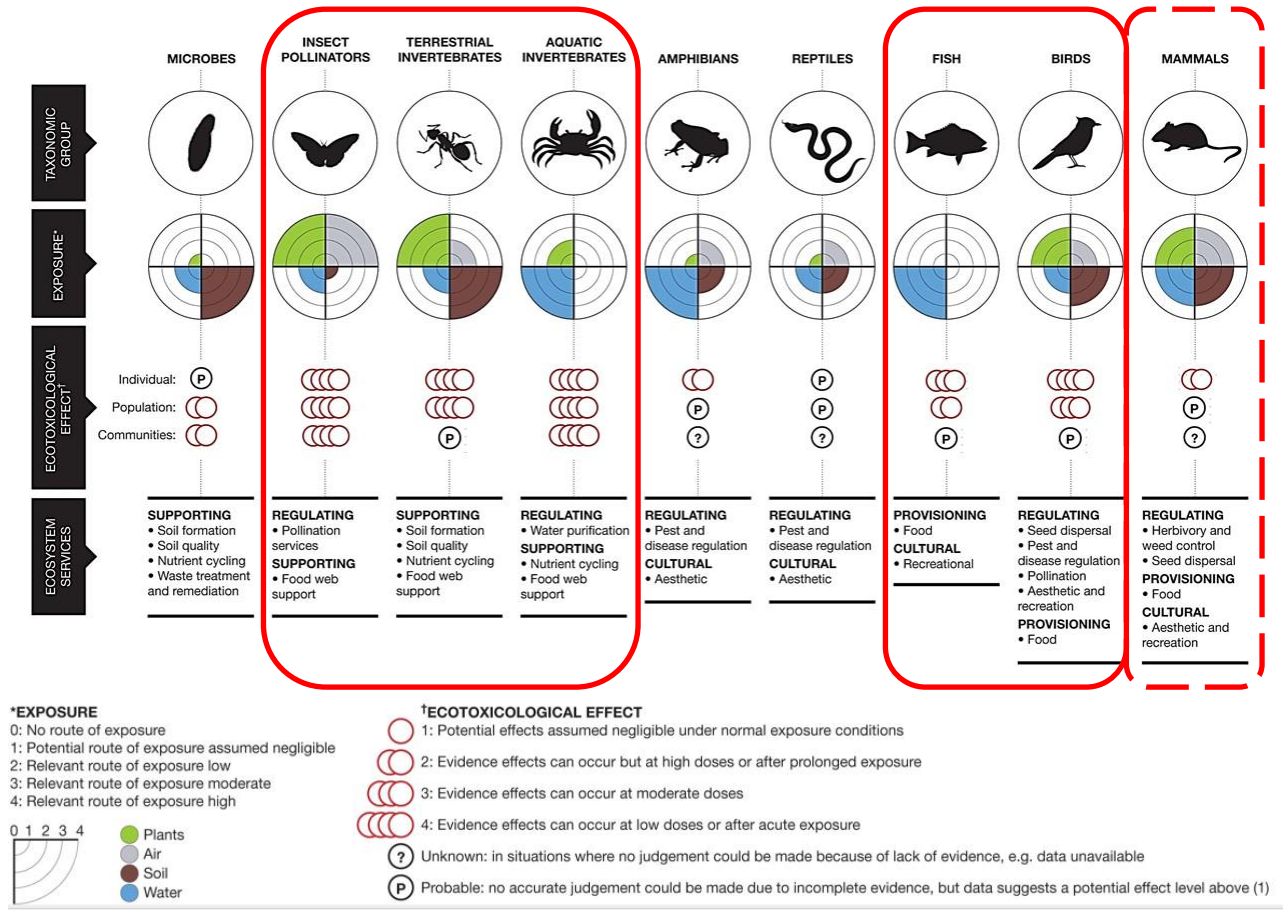

Figure 2: Infographic summarizing the main findings of the WIA study on the state of knowledge on impacts of neonic insecticides on biodiversity and ecosystem services (Pisa et al., 2017:36).

The infographic in figure 2 shows for example that effects are found on **vertebrate wildlife (birds):** Some bird species may consume seeds coated with neonics or forage on plants or seeds with residues, but indirect effects on insectivorous birds as a consequence of reduced insect abundance is also a ground for concern, but there is still limited evidence and many uncertainties remain because the impacts have only been examined in a handful of species. Since 2014, studies have found negative impacts of the neonicotinoids imidacloprid and clothianidin on vertebrate wildlife, such as birds who ingest treated seeds left on the surface at sowing (Gibbons et al., 2015; Hallman et al., 2014). A recent study shows that field-realistic imidacloprid exposure reduces fueling and delays migration in songbirds (Eng et al, 2019). Effects are also found on **Terrestrial invertebrates such as earthworms** (see Chagnon et al., 2015), which provide a range of ecosystem services (e.g. decomposition of organic matter in soils for nutrient cycling). Another increasing worry is the effects of neonics on **Aquatic invertebrates**, which also provide significant ecosystem services (van Dijk et al., 2013; Sánchez-Bayo et al., 2016A). Entire ecosystems may be impacted as invertebrates constitute the main food source for many insectivorous vertebrates and fulfil an essential role in recycling organic matter in the soil as well as in water (Pisa et al., 2017)

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 (Cimino et al., 2017; Zang et al., 2018). There is also emerging evidence that at least some neonicotinoids are not only nerve poisons but are also endocrine disruptors (Caron-Beadoin et al., 2017).

Despite the accumulating amounts of studies, there are many uncertainties and large controversies. The controversies will be further explained in the following section, highlighting that the complexity of the issue.

3.2 Scientific analysis

The first observations (early-warnings) of the negative effects of neonics on pollinators came from beekeepers in different European countries, who started to report large amounts of bee-deaths (and colony losses) in hives located near fields sown with neonicotinoid-coated seeds. 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 (Maxim and van der Sluijs, 2007; 2013). Of particular importance was the scientific assessment by the French Scientific and Technical Committee for the Multifactor Study of the Honeybee Colonies Decline (CST)[9] from 2003. Based on the analysis and synthesis of 338 scientific publications, the CST concluded that seed-dressing sunflower and maize posed serious risks to honeybee colonies via larvae feeding, pollen consumption by nurses, nectar ingestion by foragers, and honey consumption by honeybees living inside the hive. The CST based the assessment on comparison between the levels of exposure (Predicted Exposure Concentration — PEC) and toxicity (Predicted No Effect Concentration — PNEC) of imidacloprid for honeybees considering both lethal and various sublethal effects. It concluded that the exposure in the field exceeds the known no-effect concentrations and are therefore of concern (CST, 2013).
The use of different types of neonics in different kinds of crops expanded in Europe during the 2000s. In the spring of 2008, serious bee-colony losses were reported in Italy, Germany, Netherlands, Slovenia and France. This led to national bans or restrictions of products containing neonics for certain kinds of crops. Further, the incidents of colony collapses in Europe were followed by increased research and monitoring on the effects of neonics on bees. In Italy, a 3-year monitoring research project (APENET) was conducted between 2009 as initiated by Italian authorities in order to clarify the causes bee-deaths (EFSA, 2012a).

Independent peer-reviewed research: Beekeepers suspicion that colony collapses were related to the use of neonics in the fields close to beehives, inspired independent researchers to investigate the matter. Particularly three studies received much attention, finding that imidacloprid (Whitehorn et al., 2012), thiamethoxam (Henry et al., 2012) and clothianidin (Schneider et al., 2012) at field-realistic concentrations had significant impacts on bee colony stability and survival of honeybees and bumblebees. Since 2012, and especially after the decision of EC to implement a partial ban on three neonics in 2013 (outdoor use on crops that are attractive to bees), research on the risks of neonics expanded massively. There have been several review studies assessing and evaluating the amount of detailed studies generated, including Godfray et al., (2015), Lundin et al., (2015), and Wood and Goulson (2017), EASAC (2015). As example, Lundin et al. (2015) provide a systematic review of research approaches, evaluating 268 publications on bees in general (honeybees, bumblebees, solitary bees). The International Task Force on Systemic Pesticides published a synthesis of 1,121 published peer-reviewed studies spanning the last 5 years at that time, including industry-sponsored ones in 2015. This seminal report is called the "World Wide Integrated Assessment of the Impacts of Systemic Insecticides on Biodiversity and Ecosystem Services" (WIA). The WIA was published in the form of 8 scientific papers in the journal *Environmental Science and Pollution Research* (Simon-Delso et al., 2015; Bonmatin et al., 2015; Gibbons et al., 2015; Chagnon et al., 2015; Furlan and Kreutzweiser 2015; Van der Sluijs et al., 2015). In 2017, the same task force published an update of the WIA in 3 papers based on more than >700 publications that had appeared since the first WIA study (Giorio et al., 2017; Pisa et al., 2017; Furlan et al., 2017).

EC mandated EFSA reviews: Mandated by the European Commission (EC), EFSA has provided a conclusion of the risk assessment for the active substance clothianidin (EFSA 2013b, 2015a, 2018d) thiamethoxam (EFSA 2013c, 2015c, 2018c) imidacloprid (EFSA 2013d, 2015b, 2018b) and thiacloprid (EFSA 2019). The context for the risk assessment was that the EC mandated EFSA, in accordance with Article 21 of Regulation (EC) No 1107/2009, to review the approval of active substances considering new scientific knowledge. Further, in accordance with Article 31 of Regulation (EC) No 178/2002, EFSA organised an open call for data in order to collect new scientific information as regards the risk to bees from the neonicotinoid pesticide active

[9]Comité Scientifique et Technique de l'Etude Multifactorielle des Troubles des Abeilles, installed by the French Ministry of Agriculture

substances clothianidin, thiamethoxam and imidacloprid applied as seed treatments and granules in the EU. The EFSA also performed an extensive updated literature search for their 2018 assessment instead of only relying on the dossier provided by the industry, as would occur in a normal authorization procedure (EFSA, 2018b). It should be noted that for re-evaluations of imidacloprid, thiamethoxam and clothianidin published in 2018, EFSA not only used far more data sources, but also got the explicit mandate to apply its new 2013 Bee Guidance (EFSA 2013e), even if it was (and at the time of writing, mid 2020, still is) not yet put into force. If the limited (and scientifically outdated) authorization tests that were in force (found in the Guidance Document on Terrestrial Ecotoxicology 2002[10]) had been used, it is unlikely that any risks would have been identified. This highlights a major problem in pesticide authorization, namely that the authorisation tests that are in force typically lag many years behind the scientific progress in the field, in this case at least 18 years.

3.3 Scientific Uncertainty

3.3.1 Complexity

Several complexities contribute to the challenges of estimating and analyzing the risks connected to neonics (esp. choosing variables and samples for analysis), and we have here categories these complexities into four categories:

First, there are complexities of the **types and applications** of neonics. There are different types of neonics and different kinds of products (including cocktails of pesticides), and different neonics are applied to different types of crops, in indoor or outdoor facilities. With a definition focusing on how the compound works, the neonicotinoid family includes imidacloprid, clothianidin, thiamethoxam, dinotefuran, thiacloprid, acetamiprid, sulfoxaflor, nitenpyram, imidaclothiz, paichongding and cycloxaprid (van der Sluijs et al., 2015). There is some ambiguity on the names of families of these chemicals, as evident in the current debate on **sulfoxaflor** (approved in 2015) (EFSA 2018f). The TFSP classifies sulfoxaflor as a neonicotinoid (Giorio et al., 2017), but the authorization dossier sent by Dow Chemical to the EFSA classified it as a sulfoximine. It has however the same mode of action, acts on the same receptor in the insect nervous system and has similar toxicity to bees as imidacloprid.

Regarding applications, neonics can be applied though either spaying, seed coating/seed-dressing, soil treatment, injection, and drenching. Seed-dressing is the most common application method, and was estimated to make up 60% of the global use in 2010 (Jeschke et al., 2010). The advantage of seed-dressing is that it requires no action from the farmer, prophylactically protecting all parts of the crop for several months following sowing (Jeschke et al., 2010). Further, neonics may be applied in different seasons, which is related to routes of exposure for bees, especially in foraging season. Particularly two seasons are important: Seeding seasons, when bees and other insects may be exposed to neonics through dust drift during the sowing/application of the treated seeds, and flowering seasons, when residues of neonics are found in nectar and pollen, exposing pollinating insects. It should also be noted that neonics may be applied not only to crops, but also in **biocides and in veterinary medicine.** Consequently, there are different regulative regimes for different uses of the same chemical – e.g. neonics as applied on crops are regulate under a different regime than neonics applied in biocides (for instance to kill flies in cattle stables) and veterinary medicine (for instance to kill fleas in pets).

Secondly, and linked to the variety of applications, there is a complexity of **residues and possible routes of exposure for** non-target species. Neonics residues are found not only in treated crops, but also in nearby wild flowering plants, including arable weeds, trees and shrubs. Research has revealed that insects may be exposed through residues of pesticides in nectar, pollen, honeydew, extrafloral nectar, guttation fluid, surface water, puddle water, soil, sediments, leaves, and through dust produced during the seeding of coated seeds or spraying (Bonmantin et al., 2015). There is therefore uncertainty on the level of chronical exposure of non-target organisms to sublethal levels of neonics also after planting, and indicated that

[10] https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_ecotox_terrestrial.pdf

pollinators may face cumulative exposure to neonics from combined residues in pollen, nectar and water (Samson-Robert et al., 2014). In a field study in Canada, it was found that honey bees in corn-growing regions were exposed to toxicologically significant levels of neonics for the majority of the active bee season despite the mandated use of dust-reducing seed lubricants during planting (Tsvetkov et al., 2017:3).

Third, there is a complexity of **species affected,** as also highlighted in section 3.1. Honey bees (managed bees) are the most researched species, but wild bees like bumblebees and solitary bees are also affected and may show different levels of sensitivity. As most European wild bees are smaller than honeybees, they may be more sensitive on a basis of a few nanogram/bee exposure (Pisa et al., 2017). The effects on solitary bees may be different than on bees living in colonies that store larger amounts of food. Bumblebees have a different biology, behaviour and ecology from honey bees, and may for example be exposed to neonics via soil or plant materials used for nesting materials (EFSA 2013c, p7). Further, as elaborated earlier, neonics may affect other wild pollinators such as butterflies, on invertebrates (like earthworms), on aquatic animals (fish, molluscs) and on birds, through various routes of exposure like residues in water, soils and seeds.

Fourth, there is a complexity of **ecological contextual factors** that affect the consequences of neonics exposure for different species. Here, we will focus on bees, as these have been given the largest amount of public and scientific attention in this case. It is found that neonics can weaken bee colonies in various ways, as the sub-lethal effects may affect the complex social and collaborative structures of a bee colony (van der Sluijs et al., 2013). As an example, bees depend on communication and collaboration, and neonics may weaken the general health of worker bees, and their ability to communicate on where to find food. Moreover, is well known that that reasons for bee deaths / declinecannot only be linked to neonics, but to a complex set of factors that may interact: it is the combined stress from parasites, pesticides, and lack of flowers that contribute to bee decline (Goulson et al., 2015). Loss of habitat is a major factor contributing to bee-deaths, as bees require access to flowering plants in their adult flight season, and undisturbed nesting sites (wild bees). The conversion of rich habitat to farmland, but also urbanization has contributed to the loss of habitat. Then there is the problem of diseases. Bees naturally suffer from a broad range of parasites, fungi, bacteria, and viruses, especially Nosema ceranae and the Varroa mite. The main general understanding there is not one cause of bee-deaths, but that the different factors work together, e.g. by that the lack of access to flowering plants decreases reduces the bee's ability to cope with both toxins and pathogens and that neonics may make bees less resilient towards these diseases (Sánchez-Bayo et al., 2016B). Further, bees are often chronically exposed to a cocktail of different pesticides (e.g. bees can be exposed both neonics and fungicides simultaneously), and this 'cocktail effect' remains poorly understood (Goulson et al., 2015).

3.3.2 Uncertainty

Scientific uncertainty may stem from a lack of data or inadequate models for risk assessment, and from the complexity of factors that may complicate determining the causal relations. In the case of neonics and its effects, the extended overview of the complexity as outlined above indicate several uncertainties. Some of these uncertainties could be attributed to a lack of data or knowledge gaps, that hamper evaluation of the full extent of risks associated with the ongoing use of systemic insecticides. However, even the fields where extensive amounts of research have been carried out, such as the effects of neonics on bees, there are many knowledge gaps and uncertainties. These uncertainties are related to the complexity of insect biology (including insect behaviour and colony mechanisms), and the environment they inhabit which increases the difficulty of determining causal relations. We will here give an overview of uncertainties related to the different aspects of complexity outlined above.

Even if bees, and especially honeybees, are well researched in relation to neonics, knowledge gaps and uncertainties remain on both the extent to which bees are exposed to neonics, and on the various effects of the exposure. 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, 2013), but there is limited

knowledge on the exact residues in different areas, as they may vary significantly. In 2017, a field study identified widespread contamination of agricultural land by neonicotinoids (Tsvetkov et al., 2017), however this may vary geographically and over time. In the TFSP study, it was found that for most countries, there are few or no publicly available data sources on the quantities of systemic pesticides being applied, nor on the locations where these are being applied (Van der Sluijs et al., 2015). Thereby, realistic assessments of ecological impacts and risks becomes challenging. Additionally, the screening of neonicotinoid residues in environmental media (soils, water, crop tissues, non-target vegetation, sediments, riparian plants, coastal waters and sediments) is extremely limited. Therefore, even if a worldwide survey found residues of neonics in 75% of honey samples (Mitchell et al., 2017), uncertainty remains on the extent of exposure in different areas.

Further, there are uncertainties on the consequences of different levels of exposure, especially of **lower sub-lethal exposure over time.** Sub-lethal effects are documented as summarised in several meta-studies to have negative effects on e.g. their growth and behavior (Cresswell, 2011; Main et al., 2018). However, effects of long-term, acute and chronic exposure are less well known, as long-term consequences of exposure under environmentally realistic conditions have not been studied (Van der Sluijs et al., 2015). It is also challenging to estimate the effects of neonics on colony strength and resilience. It has been found that exposure to neonics can affect the strength of the bee colony in different ways, for instance when forager bees are affected in a sub-lethal manner by e.g. making navigation errors, show impaired social communication, thus weakening the colony (Pisa 2017, p3-4). However, there are multiple stressors that affect bee health and colony strength, but there are few studies on synergic effects of systemic insecticides and other stressors, such as other pesticides, disease and food stress (van der Sluijs et al., 2015). Bee diseases such as the Varroa mite and Nosema may weaken the colonies significantly, and these diseases are often seen as the main causes of colony collapse disorder. An indirect relation between neonics and such diseases have been found, by that the neonics supresses the immune system and thereby opens the way to parasite infections and viral diseases, fostering their spread among individuals and among bee colonies at higher rates than under conditions of no exposure to such insecticides (Sánchez-Bayo et al. 2016B). Clearly, there can be many reasons for weak colonies. This uncertainty is also drawn on by agrochemical companies, who argue that there is no causal relation between neonics and colony collapses, but that bee health problems like the varroa mite is the main cause (see e.g. Bayer's home pages dedicated to on bee health[11]).

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 degrees are exposed to. In a review from 2015 it was found that no studies had addressed the additive or synergistic effects of simultaneous exposure to multiple compounds of the neonicotinoid family, i.e. imidacloprid, clothianidin, thiamethoxam, dinotefuran, thiacloprid, acetamiprid, sulfoxaflor, nitenpyram, imidaclothiz, paichongding and cycloxaprid (van der Sluijs et al., 2015). As all neonicotinoids bind to the same receptors in the nervous system, a cumulative toxicity could be expected, however assessments are done for each chemical separately. This is problematic because in field situations, organisms will almost invariably be simultaneously exposed to multiple pesticides as well as other stressors, so our failure to understand the consequences of these interactions is a major knowledge gap (van der Sluijs et al., 2015).

With the high degree of contextual complexities, there are several uncertainties connected to the **methods chosen for measuring the effects of neonics on pollinators**. A main method is conducting **lab studies** (or experimental studies) under controlled circumstances (inside of a lab), by feeding bees with different types of neonics and measuring their responses. Such studies have the advantage that they allow for causal arguments about exposure-effect relationships, and many of these seem to highlight a negative effect of neonics on bees. A disadvantage of lab studies is that there is a high degree of uncertainty on what a field-realistic doses of neonics would be, due to many contextual complexities. As example, bees may be

[11] https://www.cropscience.bayer.com/people-planet/biodiversity/bee-health

more exposed to neonics in some seasons more than others (also depending on farmers methods of seeding), there may be different availabilities of other flowering plants in different areas, and it is uncertain and may vary how far bees fly when foraging (while some argue 1 km, others 3 km, Beekman and Ratnieks (2000) found a median foraging distance of 6.1 km with 10% of the bees foraging over 9.5 km.). Therefore, lab-studies have been critisised for giving bees unrealistically high doses of neonics compared to what they would get in a real life (see e.g. Carreck and Ratnieks, 2014; Löfsted and Schlang, 2017). Contrasting lab-studies, **field studies** may encompass more contextual complexity, making the study more field realistic. Disadvantages of such studies are that they are challenging to reproduce and do not enable good estimations of causal effects as a multitude of factors may impact the specific case that is studied. Weather, nutrition, genetics, pathogens and diseases, presence of multiple toxic compounds, potentially contrasting behavioural characteristics of the studied colonies, and very different methodological approaches, may affect the results of the study (Pisa et al., 2017:3). The specific location of the field study may impact the study, because the floral resources (containing different mixtures of pesticides) that bees can forage on, usually within a 3 km radius around a hive, varies between locations. This becomes evident when we look at figure 3 below. Consequently, it is difficult to reproduce field experiments.

Figure 3: high variability in land-use (a key confounder) in a typical 3 km foraging area (in Belgium) around a honeybee hive, puts fundamental limitations to the reproducibility of field studies (figure source: Simon-Delso, 2017).

Field studies on the effects of neonics on bees have come to different conclusions. While some found no or little effects on bees and bumblebees (Pilling et al., 2013; Thompson et al., 2013; Peters et al., 2016), others have found varying and worrying effects (Rundlof et al., 2015; Tsvetkov et al., 2017; Woodcock et al., 2017). The uncertainty of the effects of neonics in field realistic studies are evident when comparing two of the most debated peer-reviewed articles in 2017: While Tsvetkov et al (2017) demonstrated that field-realistic chronic exposure to neonics reduced the health of honey bee colonies near corn crops in Canada, a large scale field study in Europe found more contradictory results (Woodcock et al., 2017). These studies both accounted for some of the complexity of the environment and included behavioural / sub-lethal effects.

Many of the uncertainties discussed here are reflected in the conclusions EFSA risk

assessments from 2018. The conclusions on risk varied according to factors such as the bee species, the intended use of the pesticide and the route of exposure (residues in bee pollen and nectar; dust drift during the sowing/application of the treated seeds; and water consumption) (EFSA 2018b; 2018c; 2018d). For example, the 2018 review on imidacloprid found that there was a low risk of exposure through both dust drift and residues in pollen and nectar for honeybees, but a high risk when bumble bees and solitary bees were included (EFSA, 2018b). The current focus in EFSA is to improve the risk assessment process by including larger spatial scales, multiple stressors, and different pesticide uses (Streissel et al., 2018). This is also evident in EFSA's MUST-B project, which aims to develop a holistic approach to the risk assessment of multiple stressors in honeybees[12].

3.3.3 Ambiguity

Ambiguity arises when different actors both interpret the knowledge and frame the issue at hand differently. Involved actors in the controversies over neonics include beekeepers and beekeeper associations, farmers and farmers associations, agrochemical companies and chemical industry associations, environmental NGOs, politicians, policy advisors and different groups of scientists. With the amount of stakeholders engaged and the multiple sources of uncertainties around the effects of neonics on bees, it should be no surprise that there is a high level of ambiguity – reflected by the highly contradicting interpretations of the context, the problem, and the research on the problem.

Ambiguity on the context and the problem (what is at stake)

The risks that different stakeholders relate to neonics should be seen in light of 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 way of framing PPPs is seeing them as vital tools in providing food security. With this perspective, the historical and ongoing advances in food production that are necessary to ensure sufficient food production for a growing world population is central. Often, a different contextual story used to illustrate how vulnerable food production is, e.g. referring to the Irish potato famine (Bozzini, 2017).

In the case of neonics, the risk these PPPs pose to the ecosystem services and biodiversity is particularly highlighted by beekeeper organizations and environmental NGOs. Beekeepers and beekeeper associations, including Apimondia, European Professional Beekeepers Association, BeeLife and European Beekeeping Coordination. The most outspoken (Environmental) NGOs involved in this case include Pesticide Action Network, Greenpeace, Buglife, and Slow Food[13]. In 2017, more than 80 NGOs, covering most of the European Union and comprising beekeepers, environmentalists and scientists, officially launched the 'Save The Bees Coalition', where it is stated that

> "Neonicotinoids and other pesticides are major factors causing the decline in populations of honey bees, wild bees and other pollinators. This jeopardises our food sustainability and biodiversity. Neonicotinoids have been authorised more than 20 years ago because their impacts on bees were not fully assessed as the procedures for testing the safety of pesticides used rules that were partly written by the pesticide industry itself »[14].

There have also been online petitions, the most recent one demanding Bayer CropScience to drop their court case against the EC on the ban in 2018, where it is highlighted that bees are at risk of global extinction, while companies like Bayer put their profits ahead of the planet's

[12] http://www.efsa.europa.eu/en/topics/topic/bee-health , http://www.efsa.europa.eu/en/press/news/170522-0

[13] An international grassroots organisation that supports small-scale agriculture, based on crop rotation and sustainable pest- and weed-control methods, and works directly with beekeeping communities worldwide, creating international networks of quality honey producers.

[14] https://beecoalition.eu/

health. [15] The petition received over 1.4 million signatures. Note that public debate is focused especially on honey bees, while e.g. bumble bees, solitary bees, hoverflies butterflies and moths, which also are significant pollinators, have received less public attention (EASAC, 2015).

The stakeholders promoting neonics as safe focus more on food production efficiency and in context of food security. Particularly outspoken on the matter are the agrochemical companies Syngenta and Bayer Crop Science. Their main position is that neonics are efficient and safe, and they highlight the economic importance of products containing neonics (see e.g. press releases regarding the restrictions implemented in 2018[16]). Supporters of the agrochemical companies, who also supported the court case complaints against the EC bans in 2014 (case T-429/13 ant T451/13), include industrial and farmers associations such as the British National Farmers Union (NFU), Agricultural Industries Confederations (AIC), and the European Seed Association (ESA). The European Seed Association (ESA), state in a press release regarding the ban in 2018, that neonics dramatically have improved farming in Europe and boosted yields[17]. Similarly, the head of the Agricultural Industries Confederations stated in a press release that "Effective modern crop protection products are an essential part of meeting UK government's drive to raise productivity whilst enhancing the environment"[18]. The British National Farming Union (NFU) states, in a press release commenting on the scientific report by Budge et al., (2015):

> "From this study we can see clearly that neonicotinoid use results in oilseed rape yield increases, which are vital in increasing farm productivity and profitability. This benefits everyone - as the population grows, growing the raw ingredients for affordable, wholesome food is becoming more important than ever[19].

However, the simple the dichotomy between food safety and biodiversity/ecosystem services is not clear cut between the stakeholders. As example, Bayer highlights their concern about pollinators at their webpages[20] where they focus on bee health, where they also underline that neonics is not the cause of pollinator declines. On the other hand, environmental NGOs argue that agricultural productivity can increase with other measures than with pesticides such as neonics. There is little ambiguity on the importance of pollinators as important ecosystem service providers that need to be protected – here all stakeholders seem to agree. Rather, the controversy centers more on the what the problem is, to what degree neonics contributes to pollinator decline, and what kinds of regulations that are necessary. As described by Maxim and Sluijs (2010), there is an overall ambiguity over what the causes for bee-losses are: While beekeepers and some scientists claim neonics is a relevant cause, the agrochemical industry argue that a bee diseases are a determining factor. As highlighted by Kleinman & Suryanarayanan (2012), university bee toxicologists, agrochemical companies, farmers, and commercial beekeepers have contrasting approaches and make different claims about the causal role of agrochemicals in Colony collapse Disorder (CCD), because they have different stakes in the regulation of the risks.

Related to this, there is ambiguity around acceptability of risk and what a "**high level of protection**" to be achieved by the EU's pesticide regulation 1107/2009 implies for the case of neonics. For instance, Greenpeace endorsed the restrictions on neonics in 2018, but also argued that regulations should be stricter as pollinators are not sufficiently protected.[21]

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[15] https://actions.sumofus.org/a/bayer-bees-lawsuit see also https://www.euractiv.com/section/agriculture-food/news/agri-giant-under-pressure-to-drop-appeal-on-neonicotinoids-ban/

[16] Syngenta press release: https://www.syngenta.com/company/media/syngenta-news/year/2018/neonicotinoid-decision-takes-european-farming-wrong-direction
Bayer press release: https://media.bayer.com/baynews/baynews.nsf/id/Neonicotinoid-ban-a-sad-day-for-farmers-and-a-bad-deal-for-Europe

[17] https://european-seed.com/2017/12/impact-ban-neonicotinoids/

[18] https://www.agindustries.org.uk/news-and-events/aic-disappointed-by-eu-court-ruling-on-neonicotinoids/

[19] https://www.nfuonline.com/pollinator-impacts-and-farming-benefits-of-neonicotinoids-on-osr/

[2020] https://beecare.bayer.com/home

[21] https://www.greenpeace.org/eu-unit/issues/nature-food/785/commission-takes-major-step-to-ban-three-bee-harming-pesticides/

Independent researchers have also criticised the risk assessment scheme in the EU for reacting too late (Sgolastra et al., 2020). Agrochemical companies on the other hand, find the regulations on neonics too strict and overprotective, as they still claim that neonics are safe if used as instructed. Further, as e.g. stated in Syngenta press release commenting on the ban in 2018, it takes Europe in the wrong direction as these chemicals are essential for farmers to ensure the supply of safe and affordable food.[22] This ambiguity is also evident in the different perceptions of the role of neonics in an Integrated Pest Management (IPM) approach. IPM plays a significant role in directive 2009/128/EC on the sustainable use of pesticides, where the overarching aim is to reduce the use of pesticides in the EU to a minimum[23]. In relation to IPM, some researchers have claimed that neonics, with their low risk for nontarget organisms and the environment and versatility in application methods, are now essential components for integrated pest management strategies (Tomizawa and Casida, 2011). It was assumed that the use of neonics would reduce the amounts of pesticides used globally. Countering this, others argue that because neonics are mostly used prophylactically - by coating all seeds with neonics as a preventative measure even if there are no signs of pests, they are incompatible with IPM (Furlan and Kreutzweiser, 2015; Tooker et al., 2017; Sgolastra et al., 2017; Veres et al., 2020). This is because the prophylactic use of neonics has increased the use of pesticides (and actually drives the worrisome trend in farmland toxicity to insects, see fig. 1 in section 3.1), contradicting previous expectations of using fewer insecticides than a decade or two ago (Douglas and Tooker, 2015). The Netherlands Bijenstichting, a bee conservation NGO argues that: "The use of neonicotinoids in seed coating is a pre-emptive strike against a possible pest before there is any evidence that a pest would have emerged if the seed had not been coated. In other words, it is a pre-emptive strike with toxic chemicals instead of a last resort, the complete opposite of IPM."[24]

Ambiguity on validity and reliability of evidence

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 (Godfray et al., 2015; Löfsted and Schlang, 2017). The claims that neonics are safe often refer to specific monitoring and field studies that have found a lack of clear evidence of harm (see eg. Pilling et al., 2013; Thompson et al., 2013; Heimbach et al., 2016; Peters et al., 2016). These studies are often referred to when criticising EFSAs application of the Bee Guidance document in their risk assessment, where field studies were disqualified. Countering this, it maintained that laboratory tests should get priority over field tests in EFSAs risk assessments, because reliable, reproducible, field tests for bees are fundamentally impossible given the size of the foraging area (van der Sluijs, 2018).[25] It is also argued that the lack of clear evidence of harm in field studies should not be interpreted as evidence for that toxicological lab-studies are unrealistic (Goulson et al., 2015). Therefore, the focus on lab studies in EFSAs reviews of three neonics have been endorsed by academics and NGOs, e.g. by Greenpeace who argue that it is the most comprehensive – though by no means perfect – testing regime to assess the potential risks to bees arising from the use of pesticides (Miller et al., 2019).

Another aspect regards how to judge what constitutes high quality and trustworthy research, especially reports that are not peer-reviewed and/or are funded by the industry, or NGOs. There have been numerous allegations by various stakeholders on the lack of validity and bias in different research reports and risk assessments (see example below). It is also argued that biased, statistically underpowered and socially over-sold reports or publications is a central challenge for making policy decisions regarding neonics (Boyd, 2018).

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[22] https://www.syngenta.com/company/media/syngenta-news/year/2018/neonicotinoid-decision-takes-european-farming-wrong-direction

[23] EU (2009) Directive 2009/128/EC of the European Parliament and of the Council, establishing a framework for Community action to achieve the sustainable use of pesticides, OJ EU L309, 71–86, 24.11.2009 https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1536580974138&uri=CELEX:32009L0128.

[24] 3rd party intervention by Bijenstichting 6 March 2019: "RESPONSE pursuant to Article 132 of the Rules of Procedure of the Court of Justice on behalf of stichting, DE BIJENSTICHTING IN: CASE C-499/18 P on the appeal brought on 27 July 2018 against the judgment of the General Court of 17 May 2018 in Case T-429/13 (PB C 381 van 22.10.2018) (Contested Judgment), BAYER CROPSCIENCE AG versus EUROPEAN COMMISSION

[25] Answer 7 in: https://www.europarl.europa.eu/cmsdata/152432/Answers_Jeroen_van_der_Sluijs.pdf

This ambiguity over evidence is also evident at a more detailed level, where specific studies are interpreted differently. An illustrative example is the scientific and public reception of the publication 'Country-specific Effects of Neonicotinoid Pesticides on Honey Bees and Wild Bees' (Woodcock et al., 2017), which is the so far largest scale field-realistic experiment of neonics effects on bees. The study was initiated and sponsored by the agrochemical companies Bayer and Syngenta and carried out by the research Centre for Ecology and Hydrology (CEH). The results were published in the journal Science in 2017, and received very contradicting interpretations by both stakeholders and researchers:[26].

- **Interpretations by NGOs:** Friends of the Earth, state in their press release that 'this Landmark study confirms neonicotinoid pesticides harm bees'[27]. Similarly, Greenpeace state in their press release that the study confirms that neonics harm bees: Dr David Santillo, states that "This novel study confirms that adverse effects on individual bees and bee colonies found in high-dose laboratory studies are also observed in the fields. It shows that industry claims that neonicotinoids do not harm bees at field-relevant concentrations are baseless". [28]

- **Interpretations by industry:** Syngenta concluded that the "CEH study shows direct effects of neonicotinoids on bee health are rare"[29]**.** Bayer highlight that some positive effects were found in Germany, but also argue that the conclusions that the researchers make differs from what the data actually reveals within the report[30]. It is also argued, in a pest management journal editorial titled 'Lies, dam lies', that sensationalist interpretations of the study in media simplifies the complexity of the data (Dewar, 2017)

- **Interpretations by Expert / scientists**: An overview of comments on the study provided by Science Media Centre illustrates how also experts in the field interpret this study differently. Although most of the experts agree that the study is important, some highlight that the study shows that neonics harms bees, while other highlight the complexity of the issue.[31]

This example clearly shows how even evidence from a study published in a highly rated journal, can be interpreted in completely different manners by different stakeholders. As found by Maxim and van der Sluijs (2010), scientific uncertainty is framed and used differently by different actors.

3.2 Relevance of the PP to the case

In this case, research confirming that neonics may pose unacceptable risk to bees, has been mounting, although there still are many scientific uncertainties on the degree of the risk for different non-target species. However, the main ground for concern 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 and irreversibility of the risk for society and environment could justify precautionary action.

It is also interesting to note that the main controversy and public debates are focused on managed honeybees, with less attention to species that may also be vulnerable.

[26] See also https://www.nature.com/news/largest-ever-study-of-controversial-pesticides-finds-harm-to-bees-1.22229
https://science.sciencemag.org/content/356/6345/1321.full
[27] https://friendsoftheearth.uk/bees/landmark-study-confirms-neonicotinoid-pesticides-harm-bees
[28] https://www.greenpeace.org/eu-unit/issues/nature-food/1108/first-pan-european-field-study-confirms-neonicotinoid-pesticides-harm-bees/
[29] https://www.syngenta.com/site-services/ceh-study
[30] https://beecare.bayer.com/media-center/beenow/detail/controversy-over-a-large-scale-field-study-shows-why-good-science-not-sensational-headlines-should-drive-research-conclusions
[31] https://www.sciencemediacentre.org/expert-reaction-to-ceh-study-of-the-effects-of-neonics-on-honeybees-and-wild-bees/

4 Risk governance and the PP – Political and juridical dynamics

In this part, we outline the risk governance of process, with particular attention to political and juridical controversies over regulative processes and the role of the PP.

4.1 Early precautionary regulations of neonics in Europe

As mentioned in the timeline in section 1.2, neonics have been available on the European market since 1991. Due to beekeeper reports and subsequent scientific risk assessments finding that neonics seemed to be a central factor in causing bee-deaths, the PP was applied to regulate neonics in several countries in Europe. The first national legal restrictions were implemented in France in 1999, where a two-year ban on the use of Gaucho (containing imidacloprid) in sunflower seed dressing was implemented (Maxim and Sluijs, 2007). In 2008, reacting to incidents of bee-deaths that were linked to the sowing of seeds coated with neonics, National authorities in Germany took precautionary steps and regulate the use of seed corn which has been treated with the active ingredients clothianidin, imidacloprid and thiamethoxam (Notification 2009/50/D)[32](Maxim and Slujs, 2013). The same year, Italian national authorities applied the precautionary principle to temporarily suspend the use of maize seeds, oilseed rape and sunflower treated with clothianidin, thiamethoxam, imidacloprid (Sgolastra et al., 2017). In Slovenia, clothianidin, thiametoxam and imidacloprid in oilseed rape and corn seed treatment have been banned, reapproved and then banned again between 2008 and 2011 (Maxim and van der Sluijs, 2013).

4.2 Legislation in the EU on plant protection products

Precautionary regulations in the EU are closely linked to changes in pesticide authorization directives. Before 2011, the Council Directive 91/414/EEC provided a procedure authorisation of plant protection products in the Member States, but the directive was not very successful in establishing a coherent framework (Bozzini, 2017, p 19). In 2009, the framework for approving plant protection products changed with the implementation of **Regulation (EC) No 1107/2009** concerning the placing of plant protection products on the market.[33] This regulation entered into force on 14 June 2011. We will here outline aspects of regulation 1107/2009 that specifically impacted on the approval and regulation of neonics.

First, it should be underlined that the regulation is underpinned by the Precautionary Principle:

> "The provisions of this Regulation are underpinned by the precautionary principle in order to ensure that active substances or products placed on the market do not adversely affect human or animal health or the environment." (Regulation 1107/09 Article 1)

Further, the regulation introduced new requirements for the approval active substance. Particularly relevant for the neonic case are the requirements relating to the absence of unacceptable effects on honeybees as stated in annex II:

> "An active substance, safener or synergist shall be approved only if it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist:
> — will result in a negligible exposure of honeybees, or
> — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour."
> (Regulation 1107/09 Annex II, 3.8.3)

By requiring that active substances should not have 'unacceptable acute or chronic effects on

[32] https://ec.europa.eu/growth/tools-databases/tris/en/index.cfm/search/?trisaction=search.detail&year=2009&num=50&mLang=EN
[33] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32009R1107

colony survival and development', the protection of honeybees against pesticides was substantially strengthened compared to directive 91/414.
Articles 7 – 13 of Regulation 1107/09 specifies the risk assessment procedure for approving a pesticide. These requirements are also to be applied in reviews of already existing approvals. Recital 10 of this regulation states that, for active substances already approved prior to entry into force of the regulation, criteria harmonised by Regulation 1107/2009 are to be applied at the time of renewal or review of their approval. Further, and particularly relevant in this case, article 21 states **that an approval of active substances should be reviewed in light of new scientific knowledge:**

> "The Commission may review the approval of an active substance at any time. It shall take into account the request of a Member State to review, in the light of new scientific and technical knowledge and monitoring data, the approval of an active substance, including where, after the review of the authorisations pursuant to Article 44(1), there are indications that the achievement of the objectives established in accordance with Article 4(1)(a)(iv) and (b)(i) and Article 7(2) and (3) of [Directive 2000/60] is compromised."
> (Regulation 1107/2009, article 21).

Thereby, the regulation allows for a reassessment of approved pesticides before the approval period is ended, if new risks are found and estimated to be serious. In the following sections, we will outline how these paragraphs of regulation 1107/2009 and the precautionary principle was applied, and contested, in imposing bans on neonics in the EU in 2013 and 2018.

4.3 The EC process of reassessing neonics 2012 - 2018

In 2012, a reassessment process of neonics allowed on the market in the EU was set in motion. This was triggered by that member states raised concerns about neonics risks for bees, indicated both in the monitoring studies in France, Italy and Germany, and in the amounting number of independent studies. Particularly three studies published in peer review journals gained attention, by finding that field-realistic levels of the neonicotinoids imidacloprid (Whitehorn et al., 2012), thiamethoxam (Henry et al., 2012) and clothianidin (Schneider et al., 2012) had a significant effect on bee-colony stability and survival of honeybees and bumblebees. As these studies found 'new knowledge' indicating that the substances no longer satisfied the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009, the EC decided to follow a central aspect of precautionary action as laid down in Article 21 of this regulation, and started a re-evaluation process. EFSA was therefore requested to provide conclusions as regards the risk to bees for the uses of thiamethoxam, clothianidin, and imidacloprid, with particular attention to acute and chronic effects on colony development and the effects of sub-lethal doses on bee survival and behaviour (EFSA, 2013a).

Risk assessment process
Parallel to the requests to assess these neonics, EFSA was in an ongoing process of reviewing the 'EPPO Guidance'[34] for the assessment of risks posed by plant protection products to bees. In 2011, members of the Parliament and beekeeper associations had raised concerns on the validity and relevance of this guidance, and asked EFSA to review this with particular attention to the assessment of chronic risks to bees, exposure to low doses, exposure through guttation and the cumulative risk assessment (EFSA, 2012a). The problem with the EPPO guidance was that it ignored relevant risks assessments of neonics in the first place, as it was designed only for spray applications and not seed treated and soil-drenching chemicals, and as it assumed exposure to be restricted to the pesticide application period and to the treated crop (Sgolastra et al., 2020). In addition, the scheme was criticised for not including the views of bee experts (and instead including many representatives from agrochemical companies into the working (ICPBR) group that assessed the impact of pesticides on bees)[35]. When EFSA provided a Scientific Opinion on the science behind the development of a risk assessment of Plant

[34] The EPPO Guidance was drawn up by the European and Mediterranean Plant Protection Organisation (EPPO), and was first issued in 1992 and updated in 2002 and 2010.
[35] COE and BeeLife (2010) *Is the Future of Bees in the Hands of the Pesticides Lobby*?, 2010: https://docs.wixstatic.com/ugd/8e8ea4_40071cca1f974a988a6e484c5590ac07.pdf

Protection Products on bees (EFSA, 2012a), it was confirmed that the EPPO risk assessment guidelines had several weaknesses when applied both in field tests and lab tests. For field test, problems included "*the small size of the colonies, the very small distance between the hives and the treated field, the very low surface of the test field, leading to uncertainties concerning the real exposures of the honey bees".* (EFSA, 2012a:133). It was found that the EPPO guideline *were better suited to the assessment of spray products than of seed- and soil-treatments.* For lab-tests, problems included that several exposure routes of pesticides are not evaluated in laboratory conditions: the intermittent and prolonged continuous exposures of adult bees, exposure through inhalation and the exposure of larvae. Likewise, the effects of sub-lethal doses of pesticides were not evaluated in the conventional testing (EFSA, 2012a:132). In short, it became evident that the EPPO scheme for risk assessments did not account for the complexity and uncertainty of exposure and effects. Due to these limitations, the EFSA drafted a new guidance document (the so-called 'Bee Guidance document') for assessing the risks of neonics for bees (EFSA, 2013e). A preliminary version of this guidance was published for public consultation on 20 September 2012, and the amended document was published on 4 July 2013. As mentioned in section 3.3.3. on ambiguity, and as also will be discussed in the court case section, this (Bee Guidance) risk assessment scheme is one of the major grounds for controversy between stakeholders.

On the 16th of January 2013, EFSAs Panel on Plant Protection Products and their Residues (PPR Panel) presented their conclusive risk assessment reports examining the risks for bees of clothianidin (EFSA 2013b), thiamethoxam (EFSA 2013c) imidacloprid (EFSA 2013d) to the EC. In general, the conclusions estimate a high risk for some uses of neonics on cereals, maize and oilseed rape for honey bees (see detained table on eg. clothaniadin in EFSA 2013b:38-44). A high acute risk for honeybees from exposure via dust drift as a result of the sowing was estimated (e.g. for sowing of maize and cereal seeds coated with clothianidin, imidacloprid, thiamethoxam). Additionally, a high acute risk for bees from exposure to residues in nectar and pollen for the uses in oilseed rape (clothianidin, imidacloprid) as well as cotton and sunflowers (imidacloprid), and a high acute risk from exposure to guttation for uses in maize (thiamethoxam) was estimated. However, EFSAs conclusions also underlined that uncertainty remains on many risk aspects due to shortcomings of data to a lack of a finalised risk assessment guidance document[36]. It is also highlighted that there is a knowledge gap on the risks for pollinators apart from bees. EFSAs conclusions gained some debate, and agrochemical companies disputed the conclusions and referred to studies they had funded. EC requested EFSA to review one of these field studies - Thompson et al. (2013) - that found few effects of neonics on bumblebees in a UK field study. However, EFSA evaluation of the filed study concluded that it contained weaknesses in design and methodology, and thus would not change any of the conclusions made in the EFSAs risk assessment (EFSA 2013d).

Risk management 2013 – EC implements restrictions

As the risk assessment were provided, the risk management process was initiated. After reviewing EFSAs risk assessments reports, the EC proposed to adopt a ban on these three substances (regulation 485/2013) and asked the Member States to vote over the regulation. The main reasons for proposing to apply the PP seemed to be the seriousness of the risk. In a speech by the Commissioner responsible at the Council's 'Agriculture and Fisheries' meeting on 28 January 2013, the urgency of the matter is highlighted after reviewing EFSAs conclusions:

> "In its conclusions, EFSA has identified a number of concerns and [has] Confirmed serious risks linked with the use of the three neonicotinoids used on several important crops grown across the [European Union]. These concerns call for swift and decisive action! The time is now ripe to act to ensure an equally high level of protection of bees across the [European Union]. The Commission will propose a set of ambitious but proportionate legislative measures to be presented for first discussion at the meeting of the [Standing Committee] that will take place on Thursday of this week. There is one particular point I want to be clear: Our proposal will call for EU harmonised and legally binding measures, inspired by the precautionary principle, but also by the principle of proportionality! In fact, a number of safe uses of these substances as regards bees have been identified by

[36] https://www.efsa.europa.eu/en/press/news/130116

EFSA. A total ban would not therefore be justified.'"
(Cited in Judgment in cases T-429/13 and T-451/13, para 427)[37]

It should be noted that this quote not only suggests applying the PP in relation to the seriousness of the risk, but also in reference to proportionality. In line with this, the proposed regulation suggested to ban most uses of imidacloprid, clothianidin and thiamethoxam, but to still allow some as the probability of effects on bees seemed lower. This was the case for indoor use (in greenhouses) and for winter crops. Consequently, it could be argued that some measure of proportionality, in terms of 'tailoring measures to the chosen level of protection', was taken.

On the 15 March 2013, the Member States voted over proposed regulation 485/2013, but the voting resulted in a stalemate (13 voted in favor of ban while 9 opposed the ban (McGrath, 2014:3)). Hence, another round of voting was requested. The interim period between the first and second voting was marked by an intense period of political lobbying in different member states, where it seems that industry stakeholders and/or NGOs/associations (lobbyism) may have affected outcomes in the risk management phase (McGrath 2014, Patterson and McLean, 2019, Boyd, 2018). In the UK, it seemed the industry lobby influenced government opinion in the first phase (Boyd 2018), although government's approach changed towards a more precautionary stance (Patterson and McLean, 2019).

On 29th of April 2013, the second round of voting was held, and 15 countries voted for the ban, eight against, and four countries abstained (EC press release 2013A). Following the absence of an agreement (qualified majority) between Member States, the Commission announced that it would proceed with the process, basing its decision on the evidence presented in the EFSA reviews (ibid). On the 24th of May, the Commission implemented **Regulation (EU) No 485/2013[38], banning all outdoor use of 3 of the 6 neonicotinoids** that are marketed in Europe in crops attractive to bees (EC press release 2013B). For acetamiprid, EFSA established a low risk to bees, and restrictions of this substance were therefore considered inappropriate[39]. Also, Member States were allowed to apply for exceptions, and several Member States have repeatedly granted emergency authorisations for some of the restricted uses (including Romania, Bulgaria, Lithuania, Hungary, Finland, Latvia and Estonia)[40].

After imposing restrictions, EC also commissioned EFSA to assess foliar spray and all uses other than seed treatments of the 3 neonicotinoids Conclusions were submitted in 2015 (EFSA 2015a; 2015b; 2015c).

The implementation of regulation 485/2013 was followed by highly polarized debates. The restrictions were endorsed by many NGOs and institutions, including the European Environmental Agency[41], and contested by the agrochemical industry, who following a series of field studies argued that these products were safe under field conditions (Campbell, 2013). Some of these controversies will be further elaborated in the section on the court cases below.

2018 Reassessments

For the reassessment, the EC requested EFSA to apply the bee guidance risk assessment scheme (EFSA 2013e). Further, as foreseen in recital 16 of Implementing Regulation (EU) No 485/2013, the Commission initiated a review of new scientific information in 2015 by mandating EFSA to organise an open call for data (EFSA 2015d). This open call represented a significant procedural change in the evaluations, as it provided all interested parties, like

[37]For full reference and link to the judgement, see the reference section.
[38]Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances https://eur-lex.europa.eu/eli/reg_impl/2013/485/oj
[39]https://ec.europa.eu/food/plant/pesticides/approval_active_substances/approval_renewal/neonicotinoids_en
[40] https://ec.europa.eu/food/plant/pesticides/approval_active_substances/approval_renewal/neonicotinoids_en
[41] https://www.eea.europa.eu/highlights/neonicotinoid-pesticides-are-a-huge

NGOs, beekeeper organizations and agrochemical companies, with an opportunity to contribute. In earlier evaluations, this process was entirely based on data provided by agrochemical companies (Auteri et al., 2017: 970). As result, 376 contribution from 48 different sources were submitted and reviewed. Thereby, stakeholders had several possibilities to influence the decision-making process especially in the risk assessment stage, due to the arrangements of open calls. Stakeholders were also involved in funding, encouraging or producing risk assessments that had to be considered, such as e.g. Thompson's (2013) field study. The degree of influence the involved parties had in the final decision-making process is hard to estimate, but other studies have indicated that stakeholder interactions / lobbyism did play a role in national policy formulations on neonics the UK (Boyd, 2018; McGrath, 2014) and in France (Maxim and Sluijs, 2013).

In February 2018, EFSAs updated risk assessments of clothianidin, imidacloprid and thiamethoxam (EFSA, 2018a, 2018b and 2018c) were presented to the EC and the Member States, who were to consider potential amendments to the 2013 restrictions[42]. These assessments found that "for all the outdoor uses of these substances, there was at least one aspect of the assessment indicating a high risk, leading to the conclusion that overall, these neonicotinoids represent a risk to bees" (EFSA, 2018e). It is highlighted that the risks vary due to factors such as bee species, the intended use of the pesticide and the route of exposure, but that taken as a whole, the conclusions confirm that neonicotinoids pose a risk to bees.

After examining EFSAs conclusions, the Commission maintained the proposals to completely ban the outdoor uses of the three active substances. This was supported by a qualified majority of Member States[43] in the Regulatory Committee on 27 April 2018[44]. On the 29th of May 2018, the Commission implemented **Regulations (EU) 2018/783, 2018/784 and 2018/785)**[45] limiting the marketing authorizations for PPP containing imidacloprid, clothianidin and thiamethoxam[46] with exception for the following uses: insecticide on crop staying within a permanent greenhouse during its entire life cycle or seed treatment to be used only in permanent greenhouses. Several EU member states notified emergency exemptions, as farmers complained that the ban would lead to a severe loss of production of e.g. sugar beet.[47]

4.4 Court cases – Agrochemical companies against the EC

Following the implementation of the restrictions in 2013, three of the major Agrochemical companies filed court cases against the European Commission seeking to annul Regulation 485/2013 (Case T-429/13 by Bayer Crop Science, Case T-451/13 by Syngenta Crop Protection AG, and Case T-584/13 by BASF Agro BV[48]). On May 27, 2018, the court dismissed the actions brought by Bayer and Syngenta in relation to the neonicotinoids clothianidin, thiamethoxam and imidacloprid. Two months later, Bayer CropScience made an appeal (Case C-499/18)

[42] http://www.efsa.europa.eu/en/press/news/180228
[43] In the voting 16 countries (Germany, France, UK, Spain, Italy, The Netherlands, Sweden, Greece, Cyprus, Austria, Portugal, Ireland, etc), voted in favour, while Romania, Denmark, Czech Republic, Hungary) opposed the ban, and 13 countries abstained (including Poland, Belgium, Finland)
[44] https://ec.europa.eu/food/plant/pesticides/approval_active_substances/approval_renewal/neonicotinoids_en
[45] Official Journal of the European Union L132, (30 May 2018) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2018:132:FULL&from=DA
[46] As specified in Article 1, the following restrictions were implemented for the three neonics:
- prohibition of any non-professional use, indoors or outdoors;
– prohibition of uses for seed treatment or soil treatment on the following cereals when these are to be sown from January to June: barley, millet, oats, rice, rye, sorghum, triticale, wheat;
– prohibition of foliar treatments for the following cereals: barley, millet, oats, rice, rye, sorghum, triticale, wheat;
– prohibition of uses as seed treatment, soil treatment or foliar application for around 100 crops, including rapeseed, soya, sunflowers and maize, with the exception of uses in greenhouses and of foliar treatment after flowering.
[47] https://www.reuters.com/article/us-eu-sugar-neonics/insecticide-ban-to-hit-eu-sugar-beet-crops-farmers-say-idUSKBN1I41FI
[48] For links to the court documents, see 'court case documents' under references in chapter 8, p 48.

against the judgment of the General Court in Case T-429/13.

The main complaints of Bayer CropScience and Syngenta are grounded in their understanding that neonics, when used properly, does not affect bees. However, many of the complains also argue that the Precautionary Principle had been misused and misinterpreted. As summarised by the judgment of the court cases, the companies complained that the criteria for the PP was not met because "purely hypothetical risks were taken into account, that there was no adequate scientific assessment or cost/benefit analysis, and that the measures taken were disproportionate" (Judgment in cases T-429/13 and T-451/13, para 335). John Atkin, Syngenta's chief operating officer, stated in a press release, that "In suspending the product, [the European Commission] breached EU pesticide legislation and incorrectly applied the precautionary principle,".[49] In the following sections, the complaints and the courts responses on the arguments relating to the PP will be examined.

First, many of the complaints relate to EFSAs **risk assessment** process and alleged that "EFSA's Conclusions are not based on as thorough a scientific assessment as possible or on the best available data, and that EFSA took **a purely hypothetical approach** to the risk" (Judgment in cases T-429/13 and T-451/13, para 342). According to the complaints, the risk assessments that inspired the ban were invalid and not sufficiently scientifically verified. Bayer CropScience states, in the last of their six pleas:

> "Sixth plea in law, alleging that that the adoption of the Contested Measure breaches the precautionary principle, because:
> — inter alia, it involved the Commission, as risk manager, taking a purely hypothetical approach to risk, which was founded on mere conjecture and which was not scientifically verified (a result, in large part of the risk assessments not constituting a thorough scientific assessment), and it involved the Commission refusing to conduct any analysis of the potential benefits and costs of its actions."
> (Case T-429/13, plea 6)

The complains about the EFSAs risk assessments are detailed and relate to the uncertainties as outlined in section 2. Some concerns are raised about estimated rates of exposure in experiments, and about how the effects of different exposure rates are measured. As example, one complaint is that the high risk on exposure via guttation for maize was based on unrealistic assumptions (Judgment in cases T-429/13 and T-451/13, para 408). In the judgment of the case, the complaint about different details on risk assessment process were considered. In conclusion, the complaint alleging a purely hypothetical approach to risk was entirety rejected and EFSAs risk assessments were considered comprehensive and realistic (ibid, para 415).

In relation to this, it is interesting to note that in some of the complaints on the risk assessment procedures, it seems to be indicated that the risk assessment was too comprehensive. Particularly, the use of the Bee-Guidance document instead of the EPPO Guidance is criticised. As stated by Bayer complaint in 2018, if the EPPO Guidance had been applied:

> "(i) monitoring studies would have been considered "decisive", rather than "of limited use"; (ii) "data gaps" would only have been concluded where there were previous data requirements; (iii) only risks in relation to honeybees would have been considered; (iv) only risks of relevance at the colony level would have been considered; and (v) risk mitigation measures would have been taken into account where they gave rise to differences in the normal use of a product"
> (Case C-499/18, para 126).

Point (i) and (v) suggest that the assessment should have been added on different kinds of research, specifically monitoring studies and risk mitigation. Regarding the monitoring studies, the Court finds that EFSA did consult them but did not included in the assessment because they could not provide valid conclusions on correlations between cause and effects (Judgment in cases T-429/13 and T-451/13, para 208, 209 and 380). The point on including risk mitigation studies overlaps with the point on the proportionality argument (see section below). Point number (ii), (iii) and (iv) indicates that the if EPPO guidance had been used, there would have been less consideration of the complexities of bee behaviour and of other species than honeybees. In other words, the risk assessment had been much more limited if the EPPO

[49] https://www.sciencemag.org/news/2013/08/pesticidemakers-challenge-eu-neonicotinoid-ban-court

guidelines would have been applied.

A second set of arguments relate more to the **risk management** process and the relation between the Precautionary Principle and the **principle of proportionality.** The principle of Proportionality implies that measures adopted should not exceed the limits of what is appropriate and necessary. The agrochemical companies alleged that the PP had been misused or misinterpreted by not taking proportionality into account. As example, Syngenta states, in the second of their three pleas:

> Second plea in law, alleging that the Contested Regulation imposed disproportionate and discriminatory restrictions on TMX, based on purely hypothetical risk, without conducting a thorough scientific assessment or any impact assessment at all, in violation of the precautionary principle and the principle of proportionality.
> (Case T-451/13, plea 2)

Here, it is indicated that proportionality was neglected because a formal impact assessment (in the form of a cost-benefit analysis) was lacking. It is referred to that carrying out an impact assessment is mentioned in the 'Communication on the Precautionary Principle' (EC 2000). Indeed, the Commission did not mandate a formal impact assessment or cost-benefit analysis to evaluate the economic consequences of Regulation No 485/2013 before its adoption (Bozzini and Stokes, 2018). However, in the judgment, the Court underlines that Communication on the PP (EC 2000) point 6.3.4 states that cost-benefit analysis can be included where appropriate and feasible, and that the scope and format of such an analysis is not defined (Judgment in cases T-429/13 and T-451/13, para 458). Further, while the Communication specifies that an economic cost-benefit analysis could be carried out where appropriate and feasible, it also underlines that an assessment "cannot be reduced to an economic cost-benefit analysis. It is wider in scope and includes non-economic considerations" (ibid, para 458). In the case of neonics, it was found that a cost-benefit analysis was not appropriate, nor feasible, because long term economic and ecological effect are very difficult to measure. Therefore, it was concluded that it was sufficient that the Commission was informed about different impacts of a restriction, and that the requirements of the Communication on the PP thereby were satisfied. Specifically, it is stated that it was sufficient that the commission had "acquainted itself with the effects, positive and negative, economic and otherwise, to which the proposed action, as well as the failure to act, may lead, and has taken that into account in its decision." (Judgement in cases T-429/13 and T-451/13, para 406). It is further underlined that it was not necessary to estimate these effects precisely, because "such precise calculations will in most cases be impossible to make, given that, in the context of the application of the precautionary principle, their results depend on different variables which are, by definition unknown" (ibid, para 460). Interestingly, a paper evaluating this process highlights that the process may have been different if the updated 'Better Regulation package' had been applied, as it interprets the PP different from the earlier Communication (Bozzini and Stokes, 2018). The Better Regulation package mentions that all acts based on the precautionary principle should be based on a formal impact assessment, instead of a general balancing of issues. What such a formal impact assessment of neonics should look like is however not specified, and it would probably contain many uncertainties connected to the measurement and prediction of different developments. Further, as outlined in section 2 and 5.1 in this paper, there is already much uncertainty and ambiguity around the research on economic aspects of neonics (and their restrictions).

Another aspect of proportionality is related to the complexity of neonics and their use, as some applications contain lower risk than others. Bayer Crop Sciences claimed in their fifth plea, that the regulation breaches the principle of proportionality as the "contested Measure goes beyond what is appropriate to the achievement of its legitimate objectives and may even undermine them, and the Commission failed to consider less restrictive options for regulation that were available to it" (Case 429/13, plea 5). The objections concern e.g. the use of foliar sprays and the prohibition of non-professional uses outdoors and indoors, uses that were considered to give less exposure to bees.

In replying to this, the Commission denies that the contested measure was adopted in a rushed manner and that risk mitigation measures were not considered (Judgment in cases T-429/13 and T-451/13, para 418). Further, it is pointed out that the uses of neonics that the Commission restricted, correspond largely with those that EFSA had either identified an acute

risk, or had been unable to rule out a risk because the necessary data were unavailable (ibid, para 422). As stated in the last part of that paragraph, the uses of neonics that were deemed inconclusive because there was a lack of data, were also restricted. In the judgment, EC's Communication on the PP (EC 2000) is referred to, where it is mentioned that

> "when the available data are inadequate or non-conclusive, a prudent and cautious approach to environmental protection, health or safety could be to opt for the worst-case hypothesis. When such hypotheses are accumulated, this will lead to an exaggeration of the real risk but gives a certain assurance that it will not be underestimated."
> (Judgment in cases T-429/13 and T-451/13, para 114).

Thereby, it is underlined that the PP allows for a cautious approach when knowledge is uncertain. This points to that there are different understandings of the role of **scientific uncertainty** in the application of the precautionary principle. The applicants (Bayer and Syngenta) often refer to the fact that EFSA's 2013 conclusions identified several uncertainties where further research was needed, and problematised that the risks were 'inconclusive'. Thereby, they insinuate that there should have been a higher degree of scientific certainty on the actual risks before the PP could be applied. This focus on scientific uncertainty reappear in Bayer's appeal in 2018, where it eg. is argued that an "appropriate level of scientific certainty" was not set (Case 499/18). Again, it was argued that EFSAs assessments were rushed and insufficient, that the standards of proof to adopt precautionary measures were misinterpreted, and that the PP therefore was wrongly applied.

In the judgment of the case in 2018, a different interpretation of the role of scientific uncertainty is found. As example, it is stated that the PP specifically implies that scientific uncertainty allows for protective measures to be taken:

> "Where there is scientific uncertainty as to the existence or extent of risks to human health or to the environment, the precautionary principle allows the institutions to take protective measures without having to wait until the reality and seriousness of those risks become fully apparent or until the adverse health effects materialise"
> (Judgment in cases T-429/13 and T-451/13, para 110)

This underscores that the PP should be applied when there is scientific uncertainty if the risks towards humans or nature are estimated to be highly serious. Further, it is emphasised that a fully complete and conclusive scientific risk assessment may be impossible due a lack of scientific data, but that preventive measures may be taken if the risk assessment is adequately backed up by the scientific data available at the time when the measure was taken (ibid, para 117-120). The context of application of the PP is one of uncertainty, and the Court notes that "if all the consequences of inaction and of action were known, it would not be necessary to resort to the precautionary principle; it would be possible to decide on the basis of certainties" (ibid, para 460). In such cases of certainties, the **prevention principle** applies rather than the precautionary principle[50]. A good illustration can be found in Patterson and McLean's (2019) analysis of the UK government's decision on neonics, where the approach changed from a 'sound science approach', to a 'precautionary approach' allowing regulations when scientific uncertainty prevails. Again, this underlines that scientific uncertainty is at the core of the PP.

In sum, the court case documents highlight the different understandings of the role of scientific uncertainty and different kinds of assessments when considering the PP. Besides this, it seems that Bayer puts more emphasis on the innovation argument in the appeal in 2018. In the introduction of the appeal, it is argued that "the Court of Justice's task is to guard against the precautionary principle becoming a universal incantation to block innovation" (Case C-499/18). It is further pointed out that since the ban created uncertainty in the legal framework regarding the possibilities for maintaining approvals for the period of validity, the industry is reluctant to introduce new active substances, and this contradicts the Commission emphasis

[50] In risk management based on the Prevention Principle, risks are managed by agreeing on an acceptable risk level for the activity and putting enough measures in place to keep the risk below that level. This approach is meant for risks that are well known and quantifiable in a credible way. The Precautionary Principle however has been introduced to cope with risks with poorly known outcomes and poorly known probabilities, making the prevention principle approach problematic (Van der Sluijs and Turkenburg, 2006)

on the importance of innovation in this sector. In the following sections we will discuss some takes on the balancing of the PP and innovation based on a broad review of relevant literature in addition to stakeholders' public announcements.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

In the case of restricting neonics, we have identified two major reflections/discussions regarding the application of the PP.

The first theme is related to different aspects of proportionality; adapting different restrictions more proportionate to the different uses of neonics, and that the process of applying the PP should include an impact analysis. Here, it should be noted that most of the articles that criticise the restrictions on neonics implemented in the EU are not directly discussing the PP. Rather, they are more directly criticising aspect of EFSAs risk assessment process, and/or highlighting production or economic consequences of the restrictions of neonics. Many of these articles, that often refer to each other, can be found in the journal 'Pest Science Management[51]' and the news journal 'Outlook on Pest Management', (including Walters, 2013; Kathage et al., 2018; Campbell, 2013; Dewar, 2017; Dewar, 2019; Hurley and Mitchell, 2017; Blake, 2018) while others come in the form of reports by institutes (including e.g. Nicholls, 2013, Noleppa & Hahn, 2013; Noleppa, 2017). It is argued that unforeseen consequences of the ban were that other pesticides were applied with possibly other unintended side effects, that some pests were returning and that some crops were damaged causing economic losses. Some similar critiques are also found in the field of risk research, a proportionality-related critique can be found in problematising the issue of "risk-risk trade-off": that decreasing one particular risk in one area leads to another risk appearing elsewhere which was not originally considered (Löfstedt and Schlang, 2017). Alemanno (2013) argues that the application of the PP for regulating neonics can lead to a tunnel vision, ignoring possible trade-offs between risks, and that a detailed risk-risk analysis should have been conducted before the decision on the restrictions were made. Dewar (2019) argues that for many uses (e.g. for the protection of oilseed rape against flea beetles), there are no good alternatives to the use of neonics, and that the restrictions of neonics, a large proportion of farmers started using other pesticides like pyrethroids. This argument, that the ban of neonics would have damaging effects on the environment as older and less targeted pesticides would be used instead, was also noted in the judgment of the court case of Bayer and Syngeta (Judgment in cases T-429/13 and T-451/13, para 509). Replying to this, the Commission referred to that that the Member States that suspended certain uses of neonics for several years (Germany, France, Italy and Slovenia) never reported any such adverse effects on the environment (ibid, para 514).

A different set of arguments related to the PP in this case, is that the PP measures came too late and have been too weak. This critique is not only posed by e.g. NGOs, but also by the European Parliament. In a report on the Union's authorisation procedure for pesticides, the EP strongly criticises the current practice of pesticide authorisation for failing to sufficiently apply the precautionary principle (European Parliament 2018). Different researchers also argue that the PP should have been applied earlier and that risks connected to neonics should have been detected earlier, before they entered the market in the 1990s (Boivin and Poulsen, 2017, Sgolastra et al., 2020, Shafer et al., 2019). Related to this, it is suggested that the regulation of pesticides should be modelled on the regulation of pharmaceuticals, implying that instead of letting pesticides pass a once-off test, they should undergo a long-term monitoring of adverse effects throughout the lifetime of a product (Milner and Boyd (2017).

[51] This journal is peer-reviewed, and it is part of the SCI (Society of Chemical Industry), which is 'international forum where science meets business on independent, impartial ground'

5.2 Effect of the PP on innovation pathways

In the context of food security, where industrial agriculture to a high degree depend on pesticides while pests increasingly become pesticide resistant, there is a constant need for innovative solutions. Main innovations in this context would be new and more effective products, and with this perspective, regulations are hindering innovations. Specifically, the pesticide regulation regime in the EU has been criticised for being too strict and cumbersome, especially with the change from a risk to a hazard-based approach when implementing Regulation 1107/2009 (Chapman, 2014; Bozzini, 2017). It is argued, that with the escalating costs of putting new products on the market due to increasing data requirements and test guidelines, innovation of PPPs has moved from Europe to other markets. The restrictions on neonics implemented by the EC regulations in 2013 and 2018 were met similar kinds of arguments by agrochemical companies. As highlighted by a spokesperson for Bayer, it is important for the firm's investment decisions to have guidance and clarity regarding the European Union's regulatory framework.[52] Bayer also noted in the court case appeal that the ban on neonics would have "severe consequences for innovation in the crop protection sector in Europe." (Bayer appeal C-499/18, para 2)[53]. It is argued that because neonics were banned before their approval application was up for review (enabled by article 21 of regulation 1107/2009 allowed the commission to revaluate the approval of neonics approval before the approval period had ended), producers of plant protection products became reluctant to invest in applying for approval for new products. It seems plausible that regulatory stability is valuable for innovation processes in large agrochemical companies. However, in the following sections, we will take a broader view on innovation and illustrate some different innovation pathways for pest management that have appeared/are foreseen under the condition of the restrictions of neonics in the EU.

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. The most evident case is how the banning of DDT (partly banned in Europe in 1978 and totally banned for agricultural use in Europe in 1983[54]) resulted in innovations of other pesticides (Bouwman et al., 2013). In this case, as DDT was not patented, banning this toxic substance was actually good news for companies who could introduce new patented pesticides[55](Davis, 2019).

Secondly, Milner and Boyd (2017) mention that, if not done too abruptly, the withdrawal of pesticides can incentivise innovations, not only of new types of pesticides but also of cultivation methods. This opens up for a broader perspective on innovation, not only seeing innovation as developing new types of plant protection products. Different innovations may take place within strategies for 'Integrated Pest Management' (IPM) which is promoted in the EU through the 2009 sustainable use directive[56], aiming to reduce the use of pesticides through several innovative multi-faceted methods.

Regarding the application of 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 (Foster, 2011; Bonmantin et al., 2015). Spraying technology has also innovated such that spray-drift to outside the fields is reduced and more of the spray lands on the targeted crop and less on the soil (see e.g. Liu et al., 2005). There are also innovative ways of applying neonics to seeds by pelleted seeds (the common way of applying imidacloprid to sugar beets, where the poison not on the outside of a pellet around the seed. In pelleted beet seed, the insecticide is not on the surface but underneath the outermost layer of the beet seed pellet, with a high resistance to abrasion and thus a lower

[52] https://www.sciencemag.org/news/2013/08/pesticidemakers-challenge-eu-neonicotinoid-ban-court
[53] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62018CN0499
[54] https://ec.europa.eu/commission/presscorner/detail/en/MEMO_03_219
[55] E.g parathion, malathion andnchlorprifos
[56] EU (2009) Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides, OJ EU L309, 71–86, 24.11.2009

risk for dust emission[57]. However, the dust emissions are not the only concern: only a small fraction (between 1.6 and 20%) of the neonics in the seed coating is absorbed by the plant, meaning that 80 to 98.4% of the pesticide ends up as pollution in soil and water (Van der Sluijs et al., 2013). Therefore, and also due to the complexity of the usage of neonics (on different crops, using different methods), and the uncertainty around levels of residues (especially in soil and water), it is difficult to estimate how effective these mitigation efforts are. Furthermore, seed coating implies a prophylactic use, which does not fit well with the IPM approach of reducing the need of pesticides to a minimum and using them only as a last resort, as implemented in directive 2009/128/EC on the sustainable use of pesticides[58](see explanation of IPM in section 3.3.3). Thereby, it could be argued that the use of seed coated systemic insecticides closes possibilities for other kinds of innovations.

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 nano-pesticides (Kah et al., 2018) and RNA interference (RNAi) (Rodrigues and Figueira, 2016; Price and Gatehouse, 2008; Yu et al., 2013). The aims of nano-pesticide formulations are generally (a) to increase the apparent solubility of poorly soluble active ingredients or (b) to release the active ingredient in a slow/targeted manner and/or protect the active ingredient against premature degradation, which all could contribute to reduction of the amount of active ingredient needed to effectively protect plants. RNA interference is a gene silencing mechanism triggered by providing double-stranded RNA (dsRNA), that when ingested into insects can lead to death or affect the viability of the target pest. The advantage is that is highly specific to the target pest and has in theory almost no impact on non-target organisms. It can target insect specific genes. When target sequences are chosen that are unique to the pest insect, it can only kill the target pest insect, so in theory high selectivity is possible. It can also be used in transgenic plants, or it can be applied to non-GMO crops (Price and Gatehouse, 2008; Rodrigues and Figueira, 2015).

However, there are also **innovations of non-chemical alternatives to neonics** for pest management. The argument that there are no alternatives to neonics has been contested, and several non-chemical methods are found in different studies (Jactel et al., 2019; Furlan and Kreutzweiser, 2015; Lundin et al., 2020; Veres et al., 2020). Furlan and Kreutzweiser (2015) outline examples from management of three insect pests in maize crops and an invasive insect pest in forests, including diversifying crop rotations, altering the timing of planting, tillage and irrigation, using less sensitive crops in infested areas, applying biological control agents, and turning to alternative reduced risk insecticides. Jactel et al's (2019) review found eight categories of potential alternative methods to neonics (including synthetic or natural chemical insecticides, biological control with microorganisms or macroorgamisms, biological control through farming practices (e.g. intercropping) etc.), and that in 78% of cases, at least one non-chemical alternative method could replace neonicotinoids. When acknowledging such alternatives, it can be argued that the prophylactic use of neonics may hinder innovation and experimentation with alternative pest management and non-chemical alternatives (Furlan et al., 2017; Veres el al., 2020). The complexity of crops that need protection and the complexity of pests indicates that much more research is needed, and innovations of e.g. prognosis tools for pests may also be relevant in this regard (Lundin et al., 2020).

Lastly, the IPM framework also includes the possibility of '**social innovations'**. Furlan et al. (2017) describes a large-scale example of this, where mutual funds and IPM increased profits for maize crop farmers in Italy, reducing the use of pesticides without negative impact on average yields and at the same time avoiding environmental impacts. Importantly, the farmers started an economic insurance initiative that insured them from large economic losses in bad

[57] See document by CIBE on The case for neonicotinoids in pelleted sugar beet seeds: https://www.cibe-europe.eu/img/user/058-18%20CIBE%20The%20case%20for%20neonicotinoids%20in%20pelleted%20sugar%20beet%20seeds%20April%202018.pdf

[58]EU (2009) Directive 2009/128/EC of the European Parliament and of the Council, establishing a framework for Community action to achieve the sustainable use of pesticides, OJ EU L309, 71–86, 24.11.2009 https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1536580974138&uri=CELEX:32009L0128.

years, without having to use insecticides.

5.3 Innovation Principle

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), argues 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 growth should be assessed and addressed. 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 (Van der Sluijs and Turkenburg, 2006).

Nonetheless, it is likely that the IP could be brought into the controversy on neonics, as many of the agrochemical companies producing insecticides containing neonics, including Bayer, BASF and Dow AgroSciences, were engaged in the European Risk Forum and signed the letter to the Presidents of the three EU institutions proposing adoption of the Innovation Principle in 2013[59]

6 Synthesis

In synthesising this case, we will focus on the role of complexity, ambiguity and uncertainty in the risk governance that led to the bans implemented in the EU, and discuss how this case illustrates the tension between innovation and precaution.

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. As outlined in section 3, there is a complexity of types of products containing neonics, applied to different kinds of crops with different methods, and there is much uncertainty and a lack of knowledge on residue levels. Thereby, it is also difficult to estimate a realistic level of exposure for different types of insects. The main uncertainty thereby stems from multi-causality - the complexity of interacting causes that together produce the ongoing global trend of pollinator decline. Thereare uncertainties regarding the sub-lethal effects on different kinds of species, and a complexity of factors (including a cocktail of pesticides) that impact different species. The scientific assessment of the relative importance of neonics in pollinator decline is highly contested. A main debate has been how to estimate and measure causes and effects, and what kinds of studies (field vs lab studies) that are valid and/or reliable. This has led to controversies around how to interpret different studies, and around different details of EFSAs risk assessments.

In 2013 and in 2018, precautionary measures were taken and the uses of three neonics (imidacloprid, clothianidin and thiamethoxam) were restricted. A main background for these

[59] http://www.riskforum.eu/uploads/2/5/7/1/25710097/innovation_principle_one_pager_5_march_2015.pdf

restrictions, was the implementation of EC Regulation 1107/2009 concerning the placing of plant protection products on the market. The regulation is underpinned by the PP, and as this regulation went into force in 2011, it enabled a reassessment of the approval of an active substance if new knowledge indicated severe risks to health or the environment. Notably, the protection of bees is particularly mentioned in this regulation. Thereby, as risk assessments increasingly found that neonics could contribute to large scale bee-deaths and colony collapses, the EC requested the European Food Safety Authority (EFSA) to conduct a formal risk assessment. In 2013, after receiving EFSAs conclusions, the Commission implemented Regulation (EU) No 485/2013 - banning outdoor use of 3 of the 6 neonics that were allowed on the market (imidacloprid, clothianidin and thiamethoxam). These restrictions were reinforced in 2018 when the Commission implemented Regulations 2018/783, 2018/784 and 2018/785)[60].

The restrictions on neonics were contested by the agrochemical companies Bayer, Syngenta and BASF, who filed a court case against the regulation in 2013. A main critique of the application of the PP was that the risk assessments contained scientific uncertainty. At the same time, it was also argued that an economic impact assessment was neglected. However, as argued in the court's decision, an economic impact assessment would also entail many scientific uncertainties, as many factors could impact on economic developments. Thereby, adding an economic impact assessment to the process could increase complexity and uncertainty. Also, the economic impact of a significant decline of pollinators would be very challenging to assess.

Further, when considering the PP in the risk management process, scientific assessments of risks only play one part. In addition to estimations of risk, risk managers have to consider possible wider consequences for both economy and society, and consider the societal acceptability of the risks and possible consequences. In this case, the irreversibility of a possible pollinator decline and its potentially wide-ranging consequences for food production was a major ground for taking precautionary measures.

Regarding the second main theme, the balancing of the PP and the IP, it should first be underlined that IP is rarely referred to in this case, except for the reference to IP made by a researcher related to the industry (Blake, 2018). There is however a tension between precaution and innovation more generally. In our industrialised food production system, there is a constant need for innovative plant protection products, as pests continue develop resistance to established pesticides. If precautionary measures can be applied at any times, the concern is that the companies will be reluctant to invest in new innovations.

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 impact and for whom'?. One could argue that a proper impact assessment should be broader than only economic impacts for the industry, to include impact on society more widely. That would also imply including many complexities, uncertainties, and the acknowledgement that there are fundamental limitations in assessing future impacts and that economic and statistical models contain many potential flaws and biases (Saltelli et al., 2020). A further problem is that if one aims too much towards a 'sound

[60] Official Journal of the European Union L132, (30 May 2018) https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2018:132:FULL&from=DA

science approach' that suppresses uncertainty, the PP is compromised to such a large degree that one risk losing the PP and being left with the Prevention Principle. One should not forget that the Precautionary Principle was introduced for the very reason that the Prevention Principle failed repeatedly in cases characterized by high uncertainty, ambiguity and complexity.

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)? This could include mitigative innovations such as those that have taken place for reducing the emissions of neonics, innovations of non-chemical alternatives to neonics, innovations of e.g. technical tools such as pest prognosis tools, and social innovations such as the mutual funds (Furlan et al., 2017).

Other lessons that can be drawn from the neonics case study are:

- Key promises of the neonic innovation included: carefully targeted, high specificity. Both proved to be wrong. Neonics became the most widespread insecticide-pollutant in surface water and it seems to be the class of insecticides that has produced the most severe collateral damage on non-target invertebrates ever.

- 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.

- There are major epistemic controversies on weight of evidence. What knowledge is relevant and whose knowledge counts (e.g. field tests vs labtests; GLP versus Academic Peer Review)? The neonic case raise questions about the current social organisation of expertise. The problem is that it leads to a practice where certain knowledge is systematically privileged (e.g. industry studies with GLP certificate) while other highly relevant knowledge is systematically excluded (e.g. peer-reviewed academic studies) from the decision making process. In this case this has led to ignoring a wide range of early warning signals and delayed action, which hampered the timely application of the PP.

7 Conclusion

This case study illustrates how the PP has been applied, and contested, in processes around regulating a specific group of insecticides. In 1999, France was the first member state that used the PP to ban a neonic (imidacloprid) in sunflower seed-dressing. Since then, many member states have taken precautionary measures and restricteded various neonics. At the European level, the PP was first invoked in 2013 when the European Comission Implemented Regulation (EU) No 485/2013, where outdoor use of 3 of the 6 neonicotinoids that are marketed in Europe in crops attractive to bees were banned.[61] Referring to Article 4 of Regulation (EC) No 1107/2009, it was considered that the approved uses of clothianidin, thiamethoxam and imidacloprid no longer satisfied the approval criteria provided for in with respect to their impact on bees and that the high risk for bees could not be excluded except by imposing further restrictions (Regulation 485/2013 (7).

[61]Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances https://eur-lex.europa.eu/eli/reg_impl/2013/485/oj

The reason for applying the PP in this case, was the risks that neonics pose to pollinators in particular. Since the introduction of neonics on the market in the 1990s, an increasing number of studies indicated risks of irreversible damage to biodiversity, especially for insects providing significant ecosystem services like pollination. It should be noted that there are also emerging concerns that continued use of neonics can cause a collapse of the entomofauna (all insects) and species that feed on insects (e.g. birds), and even affect human health. The main concern in public debates, and the main reason for applying the PP however, was the contribution of neonics to pollinator decline, which poses risks to food production and ecosystem functioning and stability. The PP is relevant here due to several scientific uncertainties. Pollinator decline has a multitude of causes and drivers and scientific assessments of the relative importance of neonics in the complexly interlinked set of causal factors is contested and plagued by uncertainty. Moreover, although neonics have been praised for being innovative, precise, and cost-effective, ambiguity has also emerged in research on the actual benefits of these insecticides.

The application of the PP was contested for several reasons. A large degree of controversy surrounds the EFSAs risk assessment process. Agrochemical companies complained that the risk assessment was inconclusive, and that the principle of proportionality was neglected due to a lack of formal economic impact assessment. But the latter belongs more to the domain of the prevention principle, not the precautionary principle, because when risks and benefits are highly uncertain, ambiguous and complex, one cannot balance fundamentally unknown costs against fundamentally unknown benefits.

Other controversies relate more to the balancing of innovation and precaution, and often centre around the legal framework (specifically article 21 of regulation 1107/2009) that enables pesticides already approved on the European market to be reassessed if new evidence on risks are found. This was one of the main arguments in the court case filed by agrochemical companies Bayer Crop Science, Syngenta and BASF (supported by industry/seed associations and different European farmers unions). It was argued that this would send negative signals to the industry, which could be more reluctant to invest if they would worry that re-evaluation procedures could occur at any time dismissing their approvals. However, with a different and broader framing of innovation, there have been several suggestions on how innovations could minimise the use of neonics. This includes mitigative innovations have taken place for reducing the emissions of neonics, innovations of non-chemical alternatives to neonics such as e.g. diversifying crop rotations, altering the timing of planting, using less sensitive crops in infested areas, applying biological control agents, and social innovations.

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Nanotechnologies

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Abstract

Nanotechnology has been established as a new field of interest at the beginning of the new century to foster interdisciplinary research and bringing together different scientific disciplines and approaches such as material physics, life sciences and toxicology. As an emerging technology and an important group within the so-called advanced materials, nanotechnologies are characterized by manifold areas of application and high uncertainty. The European Commission pointed out that nanotechnologies and nanosciences will offer promising solutions for a wide variety of technical problems in a socially acceptable and environmental-friendly way. Therefore, the nanotechnology research programmes have been associated by safety and sustainability research from the very beginning. National nanotechnology research strategies and action plans followed this policy very soon. Moreover, it has been emphasised that a transparent public communication and a serious inclusion strategy has to be applied to inform the interested public and all concerned parties about the benefits but also about possible disadvantages of these new materials and products. Additional to the nanotechnology research programmes most of the member states opened calls for safety issues mainly focussing on worker safety, consumer protection and toxicology. The European Commission and the European Parliament debated and published detailed nanospecific regulation on topics of high concern like cosmetics, novel food and food contact materials at an early stage. Finally, these activities were carried out by establishing national and international networks to include all relevant knowledge. This tight interaction between organising and evaluating the available knowledge on nanotechnologies and their effects on different systems, translating and disseminating these results on possible benefits and adverse effects to all interested parties and setting up specific communication and working processes such as nanotechnology commission in Austria are an illustrative example how the precautionary principle and its following concepts like responsible research and innovation can be successfully applied.

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List of abbreviations

AG	Silver
AFNOR	Association française de normalisation (French standardisation authority)
ANSES	Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement et du travail (France)
ASI	Austrian Standardisation International
AUVA	Allgemeine Unfallversicherungsanstalt (Austria) – Austrian Workers' Compensation Board
BfR	Bundesinstitut für Risikobewertung (Germany)
BSI	British Standards Institution
CA	Consortium Agreement
CC	Consortium Committee
Cd	Cadmium
CdTe	Cadmium Teluride
CdSe	Cadmium Selenide
CEN	European Committee for Standardization (Comité Européen de Normalisation)
CNT	Carbon nanotube(s)
DIN	Deutsches Institut für Normung (German standardisation authority)
DOA	Description of Action
ECHA	European Chemicals Agency (EU)
EC	European Commission
EFSA	European Food Safety Agency (EU)
EHS	Environmental, Health and Safety
ENM	Engineered nanomaterials
ENP	Engineered nanoparticle
EUON	European Union Observatory for Nanomaterials
FCM	Food contact material(s)
GA	Grant Agreement
IRGC	International Risk Governance Council

ISO	International Organization for Standardization
ITA-OAW	Institute of Technology Assessment, Austrian Academy of Sciences
KET	Key enabling technology
MWCNT	Multi-walled carbon nanotube(s)
NBIC	Nanotechnology, Biotechnology, Information technology and Cognitive science (part of the so-called "converging technologies")
NIOSH	National Institute for Occupational Safety and Health (US)
N&N	Nanotechnology and nanosciences
NOM	Natural organic matter
ÖAW	Österreichische Akademie der Wissenschaften - Austrian Academy of Sciences
ÖNAP	Österreichischer Aktionsplan Nanotechnologie (Austrian Action Plan Nanotechnology)
OSHA	Occupational Safety and Health Authority (EU)
PCG	Project Coordination Group
PO	Project Office
PV	Photovoltaic
QD(s)	Quantum Dot(s)
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROS	Reactive Oxygen Species
RRI	Responsible Research and Innovation
SbD	Safe-by-Design
SDG	Sustainable Development Goal(s)
SCCP	Scientific Committee for Consumer Products (EU)
SCENIHR	Scientific Committee on Emerging and Newly-Identified Health Risks (EU)
TC	Technical Committee
TiO_2	Titanium dioxide
WP	Work Package

1 Introduction

1.1 Introduction

The term nanotechnology (as singular) has been introduced by several reports by the US National Science Foundation which strived to establish a new and attractive research field at the end of the 1990ies. This happened mainly in the wake of the winning of the Nobelprice for chemistry 1996 by Richard Smalley (together with Robert F. Curl and Harold Kroto) for their seminal work on fullerenes. As a consequence, there were certain hopes to revitalise research in several fields such as material physics, powder metallurgy or polymer chemistry. From an early stage on these scientific attempts were accompanied by intensive discussions on societal, economic and ethical considerations. The main focus of the US-American debate lay on the development of new materials, especially for the use in automotive and aerospace applications, but also on medical applications (diagnostics and drug delivery) including the improvement of human performance [1].
Nanomaterials range from 1-100nm in size and can be found in the form of platelets, fibres or particles. They can occur naturally, or they can be manufactured deliberately to benefit from the novel functionalities which nanomaterials exhibit as a result from their increased surface-to-volume ration and subsequent higher reactivity of particle surfaces. The commercialization of such synthetic nanomaterials or "engineered nanomaterials" (ENMs) began in the early 2000s but neither short-term nor long-term potential consequences for human health and the environment are sufficiently known [2]. Nanotechnology is considered a key technology of the 21st century with an annual market growth of up to 20.7%. It represents a very complex and multifaceted topic, the term being an umbrella for a multitude of products and processes rather than a single technology or application, simultaneously being regarded as an "emerging technology" as well as an "emerging issue of environmental concern" [3].
New nanomaterials or -products can have a high degree of potential beneficial uses resulting from their new functionalities, but at the same time they are characterized by high uncertainty, which entails unpredictable risks. When faced with uncertainty, valid data for the level of damage and probability of occurrence cannot sufficiently be provided, which hinders risk assessments and confronts regulators with the situation that there is lacking evidence to base decisions upon. At the same time, the increasing use of engineered nanomaterials (ENMs) in products and applications, ranging from electronics and automotive technology to consumer products and environmental technology [4][5][6], leads to an increased likelihood of exposure of humans and the environment, as ENMs can be released at different stages of their life cycle - during production, processing, use or disposal [7][8]. Seeing as adverse effects, biological interactions and toxicity mechanisms are not comprehensively understood, they can also not be excluded [9][10]. Faced with these circumstances, several public authorities on EU as well as on national level have chosen to apply the precautionary principle (PP) and explore governance approaches with strong interdisciplinary, cooperative and network-oriented elements over the past decade.
In the case of the extraordinary diverse field of nanotechnology, it became apparent very quickly that risk and safety issues were not or at least not sufficiently addressed under the existing regulatory regimes (food safety, workplace safety, chemical regulation) and the existing approaches to hazard identification, evaluation and risk management. Therefore, traditional exposure and risk assessment (including e.g. modelling or testing approaches) were not applicable for nanomaterials and risks for human health and/or the environment could not be estimated.
From an early onset the European Commission (EC) propagated an "integrated and responsible approach" on nanotechnology in its Nanoscience and Nanotechnology Action

Plan of 2005 based on the precautionary principle [11]. Simultaneously, it strives to integrate innovation and sustainability (safety being one important aspect of sustainable development) by requiring the provision of favourable conditions for industrial innovation on the one hand and the respect of ethical principles, integrate societal considerations into the R&D process at an early stage. In chapter 5 and 6 of its Action Plan, after discussing issues of research policy and educational prerequisites in the previous chapters, the EC states that an essential element of a responsible strategy for nanotechnology research will be to integrate health, safety and environmental aspects to the technological development and to establish an effective dialogue with all stakeholders. This will be based on three cornerstones, i.e. the advancement of an independent nanotechnology risk research, the establishment of a transparent public communication strategy on nanotechnologies and the support of national and international network building on risk and safety issues regarding the development and use of nanomaterials and nanotechnologies. Several national nanotechnology action plans were to follow this outline, such as Germany (2006), Switzerland (2008) and Austria (2010).
It is not really a surprise that the application centred debate on nanotechnologies which has dominated the US-American discourse was very soon focused on health and safety aspects, mainly gathered around risk and precautionary aspects. This realignment of the driving concepts behind the development of nanotechnologies started very early during the establishment of the national nanotechnology research programmes, e.g. the NanoInitiative in Austria. Secondly, the public discussion about the development and use of nanotechnologies was concentrating on the use of nanomaterials and production processes rather than on nanotechnologies and finally the discussion moved through the years out of the public sphere and has been active since in professional discourse dealing with e.g. food and workplace safety. The main topics chosen were the most commonly used substances (such as nanosilver, titanium dioxide or carbon nanotubes) and their incorporation into everyday products, such as compound materials, special paints and varnishes, food, cosmetics and functionalised textiles. This kind of "normalisation" of the discourse by establishing appropriate expert panels and specific commissions (i.e. the Austrian Nanoinformation Commission of the Federal Ministry of Social Affairs) accompanies the nano research and development since at least one decade.

1.2 Key timeline

Political	***Legal***	***Science/risk assessment***	***Public debate***	***Other***
Year	**Event**	**Relevance to case study**		
1997	5th Research Framework Programme (FP5) 1998 – 2002 [12]	First mention of nanotechnology within an EU-level strategic document		
2000	Communication from the Commission on the precautionary principle [13]			
2002	6th Research Framework Programme (FP6) 2002-2006 [14]	First research projects on EHS-issues regarding the use of nanotechnologies		
2003	Start of the Austrian nanotechnology research programme NanoInitiative	The Austrian NANO Initiative is a multi-annual funding programme for Nanoscale Sciences and Nanotechnologies (NANO) in Austria and is focused on applied research and public outreach projects (mainly funded by the Ministry of Traffic, Innovation and Technology). First discussions on risk and safety issues to be integrated into nanotechnology F&E		
2004	Communication from the EU Commission - Towards a European strategy for nanotechnology [15]	This Communication proposes actions as part of an integrated approach to maintain and strengthen European R&D in nanosciences and nanotechnologies. It considers the issues that are important to ensure the creation and exploitation of the knowledge generated via R&D for the benefit of society		

2005	Report "Nano 2005 – 2006" (BMVIT) by the Institute of Technology Assessment (ITA) at the Austrian Academy of Sciences [16]	The Ministry of Technology begins to draw its attention to environmental, health and safety topics regading nanotechnologies
2005	Action Plan for Europe 2005 – 2009 for nanosciences and nanotechnologies [11]	An essential element of this responsible strategy is to integrate health, safety and environmental aspects to the technological development of nanotechnologies and nanosciences
2006	Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency [17]	REACH is the over-arching legislation applicable to the manufacture, placing on the market and use of substances on their own, in preparations or in articles. Nanomaterials are covered by the definition of a "substance" in REACH, even though there is no explicit reference to nanomaterials. The general obligations in REACH, such as registration of substances manufactured at 1 tonne or more and providing information in the supply chain apply as for any other substance. Information on the implementation of REACH for nanomaterials, including guidance and the application of the REACH evaluation processes, can be found on the ECHA website.
2007	7th Research Framework Programme (FP7) 2007 – 2013 [18]	Nanosafety projects on workplace safety, cell biology and environmental toxicology
2007	Federal Chancellery Austria: Decision of the Bioethics Commission at the Federal Chancellery of 13 June 2007 – Nanotechnology Catalogue of ethical problems and recommendations [19]	Considering the precautionary principle, the main question for the political discourse is whether the legislator should develop a special legal framework (analogous to the Genetic Engineering Act) or whether it should limit itself to active research policy and/or information policy towards the population. The Bioethics Commission acknowledges the fact that there is a gap of knowledge regarding the dangers of nanotechnology, but believes that a sufficient risk-benefit balance, both for the medical sector and for the food and technology sector, will be ensured within the existing authorization procedures. Nevertheless, the Bioethics Commission recommends within the framework of the public-sector research policy, both risk research and the intensify accompanying research, including ethics.
2007	Nano safety Project: NanoTrust 2007 – 2010 at the ITA (Austrian Academy of Sciences)	In Austria NanoTrust project of the Institute of Technology-Assessment (ITA) at the Austrian Academy of Sciences (ÖAW) is launched. The main goals of the project are to identify scientific needs in nanosafety research and to provide an independent platform for discussion on nanosafety issues
2007	Behördendialog (Dialogue of	The "Behördendialog" is held for the first time as a German speaking platform for knowledge exchange on nanosafety issues, initiated by the German Ministry of Environment (BMUB), the Swiss Ministry of Health (BAG) and the Austrian Ministry of Environment (BMLFUW). It will take place annually in in one of the member countries (D, A, CH; FL and LUX will follow a few years later). It will take place for the 14th time in November 2020.
2008	EC Communication on Regulatory aspects of nanomaterials [20]	The Commission announces a regulatory review of EU legislation in relevant sectors. The present Communication reflects this commitment. It covers nanomaterials currently in production and/or placed on the market
2008	Food Additive Regulation (Regulation No. 1333/2008) [21]	Regulation (EC) No. 1272/2008 on classification, labeling and packaging of substances and mixtures CLP [13]
2008	European Parliament Resolution of 24 April 2009 on regulatory aspects of nanomaterials [22]	The European Parliament in its resolution of 24 April 2009 on regulatory aspects of nanomaterials called, inter alia, for the introduction of a comprehensive science-based definition of nanomaterials in Union legislation

2009	Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products [23]	First nanospecific law introducing a working definition for nanotechnologies
2009	EU Commission Recommendation on a code of conduct for responsible nanosciences and nanotechnologies research [24]	Code of conduct on a voluntary basis for the use in nanoproduction
2010	Austrian Actionplan for Nanotechnology (ÖNAP) [25]	Consisting of 50 recommendations regarding the safe and sustainable use of nanotechnologies and nanomaterials which are still implemented (EHS research programme, nanoinformation web site, nanoinformation commission)
2010	Report: Nanotechnology in Vienna's procurement system - initial assessment of opportunities and risks [26]	This paper is intended to give decision-makers within the procurement system of the Municipality of Vienna a brief overview of products and applications attributed to nanotechnology, especially with regard to their propagated environmental benefits and their potential risks for health and the environment. Priority will be given to those product groups that are available on the Austrian and European market and that are important in the procurement of the municipality of Vienna.
2010	Establishment of the Austrian Nano Information Platform (NIP)	Lead by the Austrian Ministry of Health, consisting of members from various organisations (ministries, agencies, research institutions, NGOs)
2010	ITA Project: NanoTrust 2 – 2010-2013 (BMVIT)	First prolongation of the long-term research project on nano risk governance at the Austrian Academy of Sciences
2010	EU Commission: Eurobarometer Biotechnology – Awareness of Nanotechnology [27]	The key findings of this survey are that Europeans are generally unaware of nanotechnology, do not have a solid view of benefits but are not excessively alarmed about potential negative consequences. Even though understanding of nanotechnology is low, Europeans feel that it should be encouraged. [20]
2011	EU Commission Recommendation on the definition of nanomaterial [28]	
2011	Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers [29]	amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004
2011	Regulation (EU) No, 10/2011 on plastic materials and articles intended to come into contact with food [30]	First nanospecific regulation concerning food packaging materials
2011	Austrian research programme "Sparkling Science" - Youth research on opportunities and risks of Nanomaterials [31]	In this research project, under the direction of the Federal Environment Agency, high school students from Vienna and Salzburg dealt comprehensively with the perception of nanotechnology
2011	Directive 2011/65 on the restriction of the use of certain hazardous substances in electrical and electronic equipment [32]	As soon as scientific evidence is available, and taking into account the precautionary principle, the restriction of other hazardous substances, including any substances of very small size or with a very small internal or surface structure (nanomaterials) which may be hazardous due to properties relating to their size or structure, and their substitution by more environmentally friendly alternatives which ensure at least the same level of protection of consumers should be examined
2011	Establishment of a permanent working group "Nanotechnologies and Workplace Safety" by the Austrian Workers Compensation Board under participation of the ITA	This working group is active until today (2020) and meets on a regular basis

2012	Regulation (EU) No. 528/2012 concerning the making available on the market and use of biocidal products [33]	The Biocidal Products Regulation contains specific provisions for nanomaterials
2012	The Austrian Workers Compensation Board (AUVA) Code of practice: Nanotechnologies – Health and Safety at Work [34]	Nanomaterials in the workplace are completely different working materials with different physical, chemical and toxicological properties. It is therefore important to provide workers with as much specific information as possible, through training and instruction, about the substances used, the tasks they perform and the processes that may lead to inhalation, dermal or oral exposure
2012	Austrian Nanotechnology Action Plan - Implementation Report 2012 [35]	In adopting the Austrian Nanotechnology Action Plan on 2 March 2010, the Federal Government provided a clear mandate for its implementation and required the presentation of a progress report on the Plan's implementation by the end of 2012
2012	Directive 2012/19 (EU) on waste electrical and electronic equipment (WEEE) [36]	First systematic considerations of the fate and behaviour of nanomaterials in waste streams
2012	NanOpinion (EU-FP7) 2012 - 2014	
2013	Austrian Nano Information Commission (NIK) at the Austrian Ministry of Health, first term of office	In order to intensify and consolidate the transdisciplinary risk evaluation and communication processes between ministries, authorities and science, the Austrian Nano Information Commission (NIK) was founded in 2013. ITA has been appointed to chair the Commission
2013	ITA Project: Nano Trust 3 – 2013-2016 (BMVIT, BMLFUW, BMG, BMASK)	2nd prolongation of the long-term nano risk governance project "NanoTrust" at ITA, supported by several ministries and the Austrian workers compensation board (AUVA)
2013	German Federal Ministry for Risk Assessment: Nanoview [37]	Factors influencing the perception of nanotechnologies and target group-specific risk communication strategies
2013	European Commission: Guidance on the protection of the health and safety of workers from the potential risks related to nanomaterials at work.[38]	Guidance for employers and health and safety practitioners
2014	Horizon 2020 Framework Programme 2014-2020 [39]	
2013	European Commission: Working Safely with Manufactured Nanomaterials [40]	Guidance for Workers
2015	Regulation (EU) 2015/2283 on novel foods [41]	To ensure a high level of protection of human health and consumers' interests, food consisting of engineered nanomaterials should also be considered a novel food under this Regulation
2016	ITA Project: Nano Trust 4 – 2016-2017 (BMVIT, BMLFUW, BMGF)	3rd prolongation of the long-term nano risk governance project NanoTrust at ITA, supported by several ministries and the Austrian workers compensation board (AUVA,)

2017	Regulation (EU) 2017/745 on medical devices [42]	There is scientific uncertainty about the risks and benefits of nanomaterials used for devices. In order to ensure a high level of health protection, free movement of goods and legal certainty for manufacturers, it is necessary to introduce a uniform definition for nanomaterials based on Commission Recommendation 2011/696/EU (4), with the necessary flexibility to adapt that definition to scientific and technical progress and subsequent regulatory development at Union and international level. In the design and manufacture of devices, manufacturers should take special care when using nanoparticles for which there is a high or medium potential for internal exposure. Such devices should be subject to the most stringent conformity assessment procedures. In preparation of implementing acts regulating the practical and uniform application of the corresponding requirements laid down in this Regulation, the relevant scientific opinions of the relevant scientific committees should be taken intoaccount.
2017	ITA Project: Nano Trust 5 – 2017-2020 (BMVIT, BMNT, BMASKG, AUVA)	4th prolongation of the long-term nano risk governance project NanoTrust at ITA, supported by several ministries and the Austrian workers compensation board (AUVA)
2018	Amending Regulation (EC) No 1907/2006 (REACH) as regards Annexes I, III, VI, VII, VIII, IX, X, XI, and XII to address nanoforms of substances	In force since 2018 – it shall apply from 1 January 2020, concerning new and already existing registrations, explicitly addresses nanoforms of substances. For nanoforms, specific minimum characterisation information should be provided as part of the composition information under the substance identification. Particle size, shape and surface properties of a nanoform may influence its toxicological or ecotoxicological profile, exposure as well as behaviour in the environment.
2020	Austrian Nano Information Commission (NIK) at the Austrian Ministry of Health, second term of office (until 2023)	
2020	Horizon Europe Framework Programme – 2021-2027	

2 Nanotechnologies

2.1 The field of nanotechnologies

Because of their high variability and universal use nanotechnologies are among so called key enabling technologies (KET), the others being advanced materials, advanced manufacturing and production technologies and biotechnology. KETs are technologies which are meant to retain the competitiveness of the European industries and capitalise on new markets worldwide. Originally part of a cluster called converging technologies (Nanotechnology, Biotechnology, Information technology and Cognitive science (NBIC)), nanotechnologies are now one important part in the field of advanced materials. The developing European research framework programme Horizon Europe will contain nanotechnologies mainly in the cluster "Digital, Industry and Space", the areas of intervention being "manufacturing technologies", "advanced materials" and "emerging enabling technologies". But nanotechnologies and nanomaterials are modifiable in shape, structure and functionality for special purposes that one can expect nanotechology research to be carried out also in other Horizon Europe clusters, such as "Health" (diagnostics and drug delivery), "Climate, Energy and Mobility" (e.g. water treatment and printable batteries) or "Food, bioeconomy, natural resources, agriculture and environment" (indicators for food quality). It is obvious that nanotechnology is not "one" technology but is getting more and more important in a vast majority of technological sectors.
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 (see Figure 1). At present, their use and production are increasing rapidly, although much safety-relevant information is still missing, such as whether, how much and when nanoparticles can be released during the product life cycle. To give an example about the diverse field and applications of nanotechnology we give the example of Quantum Dots (QDs) and their specific application possibilities within different technology sectors. Due to their unique mechanical, magnetic, electrical and optical properties they are of interest for a wide range of materials, products and applications. They can foster innovation in various field but depending on use and application, they can be released into the environment during their life cycle and negative effects such as ecotoxicity cannot be excluded [43].

Quantum Dots (QDs) and their specific application possibilities
QDs are fluorescent nanocrystals, the size varies depending on composition and production method and is approximately 2 to 10 nanometers (nm). These synthetically produced nanoparticles such as cadmium teluride (CdTe) or cadmium selenide (CdSe) usually consist of one or more layers of inorganic semiconductors to which organic ligands are attached, which serve for surface modification. By means of surface modification, nanoparticles can be more or less "tailor-made" according to the area of application and desired properties [44]. Due to their small size, among other things, QDs exhibit specific fluorescence, whereby they emit a specific wavelength after excitation with electromagnetic waves. Their characteristic first exciton absorption peak and a very sharp fluorescence peak are particle size dependent and therefore tunable by the reaction time during their synthesis. They are also photochemically robust (photostable) and allow localization at the molecular level and thus the tracking of complex biological processes over a long period of time. Due to this unique optical property, which is mainly due to the size of the nanocrystals, they are used for energy generation in solar cell technology [45][46], environmental analysis methods [47], biomedicine [48] and nanotoxicology[49] as fluorescent markers. For example, it has been shown that QDs can be clearly detected in living cells [50] and in complex media such as waste streams [47] due to their characteristic fluorescent properties. QDs therefore offer great potential as fluorescent markers or so-called tracer materials.

Although the unique properties of QDs make them suitable for a variety of applications, the semiconductors of most QDs consist of compounds with heavy metals, such as cadmium (Cd), and both the uptake of these nanoparticles and the uptake of dissolved Cadmium ions can be toxic. QDs can, for example, be absorbed into the cytoplasm via endocytosis, where their presence creates oxidative stress and causes the cell to produce reactive oxygen species (ROS), which can damage or kill the cell [51]. On the contrary, it is precisely these reactive oxygen species that enable QDs to be used as probes for photodynamic therapy (PDT), whereby tumor cells can be destroyed in a targeted manner. QDs can also accumulate in the body or in individual organs and thus, apart from their toxicity for individual cells or organisms, can reach higher levels of the food chain by means of trophic transfer. This represents a potential danger for the entire food chain, right up to humans. Despite the expected increase in industrial production and the associated increased release into the environment, there is as yet little information about their fate or potential toxicity [52].
Nevertheless, the use of QDs in the electronics industry or for power generation in solar cell technology is increasing. Likewise, QD marking has become a fundamental tool in various fields of research to quantify and localize nanomaterials in cells and complex media and to better understand their endpoints and effects. In order to guarantee more safety in the future and to be able to understand and thus reduce environmental pollution, the development of standardized analysis and measurement methods as well as reference materials is an important step [47]. However, this poses a problem because the statements of the various ecotoxicity tests are currently often contradictory and not reproducible and therefore do not allow general statements at present.

Solar Cell Technology
Photovoltaic (PV) technology in particular offers a future field of application as it needs to be developed very rapidly in order to achieve the Paris climate targets for 2050 (100% electricity generation from renewable energy). Since this goal cannot be achieved by using classical silicon-based solar cells, novel PV technologies are required to offer flexible, ultra-thin and above all lightweight PV modules. Such flexible systems are based, for example, on perovskite silicon tandem solar cells (multi-junction solar cells) or single-junction perovskite QD cells. Perovskite is a mineral that has unique structural properties and in combination with QDs has great potential in solar cell technology. These novel PV technologies therefore also have a high potential to open up new fields of application - beyond classical energy production - for e.g. portable intelligent small devices or sensors.
For example, research is currently being carried out on so-called colloidal perovskite quantum dots to increase the efficiency of perovskite QD solar cells. However, this research is still in its infancy and does not yet come close to conventional silicon-based PV technologies. Today, commercial silicon PV modules typically have an efficiency of more than 19% over an area of one square meter, while small single junction perovskite QD cells only achieve 16.6%.[1] In addition to further improvements in efficiency and stability, the development of high-throughput coating processes and the reduction of material costs are significant challenges for the commercialization of QD solar cells [45]. A further factor is that perovskites often consist of lead-containing compounds that are harmful to the environment and health, so-called halides [46], which can lead to negative environmental effects if accidentally released. Although the lead emitted by such a solar cell is said to account for less than 0.3 percent of the ecotoxicity of the entire module[2], it is to be replaced by more environmentally friendly elements in the future.

[1] https://www.solarify.eu/2018/04/08/886-effiziente-perowskit-solarzellen/
[2] https://www.solarify.eu/2018/04/08/886-effiziente-perowskit-solarzellen/

Biomedicine

Imaging techniques that use fluorescence are widely used and important methods in biomedicine. QDs can be used as fluorescent labels in bioimaging, as experiments on mice show [53]. In recent decades, cell biology, for example, has often worked with short-lived organic dyes such as rhodamines or cyanines. These organic dyes exhibit photon-induced "chemical degradation", so-called "bleaching", which is an unintended and undesirable effect of prolonged exposure to high light intensities. The instability of the organic dyes thus hinders the long-term absorption and also the tracking of the particles in complex biological processes or in complex media. Organic dyes also have a very broad emission spectrum, which makes the detection of several labels at the same time difficult. On the other hand, different QDs can be detected in parallel due to their narrow, symmetrical emission spectrum. However, organic dyes have been in use for so long that there are commercially available functionalized dyes that are already very well characterized and applicable, which is not the case with QDs and has to be determined very precisely from case to case [54].

However, the biocompatibility of the dyes (organic or inorganic) is essential for their biological and biomedical application, whereby coating materials or "capping layers" can modify the surface properties of QDs to give them water solubility, water stability, photostability and biocompatibility. In addition, QDs can also be conjugated with specific peptides, antibodies and other small molecules targeting a specific cell type, cell structure or tissue. Therefore, QDs are increasingly used in medical diagnostics, e.g. as contrast agents. The successful use of QDs for the detection of tumor biomarkers and the imaging of tumor cells has great potential for application in the early detection of cancer and, due to a possible accurate visual tracking, also in tumor elimination [48].

Due to their specific properties, they are also used in cancer therapy. Photodynamic therapy (PDT) is a very promising method for cancer treatment. In this construct, the QDs serve as antennas to absorb light and transfer the energy via energy transfer to the closely linked photosensitizer to initiate the production of ROS, thereby damaging the cell. Photothermal therapy (PTT) is a new technique for cancer treatment in which QDs can efficiently convert light energy into heat when exposed to laser radiation to inhibit the tumor's growth [55].

Due to their unique properties, QDs can play several roles in the development of drug delivery systems. They can serve as a means of monitoring drug delivery and they can act as carriers, which transport the drug to the target site to increase the dose of the drug in the target organ [56].

Environmental analysis methods

It is being investigated whether quantum dots are potentially suitable as detectable and clearly identifiable so-called "nanotracers" to determine the final fate of synthetically produced nanomaterials in environmentally relevant media such as wastewater or landfill leachates. By labelling nanoproducts containing synthetically produced nanomaterials with nanotracers, it would be possible to estimate the potential input into the environment and predict environmental concentrations. Studies show that the unique optical properties of QDs using fluorescence spectroscopic detection methods in complex environmental matrices, such as waste samples, make it possible to clearly identify and track [47]. In addition, these nanoscale tracers can be clearly distinguished from naturally occurring nanomaterials due to their spectroscopic "fingerprint" and can be observed over a longer period of time due to their persistence. By tracing the QDs, insights can be gained into how synthetically produced nanomaterials behave in relevant environmental samples over long periods of time. Conclusions can also be drawn about interactions with natural, organic substances such as proteins, fulvic or humic acids, whereby such potential transformation processes in turn play a decisive role in terms of mobility and toxicity [57].

QDs have also been successfully used as highly sensitive and pH-dependent fluorescence probes (biosensors), e.g. to detect dissolved ions in water samples, since their adsorption on the QD surface is very selective [58].

Nanotoxicology

The visualization and quantification of the dose of nanoparticles in organisms as well as in the environment are topics of utmost importance for the toxicological evaluation of nanomaterials. Visualizing the fate of nanomaterials can provide information describing the interaction mechanisms of nanomaterials with biological matter and finally their toxicity. At the same time, the quantification of the dose of nanomaterials is essential for toxicological evaluation in order to establish a relationship between dose and endpoints and to contribute to the development of models and standardised analysis and testing methods. Despite the great advantages, there are still obstacles to this method, such as the choice of the right label, the stability of the bond with the label over time, or the presence of unbound labels in the solution, which can falsify the results. Therefore, the reproducibility of the studies is often not given and standardisation is difficult [49].
However, there is a need for reliable and reproducible results of ecotoxicological experiments to identify, quantify, classify and rank the environmental hazards of nanomaterials and to set environmental predicted no-effect concentration (PNEC) limits. Standardised analysis and test methods are required for this purpose, which can then be used as a basis for regulatory decisions to ensure the protection of the environment from unintended harmful effects [59].

The future increased use of nanomaterials in innovative application areas such as solar cell technology, biomedicine or environmental analysis is a great opportunity but also carries risks due to the high uncertainties that innovative technologies entail. 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. Reliable, scientifically based and legally binding characterization and measurement method as well as a definition and mandatory registration would create data for quantitative risk assessment, which is currently still vague. A proper risk assessment could contribute to transparency and thus trust in nanotechnology, which foster innovation instead of slowing it down. But as long as this isn´t the case, the safety of nanotechnology will always be questioned, although there is often no reason for this.

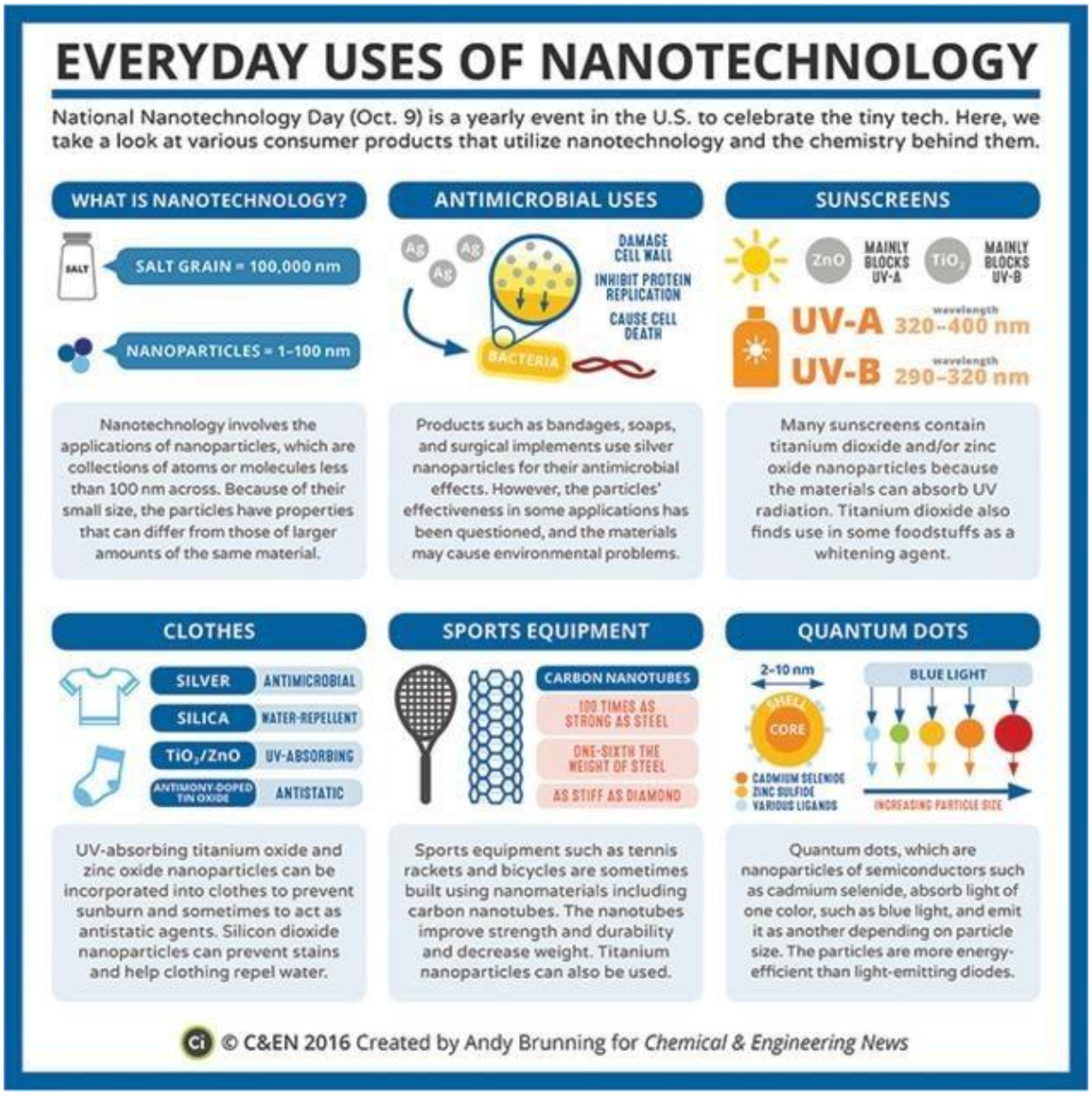

Figure 1: Nanotechnology Uses. [60]

2.2 Precautionary considerations

Because of the high variance of involved disciplines, envisioned scientific problems and possible applications and their innovation level, the transdisciplinarity of the discourse which tried to include a broad variety of stakeholders (research, regulatory bodies and authorities, producers and the interested public (including e.g. civil society and NGO´s)) and the somewhat blurred borders as to what nanotechnologies are encompassing, the EC was eager to open up the interaction between all parties concerned to bring in all safety relevant information as early as possible. In its communication to the Council, the European Parliament and the Economic and Social Committee (Action Plan) the EC emphasises these needs very clearly, especially in points 5 and 6.[61] Following the EC the safe and responsible development of nanotechnologies should be necessarily linked to the integration of the societal dimension and the appropriate assessment of public health, safety and environmental health aspects as early as possible. This needs to be done in a most efficient and effective way by fostering the international cooperation of EHS-research.

The statements of the Commission were clearly based on precautionary considerations. The scientific and technical development of nanotechnologies should be carried out in a responsible manner e.g. via the use of ethical reviews to include possible concerns regarding medical uses. Studies and foresight activities into future nanotechnology scenarios should provide useful information about the possible risks to, and potential impacts on, society. Furthermore, appropriate conditions for and pursue a true dialogue with the stakeholders concerning nanotechnologies should be created. In support of this dialogue, special Eurobarometer (EB) surveys were launched to study the awareness of and attitudes towards nanotechnologies across Member States.

The Commission called upon the Member States to encourage the industry to consider the wider economic, societal, health, safety and environmental impacts of their commercial activities as integral part of their Corporate Social Responsibility strategy [62].

A regular dialogue on nanotechnology application with the public should be opened, in particular via the media. Part of these efforts should be aimed at consumer education projects hoping to raise awareness and – maybe – also the acceptance of these new technologies. Regarding research the EC encouraged the Member States to identify and address safety concerns associated with applications and use of nanotechnologies at the earliest possible stage. The main focus should be the possible exposure to nanoparticles and nanofibers by consumers and workers. The responsible organisations and research institutions should develop guidelines, models and standards for risk assessment throughout the whole lifecycle of nanotechnology products.

As a consequence, several member countries started an open discussion how to deal with the development of nanotechnologies as a society, engaging a great variety of stakeholders. In Austria for example the "Nanonet" of the Ministry of Environment was established, which does not exist in this format today. Subsequently this discourse led to the constitution of a national Action Plans in some Member Countries. Not surprisingly, these national Action Plans contain many of the recommendations such as the establishment of an independent nanosafety research programme, the organisation of a transparent and informative public dialogue (either informal or consultational, but seldomly in a really cooperative manner) [25].

Therefore, the main activities on European and Member State level have been gathered around the research of possible health and environmental effects of nanotechnologies on the one hand, and communication processes on possible effects of nanotechnologies including all conceivable concerned parties.

3 Risks and scientific uncertainties

3.1 Risk/threat and scientific analysis

3.1.1 Human Health Risks

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 because they can come into contact with nanomaterials via nanoproducts.
The intake of ENMs can occur through inhalation, dermal absorption or oral ingestion. Furthermore, due to their small size and large surface-to-volume ratio, ENMs can migrate via the bloodstream to different parts of the body. For example, it has been estimated that around 400,000 workers worldwide are affected by occupational exposure to nanomaterials in 2008 and the number will rise to 6 million in 2020 [63]. In terms of worker protection, there is thus a need to quantitatively assess and manage potential health risks, if possible [64].
ENMs can be used as powders, in dispersions or in a matrix and release primary particles. Products containing ENMs can be subjected to mechanical or chemical processes, such as spraying, washing, weathering, burning, etc., which can lead to the unintentional release of secondary ENMs, which can be inhaled, absorbed through the skin or via the gastrointestinal tract. Due to the exposure pathways, pulmonary, dermal and/or gastrointestinal exposure to nanomaterials may therefore occur.
Studies from 2000 onwards on e.g. nanoscale silver and silicon dioxide (nano-Ag, or SiO^2) have already stated that the greatest risk is posed by inhalation intake of ENMs [65][66][67]. A survey of nano-safety experts showed that 60% of respondents were concerned with inhalation exposure to ENMs – again reflecting the greatest safety concerns – followed by oral (30%) and dermal (20%) exposure [48]. Both inhalation uptake and deposition in the lungs are strongly dependent on particle size. 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 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. For example, inhalation of asbestos fiber-like ENMs, such as certain carbon nanotubes (CNTs), can lead to a malignant mesothelioma, the cause of which is related to the length, width and chemical composition of the fibers and their ability to remain in the lungs [65]. However, CNTs not only cause asthmatic inflammation [73], but several publications on bioassays in rats suggest that CNTs have carcinogenic effects as well [74][75]. These described health effects are not restricted to nanomaterials and can also be caused by non-nanomaterials but the nanospecific properties changes response, interaction, behaviour and toxicity and make risk assessment – if possible - more cost and time intensive [76].

3.1.2 Environmental Risks

As the described nano-safety research show, some nanomaterials can have negative effects on health and the environment, such as respirable asbestos-like particles and fibers. 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 [74]. Thus, very little information is available about uptake mechanisms in living organisms and trophic transfer [52][77] as well as on specific toxicity [58], and it is very challenging to detect released nanomaterials in complex environments such as relevant technical compartments e.g. effluents, waste waters, and landfill leachates [78][79]. The expected future increase of environmental release and the consequent dissipative loss [80][81] demands not only a comprehensive analysis of nanospecific effects but an ongoing application of governance measures according to the precautionary principle.
Ecological research on the behaviour of ENPs can rely on numerous studies from the geo-sciences that have examined the behaviour of naturally occurring nanoparticles in the environment. Nonetheless, ENPs differ in certain respects from those occurring naturally. While natural nanoparticles are randomly structured and diffusely distributed in the environment, industrially produced suspensions or powders contain pure nanomaterials of very uniform size, shape and structure. Such nanomaterials have unique properties such as the high tensile strength of CNTs or the photocatalytic activity of nano-TiO2, which make them interesting for novel products and applications but also unpredictable when they enter the environment. Precisely these special features make it so difficult to predict the fate and behaviour of ENPs in the environment.
A short overview over the behaviour of nanoparticles in different environmental media, especially the fate of certain nanoparticles such as nano silver, titanium dioxide and carbon nanotubes is given below [82].
In the environment, nanomaterials can undergo a range of chemical processes that depend on many factors (e.g. pH value, salinity, concentration differences, the presence of organic or inorganic material). The characteristics and properties of a nanomaterial also play a major role. Bioavailability is decisive in determining potential toxicity. This depends strongly on whether nanoparticles remain stable in an environmental medium or are removed from the respective medium through agglomeration and deposition or are transformed into a form that organisms cannot take up.
Air: When nanoparticles enter the atmosphere, they move from zones of higher concentration to zones of lower concentration (diffusion). Air currents distribute the particles rap-idly; these can migrate great distances from their original source. Nonetheless, nanoparticles tend to aggregate into larger structures (agglomeration). Detecting nanoparticles in the air is very difficult because simple measurements of size distributions can hardly distinguish such agglomerates from natural particulates. The speed with which particles in the air are deposited on the ground, in the water or onto plants (deposition) depends on particle diameter. Nanoparticles from the air are deposited much slower than larger particles due to their smaller diameters.
Water: The general rule is that nanoparticles distributed in the water behave much like colloids, which are well described in the chemical literature. Colloids are droplets or particles that are finely distributed in a medium; they are relatively unstable because they rapidly adhere to one another due to electrostatic attractive forces and then sink as a result of gravity. Natural water bodies typically contain dissolved or distributed materials, including natural nanomaterials. As expected, synthetic nanomaterials that enter a natural water body bind themselves to such natural materials. The fate and behaviour of nanomaterials in the water, however, are also influenced by factors such as pH, salinity (ionic strength) and the presence of organic material. Naturally present organic material (NOM) can lead to the decomposition of C60-fullerenes or of their aggregates and thus alter particle size and shape. A NOM such as humic acid can stabilize certain carbon nanotubes (MWCNT) in the water and thus prevent their settlement. Some CNTs are also deliberately produced through special surface changes

so that they do not aggregate. The type of such functionalisation helps determine whether CNTs can be removed from a natural water body through sedimentation. As CNTs are very polymorphic, it is usually impossible to provide generally valid statements about their fate and behaviour in the environment. A strong influence of the surrounding environment on behaviour, in particular the presence of NOM, has also been determined for other nanomaterials such as metals or metal oxides [83].
Soil: Nanomaterials in the soil and in sediments are assumed to bind themselves to solids. The generally very low concentrations of particles in the groundwater support this notion. The bioavailability – and therefore the potential toxicity – of a nanomaterial for soil organisms apparently depend strongly on whether it binds to NOM. The bioavailability of nanosilver in complex media such as soil is considerably lower than in water because the reactive silver ions can bind to components in the soil (e.g. NOM) [84].

3.1.3 Nanowaste

A very important issue which turned up rather late both 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. This topic is insofar significant because it takes up a central recommendation of the European Commission to develop models and standards for risk assessment "throughout the whole life-cycle" of nanotechnological products. This discussion started in the member states alongside the discussion of overarching ideas connected to sustainable development, the application of safe-by-design principles and circular economy embedded in the political adaptation process of the sustainable development goal (SDG) debate.
Nanomaterials that enter the environment from diffuse sources can be classified as potential "nanopollutants" (for example titanium dioxide nano particles released from sunscreen lotions in surface waters) [85]. "Nanowaste" are materials that come into contact with solid wastes and can be collected separately. Titanium dioxide nanoparticles therefore become waste only when they are for example eliminated in wastewater treatment plants after the biological purification phase.
The behaviour of nanomaterials in waste incineration plants can be characterised as following: when incinerated nanomaterials can either be destroyed, converted into other nanomaterials (e.g. oxides, chlorides) or be released unchanged. Nanomaterials in the size class 100nm and larger are most efficiently removed in the filters of waste gas purification systems. Nanomaterials smaller than 100nm are only partially retained by filters. An estimated up to 20% can be released. Incinerating nanomaterials can accelerate the formation or destruction of undesired by-products (e.g. polycyclic aromatic hydrocarbons). Nanomaterials can be retained in the solid wastes (ash, slag, filter residues) produced by waste incineration plants. A leaching of nanomaterials from such wastes, for example when subsequently dumped in a landfill, should be avoided [86][87].
Various nanomaterials are currently incorporated in a wide range of products. It remains largely unknown whether these can pose an environmental or health risk when they end up in waste treatment plants or in landfills via various waste streams at the end of their life cycle. In a precautionary approach, several experts and organizations have therefore formulated first recommendations designed to minimize nanomaterials in wastes. Future research efforts should increasingly focus on the disposal phase of „nanoproducts" in order to better estimate potential risks. The possible environmental effects of nanomaterials and their fate in waste treatment has been a specific research topic in the Austrian nano-EHS-programme and an overview is given in several publications [88].

3.2 Scientific uncertainty

3.2.1 Complexity

According to the International Risk Governance Council (IRGC) complexity refers to the difficulty of identifying and quantifying causal links between a multitude of potential causal agents and specific observed effects in a system or a system component.[89] This may be valid to an extraordinary high level for 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. Only the C60-compunds are forming a vast field of research (Fullerenes and others) for which the Nobel prize has been awarded in 1996 to Smalley, Curl and Kroto. 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 systematics of the EFSA risk assessment scheme might serve as an illustration for the complexity of nanomaterials, although in this case only the application field of food and food contact materials are brought to attention (see Figure 2) [90]. This guidance document provides an overview on information requirements and how to perform risk assessment of nanomaterials in the food and feed area (e.g. novel food, FCMs, food/feed additives and pesticides). The EFSA Guidance is aimed at providing a structured pathway for carrying out safety assessment of nanomaterials in the food and feed area. Under the EU Regulation on Novel Food (EU) No. 2015/2283, a food consisting of engineered nanomaterials will be considered a novel food and as such will require respective authorisation. The Regulation stipulates that risk assessment of novel foods shall be carried out by EFSA, which shall also be responsible for verifying that the most up-to-date test methods have been used to assess their safety. 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. 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:

- 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);
- complex transformations (e.g. ageing, changes in surface properties, porosity) or metabolites or de novo formed particles from ionic species
- altered hydrophobicity/hydrophilicity;
- persistence/high stability (e.g. in water, fat, or body fluids, lack of degradation/dissolution);
- increased reactivity compared to equivalent non-nanomaterial (e.g. catalytic, chemical, biological);
- targeted or controlled release by the nanomaterial;
- nanomaterials having antimicrobial activity;
- 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);

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

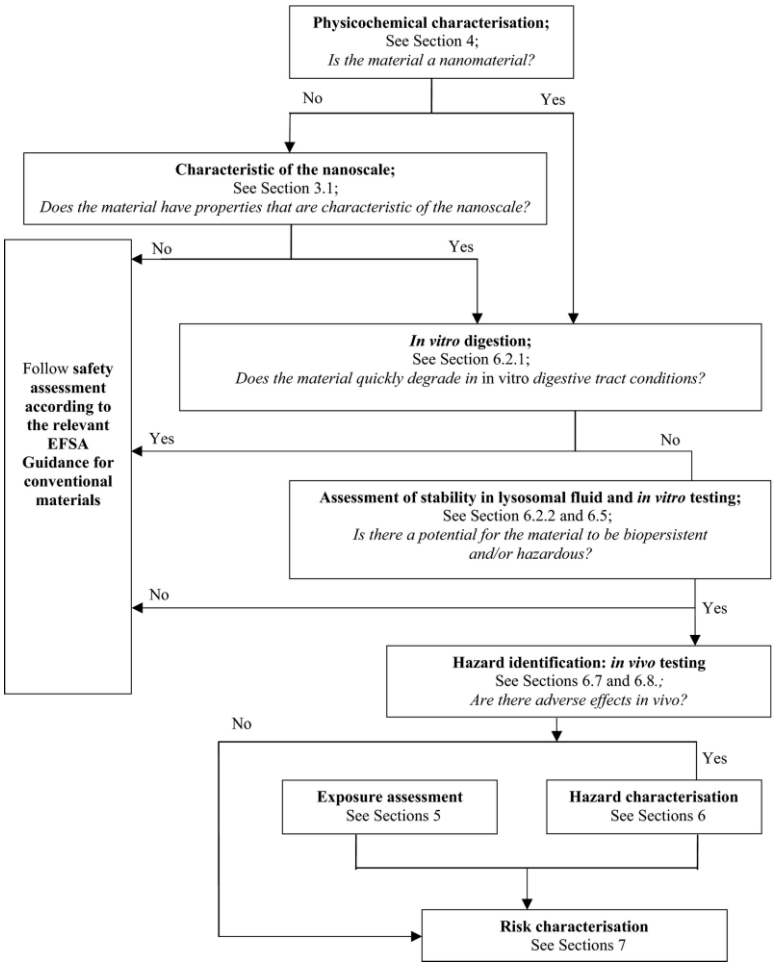

Figure 2: Example for complexity: EFSA schematic outline of risk assessment of ingested nanomaterials. [90]

3.2.2 Uncertainty

Silvio Funtowicz and Jerome Ravetz pointed out that in the context of technological systems and their impacts, human knowledge is always incomplete and selective and thus contingent on uncertain assumptions, assertions and predictions [91]. 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 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 the implementation of these new materials and products increases the pressure on decision-makers.

Seen in this light nanotechnology regulation has so far been rather the management of uncertainties than of risks and will for a long time stay like that. In the aftermath of the controversies surrounding genetically modified foods in the 1990s, nanotechnology faced calls for moratoriums and the need for a different approach to regulating new technologies with risks which cannot be fully characterized had become apparent [92]. This gave rise to self-regulatory cooperative approaches of actors in the field of nanotechnology, summarised under the term "nano governance", entailing a number of organised public and expert nano dialogues [93]. In Austria the nanosafety TA-project NanoTrust of the Institute of Technology-Assessment (ITA) at the Austrian Academy of Sciences (ÖAW) was an endeavour to foster such cooperative approaches. This project started in 2007 and is still in operation. It is described in detail in chapter 4.1.7 (risk management by network).

Technologies like nanotechnology and advanced materials are defined by uncertainties rather than risks. Governance processes of a technology characterized by a dominant risk frame will also be shaped by the availability of risk-relevant knowledge. While risks allow knowledge on possible outcomes and an expression in probabilities, uncertainty does not allow the assignment of probabilities to outcomes. Inter and trans-disciplinary deliberative expert dialogues can be a form of organising the process of knowledge creation and exchange when the prevalence of uncertainty is high [94].

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. Therefore, appropriate strategies to secure neutrality and independence are absolutely vital because of the threat to lose the necessary variety of potential aspects and the possibility to be instrumentalised by other, often funding organisations. In the case of NanoTrust the securing of independence and neutrality [94] has been achieved by several measures, such as

- Expanding the basis of support: while initially the project was funded exclusively by the BMVIT, it went on to include contributions of the Federal Ministry of Health (BMG), the Federal Ministry of Agriculture, Forestry, Environment and Water Management (BMLFUW), the Federal Ministry of Labour, Social Affairs and Consumer Protection (BMASK) and the Austrian Workers' Compensation Board (AUVA).
- Introducing an international advisory board, which convenes on an annual basis (twice annually during the first years) and is tasked with monitoring the strategic development of the project.
- Open and transparent communication: maintaining a culture in which it is possible to openly communicate is vital to ensure that the project tasks can be pursued appropriately, since it enables the project members to set boundaries for the NanoTrust work in a flexible manner, as is required when following a moving target. This necessitates the presence of trust between the funding bodies and project team. It is also important to communicate the exact roles of all involved people and also to clarify the functions to the network, allowing for transparency and accountability.

- Focus on a scientific basis: an example is provided by the NanoTrust dossiers, serving to disseminate fact-based information. The dossiers seek to summarize information on a specific topic in the area of nano-specific risks, primarily in the areas of health and environment.
- Official commitments and functions in official and federal committees and working groups, which on the one hand broadens the perspectives and options and on the other hand increases the perceived reliability of the participating project members.

3.2.3 Ambiguity

As the IRGC points out ambiguity includes two different aspects. Firstly, it denotes the variability of reasonable interpretations based on identical observations or assessments. This is the normal situation in research, especially in emerging fields which are on the brink of defining their research object. This type of ambiguity can only be solved by increasing research, generating data and fostering cognitive debate. The second aspect of ambiguity reaches far beyond the limited sphere of science and indicates situations where normative decisions have to be taken. In this case different appraisal of the same set of information is based on different values or world views.
The methodological debate following the seminal publication of Poland et al. [95] on CNT-toxicity in mice might serve as an appropriate example for scientific ambiguity. The authors found an increased propensity of mice to develop granuloma as consequence of chronic inflammation after inhalation (or rather instillation) of a certain type of carbon nanotubes. Whereas the authors insisted that their findings should be treated as preliminary result a lively debate developed focusing on issues like the application of different CNT tapes, the technical way of bringing the fibres into the mouse lung and even the applicability of the mouse model on human pathophysiological processes.
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 (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. In the case of nanomaterials, it has been suggested to apply the surface reactivity as the most important parameter. Up to now, the area and the surface reactivity have been considered the most important quantities in terms of dose. However, it is still unclear whether this understanding is actually accurate [96].
The last example illustrates decisional ambiguity and refers to the definition of threshold levels in workplaces where nanomaterials are used, manipulated and processed. Although there are still no binding workplace limit values for most fine dusts and dusts from nanomaterials, recommendations for significantly lower threshold values have already been proposed for some nano-substances. These recommendations vary depending on the responsible authorities even if they concern the same substances. For example, threshold levels for silica fine dust (SiO2) are recommended to be below 0.025mg/m^3 by the US National Institute for Occupational Safety and Health (NIOSH), while the European OSHA (Occupational Safety and Health Administration) establishes

0.100 mg/m^3.[3] In Germany even lower values are valid since 2016. The threshold level recommended by German authorities lies at 50% of the OSHA value or 0.050 mg/m^3.[4]

Especially in the case of new and emerging technologies such as the nanotechnologies the occurring various uncertainties lead necessarily to a well-balanced application of the precautionary principle as long as the scientific evaluation is not fully clarified and reasonable assumptions of possible threats to human health and the environment exist.

3.3 Relevance of the PP to the case

The first mentioning of nanotechnology within an EU-level strategic document can be found in the 5th Research Framework Programme (FP5) of the European Commission (EC) for the period of 1998-2002 [12], articulating the priorities for the European Union's research, technological development and demonstration activities: *"In order to develop from a visionary perspective future and emerging technologies with a potential industrial impact, research topics could include, in a non-prescriptive way: [...] nano-scale, quantum, photonic, bio-electronic technologies, including future generation integrated circuits, ultrahigh performance computers and super-intelligent networks".*
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 European Commission formulated a series of interconnected actions for the immediate implementation of a safe, integrated and responsible approach for nanoscience and nanotechnologies in 2005 [61] and adopted the Communication "Towards a European Strategy for Nanotechnology" mentioned here.
Within the action plan for Europe 2005-2009 for nanosciences and nanotechnologies, the European Commission reviewed relevant EU legislation to determine the applicability of existing regulations to the potential risks of nanomaterials. The Commission published a Communication in 2008 which stated that, despite the fact that the term "nanomaterials" is not specifically mentioned in EU legislation, the existing legislation covers the potential health, safety and environmental risks in relation to nanomaterials in principle [20] (see also chapter 2).
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."* [13]

[3] U.S. OSHA: Standard No., 1926. 1153 -Respirable crystalline silica (March 2016),https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.1153
[4] Nanoinformation.at, https://nanoinformation.at/fileadmin_nanoinformation/user_upload/Arbeitsplatzgrenzwerte_2019.pdf

Nanotechnology opens up many opportunities and its fields of application are already numerous. However, human health and the environment must be protected - only in this way can the opportunities offered by the new technologies be exploited in the long term and in a sustainable manner. At the 11th Nano Authorities Dialogue in March 2017, which took place in Vienna, the representatives of the authorities of Austria, Luxembourg, Liechtenstein, Switzerland and Germany agreed on a catalogue of measures to promote the sustainable and safe development of nanotechnology. The "Vienna Declaration" was presented to the Council of the European Union (Environment) in June 2017.[5]

[5] https://nanoinformation.at/bereiche/regelungen/

4 Risk governance and the precautionary principle

4.1 Political and juridical dynamics

4.1.1 Legal acts

In this chapter, we focus on the political and juridical dynamics of nanomaterials with special emphasis on the EU and Austria. National legislation in the field of nanomaterials and chemicals regulation is highly dependent on EU-wide regulations. 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. Additionally, some of the Member States established national mandatory reporting systems for nanomaterials, which is addressed in chapter 4.1.2.

The first mention of nanotechnology within an EU-level strategic document can be found in the 5th Research Framework Programme (FP5) of the European Commission (EC) for the period of 1998-2002 [12], articulating the priorities for the European Union's research, technological development and demonstration activities: *"In order to develop from a visionary perspective future and emerging technologies with a potential industrial impact, research topics could include, in a non-prescriptive way: [...] nano-scale, quantum, photonic, bio-electronic technologies, including future generation integrated circuits, ultra-high performance computers and super-intelligent networks".*

Regulation of Chemicals: The instruments concerned with the legislation of nanomaterials in the European Union are the REACH Regulation (EC) No 1907/2006 (Registration, Evaluation, Authorisation and Restriction of Chemicals) [17], which has been in force since 2007, and Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of dangerous substances and mixtures [97], which entered into force in 2009. Nanomaterials are not explicitly mentioned but covered by the "substance" definition in both regulations, nor is the PP but *"REACH is based on the principle that manufacturers, importers and downstream users have to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle."* [98]. REACH requires companies that produce or import chemical substances in quantities equal or more than one ton per year to register these in a central database. Since 2009, the European Parliament has called for the introduction of a comprehensive scientifically based definition of nanomaterials in EU legislation, as well as a European nano-registry containing information on nanomaterials and their use on the European market. In 2011, the European Commission published a recommendation on the definition of "nanomaterial" [28], which was and still is not legally binding, but currently under review [99] but stated no need for a harmonized EU-wide registry. Since 2013, the European Commission has been examining to what extent REACH can be adapted to regulate nanomaterials and finally amended REACH Annexes in 2018, concerning new and already existing registrations and explicitly addresses nanoforms of substances. More specific requirements are thereby provided within the framework for the risk management of nanomaterials [100]. Nanoforms must be identified and characterised within the registration, whereby they can be documented individually or in joint sets of similar nanoforms. Information is to be provided on particle size, shape and surface properties of the nanoforms, as well as on volumes and uses of nanoforms.

Calls for a harmonised regulation on nanomaterials now go back a decade, referencing the unique aspects of nanotechnology [101]. Nevertheless, within the European Union the precautionary principle, as detailed in Article 191 of the Treaty on the Functioning of the European Union [102], sets high standards regarding the health of humans and the environment, as well as consumer protection. This means that only products which have

their safety tested may be placed on the market. Products containing nanomaterials are currently explicitly regulated within sector-specific legislation. To date, nanomaterials are specifically addressed within regulations for cosmetic products, novel foods, food contact materials, food additives, medical devices and biocidal products, including requirements for information on nanomaterials (labelling) and the safety assessment of these materials. In addition, there is a directive on disposal of electronic waste in which nanomaterials are mentioned [36]. The various sector-specific regulations are listed below and taken from our latest Dossier [103]:

Cosmetics: The Cosmetics Regulation (Regulation No 1223/2009) [23] stipulates that the European Commission is to be notified of the content of nanomaterials in cosmetic products. The content is to be declared in a list of ingredients by its chemical name followed by nano in brackets, e.g. "titanium dioxide (nano)".

The term nanomaterial is defined as *"an insoluble or bio-persistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm"*. The Cosmetics Regulation stated that all actions by the Commission and Member States relating to the protection of human health should be based on the precautionary principle.

Biocides: The Biocidal Products Regulation (Regulation No 528/2012) [33] requires specific assessment and approval of the nanoform. Nano silver, for example, must therefore be addressed specifically and does not fall under the assessment and approval of silver as such. Furthermore, the regulation requires the labelling of chemically active substances in nanoform.

The term nanomaterial is defined as *"a natural or manufactured active substance or non active substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm"*. The Regulation is underpinned by the precautionary principle to ensure that the manufacturing and making available on the market of active substances and biocidal products do not result in harmful effects on human or animal health or unacceptable effects on the environment.

Food and Feed: The Food Additive Regulation (Regulation No 1333/2008) [21] and the regulation on plastic materials and articles intended to come into contact with food (Regulation No 10/2011) [30] stipulate the specific assessment and approval of the nanoform of approved substances. In this regulation the PP is not explicitly mentioned.

Furthermore, the Novel Food Regulation (Regulation No 2015/2283) [41], comprising considerations in relation to specific requirements regarding nanomaterials: *"Novel foods should be safe and if their safety cannot be assessed and scientific uncertainty persists, the precautionary principle may be applied."*

The regulation on the provision of food information to consumers (Regulation No 1169/2011) stipulates that nanomaterials shall be clearly indicated in the list of ingredients. Regulation No 1169/2011 on the provision of food information to consumers defines engineered nanomaterials as *"any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale".* The regulation does not explicitly mention the precautionary principle.

Medical devices: The Medical Devices Regulation (Regulation No 2017/7745) is also undergoing revision with serious reflection regarding the introduction of requirements for labelling and specific assessment of devices that contain nanomaterials.

The term nanomaterial is defined as *"a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm; Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials"*. The regulation does not explicitly mention the precautionary principle.

Electronics: The directive on restriction of certain hazardous substances in electrical and electronic equipment (RoHS Directive 2011/65) and the directive on disposal of electronic waste (WEEE Directive 2012/19) mention nanomaterials but have not introduced specific requirements.
The European Commission has, however, introduced the Observatory for Nanomaterials to provide information about existing nanomaterials on the EU market.
European Union Observatory for Nanomaterials: While there is no EU-wide nano-registry, the objective of increasing the transparency of nanomaterials on the EU market has prompted the establishment of the European Union Observatory for Nanomaterials (EUON), an online initiative funded by the EU Commission and maintained by the European Chemicals Agency (ECHA) since its formal kick-off in December 2016. The EUON gathers existing information but does not collect new data on the occurrence of nanomaterials and therefore cannot replace an EU-wide registry. The website began operation in the summer of 2017. The aim is to provide "reliable and neutral information" about nanomaterials available on the EU market. The website contains summary descriptions of product categories, uses, regulations as well as references to studies and reports, including details of existing national reporting systems. However, concrete data on individual products containing nanomaterials are missing.

4.1.2 National Nano-Registries

A quite different approach to regulate the production and use of nanomaterials and nanotechnologies is national mandatory registries. These registries, which have been established in several countries within the EU and the EEA (France, Denmark, Belgium, Sweden, Norway) operate in rather different ways (e.g. different trasholds and requirments). According to a current comparative analysis of EU/EEA Member States, Germany, The Netherlands and Italy have considered but not established a national registry so far [104]. The decision to not develop or implement nano-registries at this time can be related to concerns of creating trade barriers.
France: The French nano-registry "R-Nano" was issued in 2012 and has entered into force on 01. January 2013. It was the first European national registry for nanomaterials. The aim is to ensure the traceability of sectors using these substances, to improve the knowledge of the market and the volumes sold, and to obtain available information on toxicological and ecotoxicological characteristics.[105] Subject of the registration are artificially produced nanomaterials as defined by the European Commission, which are circulated in quantities of at least 100 g per year. Amongst the required information is the identity of the registrant, the substance identity, quantity, use and professional users. The "Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement et du travail" (ANSES) is responsible for managing the registry.
Belgium: The establishment of the Belgian nano-registry was decided by decree in 2014 and came into force on 01. January 2016. As of 01. January 2017, the registration of substances or mixtures produced in nanoparticle states (such as paints and sunscreens) is also obligatory. The registry is regulated by Royal Decree concerning the Placing on the Market of Substances produced in nanoparticle state from 27. May 2014.[106] The creation of the registry is regarded as the first step in the management of nanomaterials and their impact on humans and the environment. The aim is to provide higher transparency about nanomaterials found on the market and about possible health risks. Traceability allows authorities to intervene, for instance in the case of a public health risk for workers. This registry is also intended to improve communication on nanomaterials for employees and in the commercial supply chain, with ambitions of strengthening public confidence in nanomaterials.
Denmark: On 13. April 2014, the regulation for a nano-registry was issued, which then came into force on 18. June 2014. The Danish nano-registry was introduced via Ministerial Order published in June 2014 (Danish Ministerial Order no. 644 from13/06/ 2014). Predating this, the Danish Chemicals Action Plan (2010-2013) already contained statements on nanomaterials and called for adjustments to REACH. The Danish

Parliament consequently decided to establish an inventory of mixtures and products that contain or release nanomaterials (Danish Environmental Protection Agency Guideline for Danish Inventory of Nanoproducts).[107] The objective of the registry is to enable an overview of nano-products in Denmark and allow rapid intervention by authorities in the case of health risks.

Sweden. The Swedish Chemicals Agency (KEMI) published a proposal in 2013 where the mentioned the lack of a clear definition, inadequacy of REACH and CLP and need for a reporting system for nanomaterials. KEMI enshrined the registration of nanomaterials which entered into force on the 1st of January 2018 [108]. KEMI is also the responsible authority for the product registry. The first registration deadline was 28. February 2019 and so far there is no evaluation report available. The aim of the regulations is to create an overview of what nanomaterials are present on the Swedish market. The purpose is to gain information on the types and quantities of the nanomaterials used in Sweden [109].

Norway. Norway stated from the beginning that the existing EU legislation does not properly deal with nanomaterials and sympathised with the member state initiatives of mandatory registries. The duty to report to the Norway Product Register is determined by the "Regulations relating to the declaration of chemicals to the Product Register" [110] and information about the content of substances in nanoform must be provided, with the definition of "nanomaterials" following the EU Recommendation. The declaration of chemical products containing one or more substances in nanoform (mixture) to the Norwegian Product Register was obligatory from March 2015 and registration has to be done via an electronic declaration. The Product Register existing since 1981 is the official registry of hazardous chemicals in Norway and is managed by the Norwegian Environment Agency. The data of the registry is used to monitor chemicals, perform risk analyses related to chemical substances, compile statistics for the authorities, and to inform legislative work.

NanoTrust Dossier No.51en gives a concise overview over the recent developments regarding the use and the experiences with nanotechnology registries [103].

4.1.3 EU Code of Conduct

The Commission recommendation for a code of conduct for responsible nanosciences and nanotechnologies (N&N) research (code of conduct) dates from 2008 [24]. The code of conduct for responsible nanosciences and nanotechnologies research (code of conduct) is the Annex to the first nanotechnology-specific legal measure by the EU (2008), a Commission recommendation that is legally non-binding. The nanotechnologies code of conduct contains principles and guidelines for integrated, safe and responsible (ethical) nanosciences and nanotechnologies (N&N) research. The central control mechanisms are research prioritisation, technology assessment, ethical and fundamental law clauses/restrictions, defensibility checks and accountability [111]. The core of the code comprises seven principles.

Principle of public well-being: Under the heading "Meaning", the Commission requires that N&N research should primarily serve the interest of the well-being of individuals and society and should respect fundamental rights (Paragraph 3.1) and that research funds should only be given to research that is useful to the general public. The code encourages research institutions and member states only to pursue research "with the broadest possible positive impact" (4.1.13) and in particular support research projects "aiming to protect the public and the environment, consumers or workers and aiming to reduce, refine or replace ani-mal experimentation" (4.1.13).

Principle of sustainability: Safe and ethical research should contribute to sustainable development (3.2); N&N research should not harm or create a biological, physical or moral threat to people, animals, plants or the environment. The code of conduct encourages the denial of funding to research that could involve a violation of fundamental rights or "fundamental ethical principles" (4.1.15), and human enhancement research (4.1.16). Finally, the Commission requires funding bodies to

monitor the potential social, environmental and human health impacts of N&N research. (4.2.4).
Principle of precaution: N&N research should anticipate potential environmental health and safety impacts and maintain a high level of protection, avoiding risks without impeding in-novation (3.3, 4.1.5). As long as risk assessment studies on long-term safety are not available, nano-objects should not be intruded into the human body, food or other consumer related products (4.1.17). In order to protect workers and researchers against potential hazards and risks (4.2.1), the Commission insists on specific regulations and risk and ELSI re-search (4.2.5, 4.2.7).
Principle of democracy: The code of conduct envisions all stakeholders participating in the decision-making process (3.4, 4.1.8), research being conducted transparently (4.1.6)8, the presentation of research results being clear, balanced and comprehensible and made generally accessible (4.1.2, 4.1.4, 4.1.8, 3.1, 3.4). The EU is intended to serve as a forum for discussion to permit an appropriate debate on social concerns and hopes (4.1.1). The corresponding information and communication would be the responsibility of the Member States (4.1.1). All stakeholders are encouraged to participate in the determination of the content of N&N research (4.1.8, 4.1.10). Finally, the code requires the Member States and the research funding bodies to disseminate the code and its principles (4.3.1, 4.3.2).
Principle of excellence: N&N research should meet the best scientific standards (3.5), for which in particular the Member States and the research bodies are responsible. The Commission attempts to prevent "dubious practices" and to protect whistleblowers either through the employer or legal regulations (4.1.5). The code requires peers to verify the scientific results before they are widely disseminated (4.1.4).
Principle of innovation: N&N research should take place within an innovation-friendly environment (3.6), public authorities and standardising organisations should develop N&N research standards (4.1.11) and the Member States and research funding bodies should devote an appropriate part of research funds to risk assessment, standardisation and the refinement of metrology methods (4.1.12). The grant of funds should be preceded by a cost-benefits analysis (4.1.14) and funds should only be awarded if a risk assessment is presented together with the application for funding (4.2.3).
Principle of responsibility: Researchers and research organisations should "remain accountable for the social, environmental and human health impacts that their N&N research may impose on present and future generations" (3.7). To this purpose, researchers should conduct participatory foresight exercises (4.1.9). In order to ensure that the stakeholders actually comply with the principles of the code and other relevant legal regulations, the Commission wants the Member States to provide sufficient resources to monitor and control N&N research (4.1.6, 4.3).

4.1.4 Nano-Standards

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. The committee is chaired by a member of the Institute of Technology Assessment (ITA) of the Austrian Academy. In 2019 a support project for AG 052.73 has been established at the ITA funded by the Austrian Ministry of Technology. The project is intended to generate additional knowledge on nano R&D, nano safety research and technology assessment and to increase the engagement of Austrian nano expertise in international standardisation projects, mainly the committees ISO/TC 229 "Nanotechnologies" and the CEN/TC 352 "Nanotechnologies".
The European CEN/TC is led by AFNOR, the French standardisation organisation (Association Française de Normalisation). Its scope is to increase the understanding and control of matter and processes at the nanoscale, typically, but not exclusively below 100 nanometres in one or more dimensions, where the onset of size dependent phenomena usually enables novel applications. Additionally, the technical committee strives to

improve the utilisation of the properties of nanoscale materials that differ from the properties of individual atoms, molecules or bulk matter, to create improved materials, devices and systems that exploit these new properties. Specific tasks include developing standards for: classification, terminology and nomenclature; metrology and instrumentation, including specifications for reference materials; test methodologies; modelling and simulation; science-based health, safety and environmental practices; and nanotechnology products and processes. For the time being, 19 standards have been published since 2010, mainly on vocabulary (CEN ISO/TS 80004 series) and characterisation of nano-objects. Several specific guidelines have also been published in recent years, such as a guideline for Life Cycle Assessment (CEN/TS 17276:2018) and more recently guidelines for the management and disposal of waste from the manufacturing and processing of manufactured nano-objects (CEN/TS 17275:2018).
The technical committee at the International Standardization Organization (ISO/TC 229) is led by the British Standardisation Institute (BSI). The scope of the ISO/TC 229 is more or less congruent to the CEN/TC and focussed on a better understanding and control of matter and processes at the nanoscale and utilising the properties of nanoscale materials. The CEN/TC 229 has been founded in 2005 and 72 standards have been published up to now (April 2020), whereas 36 standards are currently under development.

4.2 Risk management

Risk management measures are dependent on the sector-specific pre-conditions 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. In the following there have been two cases chosen to illustrate sector specific risk management activities, one case shows the reaction of the French government regarding the re-evaluation of titanium dioxide by the International Agency for Research on Cancer (IARC), and the other case certain management approaches concerning the handling of nanomaterials and nano-objects at workplaces. At least the risk management by networks is explained in the case of Austria.

4.2.1 Risk management by risk managers - Workplace safety

Worker protection and laboratory safety were very soon discussed as priority topics because the most exposed persons – those who are the first to come into contact with nanomaterials – are those involved in the production, transport and processing of these materials. Nanomaterials and products containing such materials are already in widespread use because they exhibit technologically interesting, nano-specific features such as increased tensile strength, improved electrical conductivity, special optical characteristics or special medico-chemical properties. But exactly these features (high reactivity) are also major risks for those persons who have to handle them.
As early as in 2007 several studies already reported data on exposure levels of nano-substances at the workplace[112][113]. In 2011, the German Council of Environmental Advisors also emphasizes, in connection with "precautionary strategies for nanomaterials", that one should concentrate "above all on a potential exposure at production and processing worksites"[114]. According to many of the worker safety relevant publications nanomaterials and nanosubstances create special challenges: Firstly, many of their characteristics – high reactivity and small particle size – make these materials technologically interesting, but also raise concerns because they could be associated with new health risks for employees. And secondly, the lack of robust monitoring systems for identifying nano-aerosols which could be inhaled makes it very

difficult to determine contamination levels in the ambient and what measures can reduce such contamination [114].
Regulation on the international level: Internationally, a series of concise suggestions ('best practices') have been presented to deal with the risks at the workplace in the nanotechnology industry.[115][116][117] In 2013 resp. 2014 the European Commission published concise guidelines with detailed recommendations for handling nanomaterials both for workers and for employers [38][40].
Regulation at the national level: A "Guidelines for risk management in handling nanomaterials at the workplace" was commissioned by the Central Labor Inspectorate of the Austrian Ministry of Social Affairs in November 2010. It was designed to provide practically oriented and easily understandable support, especially for smaller and medium-sized businesses. This guideline orients itself according to traditional risk assessment methods for chemical agents. Beyond a list of recommended operational steps, it also contains a collection of summary-like descriptions (so-called theme sheets) on a total of 15 topics including definition and characterization, risk assessment, risk management, and measurement of nanomaterials [118]. In summer 2011, the Austrian Workers' Compensation Board (AUVA) published an official sheet "Nanotechnologies – Occupational and Health Safety" (M 310) designed to inform employees about protective measures for work-related exposure. The AUVA assumes that "the hierarchy of protective measures … is also [valid] for nanoparticles." Protective measures are to be established – as in other cases – based on a multi-level concept (substitution, technical, organizational and personal protective measures) [34].
There were also detailed recommendations published by scientific organisations (e.g. the US Research Council which focussed on laboratories) and industrial organisations (e.g. the German Chemical Industry Association or the Netherlands Federation of Chemical Industries). Together with the above mentioned governmental documents the recommendations arrive at more or less congruent statements, based on the precautionary principle (protective measures are to focus, as a precaution, on the suspected harmful features), hazard identification (safety efforts initially require recognizing potential threats although this is not always possible) and the application of cascading safety measurements (substitution, technical protection, organisational protection and personal care) [119].

4.2.2 Risk management by government - Ban of titanium dioxide in France

An example for a risk debate of nanomaterials and subsequent risk management is the case of titanium dioxide (TiO2). Already in 2006 the International Agency for Research on Cancer (IARC) of the WHO stated: „There is *inadequate evidence* in humans for the carcinogenicity of titanium dioxide", „There is *sufficient evidence* in experimental animals for the carcinogenicity of titanium dioxide", „Titanium dioxide is *possibly carcinogenic to humans (Group 2B)*" [120].
In 2017 an unexpected amount of nano-TiO_2 in food and cosmetic products was subject of public debate in France. Consumer protection groups first addressed that many cosmetic and food products do not fulfill the legal labeling requirements, having found them to contain nanomaterials without being labelled as such. The French General Directorate for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) confirmed the claims of the consumer protection groups [121], prompting a political response [122]. The debate surrounding TiO_2 (not solely nano-TiO_2) led to a petition to remove the food additive E171 (TiO_2) from the French market [121], with the French government ultimately deciding a ban on placing E171 and products containing E171 as a food additive on the market for at least the duration of the year 2020[6]. In 2019 the

[6] Legifrance (Rule No. 2018-938 vom 30. Oktober 2018) [LOI no 2018-938 du 30 octobre 2018 pour l'équilibre des relations commerciales dans le secteur Agricole et alimentaire et une alimentation saine, durable et accessible à tous]
https://www.legifrance.gouv.fr/eli/loi/2018/10/30/AGRX1736303L/jo/article_53

French Agency for Food, Environmental and Occupational Health & Safety (ANSES) points to recent studies describing damage to intestinal cells and possible genotoxic damage related to E171 and emphasized the uncertainty surrounding the oral uptake of TiO_2 due to lacking data[7]. The European Food Safety Authority (EFSA) re-investigated the use of E171 as a food additive in light of the developments in France in 2019 and concluded that there is no new evidence to support a ban [123] . Concerning the risks of inhalation of TiO_2, however, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) has proposed in 2017 to classify TiO_2 as a category 2 carcinogen through inhalation under REACH regulation, following the ANSES' proposal of a classification as a class 1b carcinogen [124]. The debate surrounding TiO2 was mainly restricted to France and did not take place in German-speaking public arenas [125]. The example shows that the size-based definition narrows the view because investigations have shown that titanium dioxide is often used in sizes very close to 100 nm, so that it does not meet the definition and does not have to be labelled as a nanomaterial in food, for example. However, the properties of the particles just above the 100 nm limit do not differ significantly.

4.2.3 Risk management by network – Nano risk governance in Austria

The Austrian nanotechnology research programme (Nano Initiative - NI) started in 2003 and an accompanying technology assessment (TA) was suggested from the Institute of Risk Research (IRR) of the University of Vienna to complete the three existing R&D oriented research program lines [126]. Despite the recommendation of the NI it took more than three years to place the first safety-relevant projects. In 2006, the Institute of Technology Assessment (ITA) at the Austrian Academy of Sciences has been assigned to produce a status report on the international environmental, health and safety (EHS) and ethical, legal and societal implications (ELSI) of research regarding nanotechnologies and nanomaterials by the Austrian Ministry of Traffic, Innovation and Technology (BMVIT) [127]. This may be interpreted as a strong indication for the fact that public debate on safety relevant issues have become more relevant to authorities by then [128]. In 2007 the NanoTrust project, dedicated to nano-safety and governance, was funded by the BMVIT.
In 2009, Austria addressed the central issues of nanotechnology by drawing up the Austrian Nanotechnology Action Plan (ÖNAP) [25], which was generated by the interdisciplinary cooperation of several federal ministries and agencies and institutions from science and economy, as a direct consequence of the ongoing discussion in the already existing nanotechnology network. The core of the Action Plan consists of about 50 recommendations for specific Austrian measures at national, European and international level and explicitly mentions the PP several times. The interdisciplinary working groups dealt with the topics 1) health and employee protection, 2) environment, 3) economy and 4) science, research and development. All interdisciplinary working groups invoke the PP. In all resumes it is implicitly mentioned.
Opportunities were seen primarily in the improvement of product properties. However, when considering nanomaterials in the work environment and worker protection, the focus is placed on the, as yet insufficiently clarified, possible risks to human health and the resulting uncertainties rather than the opportunities [25].
Nanotechnologies and products have the potential to make a significant contribution to resource and energy conservation as well as waste avoidance. When assessing the environmental impacts of nanotechnological processes and products, a life cycle-oriented approach is necessary [25]. To date, these considerations are often missing or incomplete. The results of the latest national project from the NanoEHS fund (NanoAdd)

[7] ANSES (12. April 2019): ANSES Opinion No. 2019-SA-0036,
OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the risks associated with ingestion of the food additive E171, 40 S.,
https://www.anses.fr/fr/system/files/ERCA2019SA0036EN.pdf

showed that industry (according to its own statements) tends to avoid the use of nanomaterials because of the high potential of uncertainty.
The Austrian Nanotechnology Action Plan states that nanotechnological innovations should strengthen Austria as an economic region. Resource conservation is a possible contribution to a more sustainable development of new products using nanomaterials, but this this has to be accompanied by in-depth risk research. Therefore, the national research funding program on environmental, health and safety of nanotechnologies (Nano-EHS) has been established in 2011 and is since then dedicated to foster research on safety aspects of nanomaterials.
A primary goal was to involve the public in the creation and implementation of the ÖNAP. Therefore, both the draft (2009) and the implementation report (2012) were subject to public consultation on the internet. The comments received were published and considered.
The beneficial aspect of nanotechnology seems to play an important role in terms of public acceptance as well as the safety of nanotechnological applications. The further development of safety research and regulation therefore occupies a major place in Austria and is also being pursued to date in the national NANO Environment, Health and Safety research programme and by the NanoTrust accompanying research project, which became a part of the Austrian nano risk governance landscape itself.
During the years since 2007 a complex system of different and complementary instruments to assess and to regulate the production and the use of nanomaterials has been established in Austria, engaging several dozen organizations and employing different formats and instruments such as a national communication strategy in nanotechnologies, a federal commission for nano safety and an independent nano safety research programme. The project NanoTrust has been involved in the conceptualization and practical implementation of these instruments from the very start in 2007. Figure 3 gives an overview over the main instruments of the Austrian nano governance system.

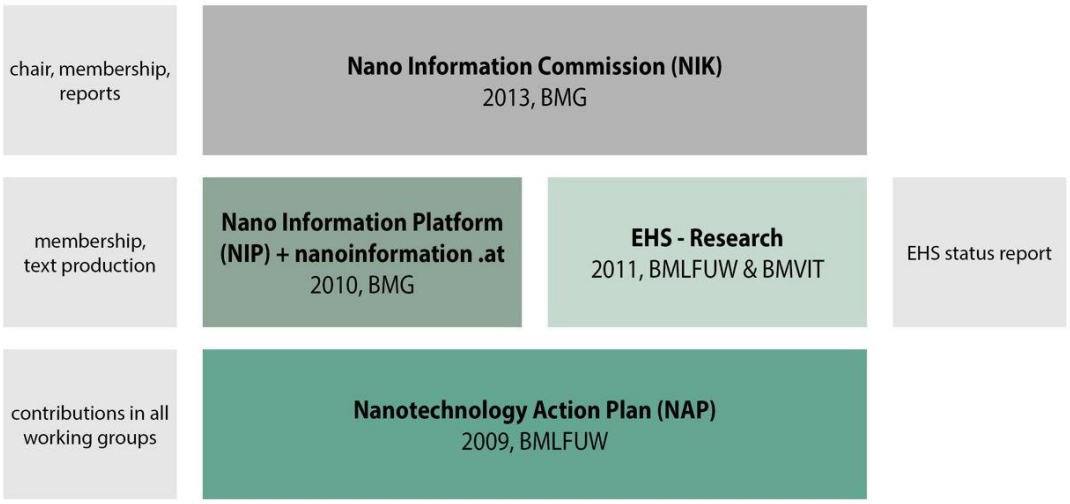

Figure 3: The Austrian nano governance system and the role of NanoTrust (grey fields) – *BMG … Ministry of Health, BMVIT … Ministry of Technology, BMLFUW … Ministry of Environment.*

The basis for the development and the core for the nano risk activities is the Austrian Action Plan Nanotechnology (NAP) published in 2010 which has been described earlier. A very important element regarding many of the conceptual aspects were drawn from the work of the long-term research project NanoTrust at the Austrian Academy of Sciences (s. above) which has since its inception in 2007 become an element of the governance system itself. NanoTrust has also played an important role in implementing and at least

partly operating many of the main elements, it is involved in shaping the nano-EHS-research programme (and therefore not liable to apply for its scientific calls as a project partner) and serves as regular provider of scientific content regarding nano risk and safety issues for the public information portal nanoinformation.at.
One of the concrete outputs of the NAP was the foundation of a Nano Information Platform (NIP) aiming to bring together experts from a wide variety of fields to establish transparent public communication on the safe use of nanomaterials. The NIP is a non-formalised, open (people participate on a voluntary basis and they are free to come and go whenever they want) yet stable (as in the sense of committed people who participate from the onset) group of around 10 – 12 stakeholder representatives (ministries, safety agencies, NGOs and research organisations), coordinated by the Ministry of Health. NanoTrust has taken part in this public communication network from its very beginning in 2010 [126].
The result of these NIP expert discussions was the establishment of a nano-information portal (nanoinformation.at), hosted by the Austrian Ministry of Health yet being a common project of all the concerned ministries and other organisations such as the Austrian Academy of Sciences and Austrian Food Safety Agency. Since 2012, it ensures transparent public communication on the safe use of nanomaterials through a continuous information flow between experts and the interested public. It gives people the option to interact with regulatory authorities and experts in case there are questions and concerns. Consumers' questions are collected through the portal and answered within a 2-week timeframe after establishing an intercommunication process among collaborating experts. Material for this public information platform is developed in different self-organized working groups.
A stable working group on worker safety was established in June 2011, under the responsibility of the Austrian Worker Compensation Board "AUVA", the biggest insurance company for workplaces in Austria. NanoTrust has initially suggested to install such a permanent working group and has since then been part of it and regularly takes part in their meetings until today. The nano – information portal establishes a two-way communication process by i) producing nano safety and risk relevant info addressing the interested public and ii) answering the consumers' questions. The NIP has been active since 2010, convening 2 or 3 times per year, being responsible up to date for the following tasks: operation and maintenance of the portal, public communication (consumers and the interested public), publication of risk and safety relevant documents produced by its members for use on the portal.
NanoTrust has been especially involved, from the onset, in the creation of the Nano Information Commission (NIK) of the Austrian Ministry of Health which represents the most formalised element of the Austrian nano risk governance landscape. The NIK was founded in 2013 as an advisory board to the Minister of Health. It consists of 23 members from ministries, agencies, universities as well as two NGOs. It convenes two to three times a year having as main tasks i) to provide all members with information on the current research and developments in the field of nanotechnology safety, ii) to offer an opportunity to discuss and evaluate these findings and iii) to foster safety-relevant research concerning the use of nanomaterials in Austria. The NIK is concerned with the implementation of the Austrian Nano Action Plan and represents the diversity of opinions and the professionally sound state-of-knowledge of various scientific experts. In contrast to the NIP, the NIK is not an open network: Proposals for new members can be made by the plenum. ITA designates one full membership and a substitute to the NIK. The chair is hosted for 5 years and currently held by the Coordinator of the NanoTrust project. In 2019 the Nano Information Commission started its second period of operation and the Coordinator of the NanoTrust project has been re-elected as chair until 2023.

4.3 Other governance dynamics

4.3.1 Public risk perception

Considering the public perception of risks with regard to technology controversies has increasingly become important since the debates on genetically modified organisms (GMOs) in Europe. The perception of risks by the population can differ tremendously from the expert judgement and in many cases does so. Risk Perception can be dissimilar in different cultures, societies, nationalities and between genders. Furthermore laymen (public), experts (risk community), policy makers, NGO´s and industry rate risks differently and hold different perspectives. Generally, laymen put more focus on severity of damage while experts place more emphasis on the probability of occurrence [129].
The topic of public perception of risks of nanotechnology has been studied institutions in the European region [130]. Table 1 shows a few studies on public risk perception carried out by European institutions.

Area	Title/ Name of project	Authors/ Publishing organisation	Time/ Period	Methodology
EU 27	Eurobarometer 73.1: Biotechnology[33]	TNS Opinion & Social (Brussels) on behalf of the European Commission	2010	Quantitative
GER, CH	Nanotechnology from the perspective of consumers[34]	Eidgenössisches Department des Inneren (EDI), Bundesamt für Gesundheit (BAG), Stiftung Risikodialog	2012	103 qualitative individual interviews
GER	Nanoview[35]	Bundesinstitut für Risikobewertung (BfR)	2013	Quantitative

Table 1: European risk perception studies. [130]

The European Commission regularly monitor the publics opinion on various topics. In Eurobarometer 55.2: Science and Technology in the Awareness of Europeans, nanotechnology per se was first mentioned as relevant technological future developments but the topic was met with little interest in 2001 (compared, for example, with medicine). It also revealed that the population, in their own estimation, said they had very little understanding of the technology itself [131]. In 2005s Eurobarometer 63.1: Europeans, Science and Technology the topic nanotechnology was still of little interest with 8% compared to medicine with 61% [132].
The European Eurobarometer of 2010, under the topic of "biotechnology", was inter alia concerned with nanotechnologies as one of several investigated "new" technologies. More than 26.600 personal interviews were carried out in all 27 EU member states, on a representative scale according to the respective populations. The study showed that the topic of nanotechnology was largely unknown to the population. Nanotechnology was generally significantly less known than genetic engineering, however, with large differences with regard to nationality, gender, level of education and level of information among the questioned persons.
The assessments of nanotechnology and consequences were quite unspecific. Some questions and statements were met with clear positions by the test persons: For example, they agreed that nanotechnology was "unnatural", but also that it was "good for the national economy". They quite clearly rejected that "nanotechnology makes you uneasy". With regard to other questions, the responses were less clear and more evenly distributed among "Agree", "Disagree" and "Don't know" (e.g. with regard to

nanotechnology helping people in developing countries, being safe for future generations, benefitting some peoples but putting others at a risk or constituting a harm to the environment). The majority viewed nanotechnology as good for the economy, but there were large country differences (20%-60%), whereby the level of knowledge plays a decisive role.
The study "Nanotechnology from the perspective of consumers" was conducted in 2010 in cooperation between the Swiss Federal Department of Home Affairs (Eidgenössisches Department des Innern, EDI), the Swiss Federal Office of Public Health (Bundesamt für Gesundheit, BAG) and the Risk Dialogue Foundation (Stiftung Risiko-Dialog). The study analysed 103 qualitative, open and personally conducted interviews in Baden-Württemberg (53) and in German-speaking Switzerland (50). The same contained a care-fully selected and near-representative selection of tests person with regard to gender, age and level of education [133]. The study confirmed the above generally low level of awareness of nanotechnology. Knowledge on specific fields of application and possible usage decreases with the exception of cancer treatments, paints/polishes, textiles and cleaning agents. Generally, while the population does not have a clearly more negative attitude than earlier, the topic's ambivalence has increased (49%), ambivalence has increased (49%), including the expectance of risks (67% expect health risks, 40% expect environmental risks). Overall, nanotechnology does not play a role in their perception (40%). The study also addresses the question of social trust: With regard to actors, science and authorities enjoy the largest trust.
The German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) conducted inter alia a study on the public opinion of nanotechnology in the project "Nanoview" and on possible communication strategies [37]. This study analysed a representative sample of the German population, consisting of 1200 persons. 200 of these test persons received detailed information on nanotechnology in advance in order to determine the influence of information material on risk perception. The study shows – similar to the Eurobarometer – that the unawareness of nanotechnology as well as its assessment as increasingly important. While the test persons are more critical in their weighing of risks and benefits than in an earlier study in 2008, the majority of the population still remains positive. The acceptance of nanotechnology depends on its field of application: Application distant from the body, as well as environmental and medicinal application generally are seen more positive. With regard to social factors, the most important variables of the study are gender and age: Men tend to be better informed and more positive than women, young people better than older people. Education, house-hold size, income or migration background were not found to have an influence on the attitude of the test persons.
All in all, it can be observed that with regard to the German speaking area (Germany, Austria, Switzerland) (studies ranging from 2006 to 2013) found that the topic of "nanotechnology" was largely unknown to the population with a low level of risk perception and a low level of awareness of nanotechnology. A well-established standard of high level of precautionary regulation can be seen as a positive effect on the public risk perception in this case and area [130].

4.3.2 Public dialogue

Nanotechnology has been massively influenced by dialogue.[8] 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 German federal government, according to its 2015 Plan of Action, therefore wants to conduct "a comprehensive dialogue with the public about the opportunities and effects of

[8] For a collection of dialogue projects on nanotechnology, see the European Commission webpage under http://ec.europa.eu/research/industrial_technologies/policy-dialogues_en.html

nanotechnology" [134]. Moreover, if one considers that the Synthetic Nanomaterials Action Plan adopted by the Swiss government views "communication and promotion of open dialogue about the opportunities and risks of nanotechnology" as the first and most important measure to be taken,[135] and that the Austrian Nano-Action Plan takes "developing cooperation and reinforcing the dialogue and transparency among all stakeholders, including the general public" to be a central task [25]. Public dialogue obviously has a political dimension and has become a political reality in the context of the management and regulation of new technologies, both on the transnational and national levels [136].
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 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].
Dialogue processes constitute the method of choice for risk communication activities. They enable the creation of a connection between societal actors, especially politics, the public, industry and academia and establish a platform for the institutionalised and focused exchange between the communication participants. Those dialogues can be informational, consultative or participatory. During the years every type of dialogue process has been employed on various aspects concerning the production and use of nanotechnologies and nanomaterials. Table 2 gives an overview over the most important nanotechnology dialogue processes carried out in the German speaking countries.

Type	Germany	Austria	Switzerland
information meeting	nanoTruck	NanoInformationsPortal	Expo Nanotechnologies
participatory dialogue	NanoSafety-focus groups		publicfocus
consultative or stakeholder dialogue	NanoDialog of the NanoKommission	Nanotechnologie-Informations-Plattform	BAG NANO-Dialogplattform

Table 2: Dialogue processes in German speaking countries. [137]

Political and scientific discussions on nanotechnology focused on the concern that the public or finally the consumers could respond to the newly implemented key technology with similar fears concerning risks and thus with rejection as it already was the case with some subareas of biotechnology and genetic engineering (e.g. green genetic engineering, cloning) [2].
In Switzerland, the population was surveyed using the publifocus method in 2006, which is a dialogue procedure developed by TA-SWISS. This allows an early contribution to an objective discussion of the possible consequences of technological progress. This method is not used to draw up recommendations and the results do not claim to be representative of Switzerland as a whole. However, they do reflect the population's assessment and provide concrete indications of further fields of action. Results show that there were societal concerns about ubiquitous communication technology, both ethical and social, as privacy and human rights could be threatened by nano-sensor networks, computers and microscopically small nano-cameras and nano-microphones, which could enormously increase surveillance. There were also concerns about the use of nanoscale instruments in medical diagnostic like nano-implants [138].

4.3.3 Media coverage

Media have a significant influence on the public image of science and technology, especially in areas where the public usually has no direct contact with and no immediate idea about the research field. 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. Especially in the beginning of the public discussion on nanotechnologies quality press such as the "Neue Züricher Zeitung" (Switzerland), the "Frankfurter Allgemeine Zeitung" (Germany) and "Der Standard" (Austria) introduced to central aspects of technical applications, which also include the opportunities and risks associated with the new technologies. A comprehensive media analysis study for the German speaking countries has been conducted during the cooperative project NanoPol[9], details of on the method and the results of this media analysis were published elsewhere [139].

Various actors are usually consulted by the media on their evaluation of the possible opportunities (chances) and threats (risks) of nanotechnologies. Scientists are the group of actors who are by far most frequently mentioned. This is typical for science reporting, as is the fact that the majority of the articles appeared in the science sections of the newspapers. Around 20% of the actors are persons from the field of business, a result confirmed by the strong thematic interest in commercially relevant fields of application. According to the above-mentioned study political actors played a comparatively small role, with neither political institutions nor decision-makers making a significant contribution to the media discourse on nanotechnology. This is due the fact that nanotechnology has mainly been treated as scientific topic and not as a political topic. Civil society organisations such as environment or consumer protection organisations, which tend to adopt a rather critical approach to controversial technical developments and mostly take-up opposing positions to the actors from science and business, also appeared in a rather reluctant role, at least in the German speaking media.

The reporting on nanotechnology in the media in the three German-speaking countries is largely science-centred and attracts 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].

[9] The "NanoPol" project was a cooperation between the Institute for Technology Assessment and Systems Analysis (ITAS) at the Karlsruhe Institute for Technology (KIT), the Institute for Technology Assessment (ITA) at the Austrian Academy of Sciences (OeAW), TA-Swiss in Berne and the Programme for Science Research of the University of Basel which lasted from 2010 to 2014. Several results of this cooperation were published in Gazsó, A. & Haslinger, J, 2014, Nano Risiko Governance. Der gesellschaftliche Umgang mit Nanotechnologien, Springer, Berlin

5 The precautionary principle and its future

5.1 Innovation principle

Nanotechnologies (in the beginning mentioned together with nanosciences) have been advertised as a promising new field of technology from the beginning. Future foresight experts stated that "the next big thing is really small"[141] and tried to convince interested parties to invest in innovative solutions in practically all conceivable areas of concern, starting from material physics, over new construction material, paints and varnishes, water and dirt repelling surfaces to new diagnostics and efficient drug delivery systems.
The European Commission set its hope in nanotechnologies and nanosciences in its action plan of 2005 and promotes nanotechnology as an area which will have highly promising prospects for turning fundamental research into successful innovations. But innovation is expected not only as mere art but in close connection to safety and sustainability. The Commission emphasises its will not only to boost the competitiveness of the European industry but also to create new products that will make positive changes in the lives of the European citizens, be it in medicine, environment, electronics or any other field. In the foreword to the action plan the then science commissioner Janez Potocnik mentions such applications as new engineered surfaces for better performance, new medical treatments for fatal diseases such as brain tumors or Alzheimers' disease, and new supercomputers using nanoscale components.
On the national level the innovative potential of these new group of materials has been always tightly linked to safety considerations. The German Research Strategy of 2007 lays its emphasis on the safe use of nanomaterials on workplaces and therefore seeks to foster research in the fields of human and environmental toxicology. Main goals should be the identification of nanomaterials, their chemical reactivity and their effects on living systems. Most important questions to answer are the possible exposition of persons on workplaces and the potential exposition of consumers. A necessary prerequisite for an effective risk management would be the adaptation of proper detection and measurement systems [142].
The recent updating of the common research strategy of the German authorities makes this tight interconnection between innovation and safety again clear: A safe and environmentally compatible design of innovative materials and their secondary products should largely rule out unacceptable risks for people and the environment right from the start. This can be achieved by either using inherently safe materials (safety of application) or a product design that is low in emissions and environmentally friendly over the entire life cycle (integrated application safety). Moreover, the consumer has to be properly informed and supported in applying these innovative materials and their products. Research priority 2 of the new research strategy aims at supporting the research institutions and industrial producers in developing application-safe and environmentally compatible material innovations and their use in secondary products by applying proper design processes (safe-by-design, see below) [143].
However, 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 [144].

5.2 Effect of the PP on innovation pathways

The innovation principle can be regarded as the counterpart to the precautionary principle which should be regarded in regulatory decisions whenever precautionary legislation is under consideration [145]. Critics warn of the risk that the innovation principle, whose origins lie in the industrial sector, could undermine the precautionary

principle and make it easier to circumvent EU safety requirements [146]. The juxtaposition of safety and innovation reflects a rather fundamental misunderstanding of the concept of safety which often is regarded as simple absence of risk which eventually means the absence of action. 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. 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.

In the case of nanotechnologies, the concepts of green engineering resp. green chemistry (as "green nanotechnology") and safe-by-design have been thoroughly discussed and are still under scrutiny. Projects like NANoREG, NANoREG2 and ProSafe even contain separate work packages for elaborating the concept of safe-by-design.

Green nanotechnology. United States Environmental Protection Agency (EPA) drew up the "Green Chemistry Framework", whose aim is to achieve a reduction of the production and use of hazardous substances. These principles were modified to be applied on the development of safe nanomaterials. NanoTrust lists a total of 12 Green Chemistry principles, which inter alia require real-time monitoring of synthesis processes or the development of chemicals and products that are degradable and do not accumulate in the environment [147]. The German Nano Commission lists the following green nano principles to ensure the safe and sustainable development of nanotechnologies and introduces the term "benign by design": [148]

1. Biomimetics
   i. Use of local materials and energy sources as well as renewable resources
   ii. Use of molecular self-organization as a manufacturing paradigm (e.g. biomineralisation for the manufacture of hierarchically structured, anisotropic, self-healing substances)
   iii. Physiological manufacturing conditions (e.g. aqueous synthesis)
2. Resource efficiency
   i. Atomic efficiency and molecular specificity (e.g. through preventing side reactions, use of enzymatic reactions, precision manufacturing, miniaturization/dematerialization, elimination of cleaning process, and avoidance of rare materials etc.)
   ii. Energy efficiency (e.g. improving production efficiency (electricity generation, light), reducing process temperatures, lightweight construction etc.)
   iii. Recyclability (e.g. avoiding losses through using limited range of materials, segregation/modular waste collection, minimizing use of additives and processing aids, avoiding diffuse emissions and contamination of materials)
3. Minimum risk – benign by design
   i. Avoidance of toxic substances and nanostructures or morphologies which pose a risk to health or safety or to the environment
   ii. Avoidance of problematic structures, morphologies and hazardous substances (e.g. bioaccumulation, persistence, ability to cross cell membranes)

iii. Responsible use of nanofunctionalities (e.g. preference of nanofunctionalities with less risks to human health and safety or to the environment or substitution of hazardous substances by inter alia selection of material and form, coating etc.)
iv. Prevention and minimization of potential exposure (e.g. through avoidance of mobility, bioavailability, being bound through a matrix or containment during process)

4 Energy and environmental technologies
i. Emissions reduction
ii. Environmental monitoring
iii. Environmental remediation in and ex situ
iv. Switch to renewable materials and energy sources

Safe-by-design (SbD). There are a number of concepts that use design approaches to aim for increased safety and hence can be qualified as SbD concepts, as well as those that include elements of SbD. All of them address the reduction of risks by including safety-relevant considerations in the innovation processes as early as possible and taking account of the entire life cycle of the material or product [149]. In recent years, many national and international projects have been dedicated to the SbD concept per se and to its practical implementation in industry. Alongside the strengths of the concept, such as the early addressing of safety-relevant issues, currently, however, a number of challenges concerning practical applicability have been identified. On EU level several projects like NANoREG, its follower NANoREG 2 and others have taken up the topic of SbD or focused on the earliest possible inclusion of safety in the innovation process for nanomaterials, products and processes. Table gives an overview of relevant research projects which include the elaboration of the SbD-concept.

Project title	Funding programme	Coordinator	Term
NANoREG A Common European Approach to the Regulatory Testing of Nanomaterials	FP7	Ministerie van Infrastructuur en Waterstaat, Netherlands	1.3.2013-28.2.2017
NANoREG 2 Development and Implementation of Grouping and Safe-by-Design Approaches Within Regulatory Frameworks	Horizon 2020	Institut National de l'Environnement Industriel et des Risques (INERIS), France	1.9.2015-31.8.2018
ProSafe Promoting the Implementation of Safe by Design	Horizon 2020	Ministerie van Infrastructuur en Waterstaat, Netherlands	1.02.2015-30.04.2017
NanoGenTools	Horizon 2020	Universidad de Burgos, Spain	1.01.2016-31.12.2019
NanoMile Engineered Nanomaterial Mechanisms of Interactions With Living Systems and the Environment: a Universal Framework for Safe Nanotechnology	FP7	The University of Birmingham, Great Britain	1.03.2013-28.02.2017
NanoFase Nanomaterial Fate and Speciation in the Environment	Horizon 2020	Natural Environment Research Council, Great Britain	1.09.2015-31.08.2019
EC4SafeNano European Centre for Risk Management and Safe Innovation in Nanomaterials & Nanotechnologies	Horizon 2020	Institut National de l'Environnement Industriel et des Risques (INERIS), France	1.11.2016-31.10.2019
caLIBRAte Performance Testing, Calibration and Implementation of a Next Generation System-of-Systems Risk Governance Framework for Nanomaterials	Horizon 2020	Det Nationale Forskningscenter for Arbejdsmiljø, Denmark	1.05.2016-31.10.2019

Table 3: EU projects on Safe-by-Design and the early integration of safety in innovation processes. [149]

5.3 Reflection on the PP in the literature

The Precautionary Principle has been the basis for many regulatory decisions regarding the development and implementation of nanotechnologies during the last 15 years. Even the establishment of a regulatory system as complex as the Austrian nano governance system can be interpreted as guided by precautionary considerations. As a consequence, it is reasonable to assume that all continuing concepts such as RRI which are elaborating the PP will play a considerable role in managing emerging risks in connection with new and advanced materials, nanomaterials being one important group of them.

Concepts such as the EU's Responsible Research and Innovation (RRI) shows that societal values and aspirations should be integrated stronger at the political level into the innovation process. Schomberg (2013) provides a (preliminary) definition of RRI: "Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products"[150].

On the EU level projects like Nano2All and GoNano try to fathom the relevance of the guiding principles of RRI. The European research project GoNano focuses on the public engagement dimension of RRI, especially on the aspect of co-creation of knowledge and products. It tries to unite industrial demands and public expectations applying various participatory approaches. The GoNano project analyses the framework of responsible research and innovation and its applicability for the development of emerging technologies, especially nanotechnologies, according to the four main dimensions of responsible innovation: anticipation, reflexivity, inclusion and responsiveness[10].

[10] http://gonano-project.eu/about-gonano/

6 Synthesis

The term nanotechnology has been introduced by several reports by the US National Science at the end of the 1990ies. As a new field of scientific interest nanotechnology research has been announced to serve as universal solution to many technical and non-technical problems, especially in various sectors of industrial production, but also in pharmaceutics and medicine. Because of their high variability and universal use nanotechnologies are considered to be key enabling technologies (KET). Together with other scientific and engineering approaches such as biotechnologies they belong to a cluster called converging technologies because of their high potential to be combined with other organic and inorganic matter on a small scale.

In the case of the extraordinary diverse field of nanotechnology, it became apparent very quickly that risk and safety issues were not or at least not sufficiently addressed under the existing regulatory regimes (food safety, workplace safety, chemical regulation) and the existing approaches to hazard identification, evaluation and risk management. Therefore, traditional exposure and risk assessment (including e.g. modelling or testing approaches) were not applicable for nanomaterials and risks for human health and/or the environment could not be ruled out.

From an early onset the European Commission propagated an "integrated and responsible approach" on nanotechnology in its Nanoscience and Nanotechnology Action Plan of 2005 based on the precautionary principle. Simultaneously, it strives to integrate innovation and sustainability (safety being one important aspect of sustainable development) by requiring the provision of favourable conditions for industrial innovation on the one hand and the respect ethical principles, integrate societal considerations into the R&D process at an early stage. Several national nanotechnology action plans were to follow this outline, such as Germany (2006), Switzerland (2008) and Austria (2010). All of these political approaches to develop nanotechnologies in a safe and responsible way were based mainly on three cornerstones, i.e. the advancement of an independent nanotechnology risk research, the establishment of a transparent public communication strategy on nanotechnologies and the support of national and international network building on risk and safety issues regarding the development and use of nanomaterials and nanotechnologies.

Toxicological research took up issues of human and animal health and environmental integrity regarding the fate of nanomaterials in living beings, their organs, cells and environmental media such as air, water and soil. Environmental, health and safety research (EHS) has been intensified several times during the past European and member state nanotechnology research programmes. Specific risk assessment schemes, such the ones of EFSA or ECHA, show the complexity of the topic and emphasize the uncertainties and ambiguities of the available knowledge. The enormous need of specific data makes it necessary to connect the many research programmes and specific national nanosafety projects of on to each other and in multi-level databases.

Regarding the regulatory situation at European level, there are various pieces of legislation that regulate nanomaterials in consumer products (cosmetics, novel foods, biocides, food contact materials), some of them in general and some of them in specific terms. These regulations are implemented in the member states of the European Union, within the framework of existing national legislation.

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 authorities 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. Many of these efforts have been increasingly linked to each other to exchange practical and procedural experiences, e.g. the "Behördendialog" of the German speaking countries and the nano risk governance system of the Austrian Nanotechnology Action Plan and its executing elements such as NanoTrust, the Nano Information Commission and the Nano Information Platform. Because of the high variance of nanotechnologies and the fairly universal use of nanomaterials it is not possible to give a one-for-all solution which can be applied to all applications and areas. To develop effective risk management measures, they have to be tailored to the concrete context where they have to be taken. An appropriate risk management regime will therefore tremendously differ by scope, accountabilities and responsibilities. Main emphasis has been laid upon workplace safety and consumer protection at a very early stage.

Considering the public perception of risks with regard to technology controversies has increasingly become important since the debates on genetically modified organisms (GMOs) in Europe. Keen not to live through the same mistakes which have been made in earlier cases nanotechnology research policy cared for public risk perception and participatory inclusion of consumer concerns from the start of the research programmes. This has been accompanied by the establishment of more or less open and transparent information policies, at least from side of the national and international authorities. 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.

The European commission and consequently many of the member states have made the attempt to integrate the allegedly opposing concepts of innovation and safety in the case of nanotechnology research and development. Unsurprisingly, already the European Nanotechnology Action Plan contains both provisions for fostering innovative technology development and the integration of health and safety issues to a comparable degree. In the case of nanotechnologies, the concepts of green engineering resp. green chemistry (as "green nanotechnology") and safe-by-design have been thoroughly discussed and are still part of on-going research projects. Upcoming activities are ready to make use of the guiding principles of RRI and the Sustainable Development Goals (SDG), especially the application of new and advanced materials and technologies for managing complex global challenges.

7 Conclusion

Technologies like nanotechnology and advanced materials are defined by uncertainties rather than risks. Governance processes of a technology characterized by a dominant risk frame will also be shaped by the availability of risk-relevant knowledge. While risks allow knowledge on possible outcomes and an expression in probabilities, uncertainty does not allow the assignment of probabilities to outcomes. Moreover, several aspects of emerging phenomena are influencing the available knowledge on a specific technology. 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 and motives to co-operate. Inter and trans-disciplinary deliberative expert dialogues can be a form of organising the process of knowledge creation and exchange when the prevalence of uncertainty is high. On the other hand, the integration of different interest groups and their values and concerns can contribute information that might be decisive for choosing an appropriate development path of a new technology. Finally, responsible authorities will have to take decisions on risk and safety relevant issues such as consumer protection, workplace safety and product liability which cannot be fully based on scientific understanding. This means that regulatory decisions have to be secured by additional aspects such as responsibility, accountability and social benefit.

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. In Austria this has been provided by the Austrian Academy of Sciences and its long-term research project NanoTrust which started in 2007 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 aspects and the possibility to be instrumentalised by other, often funding organisations. In the case of NanoTrust the securing of independence and neutrality has been achieved by several measures, such as expanding the basis of support: while initially the project was funded exclusively by the BMVIT, it went on to include contributions of the Federal Ministry of Health (BMG), the Federal Ministry of Agriculture, Forestry, Environment and Water Management (BMLFUW), the Federal Ministry of Labour, Social Affairs and Consumer Protection (BMASK) and the Austrian Workers' Compensation Board (AUVA).

An additional aspect which contributes to the stabilisation of risk and certainty assessment procedures is the building of national and international networks, either by establishing high level advisory boards or by forming specific working groups and committees. The involvement in the pragmatic work of international standardisation authorities (like CEN and ISO) and organisations (like OECD) increases the visibility of national expertise and contributes to the continuity of workflow and social integration.

An open and transparent communication maintains a culture in which it is possible to openly communicate is vital to ensure that one can pursue given tasks appropriately. This necessitates the presence of trust between the funding bodies and scientific assessment procedures. It is also important to communicate the exact roles and functions to the network, allowing for transparency and accountability.

Science based political counselling regarding the development and regulation of nanotechnologies demonstrated the importance to focus on a scientific basis. An example is provided by the NanoTrust dossiers, publicly available information material which is meant to serve as baseline for taking qualified decisions. The dossiers seek to summarize

information on a specific topic in the area of nano-specific risks, primarily in the areas of health and environment and will be read by political decision-makers, funding organisations, safety personnel and experts from responsible governmental organisations like ministries and agencies.
Eventually, the appropriate management of emerging technologies like nanotechnologies and their uncertainties is essentially dependent on inter- and transdisciplinary co-operation and co-production of resilient knowledge. This requires both confidence in governmental and societal regulatory processes and trust in the people who are responsible for organising and maintaining these processes. Only by the willingness of these people to contribute to a common goal, in this case the safe and responsible development of nanotechnologies, and the good-will to assume the same willingness in everybody concerned, ensures the necessary stability and continuity that is the basis for building safe systems. The development of innovative technologies which make also sense in a societal way is certainly not a short-term project and requires the support of any substantial expertise as nanotechnology risk governance systems have shown. Long-term projects like NanoTrust can help draw attention to the specific lessons we have learned by this new approach of integrating innovation and safety at an early stage in technology development.

8 References

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9 Appendix

Glyphosate case study

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Abstract

Glyphosate is the world's most widely used herbicides and the debates surrounding potential risks associated with it have dominated its recent re-approval in 2017 and will continue to play a role in the ongoing renewal procedure which was applied for in December 2019.

Paying attention to the risk assessment and risk management phase at EU level as well as the position of various stakeholders, this case study will analyse the role that the precautionary principle played in the EU procedures for the re-approval of glyphosate. It will also discuss how the application of the precautionary principle in this case interacts with innovation and especially the 'innovation principle' which is recently gaining traction in the EU discourse.

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List of abbreviations

ADI	Acceptable Daily Intake
AMPA	Aminomethylphosphonic
BfR	Bundesinstitut für Risikobewertung /Federal Institute for Risk Assessment
BEUC	Bureau Européen des Unions de Consommateurs
DAR	Draft Assessment Report
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
ERF	European Risk Forum
GBH	Glyphosate-based Herbicide
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
IARC	International Agency for Research on Cancer
NFU	National Farmers Union
NGO	Non-governmental organisation
OECD	Organisation for Economic Co-operation and Development
PAFF	Standing Committee on Plants, Animals, Food and Feed
PEST	Special Committee on Pesticides (PEST)
PPP	Plant Protection Product
RMS	Rapporteur Member State
SAM	Scientific Advice Mechanism
WHO	World Health Organisation
WP	Work Package

1 Introduction

1.1 Introduction

Glyphosate is used as active substance in herbicides (weedkillers) to control unwanted plants and is marketed since the 1970s. Because glyphosate is effective on a very broad range of weeds and not only kills the part of the plant above the surface, but also the plant tissues below the ground level, it quickly became a widely used pesticide in agriculture, landscaping, but also in private households. At the time of its introduction glyphosate was deemed relatively safe to use and even had environmental benefits, as it reduces the need for tillage, which has bad effects on the soil and releases CO^2. However, increasingly scientific studies and reports of NGOs questioned the safety of glyphosate and glyphosate-based herbicides, raising concerns about risks to human health and the environment.

This case study will examine the complexities and controversies surrounding the application of the precautionary principle in the approval of the active substance glyphosate in the European Union. It will focus on the renewal of the approval of glyphosate as an active substance in pesticides in the EU, which took place between 2012 and 2017.

The renewal of its approval beginning in 2012 was disrupted when the International Agency for Research on Cancer (IARC) published a scientific monograph which presented grounds for concern of carcinogenic potential of glyphosate. Although the European Food Safety Authority, the European Chemicals Agency, as well as other regulatory bodies around the world did not classify glyphosate as carcinogenic, the renewal process was accompanied by public outrage and controversy. The debate concerned studies that have both proven and disproven carcinogenic effects. Additionally concerns arose whether glyphosate might act as endocrine disruptor. Moreover, recently also questions are raised if glyphosate poses unacceptable risks to habitats and biodiversity in farmlands and aquatic ecosystems, because it is non-selective and potentially harmful for a range of non-target organisms.

The glyphosate renewal procedure in 2017, after a long phase of risk assessment by the EFSA and ECHA and contestation through the Member States in the comitology committee, culminated in a renewal of the approval for 5 years. The risk governance in the renewal procedure as well as the legal framework for pesticides will be analysed in this case study, with a specific focus on the application of the precautionary principle.

The main goal of the research in this case study is to understand the complexities and controversies around the application of the precautionary principle in the case of glyphosate in the EU. Therefore, it will describe the specific context of the case study: legal and/or policy discussions (environmental, economic, risk policy), as well as social and cultural context. It will examine how precaution and innovation interact in the case of glyphosate and if they in tension. It will analyse how the risk properties of complexity, uncertainty and ambiguity add to this understanding, and how they been understood by stakeholders (legal, policy makers, risk community). And finally, it will research how glyphosate challenges the innovation/precaution juxtaposition.

1.2 Key timeline

Political	Legal	Science/risk assessment	Public debate	Other

Year	Event	Relevance to case study
1950	Glyphosate creation	N-(phosphonomethyl) glycine, later called glyphosate, was first synthesised by Dr. Martin in Switzerland.
1960s	Glyphosate sold to Monsanto	Glyphosate is sold by Dr Martin to the chemical company Aldrich in 1959 and resold to Monsanto in 1960.
1970	Discovery of herbicidal properties	Glyphosate is discovered to be an herbicide by Monsanto chemist John E. Franz.
1973/74	First marketing of Roundup	The first glyphosate based herbicide is marketed.
1991	Adoption of Council Directive 91/414/EEC	Plant protection products are subjected to a harmonised authorisation procedures and a EU level approval of active substances.
2002	Glyphosate approval	Adoption of Commission Directive 2001/99/EC. Glyphosate is now an approved active substance for plant protection products in the EU. Before it was authorised in the Member Sates via national procedures.
2009	Adoption of Plant Protection Product Regulation 1107/2009	The legal framework for plant protection products is revised through the adoption of Regulation 1107/2009. Glyphosate remains approved and listed in Part A of the Annex of Commission Implementing Regulation (EU) 540/2011.
2012	Start renewal of approval procedure	Submission renewal application by the Glyphosate Task Force. The regulatory procedure for the renewal of the approval starts.
2013	Friends of the Earth briefings	The NGO Friends of the Earth publish briefings raising concerns about risks of glyphosate for human health and the environment.
2013	BfR Renewal Assessment Report	The BfR concluded that 'glyphosate is devoid of genotoxic potential' and that 'classification and labelling for carcinogenicity is not warranted'.
2015	IARC hazard assessment	The IARC classified glyphosate as 'probably carcinogenic to humans (Group 2A)', which in the evaluation scheme of the IARC means that there was 'limited evidence of cancer in humans' but 'sufficient evidence of cancer in animals'.
2015	EFSA risk assessment	Glyphosate is 'unlikely to pose a carcinogenic hazard to humans'. EFSA concluded that glyphosate can be expected to meet the approval criteria.

2016	European Parliament Resolution	Referring to the precautionary principle the Parliament called on the Commission the limit the renewal to 7 years and asked for further limiting conditions.
2017	ECHA hazard assessment	ECHA concluded that glyphosate is not to be classified as carcinogenic, moreover it is not mutagenic and also does not disrupt reproduction.
2017	European Citizens Initiative	The European Commission received a European Citizens' Initiative which called for the Commission to ban glyphosate, to reform the regulatory framework for pesticides and to set reduction target for pesticide use.
2017	European Parliament Resolution	The Parliament again referred to the precautionary principle and called for phasing out the use of glyphosate.
2017	Glyphosate renewal of approval	Approval glyphosate renewal through Commission Implementing Regulation (EU) 2017/2324.
2019	Start renewal of approval procedure	The Glyphosate Renewal Group submitted a renewal application for glyphosate. A new regulatory procedure for the approval has started.
2022	Expiry of approval	The renewal of approval granted in 2017 expires. The ongoing procedure will determine if the approval is prolonged beyond that.

2 Glyphosate

The chemical substance **glyphosate [N-(phosphonomethyl) glycine]** was first created in the 1950s by the Swiss chemist Dr. Henri Martin (Dill et al 2016). Its herbicidal properties were discovered by Monsanto (a former US agrochemical company that in 2018 has been acquired by the German chemical company Bayer), which had in the meantime bought the compound, in 1970. Glyphosate is a **pesticide**, which are substances that prevent, destroy, or control a disease or harmful organism, used on plant or plant products during their production, storage or transport. Within pesticides, it classifies as **herbicide** (or weedkiller), which are those pesticides that are used to control unwanted plants, like weeds that would compete with the crops. In the EU, the term **plant protection products (PPPs)** is used: PPPs are pesticides – including herbicides – which are applied to protect crops or other useful plants in agriculture, forestry or home gardens.[1]

Monsanto was the first to market glyphosate as **active substance** of its herbicide Roundup in the early 1970s. The active substance glyphosate is the part of the chemical mixture of the herbicide that acts against the unwanted plants, while the herbicide that is brought to the market contains other chemicals - so-called co-formulants -, like in the herbicide Roundup. Glyphosate was patented by Monsanto from 1971 until 2000, but after the patents had expired, other companies started selling glyphosate-containing herbicides, for example TouchdownTotal by Syngenta. Reportedly in the US alone 750 glyphosate containing products are on the market (IARC 2015, p.322).

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. In Europe, the agricultural use is mostly the application to fields before a crop is planted, in order to remove weeds that would otherwise compete with the crop and in some cases it is also sprayed on the crop before harvest to regulate growth.[2] Today, **glyphosate is the most commonly used active substance in herbicides** around the world (Benbrook 2016). It also is the most widely used agrochemical in the world, with a 2008 global sales of 620 000 MT and 8.3 billion US-Dollar (Pollack 2011, p.116). According to a projection made by Benbrook, in the decade between 2005 and 2014, the global use of glyphosate amounted to 6133 million kg (Benbrook 2016, p.7). In Germany, as survey carried out amongst farmers led to the estimation that in 2009, glyphosate-based products were applied to 4.3 million hectares representing 39% of total arable land (Steinmann et al 2012). Moreover, between 1999 and 2010 the use of glyphosate in Germany increased by 100% (Steinmann et al 2012).

Glyphosate works through inhibiting an enzyme which plants (but not animals) need in order to produce the amino acids necessary for the plant metabolism.[3] As this enzyme is essential to the growth of most plants, applying glyphosate leads to the plant wilting and dying. It's wide-spread use is due to its "broad spectrum perennial weed control" (Dill et al 2010, p.2), it works effectively on a very broad range of plants and not only kills the part of the plant above the surface, but also the plant tissues below the ground level. At first, as glyphosate kills all plants that it is applied to including the crops on a field, it first had limited use in traditional agriculture, but began to be more commonly used before planting and also pre-harvest for some crops to facilitate faster harvest.

[1] See: https://ec.europa.eu/food/plant/pesticides_en, last accessed: 13/4/2020.

[2] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 6.

[3] Glyphosate inhibits the enzyme 5 - enolpyruvylshikimate - 3 - phosphate synthase (EPSPS).

The use of glyphosate is also closely connected to **biotechnology**. Genetic modification has been used to make crops like maize or soy resistant to the herbicidal effects of glyphosate, which means that a field can be treated with glyphosate and all plants apart from the herbicide resistant GMO crops will be destroyed.[4] This means, that in the US, where glyphosate was already popular before the rise of biotechnology it has become even more widely used, however, in the EU where GMOs are used far less it is a very popular pesticide (Bozzini 2017). 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 (INGSA 2017). Glyphosate was presented as "relatively harmless because it bound tightly to soil constituents with little movement through either soil or groundwater, and had a short environmental half-life with no atmospheric contamination because it is not volatile" (INGSA 2017, p.2).

Bayer presents glyphosate as environmentally friendly, claiming that as shown by regulatory assessments it is not a threat to biodiversity, that it is contributing to conserving land for wildlife by ensuring a productive harvest on the land currently used for agriculture and that through reducing or eliminating the need for tillage it improves soil health and reduces carbon emissions.[5]

Bayer on its website presents glyphosate as a part of modern innovative farming:

> *" Introduced as the active ingredient in Roundup® in the 1970 s, glyphosate is a non- selective herbicide, which means that it can eliminate almost any type of plant to which it is applied – even desirable plants. It grew in prominence in modern agriculture as an important tool in Integrated Weed Management after the introduction of genetically modified crops, which allowed farmers to use the herbicide in a way that eliminated weeds without harming desirable plants. Today, glyphosate serves as an active ingredient in hundreds of crop protection products currently registered and approved for use in agriculture, vegetation management, lawn care, gardening and more.*
>
> *(…) From data gathered from drones, sensors and other digital technologies to trusted herbicides l ike glyphosate, there ar e a host of tools in the crop protection toolbox that are essential for farmers to shape a healthy and sustainable future for agriculture."*[6]

Farmer's 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). According to the NFU, they would need 49% more labour per hectare without glyphosate and would require 546,000 more hectares to grow the same amount of food (NFU 2017). Finally, Bayer as well as the NFU argues that glyphosate is safe

[4] The application of the precautionary principle to GMO's is discussed in a separate case study in the RECIPES project.

[5] https://www.bayer.com/en/about-glyphosate-based-herbicides-and-their-role-in-agriculture.aspx, last accessed: 13/4/2020.

[6] https://www.bayer.com/en/about-glyphosate-based-herbicides-and-their-role-in-agriculture.aspx, last accessed: 13/4/2020.

especially because such a thorough hazard and risk assessment has taken place and because of the sheer volume of studies carried out for this active substance.[7]

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 (Benbrook 2016). Thus, the development of glyphosate-resistant weeds might ultimately take away some of the initial benefits of using glyphosate.

3 Risks and scientific uncertainties

Generally speaking, the use of pesticides can entail risks to human health (where humans come in contact with the substance either directly or for example through residues in food) and to the environment (including ecosystems, biodiversity, as well as water and soil quality) (European Court of Auditors 2020). The risks posed by the plant protection products will vary according to the active substance used, the co-formulation with other substances and also when, how and where as well as in which amount they are used (European Court of Auditors 2020). Glyphosate was for the longest time seen as a safe pesticide and used in large quantities all over the world. However, as will be shown in this section, in the last decade concerns with regard to **risks for human health and the environment** have arisen and were simultaneously subject to scientific controversies, as will be discussed in the following.

3.1 Risk/threat

3.1.1 Potential risks

From its invention in the 1970s until the 2000s there was little concern over the use of glyphosate-based pesticides and the general public's exposure to them in the scientific and regulatory community. However, in the EU especially in the time surrounding the start of renewal of approval procedure for glyphosate in 2012, concerns about risks of glyphosate to human health and the environment were voiced by scientist and non-governmental organisations (NGOs). The NGO Friends of the Earth Europe for example in July 2013 published a series of briefings raising concerns about risks for human health and the environment.[8]

Exposure

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 weedkiller 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). This means that even the average citizen that has never applied glyphosate-based herbicides is exposed to it.

[7] https://www.bayer.com/en/is-glyphosate-safe.aspx, last accessed:13/4/2020.

[8] https://www.foeeurope.org/glyphosate-reasons-for-concern-briefing-130613, last accessed: 13/4/2020.

In 2013, the fact that glyphosate residues were found in the urine of European citizens from 18 Member States through a study commissioned by Friends of the Earth caused a public outcry.[9] However, the German competent authority BfR clarified that these concentration levels were not at a level that would cause a risk to human health.[10] In 2016, Benbrook argued that the human exposure estimates through water, soil, air and food remained below the Acceptable Daily Intake (ADI), thus not giving rise to concern (Benbrook 2016, p.11). However, with regard to exposure caused by applying the pesticide, in a more recent article Benbrook claims that the risks that might follow occupational exposure for those mixing and applying the substance, especially through hand held application by sprayers, are higher (Benbrook 2019). In this regard, the application through handheld and backpack sprayers leads to a far higher exposure then the application by tractors with cabins and air filtration systems (Benbrook 2020).

Risks: Human Health

In June 2011 the NGO Earth Open Source published a report 'Roundup and **birth defects**; Is the public being kept in the dark?', referring to a study (Paganelli et al 2010), which linked glyphosate and glyphosate-based pesticides to birth defects. In 2013 the NGO Friends of the Earth published a media briefing, in which they pointed to the **toxicity** of the substance.[11] 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).

However, the focal point of the public debate surrounding glyphosate approval was the potential **carcinogenicity** of glyphosate, i.e. the potential of the substance to cause cancer. Although publications by individual scientists began to raise concerns about the potential carcinogenicity of glyphosate and glyphosate-based pesticides (Myers et al 2016), the publication of Monograph 112 by the **International Agency for Research on Cancer (IARC)** in 2015 accelerated the debate concerning carcinogenicity. The IARC classified glyphosate as 'probably carcinogenic to humans (Group 2A)', which in the evaluation scheme of the IARC means that there was 'limited evidence of cancer in humans' but 'sufficient evidence of cancer in animals' (IARC 2015).

Next to the carcinogenicity of glyphosate, other concerns that glyphosate may be an **endocrine disruptor** emerged (Gasnier et al 2009; Krass et al 2020). Endocrine disruptors are chemicals that interfere with the hormonal system and thereby cause cancer and other harms such as birth defects or developmental disorders.[12]

A question that is debated in the scientific analysis of the risks of glyphosate is whether the health risks of glyphosate are the same for all humans or if they differ according to the **gender** of the exposed person. 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 (Arcuri & Hendlin 2019). With regard

[9] https://www.foeeurope.org/weed-killer-glyphosate-found-human-urine-across-Europe-130613, last accessed: 13/4/2020.

[10] Bundesinstitut für Risikobewertung, Glyphosate in Urine - Concentrations are far below the range indicating a potential health hazard, BfR Opinion No. 014/2013, 14 June 2013.

[11] https://www.foeeurope.org/sites/default/files/press_releases/foee_media_briefing_glyphosate.pdf, last accessed: 13/4/2020.

[12] Please see the separate case study on endocrine disruptors in the RECIPES project.

to the risk of endocrine disruption, a study in 2013 found that glyphosate stimulates breast cancer via the receptors for the hormone estrogen (Thongprakaisang et al 2013). Generally as the male and female hormonal system differ, the harm caused by endocrine disruptors can differ, but currently there is still limited knowledge especially about the effects on females.[13] With regard to animal studies, differences in the impact of glyphosate on animals according to gender have been researched. For example, in the animal studies conducted concerning carcinogenicity the IARC notes a difference in two studies which reported tumours for male but not for female rats (IARC 2015, p.396). A French study reported risks for the gut microbiome specifically of female rats (Lozano et al 2018). Overall, further research is needed to reach more clarity on gender related risks of glyphosate both in humans and animal.

Risks: Environmental

As nowadays, glyphosate is present in soil, water and air it might cause risk to non-target organisms and whole ecosystems. The European Parliament for example in its resolution of April 2016 pointed to: "a high long-term risk found for almost all uses of glyphosate for non-target terrestrial vertebrates, including mammals and birds; whereas use of the non-selective herbicide glyphosate kills not only unwanted weeds, but all plants, as well as algae, bacteria and fungi, thereby having an unacceptable impact on biodiversity and the ecosystem".[14]

Thus, the environmental risks are twofold: 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. Regarding specific species that are affected by glyphosate, Benbrook for example refers to studies which point to potential harm for microbial communities in the soil as well as for several species (earthworms, monarch butterflies, honeybees, crustaceans) (Benbrook 2016).

With regard to the risks to the ecosystems and biodiversity, the risk assessment on the EU level so far did not point to risks to ecosystems, provided that the substance is used within good agricultural practice and under the conditions under which it was approved.[15] The Commission in this regard points to the possibility of the Member States to impose conditions such as no spray zones or drift reduction technology in the authorisation of glyphosate-based pesticide. Nonetheless, as glyphosate - and any herbicide for that matter – removes unwanted plants, this could disturb interlinked food chains in the relationship between different species (so called foodwebs).[16] Two examples in this regard are mentioned by the NGO Friends of the Earth:[17] First of all, the weeds which are

[13] Please see the separate case study on endocrine disruptors in the RECIPES project.

[14] European Parliament resolution of 13 April 2016 on the draft Commission implementing regulation renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Implementing Regulation (EU) No 540/2011, P8_TA(2016)0119, Point R of the resolution.

[15] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 8.

[16] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 8.

[17] https://www.foeeurope.org/sites/default/files/publications/foee_5_environmental_impacts_glyphosate.pdf, last accessed: 13/4/2020.

removed through the application of glyphosate constitute an important food source for insects, which in turn are the main feed of birds such as the skylark. Second, the use of glyphosate-based herbicides is linked to the decline of Monarch butterflies in the US, not because it would be directly toxic to the butterflies, but because it removes the common milkweed on which the caterpillars of the butterfly are dependent as food source.

More and more, the risk of glyphosate for the environment and, specifically the risks to wildlife in meadows and rivers, is the focus of attention.[18] In an interview by the webportal Politico, Jeroen van der Sluijs (RECIPES partner) warned, concerning the risks of glyphosate, that it leads to an agricultural practice where you have monoculture with no wild plants left in the fields and thus no floral resources for bees and other pollinators, that it harms non-target plants and that it poses risks to aquatic organisms and especially amphibians.[19]

3.2 Scientific analysis

Individual scientific studies

Glyphosate has been the focus of a large and still growing number of scientific studies.[20] Initially, the toxicological testing of glyphosate-based herbicides pointed to a low risk of the substance for non-target species (Myers et al 2016). For example, in 2000 Williams et al. in a review of the safety of glyphosate, based on industry performed regulatory studies as well as published studies, concluded that they found no indication of human health concerns for glyphosate as well as the Roundup formulation (Williams et al 2000). At the time, studies were often carried out by laboratories owned or commissioned by the industry, and also the review of Williams et al. is based on these unpublished studies, while the authors were consultants associated with the industry (Myers et al 2016).

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 (Myers et al 2016). A review of such studies led to a consensus statement of several scientist concerning glyphosate-based herbicides (GBHs) from 2016 which expressed that:

> *" Collectively, studies from laboratory animals, human populations, and domesticated animals suggest that current levels of exposure to GBHs can induce adverse health outcomes." (Myers et al 2016 , p. 3).*

According to this consensus-statement, further studies of the causal link between the exposure to glyphosate-based pesticides and cancer (specifically non-Hodgkin's Lymphoma) are required, while the epidemiological data does provide evidence of heightened cancer risk (Myers et al 2016). They also state that several studies have "reported effects indicative of endocrine disruption." (Myers et al 2016, p.6).

The scientific assessment of glyphosate carcinogenicity: The International Agency for Research of Cancer (IARC)

[18] https://www.politico.eu/article/battle-over-glyphosate-shifts-to-the-environmental-front-pesticides-herbicides/, last accessed: 13/4/2020.

[19] https://www.politico.eu/article/battle-over-glyphosate-shifts-to-the-environmental-front-pesticides-herbicides/, last accessed: 13/4/2020.

[20] In its assessment the BfR reviewed over 1,000 studies, including epidemiolocal studies on glyphosate carcinogenicity.

The IARC is the specialized cancer agency of the Wold Health Organisation (WHO), which focusses on the carcinogenic properties of different substances. They do not perform their own studies, but base their assessment on compiling publicly available information, the IARC experts critically review and evaluate peer-reviewed and published studies, which they assess in terms of strength-of-evidence (of carcinogenic properties of a substance). The IARC was the first international scientific body identifying carcinogenic properties of glyphosate (Arcuri 2019). The findings are summarised in an article in The Lancet in the following way:

> *" There was l imited evidence in humans for the carcinogenicity of glyphosate. Case- control studies of occupational exposure in the USA, Canada, and Sweden reported increased risks for non- Hodgkin lymphoma that persisted after adjustment for other pesticides. (…)*
>
> *In male CD- 1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma. A second study reported a positive trend for haemangiosarcoma in male mice. Glyphosate increased pancreatic islet- cell adenoma in male rats in two studies. A glyphosate formulation promoted skin tumours in an initiation- promotion study in mice." (Guyton et. al 2015 , pp. 490 - 491)*

The scientific assessment of glyphosate carcinogenicity in EU Agencies: ECHA and EFSA

In the context of the EU procedures, glyphosate as an active substance was subject to scientific assessment by:

- the Federal Institute for Risk Assessment (BfR) (as rapporteur for EFSA)
- the European Food Safety Authority (EFSA)
- the European Chemicals Agency (ECHA)

In its assessment the BfR reviewed over 1,000 studies, including epidemiolocal studies on glyphosate carcinogenicity.[21] The BfR also found that there is 'limited' evidence for carcinogenicity in humans based on the epidemiological studies that the IARC also referred to. However, the BfR concluded that the studies in question have certain flaws and do not provide evidence for a link between the exposure to glyphosate and cancer (*non-Hodgkin lymphoma*).[22]

In October 2015, based on the assessment of the BfR and the subsequently carried out peer review, EFSA published its 'Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate' in which it concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008."[23]

[21] Bundesinstitut für Risikobewertung, Assessment of the BfR concerning epidemiological studies on carcinogenic effects of glyphosate in the context of the EU active substance review BfR background information No. 034/2015, 28 September 2015.
[22] Ibid.
[23] EFSA, Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate, 13(11) 4302 EFSA Journal (2015),pp. 1-107.

In its opinion of 15 March 2017, ECHA concluded that glyphosate is not to be classified as carcinogenic, moreover it is not mutagenic and also does not disrupt reproduction.[24] However, it did classify glyphosate with: Eye Damage (class 1, Causes serious eye damage) and Aquatic Chronic (class 2; Toxic to aquatic life with long lasting effects). The hazard classifications with regard to eye damage and aquatic toxicity were already in place before the renewed evaluation in 2016.[25]

3.3 Scientific uncertainty

This section is about the **scientific uncertainty about the risks** associated with your case.

3.3.1 Complexity

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 (Bozzini 2017). Their use has drastically increased since the 1950s due to the progressive shift towards "the agro-industrial model of farming" (Bozzini 2017, p.2).

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 (IARC 2015, p. 322). For example, concerns were raised regarding the **high toxicity of a co-formulant** of glyphosate, POE-tallowamine (Mesagne et al 2013). After a request from the Commission to EFSA to investigate this further and EFSA concluded that: "Compared to glyphosate, a higher toxicity of the POE-tallowamine was observed on all endpoints investigated."[26] The formulation of the plant protection products are commercial secrets and therefore not accessible to independent scientists (Myers et al 2016).

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. Myers et al. explain that glyphosate-based pesticides are increasingly applied together with other pesticides, while the safety levels for the active ingredients are calculated separately and without taking into account these mixtures (Myers et al 2016). As stated in a report for the European Parliament, Europe risk assessors also struggle with this issue: "(…) less attention is given to **unintentional mixtures** – like the ones that are formed during the handling of different products on the part of users – or coincidental – mixtures that get formed in the environment after the use of a variety of active substances. At present there is no systematic and integrated approach across different pieces of legislation. In the pesticide sector, guidelines are currently under development."[27]

However, not only the mixture of glyphosate with other chemicals poses risk assessment problems. The **physicochemical properties**, make it very difficult to analyse (Huhn

[24] ECHA, Committee for Risk Assessment (RAC) Opinion proposing harmonised classification and labelling at EU level of glyphosate (ISO); N-(phosphonomethyl)glycine, CLH-O-0000001412-86-149/F, 15 March 2017.

[25] ECHA, How ECHA is assessing glyphosate, ECHA Newsletter 3/2016, p. 3.

[26] EFSA, Statement of EFSA on the request for the evaluation of the toxicological assessment of the co-formulant POE-tallowamine, 13(11) 4303 EFSA Journal (2015), pp. 1-13.

[27] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, Annex II p. 8.

2018). Huhn concluded an article calling for more and enhanced analysis of glyphosate with the statement that: "our understanding of the fate of glyphosate in the environment and its impact on ecosystems and human health are still not fully understood." (Huhn 2018, p.3043). It is also pointed out that currently studies can only address individual aspects of the fate of glyphosate in the environment and that questions regarding the **bioavailability** when it is absorbed into the soil are unclear, this also leads to gaps in the understanding of its ecotoxicology (Huhn 2018).

3.3.2 Uncertainty

Added to the complexities as elaborated in the previous section, is the uncertainty of the ever-evolving **scientific methods**. Since glyphosate is already a relatively old product, it is worth reminding the reader that toxicology as a scientific discipline has rapidly evolved and has become increasingly refined, which means that today scientists are able to conduct a far more sophisticated risk assessment when it comes to toxic, ecotoxic and endocrine disruption risks of a substance (Bozzini 2017). This also influenced the regulatory framework of pesticides which reflects the increasing ability to identify these risks (Bozzini 2017). It should also be taken into account that the science of toxicology will certainly progress further and findings which are now in accordance with the most up-to-date science will be overhauled. Even in an area such as carcinogenicity testing, where a testing standard is already established since the 1960s, the assessment is complex and has been progressively refined, still causing debate.[28]

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** (Myers et al 2016). As Benbrook explains, the quantification of risks to human health and the environment is dependent on knowing how much of the substances is applied in a certain region, on which crops and in which other areas (forests, parks, industrial properties etc.), the timing of application and which method was used (Benbrook 2016). However, such a comprehensive dataset is hardly available (Benbrook 2016). Also the Scientific Advice Mechanism (SAM)[29] of the European Commission has noted that: "[i]nformation on non-dietary health risks (e.g. agricultural worker safety) and environmental risks of PPPs is commonly not fully available to all risk assessors and risk managers due to lack of systematic monitoring and data sharing."(SAM 2018, p.33). Currently, a lot of uncertainty with regard to glyphosate thus originates in a lack of data concerning the exposure to it. This applies to the exposure of citizens through food, water and air; the exposure of people that use glyphosate professionally (often in combination with other pesticides); and the exposure of the environment to glyphosate under real world conditions.

3.3.3 Ambiguity

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,[30] the **different assessment of the scientific evidence regarding**

[28] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, Annex II p. 37-41.

[29] The Scientific Advice Mechanisms (SAM) provides independent scientific advice to the European Commission. It is constituted of 7 Chief Scientific Advisors who work closely with the Scientific Advice for Policy by European Academies (SAPEA) a consortium of over 100 academies and societies across Europe.

[30] For example the article 'Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize' by Séralini et al. (in Volume 50 of Food and Chemical Toxicology) was

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.

While the IARC only takes into account publicly available studies, but does not limit its assessment to only the active substance, the regulatory authorities in the EU also use raw data from industry conducted studies but limit their assessment to the active substance. Nonetheless, this is not to say that the IARC and EFSA/ECHA would have carried out their assessment on completely different data sets, on the contrary, the information at their disposal to a large degree was overlapping.[31] What might be surprising given the divergent assessments is that in its 2015 assessment, the IARC did not only take into account peer-reviewed scientific articles but also regulatory reports from the EU and US (IARC 2015). However, what does differ significantly is how the bodies judged the quality, reliability and importance of the different studies.

The IARC, in accordance with its procedures, bases its assessment exclusively on publicly available data, mostly on scientific literature, which is identified by the Agency through systematic literature review and a public call for data. The EFSA conclusion (as well as the ECHA classification), on the other hand, takes into account published studies, but is based on the data submitted by the approval applicant, which contains studies commissioned by the applicants and therefore not publicly available. In examining the submitted studies, EFSA (and the BfR as rapporteur) used a so-called weight-of evidence assessment. According to EFSA guidance, the weight of evidence approach is: "a process in which evidence is integrated to determine the relative support for possible answers to a question."[32]

In essence for the **weight of evidence assessment**, one asks whether the studies are reproducible, how many studies support a conclusion and also how these studies are designed and conducted.[33] The reason why regulatory authorities, place a big emphasis on the studies submitted by the applicant is that those are performed according to the Organisation for Economic Co-operation and Development (OECD) standards of Good Laboratory Practice (GLP). GLP is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. It reduces the possibilities for fraud and fabrication but it is argued that it does not guarantee that a study has been designed correctly (Maxim & van der Sluijs 2013; Myers et al 2009). Academic studies, on the other hand, are often designed and carried out according to more original and less standardised designs. Most academic labs do not have GLP certificates because this is a standard for industry labs and academic studies rely on the system of peer review for the quality control of the studies. As regulatory authorities apply the so-called Klimisch criteria to assess the reliability of toxicological studies, academic studies are excluded or deemed less reliable as they usually lack the GLP certificate (Myers et al 2016).

While the EU agencies relied on the weight of evidence approach, the IARC uses a so-called strength of evidence approach, which led to different weighting of the studies in question. This is explained by Bozzini:

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retracted and then republished (in 26(14*) Environmental Sciences Europe*), after controversy about its findings.

[31] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, Annex IV p. 89 ff.

[32] EFSA, Guidance on the use of the weight of evidence approach in scientific assessments, 15(8) 4971 EFSA Journal (2017), pp. 1-69.

[33] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 87.

> *" IRAC concludes that three studies (out of 14) present evidence of a weak/ dubious – but still existent- correlation and classifies such evidence as l imited. As a consequence, according to IARC criteria, glyphosate can be classified as ' probably carcinogenic'. Whereas the IARC relies almost exclusively on this evidence, EFSA places it in the context of a much broader set of (unpublished) papers and employs a weight of evidence approach to reach its conclusion. Eventually, EFSA concluded that the evidence is very l imited and that, therefore, glyphosate cannot be categorized as carcinogenic." (Bozzini 2017 , p.89)*

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 (...)."(Bozzini 2017, p.89)

3.4 Relevance of the PP to the case

Glyphosate might be **one of the most intensely studied pesticides on the market**, however as the sections above have shown **this does not exclude scientific uncertainty**. First of all, the discussion in the previous sections has shown that not only people that apply glyphosate-based herbicides, but also average citizens are exposed to the substance. Nonetheless, the absence of systematic monitoring of its herbicide use as well as the exposure via food and water, poses significant uncertainty challenges for the assessment of its risks. These risks concern human health risks, such as carcinogenicity and endocrine disruption, as well as risks to the environment, regarding specific species as well as whole ecosystems. However, the main controversy and source of **ambiguity** surrounding the risk(s) associated with glyphosate in the recently concluded renewal procedure was the **diverging scientific assessment of the substance in terms of its carcinogenic potential**: while in its 2015 monograph the IARC classified glyphosate as probably carcinogenic to humans (Group 2A), EFSA and ECHA did not classify glyphosate as carcinogen.

The causes for this divergence in assessment have been addressed in the literature. From these sources, several factors for the diverging carcinogenicity classification can be identified (Paskalev 2019; Leonelli 2018; Arcuri 2018):

- the mandates and procedures of the bodies in question (regulatory vs non-regulatory);
- hazard identification vs risk assessment;
- approach concerning the data taken into account (published/peer reviewed vs industry composed dossiers);
- assessment of active substance and/or co-formulation;
- diverging methods/interpretations in the 'weight of evidence approach'.

What makes the glyphosate case especially interesting as a case study for the application of the precautionary principle is that not only is the science contested or at least interpreted ambiguously, but that the EU regulators have been criticised for failing to "give any substantial weight to the margins of scientific uncertainty surrounding the glyphosate case"(Leonelli 2018, p.594). For example, the President of BfR in an article in

the ZLR, explaining that the precautionary principle does not apply to the risk assessment of glyphosate as there was no unknown risk and no lack of knowledge (Hensel 2016). Concern has been voiced, for example by the Executive Director of EFSA Bernhard Url in Nature, that the public debate surrounding the scientific findings concerning carcinogenicity in the EU risk assessment was driven by political agenda rather than scientific uncertainty. He states that: "It seems to us that some campaigners contest the science of safety assessments in pursuit of greater political arguments. These arguments deserve airing — but they belong with policymaker."(Url 2018, p.381)

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.

4 Risk governance and the precautionary principle

The scope of this case study is largely limited to renewal of glyphosate as an active substance in pesticides in the EU, which took place between 2012 and 2017. The glyphosate approval was renewed at the time, however, the precautionary principle still played an important role in the risk governance process as this section will show. First, the political and legal dynamics of the risk governance process will be discussed, including an analysis of the regulatory framework as well as a detailed description of the risk analysis process. In section 4.2. the societal dynamic in the glyphosate risk governance will be introduced.

4.1 Political/juridical dynamics

Glyphosate and glyphosate-based pesticides are subject to an **extensive regulatory framework in the EU**. Plant Protection Products have to be approved/authorised before they can be placed on the internal market. [34] The **active substance**, such as glyphosate, is subject to an **approval granted on EU level** by the Commission. However, the actual plant protection products, thus the **commercial formulation** of the active substance with other co-formulants, like the glyphosate containing herbicide Roundup, have to be **authorised on Member State level**.

Pesticides are subject to harmonised European legislation only since the 1990s. A first proposal for a Directive in 1976 was not adopted due to resistance of the Member States.[35] Only with the adoption of Council Directive 91/414/EEC a common procedure for an approval of active substances and the authorisation of plant protection products in the Member States was established.[36] However, the Directive proved unsuccessful in establishing a coherent framework and was inefficient.[37] This led to the adoption of the pesticide package establishing the current regulatory framework: **Regulation (EC) No**

[34] For a comprehensive discussion of the regulatory framework for pesticides in the EU see: Bozzini 2017.

[35] European Commission, Proposal for a Council Directive concerning the placing of EEC-accepted plant protection products on the market, COM (1976) 427 final, OJ C 212, 9.9.1976, p. 3–20.

[36] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market, OJ L 230, 19.8.1991, pp. 1–32.

[37] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 19.

1107/2009 concerning the placing of plant protection products on the market,[38] and **Directive 2009/128/EC establishing a framework for Community action to achieve the sustainable use of pesticides**.[39] The following section will examine how the precautionary principle is integrated in the Pesticides Regulation 1107/2009, which applied to the glyphosate renewal.

The precautionary principle and the regulation of pesticides in the EU

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.[40] Therefore, it is not surprising that also Regulation 1107/2009 refers to the principle. First of all, the precautionary principle is mentioned in Recital 8:

> *"(8) The purpose of this Regulation is to ensure a high level of protection of both human and animal health and the environment and at the same time to safeguard the competitiveness of Community agriculture.* ***Particular attention should be paid to the protection of vulnerable groups of the population, including pregnant women, infants and children*** *.* ***The precautionary principle should be applied*** *and this Regulation should ensure that industry demonstrates that substances or products produced or placed on the market do not have any harmful effect on human or animal health or any unacceptable effects on the environment."(emphasis added)*

This is then included in Article 1 of the Regulation and specifically paraphs 3 and 4 which state:

> *' 3 . The purpose of this Regulation is to ensure a high level of protection of both human and animal health and the enviro nment and to improve the functioning of the internal market through the harmonisation of the rules on the placing on the market of plant protection products, while improving agricultural production.*
>
> *4 . The provisions of this Regulation are underpinned by the* ***precautionary principle*** *in order to ensure that active substances or products placed on the market do not adversely affect human or animal health or the environment. In particular, Member States shall not be prevented from applying the precautionary principle where there is scientific uncertainty as to the risks with regard to human*

[38] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, OJ L 309, 24.11.2009, pp. 1–50.

[39] Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticide OJ L 309, 24.11.2009, pp.71-86.

[40] See e.g.: C-616/17 *Criminal proceedings against Mathieu Blaise and Others*, ECLI:EU:C:2019:800, paras. 41and 42.

or animal health or the environment posed by the plant protection products to be authorised in their territory.' (emphasis added)

The regulation aims at the protection of humans, animals and the environment, expressing the precautionary principle in various ways:

- **The prior approval scheme:** Plant protection products can only be placed on the market when they have been authorised by the Member States, and any active substance contained in the PPPs has to be approved on EU level. As stated by Advocate General Sharpston, such a prior approval scheme is in itself an expression of the precautionary principle: "The PPP Regulation is itself a precautionary measure because it establishes a system of *prior approval* affecting a generic product category (plant protection products)."[41] Comparable prior approval schemes are used in several policy areas in the EU, including food, chemicals, and pharmaceuticals.[42] In accordance with the Commission Communication on the precautionary principle, such authorisation schemes are used exceptionally with regard to "substances deemed 'a priori' hazardous"[43].
- **The shift in the burden of proof:** The prior approval scheme also introduces a shift in the burden of proof: in the approval and authorisation procedures the safety of the product had to be proven, and this responsibility is placed on the company that wants to market the product (Bozzini 2017). Such a shift in the burden of proof is exceptional and not the general rule for all risks.[44] 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 (Bozzini 2017).
- **The authorisation criteria:** With the adoption of Regulation 1107/2009, the EU introduced a hazard-based approach as opposed to a risk-based approach.[45] This entails that a substance is first examined for certain intrinsic hazardous characteristics, the so-called 'cut-off criteria'. If in the hazard identification stage, it becomes evident that a pesticide meets one of the cut-off criteria, for example as it is carcinogenic, a risk assessment concerning the likelihood of the harm to occur is not necessary to take precautionary measures. With regard to the approval of active substances, the hazard-based approach is enshrined in Article 4(1) of

[41] Opinion of Advocate General Sharpston in case C-616/17 *Criminal proceedings against Mathieu Blaise and Others*, ECLI:EU:C:2019:190.

[42] See also: European Commission, Communication from the Commission on the European Citizens' Initiative "Ban Glyphosate and Protect People and the Environment from Toxic Pesticides", C(2017) 8414 final, p. 11.

[43] European Commission, Communication from the Commission on the precautionary principle, COM(2000)0001 final, p.20.

[44] European Commission, Communication from the Commission on the precautionary principle, COM(2000)0001 final, p. 4.

[45] For a discussion of the hazard-based approach see: Bozzini 2017, p. 29 ff.; SAM 2018,. p. 42; European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p.43.

Regulation 1107/2009 and the cut-off criteria are listed in Annex II points 3.6.2 to 3.6.4 and 3.7. According to this cut-off criteria system, an active substance will be banned if it is: carcinogenic; mutagenic; toxic for reproduction; persistent, bioaccumulative and toxic for the environment; a persistent organic pollutant; very persistent and very bioaccumulative; or an endocrine disruptor.

- **The limited approval periods:** In accordance with Article 5 of the Pesticide Regulation, if an active substance is approved for the first time, the approval cannot be granted for a longer period than 10 years. If the approval of an active substance is subsequently renewed, the maximum period is 15 years (Article 14(2)). This ensures that the scientific evidence for the safety of the substance is reviewed regularly, considering new scientific findings and evolving technology.
- **The review of approval**: In accordance with Article 21 the Commission can review the approval at any time should new scientific findings and technical knowledge point to doubts that the approval criteria are still fulfilled.
- **Emergency measures:** If an authorised product (or a substance contained in it) or approved active substance is likely to cause serious risks to human or animal health or the environment, the Commission – also on proposal of a Member State – can immediately take measures to restrict the use/sale as an emergency measure (Article 69).

Thus, the **precautionary principle is integrated in the regulatory framework applicable to pesticides**. Especially the use of a hazard-based approach is quite unusual, not only compared to pesticide regulation around the world, but also compared to other risk regulation areas in the EU, which generally are risk based (Bozzini 2017). It is argued that the hazard-based approach is not only an expression of the precautionary principle, but that choosing a hazard, rather than risk based approach is "a strong version of the principle by calling for precautions to avoid serious and possibly irreversible harm".[46] As was stated before, already the existence of the prior-approval scheme in the regulatory framework for pesticides in based on the precautionary principle. In the following section the approval procedure will be introduced, before examining the approval procedure of glyphosate.

The approval procedure for active substances

Active substances like glyphosate have to be approved before they can be used in plant protection products in the EU. An application will have to be submitted to a competent authority of a Member State, which becomes the Rapporteur Member State (RMS).[47] The RMS together with another co-rapporteur from another Member State, produces a draft assessment report (DAR), carrying out an "**independent, objective and transparent assessment** in the light of current scientific and technical knowledge" of the documents submitted by the applicant.[48] The purpose of these assessments is to establish 'whether the active substance can be expected to meet the approval criteria, as provided for in

[46] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 21.

[47] Regulation (EC) No 1107/2009, Art. 7.

[48] Regulation (EC) No 1107/2009, Art.11(2).

Article 4 of Regulation (EC) No 1107/2009.'[49] The following risk assessment steps are coordinated by EFSA Panel on Plant Protection Products and their Residues, including a peer review of the application by the other Member States and a public consultation.[50] EFSA's Conclusion is subsequently sent to the Commission, which has the decision-making power concerning the approval of active substances.

Taking into account the EFSA Conclusion, the European Commission will draft a review report and a Draft Implementing Regulation.[51] This Draft Implementing Regulation will approve or not approve the active substance, based on "the review report, other factors legitimate to the matter under consideration and the **precautionary principle**".[52] However, the European Commission's decision-making power is still subject to control by the Member States through comitology, as the comitology committees are composed of representatives of the Member States (van den Brink 2020), often being employees of national ministries. This means that the Member States will vote on the Commission proposal to approve a substance in the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee), and more specifically in the PAFFs section on phytopharmaceuticals. In case of a positive opinion of the committee, the Commission adopts an Implementing Regulation approving the substance, it will be included in the list of approved active substances in the Annex of Commission Implementing Regulation (EU) No 540/2011.[53]

In case of glyphosate, the procedure applicable in this case study was not an initial approval, but a renewal of an existing approval, which is governed by Articles 14 until 21 and further detailed in Commission Implementing Regulation (EU) No 844/2012.[54] As the first approval of an active substance is only granted for a maximum of 10 years,[55] while the maximum renewal period is 15 years,[56] such renewals are reoccurring regularly. The procedure follows similar steps as the approval procedure with an assessment by a Rapporteur MS and a subsequent peer review by EFSA. However, a core difference is that the Rapporteur Member State is not chosen by the applicant but has been assigned in the Commission Implementing Regulation.[57] Like in the case of an initial approval, the applicant company will have to provide scientific evidence that the approval criteria are fulfilled given the current scientifically and technical knowledge. The Commission again is the final decision-maker, together with the comitology committee.

[49] Regulation (EC) No 1107/2009, Art 11. Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market OJ L 252, 19.9.2012, pp. 26–32.

[50] Regulation (EC) No 1107/2009, Art. 12. See also: European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 21.

[51] Regulation (EC) No 1107/2009, Art. 13.

[52] Regulation (EC) No 1107/2009, Art. 13(2). Emphasis added.

[53] In case of approval of active substances the examination procedure is followed in accordance with Article 5 of Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers, OJ L 55, 28.2.2011, pp. 13–18.

[54] Commission Implementing Regulation (EU) No 844/2012.

[55] Regulation (EC) No 1107/2009, Art. 5.

[56] Regulation (EC) No 1107/2009, Art. 14(2).

[57] Annex of Commission Implementing Regulation (EU) No 844/2012.

Glyphosate in the EU: the timeline of glyphosate approval procedures

Glyphosate was first approved in the EU in 2002, after the introduction of the harmonised procedures through Council Directive 91/414/EEC. Before, glyphosate was used in the European Union in products authorized in Member States under their national regulatory framework. With the adoption of the Directive, a gradual work programme was set up in order to examine and approve the active substances on the market.[58] In the context of this work programme glyphosate was approved in 2002,[59] based on the scientific and technical knowledge of human health and environmental risks at the time.

In 2009, after a revision of the Plant Protection Product legislation in the EU, a new general legislative framework was introduced through the adoption of Regulation (EC) 1107/2009. The previously granted approval of glyphosate remained valid.[60] This approval originally expired in 2012 but, together with other approval dates, was prolonged to 31 December 2015,[61] in order to clarify the framework for and carry out the renewals under the new Regulation. In accordance with the applicable procedure,[62] the renewal was applied for on 25 May 2012 by the so-called Glyphosate Task Force, a collective of 24 glyphosate producing companies which included Monsanto Europe.[63]

The **Rapporteur Member State (RMS) was Germany** and its German Bundesinstitut für Risikobewertung (BfR), which was supported by Slovakia as co-rapporteur. The Renewal Assessment Report (RAR) will form the basis of the risk assessment. On 20 December 2013 the BfR provided the Renewal Assessment Report to EFSA, in which it stated that "glyphosate is devoid of genotoxic potential" and that "**classification and labelling for carcinogenicity is not warranted**".[64] Upon receiving the RAR, EFSA sent it out for consultation to the Member State and the applicant – the Glyphosate Task Force. Based on the comments received, EFSA identified "that expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology" should be carried out.[65] After consultation with experts from other Member States and the approval applicants as well as a public consultation, the BfR incorporated the comments and additional studies and submitted a revised report in December 2014.[66]

[58] Council Directive 91/414/EEC, art 8(2).

[59] Commission Directive 2001/99/EC of 20 November 2001 amending Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market to include glyphosate and thifensulfuron-methyl as active substances OJ L 304, 21.11.2001, pp. 14–16.

[60] All the active substances included in Annex I to Directive 91/414/EEC were also deemed to be approved under Regulation (EC) No 1107/2009.

[61] Commission Directive 2010/77/EU of 10 November 2010 amending Council Directive 91/414/EEC as regards the expiry dates for inclusion in Annex I of certain active substances Text with EEA relevance OJ L 293, 11.11.2010, pp. 48–57.

[62] Commission Regulation (EU) No 1141/2010 of 7 December 2010 laying down the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC and establishing the list of those substances, OJ L 322, 8.12.2010, pp. 10-19.

[63] Bundesinstitut für Risikobewertung, Renewal Assement Report, Glyphosate, Volume 1 Report and Proposed Decision, Volume 1, p.3.

[64] Bundesinstitut für Risikobewertung, Renewal Assement Report, Glyphosate, Volume 1 Report and Proposed Decision, Volume 1, p.139.

[65] EFSA, Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate, 13(11) 4302 EFSA Journal (2015), pp. 1-107, p. 2.

[66] This Renewal Assessment Report was revised twice (29 January 2015 and 31 March 2015). Bundesinstitut für Risikobewertung, Frequently asked questions on the procedure for the re-

While the assessment in the EU was ongoing, on **20 March 2015 the International Agency for Research on Cancer (IARC) published a monograph which contained findings of a carcinogenic potential of glyphosate**. Based on a mandate by the European Commission, the BfR made an addendum to the RAR on 31 August 2015 to evaluate the IARC Monograph. The BfR reassessed the studies taken into account by the IARC, but did not change its conclusion. [67] Therefore, **EFSA in October 2015 published its Conclusion**, stating that "**glyphosate is unlikely to pose a carcinogenic hazard** to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008."[68] Overall, **EFSA concluded that glyphosate can be expected to meet the approval criteria**. [69]

However, the EFSA Conclusion mentioned a data gap concerning the fate and behaviour in the environment, stating that further information is required to assess the "contamination route through run off (especially in situations where application to hard surfaces might occur) and subsequent surface water contamination and bank infiltration to groundwater".[70] Also concerning "**ecotoxicology, two data gaps** were identified to provide an assessment to address the long-term risk for small herbivorous mammals and for insectivorous birds."[71] The ecotoxic risk for aquatic organisms as well as bees, arthropods and soil micro- and macro-organisms was considered low.[72] The risk for non-target plants was considered low, given that mitigation measures are taken.[73] The EFSA opinion had also pointed out that one study showed **potential endocrine activity** and that, while data had become available there was no time to assess this information. This led the Commission to ask for an assessment of the endocrine disruption potential through EFSA.

However, when the EFSA Conclusion was presented to the Member States, as represented in the **comitology committee**, they considered it was appropriate to have an opinion of the Committee for Risk Assessment of the European Chemicals Agency.[74] ECHA and more specifically its Committee for Risk Assessment was asked to form an opinion on the hazard classification of glyphosate.[75]

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assessment of glyphosate within the framework of the EU active substance review, BfR FAQ, 12 November 2015.

[67] Bundesinstitut für Risikobewertung, The BfR has made a comprehensive check of the epidemiological studies on glyphosate, BfR Background Information No. 033/2015, 22 September 2015.

[68] EFSA, Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate, 13(11) 4302 EFSA Journal (2015), pp. 1-107.

[69] Ibid.

[70] Ibid., p.3.

[71] Ibid.

[72] Ibid.

[73] Ibid.

[74] In January 2016, the EFSA report was presented to the PAFF and in May the PAFF asked for an opinion of the Committee for Risk Assessment of the European Chemicals Agency on the carcinogenic potential of glyphosate. When the Commission in June 2016 called for a vote on the renewal proposal, neither a qualified majority for nor against the renewal could be reached. See: https://ec.europa.eu/food/plant/pesticides/glyphosate/earlier-assessment_en, last accessed: 13/4/2020.

[75] Such a hazard assessment is carried out in accordance with Article 37 of Regulation (EC) No 1272/2008. With regard to pesticides, the Pesticides Regulation 1107/2009 prohibits the placing on the market of a hazardous pesticide that is classified as human carcinogen or as mutagen, and

In April 2016 the **European Parliament** adopted a resolution concerning ongoing glyphosate approval.[76] At the time the European Commission had drafted a proposal for the maximum period of 15 years. In its resolution the Parliament stated that the Commission proposals "fails to apply the precautionary principle"[77] and called on the Commission to limit the renewal to 7 years.[78]

In the meantime, in August 2016, the **conditions of approval of the active substance were amended** in the light of new scientific and technical knowledge by Commission Implementing Regulation (EU) 2016/1313, which the PAFF has agreed to.[79] In its opinion from October 2015 the EFSA had voiced concerns regarding the toxicity co-formulant POE-tallowamine, which is often used in plant protection products containing glyphosate. Based on these findings, the conditions of approval for glyphosate were changed and Member States had to ensure that pesticides containing glyphosate do not contain POE-tallowamine. Moreover, the changed conditions of approval now stated that Member States in their assessment of PPPS should pay particular attention to (i) the protection of groundwater in vulnerable areas (particularly regarding non-crop use); (ii) risks from use in areas used by the general public and vulnerable groups (like parks, playgrounds etc.); and (iii) compliance of the pre-harvest use with good agricultural practice.

In its opinion of 15 March 2017, **ECHA concluded that glyphosate is not to be classified as carcinogenic**, moreover it is not mutagenic and also does not disrupt reproduction.[80] However, it did classify glyphosate with: Eye Damage (class 1, Causes serious eye damage) and Aquatic Chronic (class 2; Toxic to aquatic life with long lasting effects). The hazard classifications with regard to eye damage and aquatic toxicity were already in place before the renewed evaluation in 2016.[81] It should be stressed that the ECHA carries out a hazard assessment, which does not consider the exposure.

In May 2017 the Commission, therefore, restarted the discussion, which also took into account the **EFSA opinion** published on 7 September 2017, that concluded that on the basis of the data assessed, **weight of evidence indicates that glyphosate is not an endocrine disrupter**.[82] The Commission proposed the renewal for glyphosate for 10 years, and the proposal also included certain conditions of approval.[83] A **second European Parliament resolution** was adopted on 24 October 2017, one day before the

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this classification is carried out through the procedure prescribed by the CLP Regulation 1272/2008. See Annex II Regulation 1107/2009.

[76] European Parliament resolution of 13 April 2016 on the draft Commission implementing regulation renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Implementing Regulation (EU) No 540/2011, P8_TA(2016)0119.

[77] European Parliament resolution of 13 April 2016, Point 1.

[78] Ibid., Point 3.

[79] Commission Implementing Regulation (EU) 2016/1313 of 1 August 2016 amending Implementation Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance glyphosate, OJ L 208, 2.8.2016, pp. 1–3.

[80] ECHA, Committee for Risk Assessment (RAC) Opinion proposing harmonised classification and labelling at EU level of glyphosate (ISO); N-(phosphonomethyl)glycine, CLH-O-0000001412-86-149/F, 15 March 2017.

[81] ECHA, How ECHA is assessing glyphosate, ECHA Newsletter 3/2016, p. 3.

[82] EFSA, Conclusion on the peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate', 15(9) 4979 EFSA Journal (2017), pp.1-20.

[83] See: https://ec.europa.eu/food/plant/pesticides/glyphosate/earlier-assessment_en, last accessed: 13/4/2020.

meeting of the PAFF Committee, in which the Commission proposal foreseeing a renewal for 10 years was to be discussed.[84] In this resolution the Parliament again referred to a breach of the precautionary principle,[85] and also called for phasing out the use of glyphosate in the EU until 15 December 2022.[86]

In the **comitology committee**, some Member States questioned why the renewal period was shortened to 10 years and the meeting ended with the Commission requesting written comments. The discussions in the comitology committee continued throughout October, however, no majority for or against could be found.[87] On 9 November 2017, the PAFF was asked again to vote, this time the Commission had proposed a renewal for 5 years. Again, no majority could be found and the Committee delivered no opinion. The **division in the position of the Member States** becomes visible in the summary report:

> *' Several Member States voting in favour indicated that they would have preferred a longer period of renewal but agreed to the shorter period of renewal in the spirit of compromise. (…) Two Member States voted against as they wanted a renewal or extension of approval for a maximum period of 3 years. (…) Three Member States voted against due to political and societal sensitivity and environmental concerns. (…) One Member State voted against as its national parliament had adopted a formal position against any period of renewal or extension of approval. Three Member States abstained as they considered a 5 - year renewal period too short and because they saw no scientific or legal reasons justifying such a short period of renewal. One of them indicated that the resources needed at national level to review the existing authorisations of glyphosate - containing products were of concern in particular in the l ight of the short period of renewal proposed.'*[88]

Finally, on 27 November an Appeal Committee voted in favour of a 5 year renewal,[89] after Germany had changed its position from an abstention to a positive vote.[90] On 12

[84] European Parliament resolution of 24 October 2017 on the draft Commission implementing regulation renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Implementing Regulation (EU) No 540/2011 (D053565-01 – 2017/2904(RSP)), P8_TA(2017)0395.

[85] Ibid., Point 1.

[86] Ibid., Point 6.

[87] See: https://ec.europa.eu/food/plant/pesticides/glyphosate/earlier-assessment_en, last accessed: 13/4/2020.

[88] European Commission, Summary Report of the Standing Committee on Plants, Animals, Food and Feed held in Brussels on 17 July 2017, sante.ddg2.g.5(2017)4119844.

[89] See: https://ec.europa.eu/food/plant/pesticides/glyphosate/earlier-assessment_en, last accessed: 13/4/2020.

[90] https://euobserver.com/environment/140042, last accessed 13/4/2020; https://www.politico.eu/pro/glyphosate-renewal-shakes-germany-france-italy/, last accessed 13/4/2020.

December 2017 the renewal of the glyphosate approval was adopted by the European Commission.[91] This approval of glyphosate will expire on 15 December 2022.

On 12 December 2019 a group of companies referring to themselves as the Glyphosate Renewal Group[92] has submitted an application for renewal of the glyphosate approval. In deviation from the normal renewal procedure, the application will be assessed by a group of 4 Member States consisting of France, Hungary, the Netherlands and Sweden, forming the Assessment Group on Glyphosate (AGG). [93]

The precautionary principle in the glyphosate approval

As the previous sections have shown, the precautionary principle is deeply embedded in the regulatory framework for pesticides in the EU. Submitting glyphosate to an approval procedure based on the hazard-based approach, which is continuously repeated in each renewal, is an expression of the precautionary principle in itself. Therefore, it is important to stress that according to the finding of a study carried out for the European Parliament, "did not find evidence that, in the case of glyphosate, the national and EU authorities involved in the evaluation process did not comply with the relevant procedures under the approval (renewal of approval) of substances."[94]

In the case of glyphosate, after a **scientific risk assessment** by EFSA (and hazard assessment by ECHA), the **Commission as risk manager** - in accordance with the comitology committee vote - decided that a ban was not necessary, even in the face of large public pressure. The decision to grant the renewal shows that the **threshold of damage** that would have triggered a ban/non-renewal has not been met. This is due to the fact that in the risk assessment process neither ECHA nor EFSA classified the substance as carcinogenic, or meeting any of the other cut-off criteria. To a certain degree this also explains why carcinogenicity became the focal point of the glyphosate renewal procedure: Had glyphosate been classified as carcinogenic in the EU, it would have met a cut-off criterion and would have been banned immediately.

When considering the role of **cost effectiveness/ proportionality**, as glyphosate has been renewed, no cost-effectiveness assessment of a ban has taken place. The same also holds true with regard to the absence of an **impact assessment**. In this regard it can be added that for the measures taken under the Regulation, such as the approval or renewal of an active substance, no impact assessments of the risk management measures are routinely carried out in the regulatory process (Bozzini 2017).

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

[91] Commission Implementing Regulation (EU) 2017/2324 of 12 December 2017 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011, OJ L 333, 15.12.2017, pp. 10–16.

[92] https://glyphosate.eu, last accessed: 13/4/2020.

[93] Commission Implementing Regulation (EU) 2019/724 of 10 May 2019 amending Implementing Regulation (EU) No 686/2012 as regards the nomination of rapporteur Member States and co-rapporteur Member States for the active substances glyphosate, lambda-cyhalothrin, imazamox and pendimethalin and amending Implementing Regulation (EU) No 844/2012 as regards the possibility that a group of Member States assumes jointly the role of the rapporteur Member State, OJ L 124, 13.5.2019, pp. 32–35.

[94] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 47.

is warranted by new scientific findings and technical knowledge. Also the European Commission stressed in its answer to the European Citizens Initiative that "the Commission can, at any time, review the approval of glyphosate if new scientific evidence emerges that indicates that the substance no longer fulfils the approval criteria laid down in the Plant Protection Products Regulation."[95] Moreover, in case of glyphosate, the renewal was only granted for 5 year, which entails that the new dossier had to be submitted until December 2019. Thus, there is very quick review of the measure. As the Commission explains: "This renewal period is significantly shorter than the maximum of 15 years foreseen in EU legislation but the Commission also took into account the views of the European Parliament and other legitimate factors when setting the appropriate period of renewal. In fact, the Commission has taken into account possibilities of rapid future developments in science and technology: while a large amount of inform."[96]

Court of Justice of the European Union

The glyphosate approval has kept the Court of Justice of the European Union quite busy, which for a technical issue like the approval of an active substance is relatively uncommon. The glyphosate approval was dealt with by the General Court and the Court of Justice in the cases:

- T-545/11 Stichting Greenpeace Nederland and Pesticide Action Network Europe (PAN Europe) v European Commission, ECLI:EU:T:2013:523
- C-673/13 P Commission v Stichting Greenpeace Nederland and PAN Europe, ECLI:EU:C:2016:889
- T-545/11 RENV Stichting Greenpeace Nederland and Pesticide Action Network Europe (PAN Europe) v European Commission, ECLI:EU:T:2018:817
- T-12/17 Mellifera eV, Vereinigung für wesensgemäße Bienenhaltung v European Commission, ECLI:EU:T:2018:616
- Currently under appeal: C-784/18 P *Mellifera v Commission*
- T-383/18 Mellifera v. Commission
- T-178/18 *Région de Bruxelles-Capitale v European Commission*, ECLI:EU:T:2019:130 (Order of the General Court)
- Currently under appeal: C-352/19 P *Région de Bruxelles-Capitale* v European Commission
- T-125/18 Associazione Nazionale Granosalus vs. European Commission, ECLI:EU:T:2019:92
- Currently under appeal: Case C-313/19 P *Associazione GranoSalus v Commission*
- T-716/14 *Tweedale v EFSA*, ECLI:EU:T:2019:141
- T-329/17 *Hautala v EFSA*, ECLI:EU:T:2019:142
- C-616/17 Criminal proceedings against Mathieu Blaise and Others, ECLI:EU:C:2019:800

[95] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 9.

[96] Ibid.

Most cases related to access to documents, where third parties requested to see certain studies that were part of the dossiers of the original glyphosate approval procedure in 2002 as well as the renewal procedure. This line of case law has significantly contributed to the balancing of **transparency of the authorisation procedure** and the scientific assessment and commercially confidential information contained in the authorisation dossier. These developments are not directly related to the precautionary principle. However, the **Court clearly connected the increasing transparency with regard to documents to constitutional values such as democracy, accountability and participatory openness** (Morvillo 2019; Korkea-aho & Leino 2017). The Court was thus concerned with making the risk assessment stage visible to the broader public, to enhance the citizens trust in the process and also to allow for an open debate. Ultimately, this led to a reform of the transparency rules with regard to studies submitted to EFSA in the context of the approval of new active substances and in other fields of activity of the Agency.[97] The adopted Regulation now provides for publication of all studies submitted in the risk assessment process and also requires all studies commissioned to be registered, in order to prevent that unfavourable studies can go unnoticed (de Boer 2019).

In the case brought by the government of the region Brussels (T-178/18 *Région de Bruxelles-Capitale v European Commission*), it was **pleaded that the glyphosate renewal infringed the precautionary principle** claiming that the renewal fails to ensure a high level of protection of human health and of the environment, as the risk assessment would fail to fulfil the conditions of the precautionary principle. In an article published by the webportal Politico, an official of the region bringing the claim was cited to have stated: "As long as the causal link between glyphosate and harmful effects is not 100% proven, it cannot be banned. This is diametrically opposed to the precautionary principle."[98] However, as the case was declared **inadmissible** due to strict rules on standing and an absence of direct concern, the position of the Court concerning this line of argumentation is not available.

However, in the *Blaise case*, ruled by the Grand Chamber of the Court of Justice in October 2019, the Court was asked in a **preliminary reference to assess if Regulation 1107/2019 is compatible with the precautionary principle**. In the case the Court clarified the requirements of the correct application of the precautionary principle in the regulation of pesticides, stating that it should entail (i) the identification of potential risks of active substances and PPPs for health and (ii) a comprehensive risk assessment "based on the most reliable scientific data available and the most recent results of international research".[99] The Court stated the benchmark laid by the precautionary principle for the validity of the Regulation is the question whether the legislation ensures that the competent authorities have enough information to adequately assess the risk of the active substances and PPPs under review.[100] Importantly, however, the Court stressed that a finding of non-compliance of the Regulation with the precautionary principle could not be based - solely - on the circumstances of a particular case, here the alleged errors in the glyphosate approval procedure.[101] Overall, none of

[97] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, OJ L 231, 6.9.2019, pp. 1–28.

[98] https://www.euractiv.com/section/agriculture-food/news/brussels-government-takes-commission-to-eu-court-over-glyphosate/, last accessed: 13/4/2020.

[99] C-616/17 Criminal proceedings against Mathieu Blaise and Others, ECLI:EU:C:2019:800, para. 48.

[100] Ibid., para. 74.

[101] Ibid., paras 48-49.

the questions raised in the procedure led to a finding that challenged the validity of the Regulation.

Measures taken by Member States

When looking beyond the active substance glyphosate, the plant protection products – including their formulation, are assessed on Member State level. With regard to PPPs the EU operates a specific version of **mutual recognition**: the territory of the EU is divided in three zones: north, centre and south, which is based on comparability of agricultural, plant health and environmental (including climatic conditions). If a product is authorised in a Member State belonging to one zone, e.g. North, then the authorisation should also be granted in the other Member States of this zone based on the risk assessment carried out by the other Member State.[102] However, the criteria on which the authorisation procedure in the national competent authorities are based are **subject to EU harmonisation**, to ensure the same level of safety across the Union and in order to facilitate mutual recognition.[103] Nonetheless, a recent study conducted for the European Parliament, concluded that there are still significant **differences** between the standards and procedures in national risk assessments, which creates obstacles to the mutual recognition of authorizations.[104]

With regard to the authorisation of glyphosate-based herbicides in the Member States, it should be noted that **several states have communicated their plans to ban glyphosate-based herbicides**. The French competent authority in December 2019 announced that after a review of the renewal applications for PPP authorisation, 36 out of the 39 glyphosate containing products available in France will be prohibited from the end of 2020 onwards, "due to a lack or absence of scientific data ruling out any genotoxic risk."[105] Next to France,[106] there has been debate about glyphosate-bans (more precisely: bans on glyphosate containing pesticides) in several EU Member States. In Austria, the Parliament in July 2019 voted positively on a glyphosate ban from 1 January 2020 onwards. However, the ban until the time of writing has not been signed into law.[107] In Germany, the government in the so-called 'Agrarpaket' decided to ban glyphosate containing pesticides until the end of 2023 in order to protect insects,[108] but

[102] Annex 1 Regulation (EC) No 1107/2009. The North Zone includes Denmark, Estonia, Latvia, Lithuania, Finland, Sweden; the Centre Zone is composed of Belgium, Czech Republic, Germany, Ireland, Luxembourg, Hungary, Netherlands, Austria, Poland, Romania, Slovenia, Slovakia; and the South Zone is made up of Bulgaria, Greece, Spain, France, Croatia, Italy, Cyprus, Malta, Portugal.

[103] The data requirements for the dossier are set in Implementing Regulation (EU) No 284/2013 and Regulation (EU) 546/2011 establishes uniform principles for evaluation and authorisation of PPs.

[104] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018.

[105] https://www.anses.fr/en/content/anses-announces-withdrawal-36-products-containing-glyphosate, last accessed: 13/4/2020.

[106] https://www.euractiv.com/section/agriculture-food/news/french-mayors-ban-glyphosate-weedkiller-defying-government/, last accessed: 13/4/2020.

[107] https://www.parlament.gv.at/PAKT/VHG/XXVII/E/E_00004/fname_775803.pdf, last accessed: 13/4/2020;

https://www.parlament.gv.at/PAKT/PR/JAHR_2019/PK0808/index.shtml, last accessed: 13/4/2020; https://kontrast.at/glyphosat-verbot-oesterreich/, last accessed: 13/4/2020.

[108] https://www.zeit.de/wissen/umwelt/2019-09/tierwohl-label-nutztiere-insekten-glyphosat-julia-kloeckner, last accessed: 13/4/2020.

also here no binding law has been adopted yet. Only Luxemburg has adopted legislation to ban glyphosate/glyphosate-based herbicides, withdrawing the marketing authorization from 1 February 2020 onwards.[109]

Glyphosate risk governance around the world

In the literature it is argued that the European regulatory framework for pesticides is one of the strictest in global comparison and the regulatory measures taken in the EU, including both the authorizations and conditions of use of pesticides, are stricter and more precautionary than comparable decisions in the US (Bozzini 2017).

When it comes to glyphosate, it should be mentioned that its **carcinogenicity was reviewed also by other regulatory bodies outside the EU**. As stated by the Commission in its answer to the citizens' initiative the conclusion of EFSA and ECHA "is shared by other national and international bodies (from Canada, Japan, Australia and New Zealand, and also the Joint UN Food and Agriculture Organisation/World Health Organisation Meeting on Pesticide Residues."[110]

However, it should also be mentioned that in the US, and specifically in California, Monsanto/Bayer and other producers of glyphosate-based herbicides have faced **litigation**, mostly by professional users of these herbicides who developed cancer later on (Arcuri & Hendlin 2019). For example in the case Hardeman v. Monsanto (Case No 16-cv-00525-VC) from the United States District Court Northern District of California, found in favour of the applicant that Monsanto had negligently failed to place sufficient cancer warnings on Roundup bottles. Also in the cases brought by Dewayne Johnson (Dewayne Johnson v Monsanto (case No CGC-16- 550128)) and Alva and Alberta Pilliod i. Monsanto (Case No. RG17862702, JCCP No. 495), were won by the applicants as the court agreed that the exposure to glyphosate has caused them to develop cancer. However, the task of the courts in such cases significantly differs from the risk assessment of a regulatory authority, which means that the judgment regarding the scientific evidence by the courts is not easily transferred to a risk assessment (Benbrook 2020).

4.2 Other governance dynamics

Generally the **risk perception of pesticides has changed over time**: Whereas initially the early 1900's the use of chemicals in farming was embraced as it helped to alleviate hunger, this changed in the 1960s when the risk for human health and the environment associated with pesticides became clearer (Bozzini 2017). When it comes to plant protection products, Regulation (EC) 1107/2009 aims to protect human and animal health as well as the environment, while improving agricultural production.[111] These aims and whether the Regulation succeeds in achieving them is contested, as shown in a study for the European Parliament: while some stakeholders including NGOs, but also national regulators, said that the aim of improving production and trade "are no longer relevant"[112], a pesticide manufacturers association expressed their concern that the

[109] https://gouvernement.lu/en/actualites/toutes_actualites/communiques/2020/01-janvier/16-interdiction-glyphosate.html, last accessed: 13/4/2020.

[110] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 7.

[111] Regulation (EC) No 1107/2009, Art. 1(3).

[112] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 34.

Regulation is unnecessarily burdensome in terms of health and environmental protection measures and negatively impacts on the Unions agricultural industry on the global market.[113]

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**.[114] As Alexandra Brand (Syngenta) told Politico: "A lot of what we talk about pesticides is a symbol for an agriculture we are not happy with."[115] The discussion surrounding glyphosate was certainly politicised due to its connection to the very contested issue of GMOs. For example the Parliament Resolution from April 2016 in paragraphs AC and AD mentioned the connection between glyphosate and GMOs, and that the Parliament had objected to four different draft GMO authorisations.[116] Arguably, at the time Monsanto as one of the most prominent glyphosate-based herbicide producers, attracted normative critique being "the symbol of industrialized agriculture" (INGSA 2017, p.6).

Glyphosate itself is a catalyst of the shift to large industrial-style farming, which has been criticized for creating 'green deserts' of monocultures, which in turn are detrimental to biodiversity (Paskalev 2019). This concern with broader questions of agricultural policy is also very visible in the European Citizens Initiative which called on the Commission to "set EU-wide mandatory reduction targets for pesticide use, with a view to achieving a pesticide-free future".[117] In its answer the Commission made clear that the EU is not in pursuit of a zero-pesticide policies, but that it is aiming at sustainable use of pesticides.[118] As expressed by the NGO Corporate Europe Observatory:

> *" In our opinion, one of the most important – but less discussed – stakes in this process has been the possibility to put an end to the use of one the most used and efficient plant- killer on Earth while we' re experiencing the fastest biodiversity collapse ever measured. The glyphosate saga could have been an opportunity to at last discuss and regulate the use of wide- spectrum herbicides in agriculture, but this is yet to happen."*[119]

[113] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 34.

[114] See: Section 4.2. of this report.

[115] https://www.politico.eu/article/battle-over-glyphosate-shifts-to-the-environmental-front-pesticides-herbicides/, last accessed: 13/4/2020.

[116] EP Resolution P8_TA(2016)0119.

[117] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 12.

[118] Ibid.

[119] https://corporateeurope.org/en/food-and-agriculture/2016/06/glyphosate-one-pesticide-many-problems, last accessed 13/4/2020.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

The use of the precautionary principle in the approval procedure of glyphosate and the pesticides framework in general have been extensively reflected on and criticised. Many criticisms were already mentioned in the previous analysis, however, in this section some of the central reflections on the use of the precautionary principle in the glyphosate renewal procedure will be discussed.

Although the Pesticides Regulation presents the **hazard-based cut-off criteria**, like carcinogenicity, as binary 'fulfilled or not fulfilled' criteria, the reality is different: although some of the criteria are subject to such a black-or-white assessment with clear scientific indicators, most of these criteria are more openly defined and require an expert judgement, often using a weight of evidence approach (SAM 2018). Already in the section 3.3.3 discussing ambiguity of scientific findings, it was discussed that the IARC and the EU agencies assigned different importance to scientific data, and especially studies published by academics which lack GLP certification. The **weight of evidence** that EFSA and ECHA gave to certain studies and the fact that it dismissed others is not undisputed. A group of scientists led by Prof. Portier (who has also acted as invited specialist during the IARC meeting) send a letter to the European Commission in November 2015 criticising the BfR assessment for errors in their assessment and for incorrectly dismissing certain evidence.[120] Concerned scientists including Prof. Portier and Dr. Clausing (affiliated with the Pesticide Action Network) also voiced criticisms in scientific articles regarding the application weight of evidence standards and the risk assessment in the case of glyphosate (Clausing et al 2018; Robinson et al 2020). Moreover, in other articles comparing the IARC and EFSA assessment, they identified flaws in the risk assessment carried out by EFSA (Portier et al 2016; Portier et al 2017).

With regard to the glyphosate risk assessment, another core criticism relates to the **reliability of the studies provided for by the industry** in the renewal of approval procedure. Generally, concerns have been raised whether the shift of the burden of proof that requires the applicant to submit the safety evidence, guarantees correct data and an independent and transparent risk assessment.[121] The information asymmetry between the applying companies and the risk assessing public authorities raised concerns.[122] The **Monsanto papers scandal**, where Monsanto was forced to release documents including emails, peer review reports, drafts of manuscripts as well as power point presentations, in the context of tort litigation against the company in California,[123] has contributed to the questions concerning the reliability of industry financed studies (McHenry 2018). The publication of these documents showed that Monsanto actively interfered in the supposedly objective scientific debate by ghost-writing scientific articles and intruding in peer review process (McHenry 2018). McHenry (2018, p.202) in this regard concludes

[120] https://www.baumhedlundlaw.com/pdf/monsanto-documents/johnson-trial/DX-2735-Portier-Letter-EFSA-BfR-Glyphosate.pdf; last accessed: 13/4/2020. Portier followed up with another letter in 2017 after the Monsanto papers: https://corporateeurope.org/sites/default/files/attachments/letterjuncker28may2017.pdf, last accessed: 13/4/2020.

[121] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 40f.

[122] Ibid., p. 41.

[123] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, Annex II p. 58.

that Monsanto has "poisoned the [scientific] well by flooding the scientific journals with ghost-written articles and interfering in the scientific process at multiple levels."

Moreover, **the lack of transparency of the approval process** and the confidentiality of the submitted studies was criticized.[124] To address some concerns raised by shifting the burden of proof on the industry the Commission promised to enhance the auditing of the studies and their compliance with the GLP, to increase the transparency concerning the studies taken into account and to create the possibility to exceptionally commission studies in case of serious doubts.[125] These measures were taken through adoption of Regulation 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain.[126]

Not only the risk assessment process was criticized for a lack of transparency, but also the **risk management process was deemed to lack transparency**. These transparency concerns are important with regard to the application of the precautionary principle as it is in the risk management stage that the principle is applied, in accordance with Article 13 of the Pesticide Regulation. A report for the European Parliament for example points out: "Evidence shows that there is a need for a more transparent and comprehensive risk management stage since most of the time the reasoning behind risk management decisions, the regulatory criteria adopted and how the discussions among decisions-makers unfolded is not made explicitly public."[127] This concern is also voiced by stakeholders.[128]

However, the transparency of the application of the principle is in practice challenged by two factors: first of all, the **criteria for decision-making in the risk management task are not clearly laid down**. While this allows for flexibility and a wide margin of appreciation in the decision-making, which may be necessary in the face of complex risks, it also hinders legal certainty and the meaningful accountability for the decision made (Bozzini 2017; Morvillo 2020). Second of all, the actual reasons for concrete decisions made in the approval of an active substance, like glyphosate, are not openly communicated.[129] The Scientific Advice Mechanism therefore recommended that the goals protected by a measure and factors that were taken into account should be clearly communicated (SAM 2018). Also the European Parliament called for transparency of the comitology procedure.[130]

In the aftermath of the glyphosate renewal the European Parliament decided to investigate the functioning of the pesticides approval and authorization procedures

[124] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, Annex II p.73 and Annex IV p. 57; Korkea-aho & Leino, 2017.

[125] European Commission, Communication from the Commission on the European Citizens' Initiative "Ban glyphosate and protect people and the environment from toxic pesticides", C(2017) 8414 final, p. 12.

[126] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, OJ L 231, 6.9.2019, pp. 1–28.

[127] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 50.

[128] Ibid.

[129] Ibid.

[130] European Parliament resolution of 16 January 2019 on the Union's authorisation procedure for pesticides, P8_TA(2019)0023, Point 79.

through a committee devoted to this topic, the **Special Committee on Pesticides (PEST).**[131] Based on this report, the European Parliament on 16 January 2019 adopted a resolution, which amongst many other issues also addresses the role of the precautionary principle in the pesticides procedures. The Parliament asked the Commission and the Member States to "in their role as risk managers to duly apply the precautionary principle when, following an assessment of the available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, by adopting provisional risk management measures necessary to ensure a high level of protection of human health."[132]

Finally, in an article in King's Law Journal, Arcuri and Hendlin (2019), argue that the regulatory approach taken in the case of glyphosate **fails to sufficiently protect vulnerable populations and non-human organisms**. They argue (Arcuri and Hendlin 2019, p. 236) that in the risk determination of environmental toxicology "legal frameworks (…) frequently minimise risks and overestimate the certainty and accuracy of assessments, leading to downplaying the exposures of those populations most threatened by toxic chemicals." The risk assessment of glyphosate, and pesticides in general, according to their view is flawed as it suffers from compartmentalisation and anthropocentrism (Arcuri and Hendlin 2019). They criticise that, with the regulation being anthropocentric, vulnerable groups in the human population as well as animals are not adequately protected in the current exposure and harm thresholds.

5.2 Effect of the PP on innovation pathways

As far as pesticides are concerned, next to weeds becoming resistant to certain pesticides, the **increasingly demanding regulatory framework and the banning of substances has led to innovation** (Bozzini 2017). While the sector remains very profitable, it is argued that research and development costs have dramatically increased (Bozzini 2017). As explained in an article by the legal scholars Garnett, van Calster and Reins (2018, p.6): although no piece of EU legislation directly and exclusively addresses innovation, general rules such as the precautionary principle and sector specific legislation, like the Pesticides Regulation, has an effect on how innovation is approached is certain sectors and companies. The balance that is struck in the legislation between protection human health and the environment and promoting trade industrial interests, and therefore innovation, is a core struggle in the innovation pathway for pesticides.

Whether the debate surrounding the risks of glyphosate will lead to innovation in changing the product or leading to its replacement is currently not foreseeable. Concerns have been voiced that in case of a ban, glyphosate might not be easily substituted. Euractive published an article citing Bayer official Dr. Bob Reiter as referring to glyphosate as a 'once in a lifetime product' and that it has properties that even after intensive research so far have not been discovered in another substance.[133] According to this interview, Bayer is aiming to prevent a complete replacement of glyphosate and instead is trying to advocate to complement it with other substances.[134]

[131] European Parliament, European Parliament decision of 6 February 2018 on setting up a special committee on the Union's authorisation procedure for pesticides, its responsibilities, numerical strength and term of office, P8_TA(2018)0022.

[132] European Parliament resolution of 16 January 2019 on the Union's authorisation procedure for pesticides, P8_TA(2019)0023, Point 6.

[133] https://www.euractiv.com/section/agriculture-food/news/no-magical-alternative-to-glyphosate-in-the-next-5-years-bayer-official-says, last accessed: 13/4/2020.

[134] https://www.euractiv.com/section/agriculture-food/news/no-magical-alternative-to-glyphosate-in-the-next-5-years-bayer-official-says, last accessed: 13/4/2020.

However, as was already discussed in section 4.2., the glyphosate debate is very much influenced by border concerns of agricultural policy and the questioning of the future use of pesticides. Stakeholders call for new objectives in the pesticide regulation, including: "developing new technologies, investing in the use of naturally occurring substances and the protection of farm ecosystems, stimulating use of substances with low risk, or promoting non-animal methods for assessment of risks of substances and mixtures".[135] Also the **European Green New Deal** promoted by the von der Leyen Commission in this regard states:

> *" The strategic plans will need to reflect an increased level of ambition to reduce significantly the use and risk of chemical pesticides, as well as the use of fertilisers and antibiotics. The Commission will identify the measures, including legislative, needed to bring about these reductions based on a stakeholder dia logue. The area under organic farming will also need to increase in Europe. The EU needs to develop innovative ways to protect harvests from pests and diseases and to consider the potential role of new innovative techniques to improve the sustainability of the food system, while ensuring that they are safe." [136]*

Thus, some form of innovation will have to occur in the pesticides industry, given the public and political pressure. In this regard, **the application of the precautionary principle - through the strict regulatory framework for pesticides- can be seen as fostering innovation**. The Bureau Européen des Unions de Consommateurs (BEUC) more generally expressed it in the following way: "The precautionary principle pushes industry to research and innovate in safer or greener alternatives, which benefits both consumers and the economy."[137]

5.3 Innovation principle

This study **has not found evidence that the innovation principle has been invoked** formally in the context of the debate surrounding glyphosate. However, when in 2013 12 CEOs wrote a letter to the Presidents of the Commission, European Council and European Parliament to introduce and promote the innovation principle the CEOs of several companies producing glyphosate-based pesticides were amongst the signatories Bayer, BASF, Dow AgroScience, and Syngeta.[138] Many companies participating in the **European Risk Forum** (ERF), which is central in proposing and lobbying for the innovation principle are producers of pesticides and biotechnology.[139] Although not specifically referring to

[135] European Parliament Research Service, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market – European Implementation Assessment, PE 615.668, April 2018, p. 34-35.

[136] European Commission, Communication from the Commission – The European Green Deal, COM(2019) 640 final, 11.12.2019, p. 12.

[137] https://www.beuc.eu/publications/beuc-x-2018-112_precautionary_principle_under_attack_please_delete_so-called_innovation_principle.pdf, last accessed: 13/4/2020.

[138] https://corporateeurope.org/sites/default/files/corporation_letter_on_innovation_principle.pdf, last accessed: 13/4/2020.

[139] http://www.riskforum.eu/uploads/2/5/7/1/25710097/businesseurope-erf-ert_innovation_principle_joint_statement.pdf, last accessed: 13/4/2020.

pesticides a joint position of the ERF, Businesseurope and the European Roundtable of Industrialists states:

> *" Regulation which solely concentrates on risk avoidance a nd removal of scientific uncertainty and fails to consider both risks and benefits, stifles technological innovation. This type of regulation tends to result in companies directing l imited budgets towards ' defensive R& D', for compliance, at the expense of more innovative and discovery oriented research."* [140]

Thus, the argument is advanced that strict regulatory frameworks, like the approval and authorization scheme for pesticides with heavy scientific data requirements hinders innovation, as money is spent on proving safety for the regulatory procedures rather than innovating.

As argued by Garnett, van Calster and Reins (2018, p.11), large biotech companies would use the innovation principle to side-line the precautionary principle, where they "have been finding it increasingly hard to see their products approved for use in the EU and in some cases are fighting long legal battles to see their product licenses renewed (such as with glyphosate, bisphenol A or endocrine disrupters)." They point out that the industry, like in the case of glyphosate, has to go through lengthy and demanding risk assessment procedures which still might not disperse doubts with regard to the safety of the products, which explains why those companies might be inclined to shift the focus of the debate to innovation and job creation (Garnett, van Calster and Reins 2018).

Also Corporate European Observatory (CEO) warns that: "(…) these industries are trying to use this principle to undermine EU laws on chemicals, novel foods, pesticides, nano-products and pharmaceuticals, amongst others, as well as legal principles of environmental and human health protection which are enshrined in the EU Treaty."[141] CEO refers to an event organized by the ERF and cites a representative of the pesticides industry as arguing that there is an incompatibility between regulations promoting innovation and those regulations that prohibit innovative or indispensable substances.[142] The 'indispensable substances' is interpreted by CEO to refer to glyphosate.[143]

6 Synthesis

The glyphosate case study illustrates very well that a **relatively old technology**, widely used around the world since the 1970s, can with new scientific findings become the center of an extensive controversy. In the last decade, concerns have been raised with regard to glyphosate and risk for human health, such as carcinogenicity and endocrine disruption, as well as risks to the environment, regarding specific species as well as whole ecosystems. However, these risks are subject to **scientific uncertainty** even decades after its invention. This is caused by uncertainty through absence of systematic monitoring of glyphosate use and exposure. Moreover, the case clearly illustrates that scientific uncertainty also can exist and persist, in case of an **intensely studied** chemical substance, with over 1,000 studies performed and continuous scientific interest leading to an ever-increasing number of studies. In the glyphosate case, the scientific

[140] http://www.riskforum.eu/uploads/2/5/7/1/25710097/businesseurope-erf-ert_innovation_principle_joint_statement.pdf, last accessed: 13/4/2020.

[141] https://corporateeurope.org/en/environment/2018/12/innovation-principle-trap, last accessed: 13/4/2020.

[142] Ibid.

[143] Ibid.

uncertainty is mostly fueled 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.

What is remarkable about the **risk governance on EU level** is that 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. This leads to the conclusion that in the EU assessment of the glyphosate debate, the legislation and the regulatory framework, with the weight of evidence approach as operated in the scientific assessment, has significantly influenced and shaped the risk assessment process (Paskalev 2020; Morvillo 2020). As explained by Paskalev (2019, p.3) who compared the IARC and EFSA/ECHA findings: "the decision of each agency is affected by its own governing documents, terms of reference, set functions and mission statement and this is why even if they all appeared to be considering the same issue – carcinogenicity of a certain substance – they were bound to reach different conclusions." Thus, **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**. This has brought to the forefront 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" (Arcuri, p.243).

As was shown in this case study, although not all of **main components of the precautionary principle** as defined in the **WP1 Report: Taking stock as a basis for the effect of the precautionary principle since 2000**,[144] including scientific uncertainty and risk, scientific evaluation, threshold of damage, cost-effective measures/proportionality and burden of proof, were directly applicable in the case of glyphosate as the substance was not banned. However, in principle **the regulatory framework applicable to glyphosate does incorporate these characteristics**. Nonetheless, it also became clear that the **application of the precautionary principle in the risk management stage is not clearly regulated**. Although the legislation specifically mentions taking into account the PP in the decision on approval and renewal of active substances, how this should happen is not clearly defined and also not well communicated.

In the case of glyphosate, after a hazard and risk assessment by EFSA and ECHA, it was decided that a ban was not necessary, even in the face of large public pressure. While this is criticized by some stakeholders, it is also a **sign that innovation and innovative industries do not need to be specifically protected** against 'laws of fear'[145]. The build-in mechanisms in the process leading to the application of the principle, like the thorough risk assessment, in itself protected against a disproportionate precautionary measure.

The glyphosate case also shows how a very technical and scientific debate – surrounding the carcinogenicity assessment and the underlying scientific methods, can be easily **politicized**. With regard to the glyphosate, this is caused, first of all, by the fact that **exposure** is in essence unavoidable for everyone, given the residues of glyphosate in

[144] E. Vos & K. de Smedt, '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: 13/04/20.

[145] The term was coined by Sunstein (2005).

food and water. On the other hand, the **debate surrounding glyphosate is deeply entangled with bigger questions on the future of agriculture and GMOs**.

This also has an impact on how the application of the precautionary principle interacts with **innovation**. While glyphosate has not been banned on EU level, a ban of the substance or the further limitation of its use will pose challenges to the chemical industry and farmers. It is debated if glyphosate would be (easily) replaceable and how innovation with regard to the substance or a possible substitute will look. What is clear is that the glyphosate controversy, together with the debate surrounding other pesticides such as neonics,[146] has reinvigorated the public and political pressure to rethink the use of pesticides in European agriculture. In this regard, the **precautionary principle has been a catalyst for innovation**.

7 Conclusion

The safety of glyphosate, and especially its effects on human health and the environment, have been called into question in the recent decade by scientific studies. However, these studies are debated in terms of their methodology and in how far they should be taken into account in the risk assessment by regulatory bodies. In the EU, the assessment of glyphosate in the context of the renewal of approval procedure ended with a re-approval of the substance for 5 years in 2017. This decision was based on the risk assessment carried out by EU agencies, which came to the conclusion that glyphosate is not carcinogenic and also does not pose other risk that would justify banning the substance. However, this finding is contested by individual scientists and also opposes the finding of the IARC. This creates scientific uncertainty through ambiguity.

The precautionary principles shapes the approval procedure and regulation of pesticides as such, however, as in the risk assessment of glyphosate on EU level no risk was determined, no precautionary measure in the form of a ban was taken. This is contested by various stakeholders. The politicisation of the glyphosate renewal procedure has to be seen in the context of the larger debate surrounding the future of EU agriculture and the use of pesticides. In this regard, the application of the precautionary principle has led to increased political pressure, which is highly likely to result in some form of innovation in this area in the long run. As for glyphosate itself, whether innovation will be necessary will be determined in the currently ongoing renewal procedure.

[146] Please see the RECIPES case study on neonicotinoids.

8 References

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9 Appendix

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Precaution and Financial Risks in Implementing the Urban Waste Water Treatment Directive: Cities Investing in Water Infrastructures

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Abstract

This study aims to understand the complexities and controversies around the application of the precautionary principle in the context of urban waste water infrastructure provision. It examines these dynamics by example of case studies in London and Milan. It begins by outlining the risks and threats associated with the cases and relates them to the conceptual core of the precautionary principle, the risk governance process, and the regulatory and legal history. It argues that the application of the precautionary principle through the WFD has significant impacts on urban development and that its application shifts risks from environmental impacts towards long-term planning risks and economic vulnerability of cities. The examination of the risk governance process further shows how the complexity of the water sector challenges good governance practices and how external pressures such as those instigated by the precautionary principle can lead to undesirable reconfigurations. This study further examines the innovation dynamics in the cases. 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 sector have enabled an environment for sustainable financial innovation. The innovation section concludes with a perspective on the innovation dimension inherent in the precautionary principle and how it has affected the two case studies. The study closes with a synthesis of the findings and concludes that the role of transparency and good local governance practices are essential for a successful implementation of precautionary principle requirements in a city's water sector. A common dynamic in compromised planning processes is the creation of 'white elephants', which can be avoided by harnessing the innovation dimension of the precautionary principle in a conscientious manner.

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List of abbreviations

AEEGSI	Autorità per l'energia elettrica il gas ed il sistema idrico
ARERA	L'Autorità di Regolazione per Energia Reti e Ambiente
BWD	Bathing Water Directive
BTL	Bazalgette Tunnel Limited
BOT	Build - Operate - Transfer
DEFRA	Department for Environment, Food and Rural Affairs
DWD	Drinking Water Directive
EE2	Eethinyl Estradiol
EIB	European Investment Bank
FD	Floods Directive
IP	Innovation Principle
JRC	Joint Research Centre
MSFD	Marine Strategy Framework Directive
MM Spa	Metropolitana Milanese S.p.A.
ND	Nitrates Directive
PP	Precautionary Principle
TTT	Thames Tideway Tunnel
TW	Thames Water
UWWTD	Urban Waste Water Treatment Directive
WAREG	European Water Regulators
WFD	Water Framework Directive
Ofwat	Water Services Regulation Authority

1 Introduction

1.1 Introduction

Many European **cities are facing the challenges** of having to massively overhaul their urban water infrastructures. Ageing and overburdened systems first installed in the 19th century are challenged by **increasing environmental standards** imposed by European law. These standards are set within the Water Framework Directive (WFD) and its daughter directives, with direct reference to the precautionary principle, the Control at Source Principle and the Polluter Pays Principle (Art. 191(2) of the Treaty on the Functioning of the European Union). In order to meet these infrastructural challenges, **immense investments** are needed, posing their own risks and problems for cities. This dynamic is a major point of **difference towards the other case studies** in the RECIPES project: 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.**

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 not conform with the imposed waste water standards. Two of these cities are London in the United Kingdom and Milan in Italy. By example of these two cases, this report will detail how the precautionary principle affects urban water infrastructure provision, and how the regulation of the primary risk of pollution entails secondary risks that result from the highly integrated nature of a city's water infrastructure. 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 challenges of integrating water services more closely with long-term urban planning objectives has been recognised as one of the key issues for improving European water policy (EurEau 2017).

This report's main goal is to understand the complexities and controversies around the application of the precautionary principle in the context of urban waste water infrastructure provision. It examines these dynamics by example of case studies in London and Milan. Furthermore, it will examine the role of financial and organizational innovation and how it relates to the innovation principle and the precautionary principle.

The 2010 legal case against the United Kingdom centred on the **overflow of the sewage system into the river Thames** in case of minimal rainfall. The case argues that under the UWWTD London does not provide adequate infrastructure for the prevention of pollution. As a consequence, the city was presented with the challenge to fix the problem and present a solution that was both capable to cope with the difficult post-financial crisis funding situation as well as the long-term infrastructural challenges present in London. A **strategic study** was implemented by the Environmental Agency, Thames Water (TW), Department for Environment, Food and Rural Affairs (DEFRA, the responsible ministry) and the Greater London Authority to determine appropriate

solutions. Funding allocation for the different involved disciplines was questioned later, as the results were biased towards large-scale engineering solutions. The selected solution was the adaptation of the water system to and the construction of a **25km tunnel under the River Thames** that effectively acts as a secondary sewer system that catches the overflow of the first when it becomes overburdened. Construction is ongoing and the cost is estimated at **£4.2 billion** total. Controversies around the project relate to a lack of transparency in selection process following the strategic study, a weak tender-process, a questionable financial model as well as challenges to the entire raison d'être of the project, since it's services are projected to be no longer necessary.

The legal case brought against Italy in 2000 for **Milan's ongoing dumping of untreated waste water into the river system**, handles a similar issue, however it is larger in scale. The legal case results from previous cases against Italy for the failure to implement the UWWTD into national law and puts the finger on immense structural changes that had to be implemented in cities across Italy. Milan was at the time the last major European city still dumping untreated waste water. Due to these proceedings, Milan has been the subject to an infringement procedure by the EU Commission. A reason for the EU Commission's hesitance to impose a pecuniary sanction was most likely due to the belated awarding of construction contracts to private consortia. **Milan had to construct two completely new purification plants** and implement major upgrades in a third between 1999 and 2006. The awarded BOT (Build-Operate-Transfer) **contracts were surrounded by controversy** over bribery, lack of transparency and restricted competition. These events were still very much in line with ongoing fallout from the 1990s Tangentopoli phenomena ("Bribesville", referring to corruption in public works contracts). These scandals facilitated structural changes in the operation of Milan's water sector, particularly with the **transfer of the management responsibility** for the integrated water system from the Municipality to MM Spa, a multiservice company fully owned by the Municipality of Milan. Even though the way these structural changes were implemented are still not free of criticism and path dependencies resulting from the BOT contracts are still strong, today, Milan's water system has emerged from this transformation process with several **technological and financial innovations.** It has become a point of reference for a successful water system in a European city.

The following section will provide a brief overview over the timeline of the two case studies. The sections thereafter will outline the risks and threats associated with the cases and will relate these to the conceptual core of the precautionary principle, the risk governance process, and the legal and regulatory history. It is argued that the application of the precautionary principle through the WFD has significant impact on urban development and that its application shifts risks from environmental impacts towards long-term planning risks and economic vulnerability of cities. The examination of the risk governance process further shows how the complexity of the water sector challenges good governance practices and how external pressures such as those instigated by the precautionary principle can lead to undesirable reconfigurations. The legal and regulatory history section details the long-winded nature of water regulation and implementation of changes. Section five outlines the innovation dynamics in the cases. 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 sector have enabled an environment for sustainable financial innovation. The innovation section concludes with a perspective on the innovation dimension inherent in the precautionary principle and how it has affected the two case studies. Two related instances in which the

precautionary principle has been invoked are briefly portrayed. The report closes with a synthesis of the findings and concludes that the role of **transparency and good local governance** practices are essential for a successful implementation of precautionary principle requirements in a city's water sector. A common dynamic in compromised planning processes is the creation of **'white elephants'**[1], which can be avoided by **harnessing the innovation dimension of the precautionary principle** in a conscientious manner.

1.2 Key timeline

The London Case

Political	*Legal*	*Economic*	*Public debate*	*Other*

Year	Event	Relevance to case study
1989	Privatization of Thames Water	Deep structural changes to London's water system
1991	Water Industries Act	Reforming the British Water Sector
1991	Creation of Ofwat	Establishing the Regulatory Agency
2001	RWE acquires Thames Water	Begin of overleveraging of assets
2005	Case C-252/05 for definition of waste water	Begin of legal proceedings
2006	Kemble Water Holdings acquires Thames Water	More financial engineering in the operation of Thames Water
2010	Case C-301/10 for failure to comply with the UWWTD in London	Begin of specific UWWTD case
2012	Founding of Clean Thames Now and Always Initiative	Begin of public advocacy
2015	Creation of BTL and receiving operating Licence from Ofwat	Project realization begins
2016	Construction of Thames Tideway Tunnel begins	Construction phase begins, projected to last until 2024

[1] From Merriam-Webster Dictionary: "a property requiring much care and expense and yielding little profit. […] the kings of Siam […] gave white elephants as gifts to those they wished to ruin, hoping that the cost of maintaining the voracious but sacred mammal would drive its new owner to the poorhouse."

2017	Kemble Water Holdings sells all stakes in Thames water	Reshuffling of ownership and final responsibility

The Milan Case

Political	*Legal*	*Economic*	*Public debate*	*Other*

Year	Event	Relevance to case study
1992	Begin of first Tangentopoli trial	Deep structural changes to Italy's urban infrastructure sector
1994	Galli Law reforming Italian Water Sector	Redefinition of Italian Water Regulation
1995	Case C-302/95 for failure to implement the UWWTD	Case against Italy for failing to comply with EU law
1997	Case C-195/97 for failure to implement the UWWTD	Case against Italy for failing to comply with EU law
2000	Case C-396/00 for failure to comply with the UWWTD in Milan	Begin of legal proceedings related to Milan
2000	BOT Contracts: construction start for first new purification plants	Begin of financial complications
2003	Transfer of Water System from Municipality of Milan to MM Spa	Restructuring of Milan's water system operation
2006	All purification plants completed	Original plans completed
2007	MM Spa assumes responsibility for the Water System until 2037	Solidifying current practices
2014	ATO Plan update and revised investment plan	Establishing long-term commitments

2 Urban Water

As mentioned before, this case study bears a major point of difference towards the other case studies: it does not focus on a particular product or technology that stands in tension with the precautionary principle, but it **examines the impacts of a long-term precautionary principle regime over urban water infrastructure development**. Therefore this section will not portray a specific technology, but it will briefly outline some significant aspects of urban water.

Access to **clean water and sanitation has been recognised as human right** by the United Nations General Assembly in 2010. This emphasizes the significance of the close

entwinement of the human metabolism with water, and thus it could be argued that **water infrastructure is a key prerequisite for the development of cities** in history per se. From river settlements, to aqueducts, to the development of sewers, purification and desalination plants, the history of urban water infrastructure mirrors the increasing complexity of our increasingly urbanized societies. Erik Swyngedouw characterizes this relationship as follows: "Water is indispensable 'stuff' for maintaining the metabolism, not only of our human bodies, but also of the wider social fabric. The very sustainability of cities and the practices of everyday life that constitute 'the urban' are predicated upon and conditioned by the supply, circulation, and elimination of water" (Swyngedouw 2004, p.1).

This relationship sets the stage for many current issues in urban development: from climate change impacting fresh water reservoirs to sewage system development lagging behind urban growth in newly industrializing economies and aging water infrastructures in the Global North, these issues pose many a **challenge to human health and local ecosystems**. The complexity of these issues is immense, as they cut across several scales and intersect with every aspect of human life. Keeping the scale of these challenges and structures in mind, urban water infrastructure issues pose **major financial challenges to cities**. The question of what is to be built, where and why is closely tied to the question of what funds are available and under which conditions these are provided. Financial commitments set path dependencies that can impact urban development for multiple decades, as many of these infrastructures are set up to operate for well over a hundred years. This introduces a great amount of uncertainty, as the future remains unknown. The plurality of interests and opinions tied to the interpretation of this future characterize the key role of ambiguity for urban water issues.

Between the significance for the human metabolism and society, the long timescales at play and the immense financial costs of constructing and maintaining urban water systems, the **role of regulation and its legal framing** come to the fore. Here, the precautionary principle sets the stage in the European context, as its inclusion in the WFD frames the way in which urban water systems are realized within the Union.

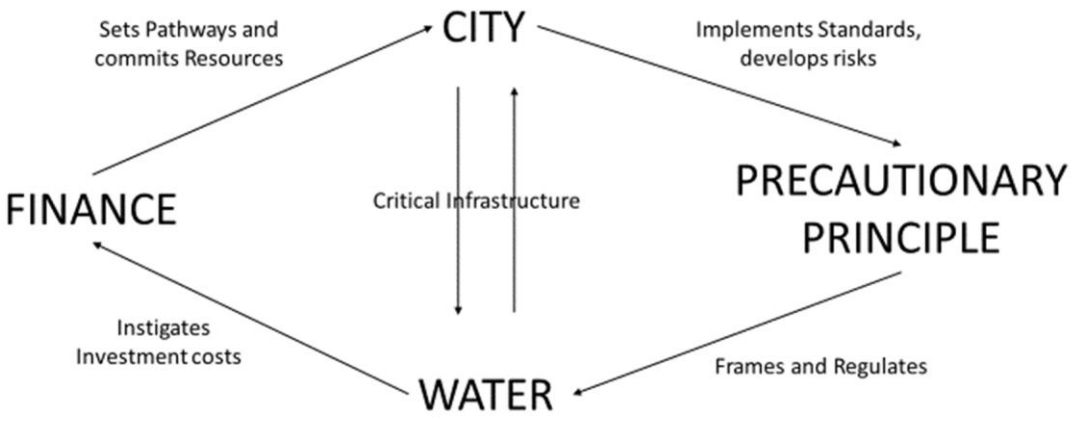
3 Risks and scientific uncertainties

3.1 Risk/threat

The precautionary principle plays a central role in regulating the relationship of cities with their water infrastructure. The **precautionary principle frames and regulates how cities are supplied with fresh water and how they deal with their waste water** through the Water Framework Directive and the associated Industry Directives (UWWTD, DWD, BWD). This legislative framework sets certain standards that must be met and can result in legal action in case cities fail comply. This has been the case in the cities of London and Milan. The ensuing situation presents cities with an enormous challenge: **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.** This situation gives rise to different financial solutions that set out pathways for future urban development. These pathways bring their own risks and threats that often go beyond the original risk that was to be regulated by the precautionary principle-based legislation.

Risks and threats thus emerge at different points within this dynamic, accompanied by uncertainties that are mostly tied to unpredictable future developments:

Figure 1: The precautionary principle, Finance and urban water



These risks and threats can be roughly allocated to the following categories, though as the graphic shows, the risks and threats in the water sector are highly integrated and often cause ripple effects in related areas.

ENVIRONMENTAL AND HEALTH RISKS

- Underfinanced infrastructure leads to lack or degradation of water supply systems which affects water quality

FINANCIAL RISKS

- Exposure of local administrations to market risk, financial health at risk
- Increased complexity in local administration operation with often scarce expertise
- Asymmetric expertise between cities and lenders creates incentives for obfuscation (socialized costs vs individualized profits)
- Current incentives discourage developers to achieve project completion to time and cost
- Water sector is characterized by quasi monopolies, who are often "too big to fail" creating further misguided incentives for effective market operation
- Conflicts of interest and corruption undermining market mechanics

PLANNING RISKS

- Pressure on cities to meet standards creates a financial burden and planning risks which restricts decision space towards other urban issues. Path dependencies are created
- Compromised decision-making process leads to sub-optimal infrastructure solutions
- Overall reduction in resilience due to increased complexity, interdependency and exposure to new vulnerabilities: systemic risk increases

3.2 Scientific analysis

Gawlik et al. provide an excellent first overview over current water issues in European cities in their "Urban Water Atlas for Europe" (2017). Within the wider literature the above risk groups can be allocated to different debates, with **environmental and health risks** as the longest established field. Here, key debates include pollution through the introduction of untreated wastewater into the landscape, securing drinking water, ecosystem management, climate change impacts and socio-economic issues (cf. Aboelnga et al. 2019, UN 2019). **Planning risks** are mostly discussed under the umbrella terms of urban resilience and vulnerability, and cover issues ranging from future challenges such as climate change to securing water resources and critical infrastructures (Revi et al 2014, O'Rourke 2007). **Financial risks** and their repercussions with regard to urban water infrastructure only entered the discourse more recently. Debates centre around changing governance practices, exposure of cities to market volatility and externalisation of costs into the future (Pike et al 2019, Grafe & Mieg 2019, Loftus & March 2016, Pryke & Allen 2019), while some authors point out the risk of corruption in water infrastructure projects (Butterworth & de la Harpe 2009). 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 (Swyngedouw, Kaika & Castro 2002).

In the context of our two example cases specifically, local research reflects these larger debates as well:

The wastewater overflow pollution occurring in London due to ground sealing and the resulting legal case, triggered research into ways to overcome the issue (Tideway Strategic Study 2005). The implementation of the proposed solution, the Thames Tideway Tunnel, has been accompanied by critical research and commentary, pointing out planning and financial risks (Loftus & March 2019, Grafe & Hilbrandt 2019, Blaiklock 2017). Aside from research on the tunnel project specifically, research further investigated financial practices and resulting risks by key water infrastructure providers (Allen & Pryke 2013, O'Brien & Pike 2015), as well as central challenges in implementing the UWWTD in a precautionary manner (Smith 2010).

The European Commission's legal case concerning Milan over ongoing lack of sufficient wastewater treatment, has caused a similar breadth of research in its wake. Early research on the case focusses on the 2000 corruption scandal and its negative effects, as well as the delayed implementation of institutional changes (Global Water Report 2001, Lobina & Paccagnan 2005). More recent publications highlight financial innovation and its effects (Cetti 2018), with the "Juncker Plan" playing a significant role in making the specific financial model work (Ref Ricerche 2017). Improving environmental impacts and implementation of the Water Framework Directive have been well documented (European

Commission 2012). While planning risks are managed in close dialogue with the city administration (Cetti 2018).

3.3 Scientific uncertainty

3.3.1 Complexity

Of the three aforementioned risk groups, **environmental impacts and health risks provide the best understood area**. Target values are established and impacts of pollution are well monitored and understood. In terms of **planning risks, complexity increases** as decisions set pathways far into the future, increasing uncertainty and introducing new dependencies. Research in the context focuses foremost on questions of critical infrastructure, that is security of highly vulnerable infrastructure for the functioning of modern societies. 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. This dynamic adds potential conflicts of interest and provides an entry-point for corruption. 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.

3.3.2 Uncertainty

Even though differences in the implementation of the European Water Directives are practiced in the different member countries (cf. Smith 2000), **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. With respect to the financial risks, the 2008 financial crisis has exposed some of the localized effects of urban investment practices, while the scientific debate on the wider impacts of financialization on urban infrastructure has only recently been taken up (cf. Pryke & Allen 2019, Grafe & Mieg 2019, Pike et al 2019). The evidence points towards a number of risks developing in this sector and includes increasing obfuscation and complexity, the exposure of municipalities to market volatility and the socialization of costs while profits are individualized.

3.3.3 Ambiguity

Ambiguity plays a key role in the water infrastructure sector. 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. One group was focussing on long-term sustainable solutions for the city, whereas the other was looking for those solutions that were financially lucrative and viable (cf. Grafe & Hilbrandt 2019).

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 corruption scandal in the early phase of the project as well as the desire to avoid putting the water service concession out for tender shows how certain actors stand to gain from keeping processes behind closed doors (Butterworth & de la Harpe 2009). The lack of legal requirements for public participation further emphasizes the structural deficiency towards making more viewpoints heard.

3.4 Relevance of the precautionary principle to the case

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.

4 Risk governance and the precautionary principle

4.1 Risk governance

The following section will examine the risk governance process, it follows the five steps of the IRGC framework, in order to find out whether these phases can be identified in the cases (see D2.1 Section 5).

4.1.1 Pre-estimation

Access to **clean water and sanitation has been recognised as human right** by the United Nations General Assembly in 2010. Thus, defining water resources and sanitation as one of the most important aspects of human life. Consequentially, the position on risks by state actors and citizens regarding water and sanitation is an absolutist one. Standards are continually raised and improved, and the public tends to be aware of the quality of service they are provided. Industry actors tend to argue the other side of the coin, as to them water tends to be primarily and industrial resource. All these interactions are tightly regulated by the European Water Directives.

This high prioritization of water quality has led to the **overshadowing of other risks**: expensive measures introduce new dependencies and open the door to financial instability. This hints at the complexity inherent in the urban water sector. The OECD gives the following issues as the **key challenges of successful water governance** (OECD 2011): institutional fragmentation, ambiguous legislation, poor implementation, limited local scientific and technical capacity, unclear allocation of roles and responsibilities, unstable or insufficient revenue and funding, no long-term strategic plans and insufficient monitoring of performance. All of this leads to weak accountability and poor transparency. Many of these issues are found in the cases and give rise to different risks.

4.1.2 Interdisciplinary risk estimation

Risk assessment was tied into long-winded legal proceedings, where after the reversal of burden of proof the cities were under pressure to present their solutions. The main aim was to provide adequate infrastructure for preventing overflows, **which infrastructures are to be built specifically was left to the cities**.

Here the stories diverge: in the case of London a strategic study was commissioned to achieve a consensus towards the most appropriate measure. The consensus process was commonly criticised, as the funding for the different sciences diverged significantly, and the resulting tunnel proposal was severely questioned by citizens favouring more sustainable long-term solutions rather than short-term technical fixes that disregard related issues such as future flood risks. As a result, the consultation process appeared to favour specific outcomes from the onset, silencing part of the discourse and discouraging input from social and environmental scientists.

Milan went about the construction of a complete waste water purification system for the city, which was overseen by a technical-scientific control committee put in place to check and verify the project for technological adequacy, reliability, costs and environmental impact. The committee itself was composed of a mix of experts and scientists from several fields from all over Italy. The entire operation of the water system was then handed over to MM Spa in 2003, an engineering company formerly in charge of the city's metro system and 100% owned by the municipality of Milan.

4.1.3 Risk characterization

As stated before, environmental risks are characterized as intolerable, whereas secondary risks such as planning risks and financial risks are treated as much more tolerable. This **tolerance varies between the two cities**, London was willing to take much bigger risks both financially as well as in future flexibility. Milan followed a more conservative approach, keeping more options available for future challenges.

4.1.4 Risk Evaluation

The risks occurring in the two cases have **not been subject to a collective risk evaluation**. Risks evaluations are spread out and differ across the early stages of the legal case, the pre-emptive studies, the tender-processes, the construction and finally the operation of the infrastructure asset. Taking these differences into account, the continued quality of service provided by the operator is still the most important risk, followed by hidden structural risks introduced by planning compromises and novel financial practices.

4.1.5 Risk management

The precautionary principle acts as the trigger for the cases at hand. The European Commission invokes the precautionary principle through the EU Water Directives and applies it in the legal cases it brings against cities for failing to comply with the standards set out therein. Once the case is brought and the reversal of burden of proof occurs, the cities are in the position to come up with their own solutions. Here, the composition of actors and decision makers differs across contexts, as this is largely dependent on the configuration of that city's water sector. Here, the level of privatization and power of regulators plays a key role. The following process and configuration of key actors is then

largely structured by the pre-emptive studies phase, the tender-process phase, construction phase and operation phase of the newly developed infrastructure. The power dynamics across this development vary widely dependent on the specific configuration of the city's water sector. In a more privatized context like London, investors hold more power at the costs of public oversight. An over-emphasis on profit maximization on their side can skew the entire development towards a more economically focussed logic, whereas the case of Milan holds strong oversight and long-term planning at the centre of the project, thus providing a more secure planning environment.

4.2 Political/juridical dynamics

This section examines those aspects of the precautionary principle that relate to regulatory measures, the section will be concluded with an overview over the cases legal history.

4.2.1 Threshold of damage

The primary risk of unmet water quality standards was put to the test in the two legal cases. Initial trigger was the continued missing of target values regarding the release of raw sewage into the environment. The legal cases thus centred on the lack of provision of adequate infrastructure according to paragraph 3,4 and 10 of the UWWTD. Both cities have since implemented different infrastructural solutions to overcome the challenge and as of 2020 meet the current standards. In the case of London questions are raised if the Tunnel project was necessary in the first place, as other regulatory changes have had an impact on improving the problem. Similarly, in Milan, the questionable BOT contracts established long-term path dependencies that heavily weighed on the flexibility and adaptability of the water system. **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. Efforts have been made to integrate it with financial regulation after the last financial crisis, but the efforts have largely been eschewed by decision makers (Crotty & Epstein 2009, Ülgen 2016). Considering the immense costs tied to infrastructure investments, an argument could be made that a **mishandling of these funds meets a threshold of damage**, as the consequences often impact other essential services cities provide.

4.2.2 Cost effective/proportionality

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. Here, the longer time frame of the Milan case provides some more accurate evidence towards the low political (delays, legal proceedings, protests), economic (transparency issues, restricted competition) and environmental (delayed implementation, binding of resources) sustainability of the awarded BOT contracts and resulting purification plants (cf. Lobina & Paccagnan 2005). **Cost effectiveness and proportionality were not met.**

4.2.3 Reversibility of the measure

As a consequence of the large investment costs, long construction periods, and far reaching financial schemes, commitments to overcome the legal challenge are not easily

if at all reversed. Significant path dependencies have been committed, the longevity of these and the on-going struggles in overcoming their fallout have been documented in the Milan case and with its problematic BOT contracts. Systemic interdependence of infrastructure systems forecloses any short-term reversals and imply significant costs if a full reversal is intended. **Obduracy and path dependencies put in place by large-scale physical structures immensely restrict the reversibility** of implemented changes.

4.2.4 Reversal of burden of proof

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.

4.2.5 Legal history

EU water legislation is defined through the Water Framework Directive (WFD) and its daughter directives (Groundwater Directive 2006/118/EC and the Priority Substances Directive 2013/39/EU). The precautionary principle is one of the core principles of the WFD and is established in article 11. These directives form the legal framework for European, national and regional policies for protecting water resources. These are further complemented by the Marine Strategy Framework Directive 2008/56/EC (MSFD), the Nitrates Directive 91/676/EEC (ND) and the Floods Directive 2007/60/EC (FD). Furthermore, the 'Water Industry Directives' (Urban Waste Water Treatment Directive 91/271/EEC (UWWTD), Drinking Water Directive 98/83/EC (DWD), and the Bathing Water Directive 2006/7/EC) provide complementary legislative tools for the safe management of sewage, the protection of drinking and bathing waters. These pieces of legislation form the backbone of water policy in the European Union and each address separate issues within the water sector. As these issues are still closely interrelated, these directives mutually impact compliance. The UWWTD fulfils an obligation of WFD to treat urban waste water (cf. EurEau 2017, p.5).

The precautionary principle was brought to bear in the two legal cases against both the United Kingdom and Italy for failing to comply with the UWWTD in the cities of London in Milan. The extensive nature of these problems and the long time necessary to overcome them characterizes the protracted legal cases. The following section summarizes these proceedings.

LONDON

The London example is characterized by two court cases, the latter of which forms the core conflict.

CASE C-252/05 (Judgement ECLI:EU:C:2007:276)

The first case can be considered a pre-amble to the latter legal case, as its subject is concerned with the definition of waste water and thus resulting obligations to improve the stormwater overflows for Thames Water.

CASE C-301/10 (Judgement ECLI:EU:C:2012:633)

The second case treats the non-compliance of the United Kingdom with the UWWTD (Urban Waste Water Treatment Directive, Council Directive 91/271/EEC) in London and Whitburn and threatens financial sanctions for ongoing breaches. The case is characterised by a long correspondence and meeting phase in which the UWWTD requirements are clarified and declared relevant for the case. The Thames Tideway strategic study is implemented, but the UK's response thereafter is still deemed lacking, thus advancing the legal procedures. The decision acknowledges the UK's failure to comply and orders it to bear the costs. Progress has been made to remedy the situation since, but problems persist. Details of the case taken from the final judgement are provided in the appendix.

MILAN

The Milanese case consists of three legal proceedings, which represent the escalation of the failure of the Italian state to implement the UWWTD first nationally and then as consequence breaching regulations locally.

CASE C-302/95 (Judgement ECLI:EU:C:1996:502)

CASE C-195/97 (Judgement ECLI:EU:C:1999:100)

These cases form the pre-amble for the Milanese case, as they treat failure to implement the UWWTD on the national level.

CASE C-396/00 (Judgement ECLI:EU:C:2002:261)

This case treats the failure to comply with the UWWTD in Milan specifically. It mirror's the British legal case to a large extent: a long correspondence phase is characterised by inaction to solve the problem at hand. Three treatment plants were planned early on but construction had not yet begun, thus triggering the pursuit of the legal case. The decision finds Italy in breach of its obligations and orders it to bear the costs. The appendix contains a detailed summary of the case taken from the final judgement.

4.3 Other governance dynamics

As mentioned earlier, the water sector is highly integrated into complex urban systems and is **regulated at several levels**. EU Level guidelines set by WFD and its related directives are implemented locally by differing institutions. Foremost are the **local regulators** for the water sector. In the case of London this is Ofwat (Water Services Regulation Authority) and in case of Milan ARERA (L'Autorità di Regolazione per Energia Reti e Ambiente, before 2018 known as AEEGSI).

There exists also a dedicated **instrument for cooperation between economic regulators** to encourage innovation and transfer of knowledge on the European Level called WAREG (European Water Regulators). So far, this network includes 31 members with shared goals of sharing common practices, improving technical and institutional cooperation, promoting capacity building, providing/creating stable regulation, protecting consumers, as well as fostering open dialogue with EU institutions and stakeholders at international levels.

BOX 1: Gender Issues and Urban Water Infrastructure

As indicated earlier, the water sector is highly integrated and touches upon a multitude of societal dynamics. This includes several gender issues, ranging from the underrepresentation of women in the financial sector to the significance of bad water accessibility for women's everyday lives in many developing countries. This section will spotlight a key gender issue that is most relevant to the two cases and that illustrates some of these dynamics in the water sector.

The Hidden cost of Birth Control

Birth control has played a significant role for sexual self-determination of women and has become an integral part of modern societies. However, this sexual revolution comes with an infrastructural cost. The active ingredient in the majority of birth control pills is **ethinyl estradiol** (EE2), a pollutant that is very **difficult to remove from waste water** with ordinary purifying infrastructures currently in place within most cities in the EU. If it enters waterways it can have adverse effects on the **reproductive systems of fish** by causing a condition known as intersex (Owen & Jobling 2012).

In 2012 the European Commission announced that it intends to regulate EE2 under the WFD, then requiring countries to limit EE2 levels in their water bodies, establishing a global precedent for regulating pharmaceuticals in the environment (Owen & Jobling 2012). In order to successfully filter EE2 out during the purification process, Owen & Jobling calculate **significant upgrade costs** for existing purification plants to be about £8 million with operational costs of about £800.000 per year for a town of 250.000 inhabitants (id.). Across England and Wales this would add up to £30 billion for the 1400 existing waste water plants (id.).

The debate around this subject is mostly held outside the public sphere and without contribution of women's voices. The UK Royal Commission on Environmental Pollution has criticised this approach advocating for an inclusion of people's values and that "it is no longer acceptable for decisions to be negotiated privately between the regulator and polluter" (RCEP 1998).

The **immense costs associated with upgrading purification plants** across the EU emphasize again the significance the precautionary principle holds for urban infrastructure development by commandeering a potential second wave of costly upgrade requirements. It further stresses the significance of transparent consensus processes in which the public can make an informed decision as to how it **balances environmental impacts, sexual self-determination and allocation of scarce resources**.

EE2 is currently on the 1st WFD watchlist, a recent JRC report concludes that it will remain there for the 2nd iteration (European Commission 2018). No legal obligation to upgrade plants has been imposed yet.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

Even though the precautionary principle lies at the very foundation of regulating urban water, it is rarely reflected upon. This has two reasons, first, as discussed in the risk governance section, it is **generally accepted that the precautionary principle applies** to the regulation of water and that the upholding of the highest standards is desirable. The significance for the human metabolism and its enshrinement as human right by the UN further solidify this rarely contested position. Second, repercussions of the application of the precautionary principle in terms of **risks generated elsewhere are rarely perceived as being directly related to the precautionary principle**. Thus, discussions often centre around issues of urban and financial sustainability in general, and less so as complex interactions of regulatory measures. Independently of water regulation, the precautionary principle is occasionally called upon as a principle for financial regulation or in the context of critical infrastructure debates (Belluck et al. 2006, Crotty & Epstein 2009, Ülgen 2016). This uncontested position has led to the **firm establishment of a precautionary principle based regulatory regime** over urban water issues.

5.2 Innovation in the water sector

Innovation in the water sector is coordinated on the EU level through the **European Innovation Partnership on Water**. It is a forum established under the Water Framework Directive (WFD) with the aim to remove barriers to innovation in the water sector. Its activities are mostly related to technological innovations in the field. This report will **focus on financial innovations**, as their impacts are underrepresented, and their repercussions can be more far reaching then technological fixes.

This case differs from the other case studies in the regard that it is not a new product or technology that challenges the precautionary principle, but that it is the **ongoing raising of standards under the precautionary principle that fosters innovation.** The basic premise is this: cities are obliged to heavily invest in water infrastructure to meet the imposed requirements, they however lack the means to fulfil this duty. In the literature this is often referred to as the **'infrastructure gap'**, and actors on all sides and levels develop strategies to overcome it. This is the main source of innovation in the case, which is why this section will focus on financial R&I of the urban water infrastructure sector.

The cases provide two different perspectives on financial innovation in the field. The **London case focusses on a specific project** that employs a highly individualized financial strategy to the benefit of investors, whereas the **Milan case presents a perspective that is more focussed on the city's long-term needs**. Both of these had to employ financial innovation to develop a viable model for the cities' infrastructure development. However, how we pay for infrastructure influences what is to be built, how it is going to be done and the location where it will happen. Thus, a novel financial model introduces new variables into a city's water system, potentially introducing new risks and vulnerabilities.

5.3 Effect of the PP on innovation pathways

As stated before, the two cities utilized different strategies for overcoming their specific infrastructure gaps. Both of these strategies resulted in specific innovation pathways, which will be characterized separately below.

London

The section on risk governance highlighted the decision-making process arriving at the Thames Tideway Tunnel (TTT) as the solution to London's water infrastructure problem. This section will move on from the pre-construction phase and will detail the specific project setup and implementation with a focus on the financial innovation occurring in this case of project finance.

Thames Water (TW) is the key actor for this project, they supply about 9 million customers with water and are responsible for the wastewater of about 15 million customers within South-East England (Thames Water 2019). TW was first privatized in 1989 and has since been subject to several takeovers and restructurings. This has resulted in lower credit ratings which mostly result from overleveraging of the underlying assets to finance these takeovers (Blaiklock, 2017). TW was first listed on the London Stock Exchange, but has since been unlisted and employed an increasingly byzantine off-shore structure, which in 2012 consisted of 10 corporate layers between shareholders and the licensed water company, further increasing complexity. For example, the off-shore subsidiary Thames Water Cayman Island Finance Ltd. holds over half of Thames Water's £10 bn long-term debt. Ultimate owner of TW is the consortium of international investment funds Kemble Holdings Limted, who mostly refinance their investment debts by securitizing household revenue streams (cf. Allen and Pryke 2013).

TW financially weak position has resulted in the fact that project delivery is being implemented by a separate entity, Bazalgette Tunnel Limited (BTL), a new special-purpose company with an off-shore holding structure similar to that of TW. The financing scheme passes a proportion of the project costs on to Thames Water's costumer bills, with an estimated £25 added per annum in the mid-2020s. Martin Blaiklock, an independent infrastructure finance expert states that this scheme where customers pay both during the construction phase as well as during service delivery is contrary to common investment principles, as it **transfers the project completion risk from utility company to the customer** (Blaiklock 2017). He concludes that "the incentive for contractors to achieve project completion to time and cost is now much diminished, if not eliminated. Furthermore, customers cannot manage, control or mitigate such risks" (id., p. 4).

Both TW as well as BTL are regulated by Ofwat (Office of Water Services), whose main responsibility lies in the negotiation of tariffs every 5 years based on Thames Water's business plans and Ofwat's internal Regulatory Assets Base Model (RAB). The relatively **weak negotiating position of the regulator** has been well acknowledged and has been much subject of recent politics within the United Kingdom's political process.

The documented increasing withdrawal from oversight mechanisms as well as the relatively weak position of oversight authorities has provided an environment in which **financial innovation occurs 'in the dark'**, and at the cost of future risks (cf. Grafe in review). The mechanism succeeds in providing the necessary financial capital but obfuscates key categories that are necessary for cities to manage their planning risks.

Milan

As the previous sections have shown, the case of Milan was characterised by a rocky start. Corruption, lack of transparency, legal proceedings as well as costly BOT contracts have provided for a burdensome heritage for MM Spa to sort through. This section will focus on the activities that are trying to overcome these challenges in more recent years.

MM Spa itself is a joint-stock company 100% owned by the Municipality of Milan. Originally primarily an engineering company and formed in 1955 for the construction of Milan's metro system, it today covers both mobility and infrastructure engineering as well as management duties for municipal housing and other public assets (cf. Cetti 2018). Outside these core activities MM Spa also engaged in international business with a joint venture in Moscow with Millenium Bank, part of the Russian Railways group, which shortly thereafter went bankrupt and lost its banking license (cf. Central Bank of the Russian Federation 2016).

The territory and duties for operations of MM Spa is defined by the restructuring of water supply and sanitation operations in Italy through the 1994 Galli Law. According to it, responsibility for water supply and sanitation is transferred to a public authority called ATO (Ambito Territoriale Ottimale). The ATO's governing body selects the water operator and determines the organizational form for water operations. It further carries the responsibility for surveying infrastructure, developing the investment program, setting tariffs, and regulating the water operator. This is done via the technical secretariat within the administrative structure of the municipality of Milan.

This sets the framework within which actors aim to provide adequate solutions despite historical baggage and pressing future challenges. Here, innovation is key for optimizing services and achieving long-term goals of the city. This section will highlight the innovative process employed in Milan to overcome this challenge.

Following the 2014/2015 updates to the ATO plan, MM Spa was presented with the challenge of developing an investment strategy to match the plan's requirements to maintain the current level of service as well as adapt the system to future technical and environmental challenges (ATO 2015).

The key innovative moment is the **bilateral development of principles for the financial strategy design and execution between MM Spa and the municipality**. This is done to balance the system's long-term requirements with financial viability and current economic opportunities. Stefano Cetti, the director general of MM Spa, summarizes these as follows (Cetti 2018, p.279):

- total IWS financial needs coverage
- source diversification
- risk and collateral minimization
- increase in debt maturity

The first aspect refers to the principle that the total financial needs of the system up until 2037 (the end of the concession of the system to MM Spa) have to be covered, while guaranteeing coherence between old and newly employed tools, acknowledging current obligations and avoiding the insurgence of refinancing risks (Cetti 2018). Source diversification refers to the fact that MM Spa aims to take advantage of favorable market conditions and be able to employ different financial instruments outside of traditional

bank loans that line up with tariff and investment projections. In order to be able to do this MM Spa acquired credit ratings at the corporate level from Moody's and Standard & Poor's. As a result of this diversification, risks are spread more widely (id.). Risk and collaterals minimization further refer to the fact that the overarching aim is self-sufficiency, thus it aims to minimize risks both to MM Spa as well as the municipality of Milan resulting from instruments that require specific collaterals. The final aspect focusses on the use of financial instruments that have the same duration as the lifetime of the underlying assets. This greatly extends the debt duration, thus heavily emphasizing long-term instruments with a duration of up to 20 years (id.).

These principles were successfully put to practice with the employ of two financial instruments: first by issuing institutional amortizing notes for an amount €100 mln , to be listed on the regulated Main Securities Market of the Irish Stock Exchange; and second the negotiation with the European Investment Bank (EIB) for a credit facility of €70 million. Both instruments are innovative on several levels in reference to Italian water sector practices (cf. Cetti 2018).

5.4 Innovation principle

The innovation principle has not been invoked in either of the two cases. The cases however make an interesting argument for the **innovation dimension already being contained within the precautionary 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 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. This stimulating effect triggered a plethora of financial innovation across Europe. A critique could be made of the fact that this **innovation is unintended and thus unguided**, often resulting in the shifting of risks from one area to the next. The resulting vacuum from the precautionary principle implementation through the UWWTD has provided an arena in which, as illustrated in the London case, financial innovation can take advantage of obfuscation strategies and profit of off an imbalance of knowledge between actors. However, the Milan case shows how even despite a difficult starting proposition, financial innovation can occur in a sustainable and impactful manner.

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 across the breadth of city possible. The project itself greatly stimulated the logistics, construction and engineering across the city. Similar patterns occurred in Milan, where individual solutions won awards for their innovative approaches (cf. Gruppo CAP 2019).

Outside of the two case studies, the innovation principle has been raised in two occasions: Firstly, an innovation principle workshop on water reuse for agricultural irrigation and aquifer recharge took place in 2017, the discussion resulted in several policy recommendations enabling effective implementation of water reuse policies in the EU (cf. European Commission 2017a). Furthermore, the interim report on the evaluation of the precautionary principle makes an argument for a recently initiated voluntary 'Innovation Deal' pilot on sustainable waste water treatment through anaerobic

membrane technology as an implementation of the precautionary principle (Renda et al 2019, European Commission 2017b). This innovation deal resulted in a report detailing hurdles for the implementation of anaerobic membrane technology for waste water treatment and argues for the initiation of pilot studies. So far this innovation deal had no impact on policy (cf. Renda et al 2019).

6 Synthesis

The invocation of the precautionary principle in the context of the European Water Directives has far reaching consequences. Not only does it facilitate precautionary measures in the regulation of the water sector, but it inadvertently triggers secondary risks in the highly complex and integrated infrastructure sector where it is to be implemented.

Given the quintessential role of water for the human metabolism, which has been codified by the UN as a human right to clean water and sanitation, the application of the precautionary principle is adequate. However, the **highly integrated nature of the water sector makes it difficult to see all repercussion of the application of the precautionary principle**. The plethora of directives born from the WFD illustrates this complexity. This report focusses foremost on issues related to the UWWTD and has shown how in this particular realm the conceptual core of the precautionary principle is put under tension. 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. 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-effective manner. The obduracy of the solutions stands in direct opposition to the reversibility of measures and outlines the significance of path dependencies born from the decision-making processes.

The **governance of these processes has differed significantly between the cases**. London's case with the focus on an individual infrastructure project has shown how across the project's phases (pre-emptive studies phase, the tender-process phase, construction phase and operation phase) risk governance has evolved and how this evolution has impacted the final infrastructure project. The longer-term perspective on Milan has shown how questionable practices have improved over time and how this experience has informed a better-balanced process for financial planning.

The legal histories represent these differing storylines: London's case begins with a private sector actor, Thames Water, contesting the definition of waste water, in order to avoid the implementation of costly infrastructure upgrades. Only thereafter does it escalate to a state level UWWTD case. This shows how the issue in London is more of a bottom up process, where local issues and actors escalate the conflict to the European level. Milan's case on the other hand is characterized by an opposite trajectory: state level implementation of the UWWTD is slow and initial legal trigger, thus causing even

more hesitance locally in overcoming the problem. Only when the state level issues become resolved does the local implementation move ahead. This exemplifies **where the decision makers are located in the two differing water systems**, and what the impacts of this dynamic are for the implementation of precautionary principle based regulation.

The role of innovation also differs significantly across the cases. As argued before, innovation occurs at different stages and levels of the process, with both cases employing technological innovations to overcome their specific issues, however, the more interesting aspect is the financial constructs they devise in order to fill the infrastructure funding gap.

London's individual infrastructure case shows how the implementation of a **market-based strategy** skews the selection of actors and the resulting decision-making process towards an **overly economically focussed solution**, that fails to address some of the long-term planning and financial risks. The viability of this strategy will only become known with time, the early phase of the Milan case though provides some evidence towards the risks inherent in this strategy.

Milan presents the longer-term perspective and the effects of past decisions in terms of path dependencies for the adaptation of the water system to future challenges. The process that was developed was informed by the complicated history of the case and innovative in the regard that it developed a **process that involved a more balanced set of opinions during the decision-making process** than the previous case.

Tensions between the precautionary principle and innovation principle are thus as follows. The **precautionary principle sets a high-level guiding principle** for the water sector with far reaching repercussions. Some of these repercussions **stimulate innovation in different areas, though not always to the benefit of the cases**. A more thorough understanding/definition of the innovation dimension inherent to the precautionary principle would equip cities with a broader arsenal of tools for overcoming the infrastructural gap.

All of these findings mirror Koop and Van Leeuwen's **key elements for good water governance** (see box 1). Particularly the first element's emphasis on a shared long-term perspective becomes evident and is further supported by the second and third element for the involvement of all affected actors and acknowledging the complexity and long-term effects. Resulting from this, better long-term solutions can be implemented (4). The sharing of data (5) and the role of financial innovation have been well documented in the cases (6). Effective monitoring (7) functions as quality assurance and as means to remain on track for long-term goals.

BOX 2: Key Elements for Good Water Governance (Koop and Van Leeuwen 2016)

1. Develop a shared long-term vision between stakeholders.

2. Involve civil society and the commercial sector, along with stakeholders: recognising that citizens and private businesses can individually contribute to success.

3. Manage the process and expertise: to address the complexity of the challenge,

conflicting interests, and the need to remain focused on a long-term vision.

4. Stop excessive focus on technology development: recognising that good governance is equally essential for success.

5. Make data accessible, and share knowledge.

6. Carry out a thorough cost-benefit analysis and remove financial barriers: Success is not dependent on simply providing more money. Limited finance can drive innovation, improve stakeholder cooperation, and help leverage new funding sources.

7. Monitor implementation: Legislation and a good strategy must be supported by a demonstration that implementation and achievements progress as intended

This case study for the role of the precautionary principle for urban waste water infrastructure provision thus stands out for several reasons:

- 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 follows the long-term impacts of a precautionary principle regime for cities
- It emphasizes the **significance of ambiguity** in a highly complex sector, and how this dimension implies the importance of transparent and effective decision-making processes for successful solutions
- It shows how **implementation strategies of EU Regulations** is effectively handled both from a bottom up process (London) and a top down implementation (Milan)
- It shows **how the precautionary principle interacts with a highly complex multi-risk environments** and how the handling of primary risks can create secondary risks elsewhere
- It **raises questions for the definition of the threshold of damage**: in the cases primary damage is not to the health of citizen, but to financial viability of cities. Immense costs and obligations significantly impact how they can maintain other essential services to citizens
- It details the **innovation dimension inherent in the precautionary principle**

7 Conclusion

The wise approach to urban planning is that cities should plan and invest in advance to prepare for future challenges. As we have shown, this is not always possible, especially in a scenario where immense costs and future commitments are put upon cities by increasing legal requirements. This often leads to more **reactive and ad-hoc implementation of infrastructural solutions**. This dynamic paired with the vested interests of certain actor groups in the water sector increases the **risk of the creation of 'white elephants'**, that is expensive infrastructure assets that are more trouble in

the long-run then they are worth in the short-term. The case of London provides a classic example of this dynamic. The case of Milan on the other hand shows how past experience and a pro-active use of the innovation aspect of the precautionary principle can foster an **innovative environment that achieves good local governance practices and transparent processe**s that help avoid the creation of further white elephants.

The precautionary principle's impact on European cities by means of the WFD and its daughter directives is immense. The repercussions of these are not yet fully explored, especially when it comes to the innovation aspect. A more thorough examination of the innovation dimension contained within the precautionary principle would further our understanding of the risk dynamics in highly integrated environments such as the water sector and consequentially qualify the precautionary principle as a mechanism that tries to evaluate the whole picture. The innovation principle on the other hand appears as even less competent in this regard, especially when viewed from an angle as complex as urban water infrastructure.

Both precaution and innovation have guided the symbiotic development of human society and its cities for centuries. As both of these grow ever more complex, the evaluation of repercussions and risks becomes ever more difficult. As the case studies have shown, open, transparent and egalitarian processes help navigating contemporary multi-risk environments with more success.

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9 Appendix

9.1 Judgment of the Court (First Chamber), 18 October 2012, ECLI:EU:C:2012:633

Judgment

1 By its application, the European Commission requests the Court to declare that, by failing to ensure that appropriate collecting systems pursuant to Article 3(1) and (2) of, and Annex I(A) to, Council Directive 91/271/EEC of 21 May 1991 concerning urban waste water treatment (OJ 1991 L 135, p. 40) are in place in Whitburn and at Beckton and Crossness in London and that appropriate treatment is provided with regard to waste waters from the Beckton, Crossness and Mogden treatment plants in London pursuant to Article 4(1) and (3) and Article 10 of, and Annex I(B) to, Directive 91/271, the United Kingdom of Great Britain and Northern Ireland has failed to comply with its obligations under those provisions.

Legal context

2 According to Article 1 thereof, Directive 91/271 concerns the collection, treatment and discharge of urban waste water and the treatment and discharge of waste water from certain industrial sectors. Its objective is to protect the environment from the adverse effects of waste water discharges.

3 Article 2 of Directive 91/271 states:

'For the purpose of this Directive:

1. "urban waste water" means domestic waste water or the mixture of domestic waste water with industrial waste water and/or run-off rain water;

…

5. "collecting system" means a system of conduits which collects and conducts urban waste water;

6. "1 p.e. (population equivalent)" means the organic biodegradable load having a five-day biochemical oxygen demand (BOD5) of 60 g of oxygen per day;

…'

4 Article 3 of Directive 91/271 provides:

'1. Member States shall ensure that all agglomerations are provided with collecting systems for urban waste water,

– at the latest by 31 December 2000 for those with a population equivalent (p.e.) of more than 15 000 …

2. Collecting systems described in paragraph 1 shall satisfy the requirements of Annex I(A). …'

5 As set out in Article 4 of Directive 91/271:

'1. Member States shall ensure that urban waste water entering collecting systems shall before discharge be subject to secondary treatment or an equivalent treatment as follows:

– at the latest by 31 December 2000 for all discharges from agglomerations of more than 15 000 p.e.,

…

3. Discharges from urban waste water treatment plants described in paragraphs 1 and

2 shall satisfy the relevant requirements of Annex I(B). …

4. The load expressed in p.e. shall be calculated on the basis of the maximum average weekly load entering the treatment plant during the year, excluding unusual situations such as those due to heavy rain.'

6 Article 10 of Directive 91/271 provides:

'Member States shall ensure that the urban waste water treatment plants built to comply with the requirements of Articles 4, 5, 6 and 7 are designed, constructed, operated and maintained to ensure sufficient performance under all normal local climatic conditions. When designing the plants, seasonal variations of the load shall be taken into account.'

7 Annex I to Directive 91/271, entitled 'Requirements for urban waste water', provides in Section A, headed 'Collecting systems':

'Collecting systems shall take into account waste water treatment requirements.

The design, construction and maintenance of collecting systems shall be undertaken in accordance with the best technical knowledge not entailing excessive costs, notably regarding:

– volume and characteristics of urban waste water,

– prevention of leaks,

– limitation of pollution of receiving waters due to storm water overflows.'

8 Footnote 1 to Annex I(A) to Directive 91/271, placed at the heading 'Collecting systems', is worded as follows:

'Given that it is not possible in practice to construct collecting systems and treatment plants in a way such that all waste water can be treated during situations such as unusually heavy rainfall, Member States shall decide on measures to limit pollution from storm water overflows. Such measures could be based on dilution rates or capacity in relation to dry weather flow, or could specify a certain acceptable number of overflows per year.'

9 Annex I(B) to Directive 91/271, headed 'Discharge from urban waste water treatment plants to receiving waters', sets the requirements that must be satisfied by discharges from urban waste water treatment plants into receiving waters. The footnote to Annex I(A) to the directive, cited in the preceding paragraph, is reproduced in Annex I(B).

Pre-litigation procedure

10 The Commission received a complaint concerning the Whitburn Steel pumping station and other complaints regarding excessive storm water overflows in other parts of the United Kingdom.

11 On 3 April 2003 the Commission sent a letter of formal notice to the United Kingdom in which it stated that the Whitburn Steel pumping station failed to comply with the urban waste water collecting obligations imposed by Article 3(1) and (2) of, and Annex I(A) to, Directive 91/271.

12 In its reply of 3 June 2003, the United Kingdom stated that the agglomeration in question met the collecting obligations set out in Article 3 of Directive 91/271. However, it accepted that, following further investigations of the collecting system in the area, it was necessary to improve the pass forward flow in that system. Moreover, the United Kingdom explained that the discharge consent conditions under which the water company was operating the Whitburn Steel sewage pumping station had been changed, as a result of which fewer discharges were to be expected. Those improvements were expected to be completed by 31 March 2004 at the latest.

13 On 21 March 2005 the Commission sent a second letter of formal notice to the United Kingdom in which it stated that the urban waste water collecting and treatment systems in the London area failed to comply with the obligations on the collecting and

treatment of urban waste water imposed by Article 3(1), Article 4(1) and (3) and Article 10 of, and Annex I(A) and (B) to, Directive 91/271. The Commission stated that untreated waste water was being discharged into the River Thames, even in moderate rainfall conditions, and that no immediate measure was foreseen to resolve that problem, which would therefore persist and even grow worse.

14 In its reply of 20 May 2005, the United Kingdom explained that the waste water collecting system for London was a combined system that collected and conveyed domestic and industrial waste water and run-off rainwater from a catchment of 557 km2 for secondary treatment at the Beckton, Mogden, Crossness, Long Reach and Riverside treatment plants prior to discharge into the River Thames. However, it accepted that there were problems related to the volume, load and frequency of wet weather discharges resulting from overflows in announcing its decision to establish the Thames Tideway Strategic Study ('the TTSS') to assess the environmental impact of such discharges.

15 With regard to its obligations to provide adequate treatment of urban waste waters, the United Kingdom stated that, while improvements would be completed as soon as possible, the treatment plants serving the London agglomeration had been compliant with the requirements in Directive 91/271 since 31 December 2000. Also, the United Kingdom explained that the discharges of August 2004 occurred due to unusually heavy rainfall.

16 Since the Commission was not satisfied with the United Kingdom's response, by letter of 10 April 2006 it sent a reasoned opinion to the United Kingdom stating that, in its view, the United Kingdom had failed to fulfil its obligations under Article 3(1) and (2) of, and Annex I(A) to, Directive 91/271 in relation to Whitburn and its obligations under Article 3(1), Article 4(1) and (3) and Article 10 of, and Annex I(A) and (B) to, Directive 91/271 in relation to the nine treatment plants serving the Greater London area.

17 In reply to the reasoned opinion, the United Kingdom, by letter of 15 June 2006, stated that the whole collecting system and the treatment plants serving Whitburn and the metropolitan agglomeration of Sunderland were in compliance with Directive 91/271.

18 Following a meeting on 6 July 2007 between representatives of the Commission and of the United Kingdom, the latter provided clarification on that issue by letter of 23 October 2007.

19 In relation to the situation in London, the United Kingdom replied that, while improvements needed to be made to the treatment plants at Beckton, Crossness and Mogden, that did not mean that those treatment plants were in breach of Directive 91/271. The United Kingdom, in accepting the need for those improvements, was simply showing its desire to provide a higher level of environmental protection.

20 At a meeting on 26 January 2007, representatives of the Commission and the United Kingdom discussed the two possible options for London, which had been suggested by the TTTS report, and the United Kingdom decided to opt for the single 30 km tunnel along the length of the River Thames and the separate tunnel for its tributary, the River Lee. The whole project was to be completed by 2020.

21 Following two further letters of 29 June 2007 and 4 February 2008 sent by the United Kingdom, the Commission, which was still not satisfied with the replies provided by the United Kingdom, issued by letter of 1 December 2008 an additional reasoned opinion in which it clarified its interpretation of Directive 91/271 in relation to the obligations on Member States to control the release of urban waste waters through storm water overflows. It also confirmed its concerns in relation to the inadequacy of the collecting system put in place around Whitburn, of the collecting systems of Beckton and Crossness, and of the treatment plants at Mogden, Beckton and Crossness.

22 However, the Commission decided not to pursue the case further with regard to the collecting systems and the treatment plants in Beddington, Esher, Crawley, Deephams, Hogsmill, Long Reach and Riverside. The Commission thus called upon the United Kingdom to take the necessary measures to comply with the additional reasoned opinion within two months of receipt thereof.

23 Exchanges of correspondence and meetings between the Commission and the United

Kingdom then ensued, but did not result in a solution.

24 Since the Commission was still not satisfied with the response provided by the United Kingdom, it decided to bring the present action.

The action

Arguments of the parties

25 The principal points of disagreement between the Commission and the United Kingdom concern the interpretation of Directive 91/271.

26 In the Commission's view, Member States are obliged to ensure that a collecting system is designed and built so as to collect all the urban waste water generated by the agglomeration it serves and that that waste water is conducted for treatment. The capacity of the collecting system must therefore be able to take into account natural climatic conditions (dry weather, wet weather, even stormy weather) as well as seasonal variations, such as non-residential populations, tourists and seasonal economic activities.

27 It submits that 'storm water overflows', referred to in Annex I(A) to Directive 91/271, are a part of urban waste water collecting systems and treatment facilities. The directive must be interpreted as providing for an absolute obligation to avoid spills from storm water overflows save for exceptional circumstances. That reasoning is reflected in footnote 1 to Annex I(A) to Directive 91/271 which provides that in practice it is not possible to collect and treat all waste waters 'during situations such as unusually heavy rainfall'.

28 The Commission puts forward factors such as the frequency and the volume of the overflows to show that there has been a failure to fulfil obligations under Directive 91/271. Contrary to what the United Kingdom fears, it does not propose a strict 20 spill rule but points out that, the more an overflow spills, particularly during periods when there is only moderate rainfall, the more likely it is that the overflow's operation is not in compliance with Directive 91/271.

29 The Commission and the United Kingdom also disagree in relation to the significance that must be attributed to the concept of 'best technical knowledge not entailing excessive costs' ('BTKNEEC') which is prescribed in Annex I(A) to Directive 91/271.

30 The Commission submits that that concept must be read in the context of Directive 91/271, of its aims and of its objectives, namely to protect the environment from the adverse effects of waste water discharges.

31 It submits that the concept of BTKNEEC allows Member States to choose between several solutions that promote compliance with both the provisions and the objective of Directive 91/271, such as building new or increased storage facilities or diverting rainwater before it can enter the collecting systems.

32 In the United Kingdom's view, Directive 91/271 must be interpreted as leaving it to Member States to determine the manner in which urban waste water should be collected and treated in order to realise the directive's objective, which is to protect the environment from the adverse effects of waste water discharges.

33 The United Kingdom considers that Directive 91/271 must be interpreted by reference in particular to the environmental impact of discharges on receiving waters.

34 So far as concerns the concept of 'unusually heavy rainfall', the United Kingdom considers that the fact that footnote 1 to Annex I(A) to Directive 91/271 expressly acknowledges that it will not be possible to avoid discharges in particular circumstances, notably when there is unusually heavy rainfall, does not impose an absolute obligation to avoid discharges in other circumstances. It considers that whether discharges are appropriate in other circumstances is to be determined by application of the concept of BTKNEEC and an assessment of the environmental impact of the discharges on receiving waters.

35 In the view of the United Kingdom, Directive 91/271 does not lay down

requirements regarding the circumstances in which or the frequency with which discharges into receiving waters may occur. To evaluate whether collecting systems or treatment plants conform with Directive 91/271, a detailed assessment of the performance of the collecting system or the treatment plant concerned must be carried out by reference to the environmental impact of the discharges on receiving waters.

36 The concept of 'sufficient performance' provided for in Article 10 of Directive 91/271 must also be assessed in light of the objective of protection of the environment as set out in Article 1 of the directive and therefore by reference to the impact on receiving waters.

37 While the Commission does not take issue with the United Kingdom's methodology for calculating what constitutes a single spill event, that does not, in the United Kingdom's submission, resolve the problem linked to the fact that the definition of a spill event may differ from one Member State to another. There would therefore be no guarantee of consistency of approach across Member States if compliance with Directive 91/271 were to be determined by reference to the occurrence and frequency of spills.

38 The United Kingdom also submits that the Commission errs by basing the determination that collecting systems and treatment plants are compliant with Directive 91/271 on the volume of spills.

39 So far as concerns, more specifically, the agglomeration of Sunderland (Whitburn), the Commission complains that, at the date of the expiry of the deadline fixed in the additional reasoned opinion, excessive storm water overflows from the Whitburn leg of the Sunderland collecting system were still occurring and that that system was therefore not compliant with Article 3 of, and Annex I(A) to, Directive 91/271.

40 While the frequency of the spills has been reduced (in the years 2002 to 2004, between 56 and 91 spills per year and annual volumes of untreated urban waste water discharges of between 359 640 m3 and 529 290 m3), the collecting system is still not compliant with the requirements of Directive 91/271, particularly given the close vicinity of the bathing waters in Whitburn and Seaham and the numerous complaints received by the Commission concerning debris on the beaches around Whitburn.

41 The United Kingdom considers that those storm water overflows are compliant with Directive 91/271.

42 The United Kingdom also submits that the bathing waters around Whitburn have been found compliant with Council Directive 76/160/EEC of 8 December 1975 concerning the quality of bathing water (OJ 1975 L 31, p. 1) and that they are thus compliant with Directive 91/271. Furthermore, it is unlikely that the debris comes from Whitburn, but rather from the Tyne where the overflow channels were not equipped with screens until the end of March 2010.

43 As regards the agglomeration of London, the Commission alleges that the frequency and quantity of discharges of untreated waste water from the Beckton and Crossness collecting systems and the Beckton, Crossness and Mogden treatment plants are of such a magnitude as to constitute a breach of Articles 3 and 4 of, and Annex I(A) to, Directive 91/271, in particular given that those spills occur even during times of moderate rainfall.

44 Also, it submits that Article 10 of Directive 91/271 requires urban waste water treatment plants built to comply with the requirements of Article 4 of the directive to be designed, constructed, operated and maintained to ensure sufficient performance under all normal local climatic conditions.

45 The United Kingdom considers that those treatment plants satisfy the provisions of Directive 91/271.

46 It also notes that the London sewerage network is very old and has been progressively upgraded since 1875. Improvements have been examined and carried out since the adoption of Directive 91/271. Furthermore, the scale and exceptional nature of the works that are being carried out on the River Thames, at a cost of GBP 4.4 billion, mean that they require a lot of time. It submits that it cannot be penalised for implementing,

in the long term, an ambitious solution.

Findings of the Court

Interpretation of Directive 91/271

47 As stated in the second paragraph of Article 1, the objective of Directive 91/271 is to protect the environment from the adverse effects of urban waste water discharges (see, inter alia, Case C-280/02 Commission v France [2004] ECR I-8573, paragraph 13).

48 The objective pursued by Directive 91/271 goes beyond the mere protection of aquatic ecosystems and seeks to conserve man, fauna, flora, soil, water, air and landscapes from any significant adverse effects of the accelerated growth of algae and higher forms of plant life that results from discharges of urban waste water (Commission v France, paragraph 16).

49 The concepts of 'sufficient performance' appearing in Article 10 of Directive 91/271, 'unusually heavy rainfall' mentioned in footnote 1 of Annex I to the directive and 'best technical knowledge not entailing excessive costs' (BTKNEEC) referred to in Annex I(A) to the directive should be interpreted in the light of that objective, but also of Article 191 TFEU.

50 First, the concept of 'sufficient performance', which concerns only treatment plants, does not have its scope defined numerically, as Article 10 of Directive 91/271 provides only that treatment plants must ensure 'sufficient performance under all normal local climatic conditions' and taking account of seasonal variations of the load when those plants are designed.

51 In this connection, the Court has already found a failure to fulfil obligations in cases where the collection or treatment rate for urban waste water amounted to 80% or even 90% of the existing load (judgments of 7 May 2009 in Case C-530/07 Commission v Portugal, paragraphs 28 and 53, and 14 April 2011 in Case C-343/10 Commission v Spain, paragraphs 56 and 62).

52 Indeed, given the objective pursued by Directive 91/271, recalled in paragraphs 47 and 48 of the present judgment, failure to treat urban waste water cannot be accepted under usual climatic and seasonal conditions, as otherwise Directive 91/271 would be rendered meaningless.

53 Thus, it is established that, in order to meet the objective of protecting the environment, the concept of 'sufficient performance', although not defined numerically, must be understood as meaning that, under usual climatic conditions and account being taken of seasonal variations, all urban waste water must be collected and treated.

54 Consequently, failure to treat urban waste water can be tolerated only where the circumstances are out of the ordinary, and it would run counter to Directive 91/271 if overflows of untreated urban waste water occurred regularly.

55 Second, the concept of 'unusually heavy rainfall' in footnote 1 of Annex I to Directive 91/271 applies to the collecting systems provided for in Article 3 of the directive and to the treatment plants provided for in Article 4.

56 By that footnote, the European Union legislature acknowledged that situations exist in which all the urban waste water will not be capable of being collected or treated. In particular, it stated that 'it is not possible in practice to construct collecting systems and treatment plants in a way such that all waste water can be treated' and it provided that failure to collect and treat waste water may be tolerated during 'situations such as unusually heavy rainfall'. However, in that case, Member States are to decide on 'measures to limit pollution from storm water overflows'.

57 It is clear that the term 'unusually heavy rainfall' is mentioned in footnote 1 of Annex I to Directive 91/271 by way of illustration only, since the term is preceded by the words 'during situations such as'. Thus, failure to collect or treat waste water may also be allowed in other circumstances.

58 However, contrary to the United Kingdom's assertions, the objective pursued by

Directive 91/271 does not permit the inference that it is normal and common for those other circumstances to arise, in particular as the word 'unusually' clearly indicates that failure to collect or treat waste water cannot occur in normal circumstances.

59 The United Kingdom's line of argument seeking acceptance that discharges might take place even outside exceptional situations cannot therefore be upheld.

60 Furthermore, it should be pointed out that, where a Member State is faced with an exceptional situation not allowing it to collect or treat waste water, it remains obliged to adopt appropriate measures to limit pollution under footnote 1 of Annex I to Directive 91/271.

61 Also, since the concept of 'unusually heavy rainfall' is not defined by Directive 91/271, it is legitimate for the Commission, in carrying out its supervision of compliance with European Union law, to adopt guidelines and, as the Court does not have jurisdiction to define numerically obligations laid down by that directive, the concept of 'unusually heavy rainfall' must therefore be assessed in the light of all the criteria and conditions prescribed by the directive, in particular the concept of BTKNEEC.

62 Third, the concept of BTKNEEC, which is mentioned in Annex I(A) to Directive 91/271, must, like the other concepts referred to by Directive 91/271 that have already been elaborated upon, be examined in the light of the objective of protecting the environment. Also, it is to be noted that the obligations of that directive which require the collection and treatment of all waste water, except in the case of exceptional or unforeseeable events, must be complied with at the date laid down by the directive.

63 Although the concept of BTKNEEC appears in Annex I(A) to Directive 91/271 only in relation to collecting systems, it nevertheless constitutes a concept inherent in all the provisions of Directive 91/271 designed to secure its objective of protecting the environment whilst avoiding too strict an application of the rules laid down. Thus, that concept is also to be extended to treatment plants in so far as in certain cases it allows discharges of untreated waste water even though the latter has adverse effects on the environment.

64 The concept of BTKNEEC thus enables compliance with the obligations of Directive 91/271 to be secured without imposing upon the Member States unachievable obligations which they might not be able to fulfil, or only at disproportionate cost.

65 However, in order not to undermine the principle set out in paragraph 53 of the present judgment that all waste water must be collected and treated, the Member States must invoke disproportionate costs of that kind by way of exception only.

66 In this connection, it should be borne in mind that, in accordance with settled case-law, a Member State may not plead practical or administrative difficulties in order to justify non-compliance with the obligations and time-limits laid down by a directive. The same holds true of financial difficulties, which it is for the Member States to overcome by adopting appropriate measures (judgment of 30 November 2006 in Case C-293/05 Commission v Italy, paragraph 35 and the case-law cited).

67 The concept of BTKNEEC must be examined by weighing the best technology and the costs envisaged against the benefits that a more effective water collection or treatment system may provide. Within this framework, the costs incurred cannot be disproportionate to the benefits obtained.

68 In that context, account will have to be taken, as the United Kingdom submits, of the effects of the discharges of untreated waste water on the environment and in particular on the receiving waters. The consequences that those discharges have for the environment would thus enable examination as to whether or not the costs that must be incurred to carry out the works necessary in order for all urban waste water to be treated are proportionate to the benefit that that would yield for the environment.

69 Should it prove impossible or very difficult to collect and treat all the waste water, it will be for the Member State concerned to demonstrate that the conditions for applying the concept of BTKNEEC are met.

70 It is true that the Court's case-law provides that in proceedings under Article

258 TFEU for failure to fulfil obligations it is for the Commission to prove the allegation that the obligation has not been fulfilled. It is therefore the Commission's responsibility to place before the Court the information needed to enable the Court to establish that the obligation has not been fulfilled, and in so doing the Commission may not rely on any presumptions (see, inter alia, Case C-494/01 Commission v Ireland [2005] ECR I-3331, paragraph 41; Commission v Portugal, paragraph 32; Case C-335/07 Commission v Finland [2009] ECR I-9459, paragraph 46; and the judgment of 10 December 2009 in Case C-390/07 Commission v United Kingdom, paragraph 43).

71 The Member States are nevertheless required, under Article 4(3) TEU, to facilitate the achievement of the Commission's tasks, which consist inter alia, pursuant to Article 17(1) TEU, in ensuring that the provisions of the FEU Treaty and the measures taken by the institutions pursuant thereto are applied. In particular, account should be taken of the fact that, where it is a question of checking that the national provisions intended to ensure effective implementation of a directive are applied correctly in practice, the Commission, which does not have investigative powers of its own in the matter, is largely reliant on the information provided by any complainants and by the Member State concerned (see, inter alia, Commission v Ireland, paragraphs 42 and 43, and Commission v United Kingdom, paragraph 44).

72 It follows in particular that, where the Commission has adduced sufficient evidence of certain matters in the territory of the defendant Member State, it is incumbent on the latter to challenge in substance and in detail the information produced and the consequences flowing therefrom (see, inter alia, Commission v Ireland, paragraph 44 and the case-law cited, and Commission v United Kingdom, paragraph 45).

73 Accordingly, for the purpose of examining the present action, the Court must, first of all, examine whether the discharges from the collecting systems or the treatment plants of the various agglomerations in the United Kingdom are due to circumstances of an exceptional nature, and then, if that is not the case, establish whether the United Kingdom has been able to demonstrate that the conditions for applying the concept of BTKNEEC were met.

Whitburn

74 With regard to the obligation to have a collecting system as referred to in Article 3(1) of Directive 91/271, it should be recalled first of all, that, according to settled case-law, the question whether a Member State has failed to fulfil its obligations must be determined by reference to the situation prevailing in that Member State at the end of the period laid down in the reasoned opinion and the Court cannot take account of any subsequent changes (see, inter alia, Commission v United Kingdom, paragraph 50, and Commission v Spain, paragraph 54).

75 The additional reasoned opinion dated 1 December 2008 prescribed a period of two months from receipt thereof for the United Kingdom to comply with its obligations resulting from Directive 91/271. On the date set in the reasoned opinion, untreated urban waste water was still being discharged through storm water overflows. The number of discharges and their volume are not contested by the United Kingdom: it merely submits that, contrary to what is put forward by the Commission, the debris found on the beaches around Whitburn cannot come from the Whitburn collecting system given that the sea outfall used for the discharge of waste water is equipped with 6 mm screens, and the debris is probably from the Tyne where the overflows were not equipped with screens until the end of March 2010.

76 In order to establish whether, as the Commission submits in its complaint, the United Kingdom has failed to fulfil its obligations arising from Article 3 of, and Annex I(A) to, Directive 91/271, the examination set out in paragraph 73 of the present judgment should be carried out.

77 It must be stated, first, that, in accordance with the letter of 2 March 2005 sent by the United Kingdom to the Commission, the number of waste water discharges indicated for 2001 was 310 with an annual volume of 561 240 m3 and that, during the period covering the years from 2002 to 2004, that number varied between 56 and 91 with volumes between 359 640 m3 and 529 290 m3. Also, it should be noted that, between 2006 and 2008, the number of waste water discharges per year varied between 25 and 47 with a

volume from 248 130 m3 to 732 150 m3, while the volume for 2009 was 762 300 m3. The Commission, basing its observations on the frequency of those discharges and their intensity, has clearly demonstrated that, both before and after the expiry of the period laid down by the additional reasoned opinion, they were a normal occurrence, as such a number of discharges cannot be linked to exceptional circumstances. Indeed, the United Kingdom does not contend in its observations that those discharges are exceptional in nature.

78 Second, it is to be noted that according to a study carried out in 2010 it would be possible, from a technological point of view, to reduce the number of waste water discharges from the Whitburn collecting system by enlarging the interceptor tunnel that already exists, a fact which has not been contested by the United Kingdom.

79 So far as concerns the costs required to be incurred and the benefits obtained, that study shows that an improvement of 0.3% in respect of the quality of the receiving waters could be achieved by the tunnel enlargement works, on the basis of 20 discharges per year.

80 Although the improvement in water quality appears marginal and, as the United Kingdom contends, Directive 76/160 is complied with, a fact which can be taken into account in the general examination of the conditions for applying the concept of BTKNEEC, it must be stated that the costs of such an enlargement of the tunnel are not mentioned at any time, either in the observations of the parties or in the reports and studies carried out.

81 Thus, the Court is not in a position to examine whether the costs of such works are excessive and disproportionate to the environmental benefit obtained

82 It follows that the United Kingdom has not demonstrated to the required legal standard that the costs of works to increase the capacity of the collecting system were disproportionate to the improvement in the state of the environment.

83 Accordingly, the Commission was right in finding that the collecting system put in place in Whitburn does not meet the obligations laid down in Article 3 of, and Annex I(A) to, Directive 91/271.

London

84 In the case of the agglomeration of London, it is not in dispute, in accordance with the contentions of the United Kingdom itself, that, at the end of the period laid down in the additional reasoned opinion, that agglomeration had neither treatment plants at Beckton, Crossness and Mogden performing the secondary treatment of all the urban waste water entering the collecting system, in accordance with Articles 4(1) and 10 of Directive 91/271, and guaranteeing that the discharges from them satisfied the requirements of Annex I(B) thereto nor collecting systems at Beckton and Crossness with a sufficient capacity, in accordance with Article 3 of the directive.

85 The Commission, relying on a TTSS report of February 2005, observes that there were approximately 60 waste water discharges from storm water overflows in London per year, even in periods of moderate rainfall; untreated water having a volume of several million tonnes was thus discharged into the River Thames every year.

86 So far as concerns the treatment plants of the collecting system for London, that report shows that their capacity is sufficient in dry weather, but not sufficient in the slightest in the case of rainfall.

87 The United Kingdom does not dispute the facts relied upon by the Commission and observes that a project is in fact underway for the construction of a new 30 km long tunnel under the tidal part of the River Thames to intercept collecting system overflow discharges and convey them for treatment at the Beckton treatment plant. Also, it is proposed to construct another tunnel, the Lee Tunnel, with the aim of reducing overflow discharges from the Beckton and Crossness collecting systems. Finally, improvement works are taking place to install extra capacity at the Beckton, Crossness and Mogden treatment plants.

88 In order to establish whether, as the Commission submits in its complaint, the

United Kingdom has failed to fulfil its obligations arising from Articles 3, 4 and 10 of, and Annex I(A) to, Directive 91/271, the examination envisaged in paragraph 73 of the present judgment should again be carried out.

89 It must be stated that the Commission, in reliance upon the TTSS report mentioned in paragraph 85 of the present judgment, which is not disputed by the United Kingdom and which indicates that the frequency and volume of the discharges come about in the case not only of exceptional events but also of moderate rainfall, has demonstrated clearly the normality of the waste water discharges into the River Thames.

90 As regards whether it is technologically impossible to reduce the number of waste water discharges from the collecting system for London and whether the costs are disproportionate to the environmental benefit obtained, it is to be noted that the United Kingdom decided, in April 2007, to carry out the works proposed by the TTSS report of November 2005 consisting in particular in the construction of a new underground tunnel. Thus, technological solutions to the problem of the collecting system for London exist and their costs cannot be regarded as disproportionate given that the United Kingdom has already taken the decision to implement them.

91 So far as concerns the United Kingdom's argument that it cannot be found to have failed to fulfil its obligations given that projects designed to ensure compliance with Directive 91/271 were examined as soon as the directive entered into force and the works decided upon are costly and achievable only over a number of years, it should be recalled that the question whether the defendant Member State has failed to fulfil its obligations must be determined by reference to the situation prevailing in that Member State at the end of the period laid down in the additional reasoned opinion and that a Member State cannot secure dismissal of the action merely because the activities and works which will, in future, cure the failure to fulfil obligations are underway. Unless a directive has been amended by the European Union legislature for the purpose of extending the periods prescribed for implementation, the Member States are required to comply with the periods originally laid down (see the judgment of 8 July 2004 in Case C-27/03 Commission v Belgium, paragraph 39).

92 It was therefore incumbent upon the United Kingdom to initiate in good time the procedures necessary for implementing Directive 91/271 in the national legal order, so that those procedures were completed within the time-limit prescribed in the first indent of Article 3(1) and the first indent of Article 4(1) of that directive, namely 31 December 2000.

93 Accordingly, the Commission was right in finding that the collecting system put in place in London (Beckton and Crossness) does not meet the obligations laid down in Article 3 of, and Annex I(A) to, Directive 91/271 and that, by failing to make urban waste water from the agglomeration of London (Beckton, Crossness and Mogden) subject to secondary treatment or an equivalent treatment, in accordance with Article 4 of that directive, the United Kingdom has failed to fulfil its obligations under the directive.

94 It follows from the foregoing that the failure on the part of the United Kingdom to fulfil its obligations that is alleged by the Commission has been established for each agglomeration referred to in the application.

95 Consequently, it must be held that, by failing to ensure:

– appropriate collection of the urban waste water of the agglomerations with a p.e. of more than 15 000 of Sunderland (Whitburn) and London (Beckton and Crossness collecting systems), in accordance with Article 3(1) and (2) of, and Annex I(A) to, Directive 91/271, and

– appropriate treatment of the urban waste water of the agglomeration with a p.e. of more than 15 000 of London (Beckton, Crossness and Mogden treatment plants), in accordance with Article 4(1) and (3) and Article 10 of, and Annex I(B) to, Directive 91/271,

the United Kingdom has failed to fulfil its obligations under that directive.

Costs

96 Under Article 69(2) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the Commission has applied for costs and the United Kingdom has been unsuccessful, the latter must be ordered to pay the costs.

On those grounds, the Court (First Chamber) hereby:

1. Declares that, by failing to ensure:

– appropriate collection of the urban waste water of the agglomerations, with a population equivalent of more than 15 000, of Sunderland (Whitburn) and London (Beckton and Crossness collecting systems), in accordance with Article 3(1) and (2) of, and Annex I(A) to, Council Directive 91/271/EEC of 21 May 1991 concerning urban waste water treatment, and

– appropriate treatment of the urban waste water of the agglomeration, with a population equivalent of more than 15 000, of London (Beckton, Crossness and Mogden treatment plants), in accordance with Article 4(1) and (3) and Article 10 of, and Annex I(B) to, Directive 91/271,

the United Kingdom has failed to fulfil its obligations under that directive;

2. Orders the United Kingdom to pay the costs.

[Signatures]

9.2 Judgement of the Court (Sixth Chamber), 25 April 2002, ECLI:EU:C:2002:261

Judgment

1. By application lodged with the Registry of the Court on 26 October 2000, the Commission of the European Communities brought an action under Article 226 EC for a declaration that, by not ensuring that by 31 December 1998 at the latest the discharges of urban waste water of the city of Milan, located within a catchment area draining into areas of the delta of the River Po and the north-west coast of the Adriatic Sea defined by Decree-Law No 152 of the Italian Republic of 11 May 1999, enacting provisions on the prevention of water pollution and implementing Directive 91/271/EEC concerning urban waste-water treatment and Directive 91/676/EEC of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources (GURI of 29 May 1999, ord. suppl., hereinafter 'the Decree') as sensitive, within the meaning of Article 5 of Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment (OJ 1991 L 135, p. 40, hereinafter 'the Directive'), were subjected to more stringent treatment than secondary treatment or an equivalent treatment prescribed by Article 4 of that directive, the Italian Republic has failed to fulfil its obligations under Article 5(2) of the aforementioned directive, as specified in Article 5(5).

Legal background

2. According to Article 1 of the directive, it concerns the collection, treatment and discharge of urban waste water and the treatment and discharge of waste water from certain industrial sectors, and has as its objective the protection of the environment from the adverse effects of waste water discharges.

3. Article 2 of the directive defines 'urban waste water' as 'domestic waste water or the mixture of domestic waste water with industrial waste water and/or run-off rain water'.

4. The second subparagraph of Article 3(1) of the directive provides that, for urban waste water discharging into receiving waters which are considered 'sensitive areas' as defined under Article 5, Member States are to ensure that collection systems are provided at the latest by 31 December 1998 for agglomerations with a population equivalent of more than 10 000. In Article 2, the directive defines one population

equivalent (hereinafter 'p.e.') as 'the organic biodegradable load having a five-day biochemical oxygen demand (BOD5) of 60 g of oxygen per day'.

5. The general rules applicable to urban waste water are contained in Article 4 of the directive, which provides in the first indent of Article 4(1):

'Member States shall ensure that urban waste water entering collecting systems shall before discharge be subjected to secondary treatment or an equivalent treatment as follows:

- at the latest by 31 December 2000 for all discharges from agglomerations of more than 15 000 p.e.'

6. Article 5 of the directive provides:

'1. For the purposes of paragraph 2, Member States shall by 31 December 1993 identify sensitive areas according to the criteria laid down in Annex II.

2. Member States shall ensure that urban waste water entering collecting systems shall before discharge into sensitive areas be subjected to more stringent treatment than that described in Article 4, by 31 December 1998 at the latest for all discharges from agglomerations of more than 10 000 p.e.

...

4. Alternatively, requirements for individual plants set out in paragraphs 2 and 3 above need not apply in sensitive areas where it can be shown that the minimum percentage of reduction of the overall load entering all urban waste water treatment plants in that area is at least 75% for the total phosphorus and at least 75% for total nitrogen.

5. Discharges from urban waste water treatment plants which are situated in the relevant catchment areas of sensitive areas and which contribute to the pollution of these areas shall be subjected to paragraphs 2, 3 and 4.

...'

7. Article 18(2)(b) and (c) of the Decree identify as sensitive areas 'the Po delta' and 'the coastal areas of the north-west Adriatic from the mouth of the Adige to Pesaro and the water courses which flow into them over a distance of 10 kilometres from the coast'.

Pre-litigation procedure

8. By letter of 18 November 1997, the Commission asked the Italian Government to provide it with information on progress in the collection and treatment of urban waste water for the agglomeration of Milan.

9. On 29 January 1998, the Italian Government replied that there were plans to build three waste water treatment plants intended to cover 95% of discharges. It attached to its reply a note from the Ministry of the Environment and a technical report on the progress of collection and treatment of urban waste water in the Milan area.

10. The Commission concluded from that reply that the agglomeration of Milan did not have a waste water treatment plant, so that the waste from a population of roughly 2.7 million was being discharged without prior treatment into the Lambro-Olona river system, a tributary of the Po, which drains into an area of the Adriatic which is very polluted and susceptible to eutrophication.

11. Taking the view that the Italian Republic had not adopted any concrete measures, the Commission sent a letter of formal notice dated 30 April 1999 to that Member State, asking it to submit its observations on a possible infringement of its obligations under the directive. It drew particular attention to the fact that the failure to subject to more stringent treatment than the secondary treatment prescribed by Article 4 of the directive the urban waste water of the city of Milan, which discharges into a catchment area of an area which should have been identified, by 31 December 1998, as sensitive within the meaning of Article 5(1) of the directive, constituted a

infringement of Article 5(2) of the directive.

12. By letters of 9 July and 27 October 1999, the Italian authorities contested that allegation, arguing inter alia that they were not required to subject the waste in question to more stringent treatment in so far as it did not, at least not directly, discharge into an area identified as sensitive by the Decree.

13. Not satisfied with that response, the Commission issued a reasoned opinion on 21 January 2000, calling upon the Italian Republic to take the measures necessary to comply with the opinion within two months of notification thereof.

14. In its reply of 6 April 2000, the Italian Government maintained its position, but stated that it had asked for a state of emergency to be declared, which would allow for the adoption of a simplified procedure to enable the city of Milan to proceed rapidly with the construction of the three planned treatment plants.

15. It was in those circumstances that the Commission brought the present action.

Merits of the case

16. The Commission is asking the Court to declare that the Italian Republic has failed to fulfil its obligations under Article 5(2) of the directive and to order it to pay the costs.

17. Anticipating the arguments of the Italian Government in its defence, the Commission considers that it is contrary to the legislative content of the directive to exclude any treatment of urban waste water originating from a city such as Milan on the sole ground that it does not discharge directly into a sensitive area.

18. The Commission argues that it is evident from Article 5(2) and 5(5) of the directive that all urban waste water originating from agglomerations having a p.e. of more than 10 000 and which discharges into sensitive areas was to be made subject, by 31 December 1998 at the latest, to more stringent treatment than that prescribed in Article 4 of the Directive.

19. The implication of Article 5 is that if the catchment areas which discharge into sensitive areas receive urban waste water originating from agglomerations of more than 10 000 p.e., this contributes to the pollution of those areas, and they should be equipped with treatment plants whose discharges meet the same requirements as discharges which reach sensitive areas directly.

20. Thus, according to the Commission, all urban waste water from agglomerations of more than 10 000 p.e. and which reaches sensitive areas, either directly or by passing through catchment areas, had to be treated using the more stringent treatment method by 31 December 1998 at the latest.

21. The Italian Government asks the Court to dismiss the action and to order the Commission to pay the costs.

22. Although the Italian Government indicates that it accepts responsibility for the urgency and gravity of the situation and will implement all possible measures to hasten the construction of the treatment facilities for the urban waste water of the city of Milan, it nevertheless points out that the city area is not part of either a sensitive area or a relevant catchment area of a sensitive area.

23. It emphasises that the Decree has not defined all of Italy as a sensitive area. Furthermore, since the definition of sensitive areas under the Decree has not been contested by the Commission, it should be accepted as an adequate criterion by which to verify the performance of the obligations under Article 5 of the directive.

24. According to the Italian Government, the area of the city of Milan is not in any of the sensitive areas identified directly by the Decree or designated as such by the Lombardy region.

25. It maintains that the fact that all of the urban waste water of the city of Milan is discharged into the Lambro-Olona river system, a tributary of the Po, which drains into an area of the Adriatic which is very polluted and susceptible to

eutrophication is of no relevance to the alleged infringement.

26. It points out that not all of the Po has been identified as a sensitive area, but rather only the delta, more than three hundred kilometres away from Milan. Moreover, no part of the Po has been defined as a sensitive area by the Lombardy region.

27. That argument cannot be accepted.

28. It is clear from Article 5(2) of the directive that all urban waste water originating from agglomerations having, like Milan, a p.e. of more than 10 000, and which discharges into a sensitive area, had to be subjected to treatment more stringent than that mentioned in Article 4 of the directive, by 31 December 1998 at the latest.

29. Contrary to the arguments put forward by the Italian Government, it makes no difference in this regard whether the waste water discharges directly or indirectly into a sensitive area.

30. The second subparagraph of Article 3(1) of the directive, which deals with discharges of urban waste water into receiving waters considered sensitive areas, and Article 5(2) of the directive, which requires urban waste water entering collecting systems to be subjected to more stringent treatment before discharge into sensitive areas, make no distinction between direct and indirect discharges into sensitive areas.

31. That interpretation is, moreover, supported by the objective of the directive, which is, according to Article 1, the protection of the environment, and by Article 174(2) EC, which provides that Community policy on the environment is to aim at a high level of protection.

32. That objective would be undermined if only waste water which discharges directly into a sensitive area had to be subjected to more stringent treatment than that mentioned in Article 4 of the directive.

33. With respect to the argument of the Italian Government to the effect that, since the definition of sensitive areas under the Decree has not been contested by the Commission, it should be accepted as an adequate criterion by which to verify the performance of the obligations under Article 5 of the directive, it is sufficient to note that the Commission's complaint does not concern the definition of sensitive areas applied by the Italian authorities, but rather the application of the measures provided for by the directive with respect to discharges of urban waste water in sensitive areas defined by the Italian authorities.

34. In the present case, the urban waste water from the city of Milan, which, as is not contested by the Italian Government, is not subjected to more stringent treatment than that mentioned in Article 4 of the directive, passes through the Po basin and ends up in the sensitive areas of the Po delta and the north-west Adriatic coastal areas.

35. In those circumstances, the action brought by the Commission must be regarded as well founded.

36. Accordingly, by not ensuring that, by 31 December 1998 at the latest, the discharges of urban waste water of the city of Milan located within a relevant catchment area draining into the areas of the delta of the River Po and the north-west coast of the Adriatic Sea, defined by the Decree as sensitive within the meaning of the directive, were subjected to more stringent treatment than secondary treatment or an equivalent treatment prescribed by Article 4 of that directive, the Italian Republic has failed to fulfil its obligations under Article 5(2) of that same directive.

Costs

37. Under Article 69(2) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the Commission has applied for costs and the Italian Republic has been unsuccessful, the latter must be ordered to pay the costs.

On those grounds,

THE COURT (Sixth Chamber),

hereby:

1. Declares that, by not ensuring that, by 31 December 1998 at the latest, the discharges of urban waste water of the city of Milan, within a relevant catchment area draining into the areas of the delta of the River Po and the north-west coast of the Adriatic Sea defined by Decree-Law No 152 of the Italian Republic of 11 May 1999, enacting provisions on the prevention of water pollution and implementing Directive 91/271/EEC concerning urban waste-water treatment and Directive 91/676/EEC of 12 December 1991 concerning the protection of waters against pollution caused by nitrates from agricultural sources as sensitive, within the meaning of Article 5 of Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, were subjected to more stringent treatment than secondary treatment or an equivalent treatment prescribed by Article 4 of that directive, the Italian Republic has failed to fulfil its obligations under Article 5(2) of that same directive;

2. Orders the Italian Republic to pay the costs.

Macken

Colneric

Gulmann

Schintgen

Skouris

Delivered in open court in Luxembourg on 25 April 2002.

R. Grass

F. Macken

Registrar

The use of AI in healthcare:
A focus on clinical decision support systems

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The RECIPES project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 824665

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Abstract

The aim of this case study is to better understand the complexities and controversies for applying the precautionary principle to the use of artificial intelligence (AI) in healthcare. The case thereby examines the theoretical applicability of the principle to a possible 'emerging' case, since there are relatively few examples of practical application of the precautionary principle to it. We focused on clinical decision support systems (CDSS). CDSS have historically been one of the main applications of AI in the medical domain and their risks are in many respects exemplary for the risks of the use of AI in healthcare in general.

Our analysis indicates that, in particular cases, the precautionary principle is theoretically applicable to the risks of CDSS. Though decision making in healthcare by humans is also accompanied by high risks, the implementation of CDSS pose *additional risks* because they often change the nature of the decision making itself. Depending on the scale of implementation and the type of decision, CDSS may harm individual health, public health and/or infringe on human rights. Moreover, there have been scientific analyses of these risks, but these analyses are characterized by a considerable amount of scientific uncertainty. This uncertainty is partially caused by the current lack of scholarship on this topic, but is also a consequence of ambiguities, complexities and uncertainties that are intrinsic to CDSS as a technology, the nature of healthcare environments and the types of risks concerned.

Our analysis of the EU risk governance shows that there have been precautionary warnings towards the necessary limits of decision making of AI in healthcare early on, that 'precaution' has been a standard for many CDSS developers and that a large collection of laws, regulations, norms and standards have emerged that partially cover the risks of CDSS. This, in addition to the fact that the precautionary principle originated from environmental law, may partially explain why the principle has not been applied to CDSS. Recently, the EU has moved from a more ethics/standards-based governance to a risk-based approach. In academic articles and public discussions there similarly is a shift visible towards a more precautionary approach towards the use of AI in healthcare, emphasizing the seriousness and uncertainties of especially data driven applications.

The precautionary principle may be useful for investigating the desirable limits of the implementation of CDSS. Policy makers, healthcare professionals and companies could ask themselves what the minimal requirements for a safe decision-making process in healthcare are and which decisions always should be 'fully' taken by humans. The principle might be instructive for reflexivity and awareness of the many uncertainties around the implementations of CDSS and could encourage anticipation, cocreation and incremental innovation, for which many possibilities exist in the innovation pathways of CDSS, as our study shows.

The innovation principle does not seem to be of relevance to this case. Careful consideration of the uncertainties and requirements of CDSS in the vulnerable domain of healthcare should have priority over the benefits of innovation in terms of jobs and economic growth or the health benefits that CDSS may offer on the long run. In many cases, moreover, it remains to be seen if the (partial) automation of decision making in healthcare is desirable and beneficial in the first place.

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List of abbreviations

CA	Consortium Agreement
CC	Consortium Committee
DOA	Description of Action
GA	Grant Agreement
PCG	Project Coordination Group
PO	Project Office
WP	Work Package
AI	Artificial Intelligence
CDSS	Clinical Decision Support Systems
GDPR	General Data Protection Regulation

1 Introduction

1.1 Introduction

In their daily practice healthcare professionals make decisions that have crucial consequences for the health and wellbeing of patients, or, in the case of communicable diseases, potential patients. Perhaps in no other domain in society is the decision over life and death so direct as in the domain of healthcare. Delegating this decision-making to machines – to clinical decision support systems – subsequently potentially brings forth direct risks towards (public) health and wellbeing.

The implementation of some CDSS moreover raises concerns with regard to human rights. The power over life that is exercised in healthcare is usually kept in check by a variety of procedures, standards and control mechanisms. A patient can for instance talk with a doctor about the decisions that are made over his body, the patient can check why these decisions are made, he/she can argue against them and he/she can trust that information about his body will not be used outside of the medical practice. Delegating decision-making in healthcare to machines can, as we will show in this case, put pressure on these assumptions. This may in extreme cases lead to violation of human rights, like access to healthcare, privacy, equality before the law and the autonomy over one's body.

A question that this case tries to answer is, do the concerns mentioned above sufficiently warrant the application of the precautionary principle? Are they serious, systemic and irreversible enough? And if so, when and how should the precautionary principle be applied? The other RECIPES cases draw lessons from how the precautionary principle has been applied in practice. This case instead examines the theoretical applicability of the principle to a possible 'emerging' case, since there are relatively few examples of practical application of the precautionary principle with regard to CDSS.

This case analysis therefore provides some unique lessons about the complexities and controversies surrounding the application of the precautionary principle on new technology. First of all, an analysis of why the precautionary principle is possibly applicable on the use of AI in healthcare forces us into reflection about what characterizes these risks in the first place. Secondly, a description of the risks, discussions about these risks and the their risk governance, illuminates controversies and complexities about why the precautionary principle is *not* applied. This case thus provides a glimpse of the theoretical and practical considerations made for not applying the principle.

To make the most of this analysis we have delimited our case ('The use of AI in healthcare') to a particular healthcare application: clinical decision support systems (CDSS). In many ways, as we will show, the use of AI in CDSS is exemplary for the general complexities and problems that surround the use of AI in healthcare. However, it should be noted that clinical decision support systems vary significantly with regard to their functionality and technical properties (see section 2). Therefore, we do not concentrate on one 'type' of CDSS technology but examine what precautionary considerations have been put forward with different types of CDSS, what risks appeared in relation to such systems and what this means for applying the precautionary principle or precaution in general.

Thirdly, in our analysis of the risk governance surrounding CDSS we focus on the European Union. The reasons for this are that, first of all, many of the RECIPES stakeholders operate on a European level, and secondly, that AI has recently become an urgent and major topic for policy makers in the EU. Lessons learned in this case may therefore be especially relevant and topical.

1.2 Key timeline

Political	*Legal*	*Science/risk assessment*	*Public debate*	*Other*

Year	Event	Relevance to case study
1942	Science fiction writer Isaac Asimov writes the Three Laws on Robotics	Asimov was one of the first to make an elaborate case for precaution towards thinking machines
1972	The development on MYCIN was started at Stanford University	MYCIN is often considered to be the first example of a clinical decision support system (a backward chaining expert system)
1976	Computer scientist Joseph Weizenbaum writes the book Computer Power and Human Reason	Weizenbaums book sparked off one of the first major debates in the AI research community about the preferable limits of AI.
2001 - present	A combination of technological developments – the rise of big data, the growth of sophisticated machine learning techniques and cloud computing – create large expectations with regard to the opportunities of AI	These developments were especially of importance for the capabilities of data driven CDSS
2017	The European Court of Justice decides that software can be seen as a medical instrument, even when the software does not have a direct effect on the human body	This made the use of AI in medical devices subject for CE marking
2017	The European Parliament adopts a resolution on the Civil Law Rules on Robotics	In the resolution the EP states that ''Robotics research activities should be conducted in accordance with the precautionary principle, anticipating potential safety impacts of outcomes and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment.'
2018	The European Commission presents its AI strategy	In the strategy the EU develops policies and risk governance more specifically focussed on AI
2018	The General Data Protection Regulation becomes enforceable	Many privacy risks of AI and CDSS are subsequently covered by the GDPR
2020	Publication of the White Paper on AI by the European Commission	The European Commission proposes a risk-based approach on AI and mentions the use of AI in healthcare as high risk. The EC asks for input from stakeholders

2 Clinical decision support systems

Clinical Decision Support System(s) (CDSS) are, in a broad sense, systems that support the decision making of healthcare professionals. Or to be more precise: 'active knowledge systems which use two or more items of patient data to generate case-specific advice.' (Wyatt and Spiegelhalter 1991). CDSS for example provide clinicians with alerts or reminders, highlight guidelines during care, provide suggested course of action and identify drug-drug interaction.

Their assistance is generally aimed at making the decision-making process for healthcare professionals easier, faster, less erroneous and more evidence based. The first CDSS were developed in the 1970's and the amount of different CDSS has grown enormously since then. Today, CDSS are often integrated with electronic health records and they sometimes make use of web-applications and/or are administered through a desktop, smartphone, tablet, biometric monitoring and wearable health technology (Sutton et al. 2020).

CDSS can differ significantly with regard to the type of medical practice they support. This can vary from administrative actions, for instance support to clinical coding and authorization procedures, to more medical procedures, such as plan processes, clinical diagnosis and condition-specific guidelines.[1] CDSS are used in both primary, secondary and tertiary healthcare. They are, for example, used by both general practitioners, specialists like cardiologists, and sometimes even by patients at home.

Because CDSS are so varied with regard to function and context of use, it is difficult to estimate how many people make use of them. Market research firm Reaction Data estimated in 2018 that 74% of healthcare organizations in the US make use of CDSS.[2] The market is dominated by large health IT firms like Cerner and EPIC.[3] According to BIS Research the global clinical decision support systems (CDSS) market generated a revenue of $1.57 billion in 2018 and is estimated to grow over $3.49 billion by the end of 2028.[4]

CDSS have historically been one of the main applications of AI technologies in the medical domain (Montani and Strianim 2019). Artificial Intelligence (AI), intelligence demonstrated by machines, is a core component of most CDSS. The support a CDSS can give to health care professionals is mostly based on the 'reasoning' that its AI provides. For instance, the CDSS's suggestion for a particular medical procedure follows from the comparison of data from the patient in question to the data in its system. According to its algorithms, the CDSS 'reasons' and comes to a particular advice.

In the context of the case study, it is important to note that there does not really exist 'one' type of CDSS technology. The properties and behaviour (and therefore the associated risks) of a CDSS are dependent on 'what kind of support' to 'what kind of decision making' they give.

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[1] OpenClinical, Decision Support Systems, http://www.openclinical.org/dss.html, last accessed, 15/6/2020.

[2] https://www.healthcareitnews.com/news/new-study-identifies-top-11-clinical-decision-support-vendors, last accessed, 15/6/2020.

[3] Cerner (25 percent), EPSi/Allscripts (14 percent), Epic (11 percent), Stanson Health (6 percent), Nuance (5 percent), Premier (5 percent), Truven/IBM (4 percent), Elsevier (4 percent), Zynx Health (3 percent), NDSC/Change (2 percent) and CPSI/Evident (2 percent). https://www.healthcareitnews.com/news/new-study-identifies-top-11-clinical-decision-support-vendors, last accessed, 15/6/2020.

[4] https://www.bloomberg.com/press-releases/2019-07-09/global-clinical-decision-support-systems-market-to-reach-3-49-billion-by-2028, last accessed, 15/6/2020.

First of all, the type of AI that a CDSS makes use of determines its capabilities and 'behaviour'. AI methodologies used for CDSS can be divided into two categories: knowledge-based AI and data driven AI (Montani and Strianim 2019). In the case of knowledge-based AI, a 'top down' attempt is made to model human knowledge in computational terms. These CDSS consist of a knowledge base, an inference engine (an 'if-then-structure'), and a mechanism to communicate. Medical diagnoses and the accompanying symptoms are for instance translated to the knowledge base and once someone consults the computer by typing in particular symptoms, the computer will show the corresponding diagnosis.

Data driven CDSS start 'bottom-up' and infer suggestions on the basis of the data that is fed to it, for instance a large amount of data about patients and the (correct) diagnoses that doctor has made. By linking variables, it learns to 'recognize' the patterns of appropriate diagnoses; which symptoms fit with which diagnoses. While in knowledge based CDSS the rules followed are coded by humans, a data driven CDSS 'finds' rules through the data. A data driven AI can therefore, in many cases,[5] not explain 'why' it follows a particular rule. Data driven CDSS can moreover be subdivided according to different types of machine learning techniques, like support-vector machines, artificial neural networks and genetic algorithms (Montani and Strianim 2019). The complexity of these types of machine learning can make them especially prone to high risks. They are more unpredictable than knowledge-based CDSS, and when something goes wrong, it is more difficult to find out 'what' goes wrong and how it can be fixed (see chapter 3 for examples).

Besides the type of AI, CDSS are categorized on the basis of system function (some systems advise on what is true/diagnose while others advise on what to do/the treatment), the model used for giving advice (passive or active), style of communication (consulting or critiquing), human computer interaction (for instance voice recognition or keyboard) and if they are used for pre-diagnosis, during diagnosis or post-diagnosis (Wasylewicz and Scheepers-Hoeks 2018).

Potential benefits of CDSS

Proponents of CDSS argue that CDSS improve the decision making in healthcare. The main argument is that the reasoning of the AI in a CDSS adds value to the overall decision-making process of healthcare systems (Verughese et al 2017). This supposed value is dependent on the specific place the CDSS gets in overall decision taking in healthcare.

Some CDSS are primarily developed to 'replace' or 'mimic' the existing reasoning of healthcare professionals. In these cases, the added value lies in the fact that the AI does the same as its human predecessor, **but faster, more accurate, with less costs and less 'human' errors**. An example would be a virtual nurse that automatically diagnoses the patient and prescribes medication through chat (or voice recognition).[6]

Secondly, there are also CDSS that are primarily developed to 'augment', human decision making. In this case, a healthcare practitioner makes use of particular capacities

[5] Due the emergence of the right to explanation, methods and techniques in the application of artificial intelligence technology are developed so that the results of the solution can be understood by human experts. This so-called 'Explainable artificial intelligence (XAI)' is still largely in the development phase and it is very much uncertain if explainability is feasible for all data driven AI applications.

[6] See for instance the 'virtual nurse'. https://www.careangel.com/ai-and-voice-powered-virtual-nurse-assistant. Automated medical/health advice is in a sense already prevalent in health apps: Niezen, M.G.H., Edelenbosch, R., Van Bodegom, L. & Verhoef, P. (2019). Health at the centre – Responsible data sharing in the digital society. The Hague: Rathenau
Instituut.

of the CDSS to **improve his decision making**; the added value here lies in how the machine complements human reasoning. Quick Medical Reference, for instance, augments the ability of a doctor to diagnose patients with a knowledge base of diseases, diagnoses, findings, disease associations and lab information.[7]

Finally, in some cases a CDSS does not 'replace' or 'augment', but makes entirely new decisions possible. Data driven CDSS can for instance provide new information based on correlations between data sets that were unobservable before. In the so-called 'Learning Healthcare Systems' data driven CDSS play a role in finding new ways to continuously learn from data about the performance of the healthcare system and make improvements accordingly (Dagliati et al. 2018).

Taken together, these advantages suggest that CDSS can make healthcare more efficient and possibly more effective. The efficiency lies in a reduction of the costs, efforts and time that has to be invested in decision making. Time which health care professionals can invest in human contact with the patient. However, it should be noted that the presumption that CDSS will provide increased efficiency is often contested.[8] In some cases researchers argue that more long-term studies are needed to measure the added benefits (like decrease in deaths or medication errors) (Jia et al. 2016). Some suggest that the use of CDSS may also take up extra time, effort and costs to instruct personnel and to maintain the necessary infrastructure.[9] Also effectiveness has to be proven still in many cases (Moja et al. 2014; Murphy 2014).

A final potential benefit is the broad scope of AI applications that CDSS can indirectly contribute to. Because AI is a general-purpose technology, investment in research and development of CDSS might trickle down into progress in other domains where AI or related technologies are used. This might increase the technological competiveness of a country, the export of innovation to other countries and attract foreign capital (like investments or researchers) (Castro and McLaughlin 2019).

3 Risks and scientific uncertainties

3.1 Risk/threat

3.1.1 Potential risks

In their daily practice, healthcare professionals make decisions that have crucial consequences for the health and wellbeing of patients, or, in the case of communicable diseases, potential patients. The augmentation, replacement and supplementation of this

[7] Open Clinical, Decision Support Systems, http://www.openclinical.org/dss.html, last accessed, 15/6/2020.

[8] It is difficult to make general conclusions on effectiveness, since this largely depends on the CDSS used and, for example, the disease in question. One study identified six medical conditions, in which CDSS improved patient outcomes in a hospital setting. Another study stated that: 'There is a large gap between the postulated and empirically demonstrated benefits of [CDSS and other] eHealth technologies ... their cost-effectiveness has yet to be demonstrated'. See respectively: J. Varghese et al. (2018). "Effects of computerized decision support system implementations on patient outcomes in inpatient care: a systematic review". Journal of the American Medical Informatics Association. 25 (5): 593–602. A.D. Black. Et al. (2011). "The impact of ehealth on the quality and safety of health care: A systematic overview". PLOS Medicine. 8 (1).

[9] It is as of yet difficult, for instance, to continually adequately incorporate the extensive quantity of clinical research in such systems.

decision-making with CDSS is in this sense accompanied by risks for individual health, public health and human rights.[10]

It should be noted though that the decision making in healthcare is *always* accompanied by risks. There is always the risk that a doctor, intentionally or by accident, prescribes the wrong treatment. Many important medical decisions moreover necessarily have to be taken in the context of considerable (scientific) uncertainty.

What concerns us in this case, however, is the *additional* risks that CDSS pose. The introduction of a CDSS transforms how decisions are made in healthcare and therefore pose *new* risks. On the basis of a literature study[11] we found four ways in which CDSS transform the healthcare system and therefore pose additional risks: 1. Because they rely on data accumulation or datafication. 2. Because they imply a loss of human control. 3. Because a human element is removed in the decisions. 4. Because they imply a new division of labour and responsibilities in the healthcare domain.

Many of the risks of CDSS are concerned with the question of what 'good' decision making in healthcare entails and to what extent things like privacy and autonomy of the patient, transparency, accountability and reflexivity are necessary to ensure that the health of patients is served sufficiently. We will first give a broad overview of these risks. The extent of which the precautionary principle is deemed applicable, will be discussed in the section 'Relevance of the precautionary principle to the case'.

1. Risks related to datafication

First of all, the augmentation, supplementation and replacement of decision making by CDSS is dependent on data accumulation. A CDSS can only come to correct suggestions when important elements of its environment have been 'translated' into discrete data. A CDSS for instance reads the biometric data of a particular patient, compares this to the data it already has about symptoms and diseases and subsequently formulates a diagnosis. In the case of data driven AI, the algorithms also are formed on the basis of the data available to the CDSS. The use of CDSS is thus dependent on a datafication (and digitization) of the healthcare system. New risks emerge that are related to the dependency of CDSS on digital data.

First of all, medical information about an individual is, by its very nature, personal, intimate and sensitive. An individual's right to privacy gives him/her a choice in whether he/she wants to disclose this information about himself/herself.[12] The risk of violating privacy is exacerbated when one takes into account genetic data or other data that not only informs about an individual, but also his family or environment. Moreover, correlations on the basis of biometric data may not always be self-evident; an iris can for instance show that someone has diabetes or high blood pressure, and irregularities in fingerprints may indicate leukaemia or breast cancer (Kool et al. 2017).

Secondly, when health-data and CDSS are used to produce and apply medical knowledge, this can change who decides on what constitutes health and disease. A CDSS that produces (medical) knowledge implies a delegation of this responsibility to the developers of these systems. The specific algorithms and data-sets these developers use to train the AI of an CDSS determines the knowledge that comes out. Especially when clinical support is used outside of the supervision of healthcare professionals, for instance

[10] The precautionary principle has been acknowledged by the European Court of Human Rights (EHRM) in relation to human rights. Tătar EHRM 27 januari 2009, ECLI:CE:ECHR:2009:0127JUD006702101 (Tătar/Roemenië). It should be noted though that the application of the principle in relation to human rights does not seems to be custom.

[11] For a full overview of the literature used, see 'References' in the back of this report.

[12] To be precise, this is about 'Informational privacy'; the capacity of an individual to control information about himself/herself.

in connection to health-apps, this gives rise to new risks. Incapable developers may unknowingly prescribe wrong health-information and developers with ulterior motives could prescribe health information that benefits them or their client, like an insurance company. As such, this brings risks for doing harm in healthcare (Niezen et al. 2019).

There is also the risk of bias that may lead to suboptimal healthcare, in particular for vulnerable groups or women. Especially in the case of gender and sex, there exist substantial biases in existing medical data. Historically, norms and classifications in the medical sciences have predominantly been based on male bodies. It is presupposed that 'anatomy' is first of all the anatomy of the male. However, researchers have found sex differences in every tissue and organ system in the human body, as well as in 'the prevalence, course and severity' of the majority of common human diseases' (Perez 2019). They have even found differences in cells (Perez 2019). Existing biases may thus be prolonged and even exacerbated in CDSS. Feminist and journalist Caroline Criado Perez notes that: 'The introduction of AI to diagnostics seems to be accompanied by little to no acknowledgement of the well-documented and chronic gaps in medical data when it comes to women.' (Perez 2019). Machine learning can amplify such existing biases.

Thirdly, the datafication of health poses new risks when medical knowledge of someone is used to have power over someone. The ability to draw conclusions from diverse data sets might make people vulnerable to the extent that knowledge of their physical, emotional, social or psychological constitution is of interest to third parties like employers, health insurance companies, scammers, and competing football teams. Used in this way, CDSS could pose structural problems in relation to profiling and discrimination. Healthcare data has already been targeted by criminal organizations to be used by extortion or for long-term identity theft (Steger, 2019).

Fourthly, the datafication of healthcare can lead to new ways to manipulate people's behaviour. CDSS based information about biological constitutions, psychological predispositions and behavioural patterns can potentially be used to extrapolate, predict and therefore influence behaviour. This might result in asymmetries of power and information (Council of Europe, 2018) and conflict with, amongst others, the right to not be measured, analysed or coached.[13] All in all, this poses risks for the autonomy of a healthcare professional over his profession and the autonomy of a patient over his/her body and health.

2. Risks related to a loss of control

A substantial difference between decision-making by a human and decision-making with the help of a CDSS, is that with the latter a machine is (partially) in 'control'.

Aspects of control taken over from healthcare professionals by a CDSS may include decision making about what to examine, reasoning about observations or control over what is done with the results. In cases where the use of a CDSS has become habitual, it can replace the considerations a doctor would have about what to examine or to do. Moreover, the autonomy to decide about what to share with, for example, other departments may be limited when a CDSS is connected with others systems and automatically shares this information with other databases.

To the extent that the reasoning of the AI is a black box (Price 2015), it might wrongly give 'objective' standardized conclusions, even in situations that require a non-standard

[13] Proposed by, amongst others, the Rathenau Institute. Van Est, R. & J.B.A. Gerritsen, with the assistance of L. Kool (2017) Human rights in the robot age: Challenges arising from the use of robotics, artificial intelligence, and virtual and augmented reality–Expert report written for the Committee on Culture, Science, Education and Media of the Parliamentary Assembly of the Council of Europe (PACE), The Hague, Rathenau Institute.

approach. Existing biases in medical knowledge that are translated into the algorithms might unconsciously become normalized because a healthcare professional might just 'trust' whatever 'objective' output the computer provides. Institutionalized racism, genderism and sexism might however be reproduced in machine learning models.

A lack of control can also result in a lack of responsibility and accountability (Price 2015). It may become unclear who, why and how a decision was made. The blame of a mistake could for instance be attributed to the developers, implementers, healthcare professional, data supplier and/or system manager of a CDSS. Responsibility, accountability, explainability and transparency are however essential in the case of justifying and communicating on medical decisions, solving problems and preventing future mistakes.

Moreover, an overreliance on AI in medical problem-solving and decision making could result in the loss of appropriate skills and knowledge among health professionals (deskilling) (Gheeshan et al. 2009). In the case of a malfunction of the AI system, this gives rise to new vulnerabilities.

3. Risks related to the lack of a human element

Another substantial difference between a decision made by a CDSS and a human is that every cognitive act of a human, a 'human element' is directly present. When a healthcare professional 'thinks' about what to do, the whole of his 'humanity' is present: self-awareness, empathy, social intelligence, emotion and sincerity.

Delegating cognitive tasks to a machine essentially could mean removing these aspects from the decision-making process. Healthcare professionals make use of implicit knowledge and subtle skills that are sometimes difficult to formalize and make computable (Coeckelbergh, 2013). This could also remove aspects of 'care' from healthcare. Far-reaching automation might consequently endanger the 'right' to human contact or even the right to healthcare to the extent that care necessitates a person that 'cares for' or is 'involved with' your suffering when decisions are made.

Healthcare professionals moreover often have to make difficult decisions on the basis of conflicting research. Such careful deliberations and reflection (meta-analysis) are difficult or even impossible to translate into the reasoning of a CDSS (Gardner, 2004).

4. Risks related to another division of labour

The replacement of decision making in healthcare with CDSS tends to be accompanied by a new division of labour. Other actors, like IT companies and data collection agencies, acquire a (more important) place in the domain of healthcare (Niezen et al. 2019; Kobie 2019). This can bring forth new dependencies and therefore new risks.

When more processes are delegated to AI systems, the health care system becomes more dependent on those that develop, maintain and update these systems, handle the data and develop algorithms. The accumulated benefits of data can lead to monopolization in the data market. As a consequence of this, expertise and possession of data resources would rest in the hands of fewer companies, which could result in higher costs. This can put a severe strain on publicly funded healthcare.

Moreover, the processing of these data often happens outside the territory of the healthcare system itself, for instance in the cloud. This could mean that knowledge-production and factual expertise in this domain is increasingly in the hands of outside actors (Niezen et al. 2019). This can make health services more dependent and vulnerable, since they are not completely under control of the healthcare organization (the so-called lock in effect).

3.2 Scientific analysis

Some form of scientific analysis has already taken place with regard to the risks of clinical decision support systems. These analyses can be subdivided into analyses about a particular system (like IBM Watson), about a particular type of system (like data driven clinical support), about a particular type of risk (like data risks) or CDSS in general.

A quick literature scoping reveals that 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.[14] These analyses are often based on the experience and intuition of experts (what they expect could/would happen), informed reasoning and by collecting the perspectives of stakeholders.

To some degree, clinical trials have been executed on CDSS. In most instances these studies seem to focus on effectivity and economic benefits (Verughese et al. 2017), and there still exists considerable uncertainty about the long-term effects (Jia 2016) 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). This is possibly related to the fact that these trials are more focussed on technical and measurable effects, while these ambiguous risks may more often play a role on a management/policy level. For instance, a clinical trial might measure if a CDSS works appropriately, but it cannot (easily) say anything about the question if the use of the CDSS significantly reduces the autonomy of the healthcare professional or leads to risky dependencies on IT developers.

Many of the main risks of CDSS seem difficult to reduce to standard risk assessment procedures. Risks related to deskilling, deresponsibilization, data-abuse or the absence of humanity in medical decision-making are difficult to formalize and standardize, especially because such risks highly differ with regard to the type of CDSS and the environment in which it is used. A definitive body of work with robust (quantifiable, testable, repeatable etc) scientific statements about 'the risks of CDSS' seems to be absent, though a variety of tests and monitoring has been done about the effectiveness of CDSS in practice.

3.3 Scientific uncertainty

Some analysis has taken place in the scientific community with regard to the risks of CDSS (see previous paragraph). However, much of the work on the risks of CDSS is characterized by scientific uncertainty. Some degree of uncertainty seems to correlate with the status of current scholarship, which is fragmented and, with regard to new types of (data driven) CDSS, relatively new. Reasoning in most work on the risks of CDSS is mostly speculative and not based on large sets of empirical data.

The lack of scientific certainty and consensus surrounding the risks of CDSS is however also a consequence of some uncertainties inherent to the use of CDSS. First of all, because CDSS make use of AI, especially in the case of unsupervised machine learning, its behaviour and effects can be complex and difficult to predict. We call this '**technological variability**'.[15] Secondly, a CDSS always interacts with the complex and uncertain environment of a healthcare system. It is thus difficult to estimate if a particular CDSS will function adequately in line with the expectations, requirements and standards of the healthcare professionals. We call this '**environmental variability'**. Thirdly, the main risks that are concerned with CDSS (see section 3.1) are difficult to measure objectively. It is difficult, for instance, to measure and estimate the outcome and the chance of 'deskilling', when a CDSS is substantially biased or when a human perspective is needed for a decision. We call this **'risk assessment variability'**.

[14] See 'References' for an overview of the consulted literature.
[15] We define variability as a lack of consistency or fixed pattern.

We will analyse the properties of the risk variabilities with regard to **complexity**, **uncertainty** and **ambiguity** in the next sections. In each subsection we distinguish between variabilities caused by the nature of CDSS technology, the nature of the environment in which they are used and the type of risks concerned.

3.3.1 Complexity

Scientific uncertainty surrounding the risks of CDSS is partially a consequence of complexity in multiple ways.[16] Both the behaviour of CDSS, the environment in which they are used and the types of risks display properties of a complex system.

Complexity of the technology
CDSS that make use of machine learning, especially in the case of unsupervised machine learning, may display emergent and self-organizing behaviour.[17] Most CDSS do not yet make use of machine learning or are still in development, but future applications that do may exhibit the same types of complexity. A CDSS that makes use of machine learning which has the generic aim to support decision making could for instance try to optimize its support and combine data or develop algorithms of which a healthcare professional had not thought of.

Complexity of the environment
Not only the CDSS, but also the environments in which they are used, are characterized by complexity. When a CDSS is implemented in a healthcare system, for instance a hospital, it has to be attuned to a system that consists of many interacting elements. For a good application it has to be attuned to the expectations, existing norms and standards of healthcare professionals. The messages of a CDSS for instance have to be readable, understandable and helpful in the context of the daily tasks of a doctor, the specific needs of a patient and the oversight of a manager and/or a privacy officer.

The complexity of the behaviour of a CDSS can moreover become more extensive because it interacts and adapts to complex and unpredictable entities: humans. An AI system can therefore encounter many forms of reflexivity.[18] In the case of a CDSS this can mean that its algorithms change on the basis of the people that operate it and the people that constitute its database.

Another cause of complexity is that a CDSS sometimes has to mediate between different standards, inputs and multiple different sets of data. Interoperability of data is necessary for the development of good AI systems. Currently, the medical landscape is however characterized by a large number of disconnected small data from different technical systems (For instance: different electronic medical records, wearables, mobile health apps) that use different standards and protocols (Lehne et al. 2019; Niezen et al. 2019).

The interaction of a CDSS with other (AI) systems can in some cases moreover lead to feedback loops. In the US, for instance, a biased medical algorithm delayed healthcare for black people (Obermeyer 2019). The algorithm was used to predict the future health of individuals on the basis of their past health records. It identified people who were

[16] See 'WP2 Conceptual framework for comparative multiple case study analysis' for an overview of our conceptualization of complexity.
[17] In the OpenAI project the AI players in a game were for example said to demonstrate 'emergent behaviour'. They developed strategies that the developers had not thought of themselves. Strickland E. (2019) AI Agents Startle Researchers with Unexpected Hide-and-Seek Strategies, Institute of Electrical and Electronics Engineers.
[18] Reflexivity describes how human agents perceive, anticipate and alter the systems in which they are participating within the specific social, cultural and technological constraints being faced. This implies that by perceiving and acting in the system, individuals alter that very system in a type of dynamic feedback loop between the course of events and agent perceptions of those events. See RECIPES WP2 Conceptual framework for comparative multiple case study analysis.

likely to need extra care in the future. For a variety of socioeconomic reasons related to access to healthcare, black patients make less use of healthcare and thereby generate lower costs than white patients. Subsequently the algorithm prioritizes white people over black people with the same health status. As a consequence of such biases, black people may tend to trust the decision making in healthcare less, which will again be reflected in the data (which will show that they apparently have less healthcare costs). Such biases are difficult to discover beforehand, because they often depend on unknown unknowns (an AI may for instance indirectly take into account the gender because of the wordings that are used), the developers of AI systems tend to ignore complex social contexts and because 'bias' and 'fairness' are in itself difficult and ambiguous notions (Hao 2019).

Complexity of risk assessment

The risks that we distinguished in section 3.1 are also characterized by complexity in multiple ways. To the extent that 'good' (and consequently safe) decision making in healthcare consists of many elements, so risks can be a consequence of multiple elements, which are itself complex. Good decision making may include respect for the privacy and autonomy of the patient, transparency, accountability and reflexivity. To the extent that a CDSS replaces, augments or supplements the decision making, it may impair the decision process with regard to each of these elements. However, what does sufficient privacy, autonomy, accountability or transparency for instance exactly entail and how should each of these elements be balanced with efficiency and effectiveness? These are complex questions.

Moreover, many of the main risks described in section 3.1 may be intertwined and their relation is difficult to assess. For instance, the risk that a healthcare system becomes overly dependent on the infrastructure and knowledge of outside actors, may pose risks related to data, loss of control or lack of human elements in the decision-making process. A commercially oriented actor may scrap human intervention as much as possible to spare costs, sell data to insurance companies and take away control from healthcare personnel to improve efficiency. But such interdependencies are very difficult to assess and predict.

3.3.2 Uncertainty

Uncertainty describes the lack of knowledge about the outcomes or likelihoods, or both, of an event or process.[19] Both the behaviour of CDSS, the context in which they are used and the risk assessment are characterized by uncertainty.

Uncertainty of the technology

In the case of machine learning, the learning capabilities of a CDSS can gives it some 'autonomy', which can make the impact uncertain: 'tasks performed by machine learning are difficult to predict beforehand (how a new input will be handled) or explained afterwards (how a particular decision was made).' (Mittelstadt et al. 2016). Moreover, to the extent that an AI system comes to conclusions on the basis of statistical inferences, its decision-making is always based on probabilities, and thus (partially) uncertain knowledge (Mittelstadt et al. 2016). Though, it should be noted, the same (often even to a larger extent) of course applies to human decision-making.

The behaviour of a CDSS can also exhibit uncertainty[20] in the sense that small variations in the initial conditions of a (learning) AI system (for instance: its core code statements) can have highly divergent results. Researchers warn for instance for cyberattacks that can change the behaviour of machine learning AI systems by using only tiny pieces of

[19] See 'WP2 Conceptual framework for comparative multiple case study analysis' for an overview of our conceptualization of complexity.

[20] 'Variability uncertainty arises because of relevant, correct, but 'random' system behaviour.' RECIPES WP2.1.

digital data. Changing a few pixels on a lung scan could for instance fool such a system into detecting a non-existing disease (Finlayson 2019).

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. This makes it harder to predict its consequences, and therefore: it's risk. IT systems depend on interoperability between different codes, protocols and applications. Especially in relation to older IT-infrastructure that are written in older programming languages, it can be difficult to ascertain how it will interact with new systems (see also 3.2.2.1 Complexity).

Uncertainty of the environment
The environment in which a CDSS is used – a healthcare system – may besides complexity also be characterized by uncertainty. Healthcare professionals often have to make decisions under uncertainty about events as well as the likelihood of these events (for instance in the case of an unknown disease). Subsequently, it can be difficult with regard to the implementation of an CDSS to take into account these uncertainties and predict the risks of a CDSS. A CDSS in principle has to be prepared for many situations, but to the extent that these uncertain situations occur a CDSS may be unsuitable (unbeknownst to personnel) and thereby potentially pose additional risks.

Due to the complexity of many healthcare systems (Panch et al. 2019) it is moreover difficult to test the likelihoods of uncertain outcomes in controlled trials; the dynamic of a healthcare system and the extent an AI systems fits is difficult to simulate realistically.

Uncertainty of risk assessment
Just like that the types of risks described in section 3.1. are complex, they are also uncertain. For instance, it is very difficult to predict what the consequences would be if large amounts of health data fall into the wrong hands both with regard to the outcomes as the likelihood. It is difficult to estimate to what extent such data sets can be traced back to individuals and to what extent or how it can be used against them. The combination of separate data sets can lead to unexpected conclusions (Kool et al. 2017). Of apparently innocent biometric information sensitive correlations may for instance be discovered with regard to biological aspects like heritable diseases, psychopathology, behavioural dispositions, preferences or pregnancy.

Similarly, it is difficult to assess the amount of harm that is caused by decisions made on (partially) defective data. It is for instance difficult to measure how many harm has occurred due to the fact that there exists a strong bias towards a particular male body in medical data (Perez 2019).

3.3.3 Ambiguity

Another cause for scientific uncertainty on the risks of CDSS is that they are characterized by interpretive[21] and normative[22] ambiguity. Both the behaviour of CDSS, the context in which they are used and the risk assessment are characterized by ambiguity. This also brings forth ambiguity with regard to what extent risks are present when a CDSS is implemented.

Ambiguity around the technology
First of all, ambiguity lingers about what AI exactly is and when a CDSS exactly makes use of it. AI is still a relatively open-ended notion about which diverse conceptualizations are used. No transnational agreement exists with a commonly accepted working definition, neither at the technical nor the legal/policy level (EPRS/STOA 2019). However

[21] 'Interpretative ambiguity refers to the situation where information, data, analyses and risk governance strategies are interpreted in different ways by different actors.' RECIPES WP2.1. Conceptual framework for comparative multiple case study analysis
[22] 'Normative ambiguity points to the diverging ethical and normative assumptions in society.' WP2.1. Conceptual framework for comparative multiple case study analysis.

in the EU there is some consensus on the policy level. There also seems to exist some ambiguity surrounding the term of CDSS, especially with regard to new systems.[23] It may thus be difficult to adequately categorize CDSS and thereby adequately examine their risks.

Ambiguity around the environment
Moreover, ambiguity exists to what extent an artificial system supports or replaces the decision-making of healthcare professionals in a CDSS (EPRS/STOA, 2019). This can be problematic when assessing to what extent an AI was responsible for a particular harm (was it, for example, the fault of the technology or the one that used it?) and how it thus can be prevented.

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 (from existing libraries for example) and treated as black boxes 'as long as it works'. The harm brought by an AI system could thus potentially be the result of a mistake from a previous developer (Mittelstadt et al. 2016) In the case of autonomous systems, the gap between a designer's control and the algorithm's behaviour can result in a situation where blame can be assigned to several moral agents simultaneously (accountability gap) (Ford and Price 2017).

Ambiguity around risk assessment
No clear consensus exists about how the possible risks surrounding AI should be characterized and ethically framed. Though the risks of AI were originally primarily framed in relation to safety, privacy and security, recent research has also pointed to the possible implications that AI (in healthcare) may have with regard to autonomy, distribution of power, human dignity, justice and control over technology (Kool et al. 2017), and the possibility as a society to guarantee certain human rights and civil liberties (EPRS/STOA 2019). The question how these values have to be weighed against each other makes the problem even more ambiguous.

Risk analysis of the use of CDSS is moreover surrounded by difficult ethical questions: what defines (human) responsibility? Can a machine really replace the essence of (good) 'care' and 'human contact'? How much of our privacy, intimacy, personal integrity, autonomy and power are we willing to trade for a healthier/longer life? These questions often do not have straightforward answers.

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. The way such a system is developed and who gets a say in its conclusions brings forth ethical and political dilemmas. Moreover, different patients, healthcare professionals, managers, insurance companies and insurance payers, will have different perspectives on what counts as a risk, who will and should carry the burden of the risks (Wagner 2017).

3.4 Relevance of the precautionary principle to the case

In this section we analyse to what extent the precautionary principle may be of relevance to the risks of CDSS. We do this by checking to what extent the risks surrounding CDSS meet the requirements for application of the precautionary principle: 1. That the risks meet the threshold of damage. 2. That some form of scientific analysis has taken place 3. That there exists scientific uncertainty about the risks (Vos and Smedt, 2020).

[23] For instance, in the literature different terms are used and overlap exists of terms that refer to CDSS, like AI-Assisted Decision-making instead of CDSS, data driven CDSS / non-knowledge based CDSS.

Threshold of damage
It can be argued that, in terms of severity, the risks concerned with CDSS are comparable to the types of risks of other cases in which the precautionary principle has been applied. In section 3.1 we showed that the risks surrounding CDSS are in principle directly proportional to the importance that decision-making by healthcare practitioners has in a society.

First of all, when a wrong decision is made on the basis of a CDSS this might thus amount to serious harm. Some argue that the precautionary principle can be understood as a modern restatement of the classical Hippocratic oath (Hanson 2018). In this respect, (a particular) use of AI in a CDSS may be forbidden because it may lead to avoidable/intentional harm. Other people even argue that a new Hippocratic oath is necessary for AI-developers (Etzioni 2018). However, it should be noted that 'human' decision making just as well can cause harm in healthcare and that CDSS may also prevent harm.

Secondly, the implementation of a CDSS can also be accompanied with public health risks. This is the case when a defective CDSS is implemented on a broad scale. If, for instance, multiple hospitals make use of the same system, it will have large scale effects when it doesn't function properly. Such risks may also spread when other technological systems (indirectly) make use of the data or the algorithms of the CDSS in question. A CDSS may also pose public health risks when its reasoning is used to support decision making that affects (large) groups, for instance in the case of support to decision making in epidemiology, population health and Learning Healthcare Systems.[24]

Thirdly, the precautionary principle has also been applied in the context of **human rights** and in particular circumstances the use of CDSS can be at odds with human rights. In section 3.1 we showed that CDSS are surrounded with a variety of data related risks, that may have implications for the right to access to healthcare, the right against discrimination, the right to respect for private and family life and the right to human dignity.

Fourthly, an implementation of CDSS can also result in severe power asymmetries and new dependencies of healthcare systems on outside actors. In some case this might lead to **irreversible consequences** that endanger the **sustainability** of the healthcare system. Precaution in this sense is prudent because the integration of AI in the decision-making of healthcare systems does have irreversible consequences on the moral principle of inter-generational equity. Legal scholar Joanna Mazur notes that there exist similarities between the nature of challenges faced in environmental law and data protection law. She argues that "if decision-making solutions were to pose a serious risk for public health or a high level of an unpredictability if applying these solutions in the policies referring to the protection of health, it might be possible to apply the precautionary principle as a legal measure to address the identified risks." (Mazur 2019).

Overall, it appears that the requirement of risks meeting the threshold of damage is met.

Some form of scientific analysis and scientific uncertainty
In section 3.2. we showed that some form of analysis has taken place with regard to the risks of CDSS. In section 3.3. we moreover described that the risks of CDSS are characterized by scientific uncertainty in a wide variety of ways. Both the technology of CDSS, the environment in which it is used (healthcare systems) and the difficulty of assessing the risks concerned, are characterized to some degree by ambiguity, complexity and uncertainty. Besides the relatively scattered status of the respective scientific disciplines concerned with these risks, the scientific uncertainty may thus be caused by a variety of aspects that are intrinsic to CDSS. All in all, it appears that some

[24] See for instance: Engler, A. (2020) A guide to healthy skepticism of artificial intelligence and coronavirus, The Brookings Institution. In which many of the hype around the use of AI for battling the corona virus are debunked and a variety of risks are addressed

form of scientific analysis has taken place and that there is substantial uncertainty about the risks of CDSS.

Considerations contra invoking precautionary principle
Though the risks of CDSS potentially meet all of the criteria that makes it justifiable to invoke the precautionary principle, a variety of arguments can also be made to not invoke the principle. First of all, it is important to note that healthcare is in itself a high-risk sector. Human decision making without CDSS just as well poses severe risks, and sometimes perhaps even more so. It is therefore crucial to assess the risks of a CDSS relatively to the risks that existing practices have, and also take into account that many CDSS may also prevent harm (see chapter 2, benefits).

Second of all, many of the reasons to invoke the precautionary principle in relation to CDSS are related to specific circumstances; the risks are highly context specific. Amongst others, they depend on the type of CDSS, their specific technical design, the situation in which they are used and the precautions that have been taken in the healthcare system. A CDSS that merely gives advice for harmless medical procedures does not seem to be in need of applying the precautionary principle. A CDSS that makes use of a good storage and authorization procedures around data has less need for precaution towards data risks. And, finally, as long as hospital keeps investing in the education of its personal, deskilling will also be less of an issue.

Relevance of the precautionary principle
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. The principle may nevertheless be useful because it can point to appropriate regulatory and technical boundary setting for CDSS. In some scenario's, the seriousness of the risks clearly indicates the need for precaution (risks to public health, human rights), even when no scientific certainty about these risks has been established. Keeping these extreme situations and uncertainties in mind can inform decision making for taking the right precautionary measures; for instance, by limiting the medical procedures in which a CDSS can be used or the amount of human oversight that is necessary for important decisions.

Our analysis also shows that the risks of CDSS are in many cases difficult to define, both with regard to their specific outcome or harm, and with regard to their statistical probability. In these cases, the precautionary principle would be more suitable than, for example, the principle of prevention.

4 Risk governance and the precautionary principle

In this chapter we examine the risk governance that has taken place in the EU with regard to CDSS and the place the precautionary principle has had in it. The precautionary principle has not formally been applied in the EU by means of legislation or policies to the use of AI in healthcare, let alone the use of CDSS. Our analysis is therefore restricted to how in the EU was dealt with the risks of CDSS and to what extent precautionary thinking played a role.

We define risk governance as: "the totality of actors, rules, conventions, processes and mechanisms concerned with how relevant risk information is collected, analysed and communicated and management decisions are taken." (IRGC, 2018). Part of the risk governance are political and juridical dynamics (like legislation, regulation and policy initiatives) but also technological dynamics (like choices in the design of the technology) economic dynamics, (for instance markets with a high demand for safety and sustainability) and societal interactions or norms (for instance standards and practices among healthcare organizations for a safe use of CDSS).

In the first part of this chapter, we give an overview of the current legislation and regulation applicable to the EU that covers the risks of CDSS. The risk governance towards CDSS in the EU is in in a certain sense surrounded by a wide variety of legislation and regulation. Precaution towards the risks that may arise with CDSS is to some extent already covered by, for instance, regulation on medical devices and patient safety. These laws and regulations do not explicitly refer to CDSS, but nevertheless effectuate or can effectuate practices, norms and restrictions that impact how the risks of these systems are governed. For instance, while the GDPR does not explicitly refer to artificial intelligence or CDSS it does prescribe practices, norms and restrictions that are important for the data related risks of CDSS (for instance: data protection by default[25]).

In the second part of this chapter, we describe how EU risk governance has historically developed. We give an overview of the technological, economic, political and societal dynamics that played a role in how the risks of CDSS inside the EU have been dealt with. This analysis starts with the first precautionary warnings on AI in the research community (which largely happened outside the EU) and ends with forthcoming initiatives of the EU concerned with the use of AI in healthcare.

4.1 EU legislation and regulation

In this section we will give an overview of the existing regulation and legislation that covers some of the risks of CDSS in the EU.

It should be noted that (as described in sections 3.1-3.4) the risks of CDSS are complex, ambiguous and uncertain. This uncertainty, complexity and ambiguity applies to both the technological properties, the environment in which it is used as the assessment of risks concerned. As a consequence, different CDSS seem to fall in between different EU legislations and regulations. For instance, a data driven CDSS for instance generally has to refer to the GDPR to a larger extent than a knowledge based CDSS.

EU responsibility with regard to public health
It can be argued that the most extreme risks of CDSS are covered by a general responsibility of the EU to protect the public health of its citizens. However, the responsibilities towards the (public) health of the EU are limited.

The competence of the EU for public health has only been explicit inserted in the EU treaties since 1993, and is today laid down in Article 168[26] of the Treaty on the Functioning of the European Union.[27] It should also be noted that Article 168 entails a so-called supplementary competence which means that the EU can only supplement the actions undertaken by the Member States. Member States thus remain responsible for public health. Hence, EU action is required to respect 'the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care'.[28]

In the same fashion, the EU has to act and legislate consistently with the Charter of Fundamental Rights, but only to the extent that the EU has established competency over it.[29]

[25] Article 25 of the EU GDPR
[26] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A12008E168
[27] Article 168 states that: 'A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities.'
[28] Article 168 (7) TFEU.
[29] https://eur-lex.europa.eu/summary/chapter/human_rights.html?root_default=SUM_1_CODED%3D13

Indirect responsibility
Precautionary action on the EU-level towards CDSS could be inferred from more specific regulation. The risks of CDSS are covered by regulation on 1. safety of 'machines' in general. 2. medical products. 3. patient or consumer health and safety. 4. 'responsible' research and development. 5. Privacy.

These regulations do not explicitly refer to CDSS and are therefore more 'technology neutral' with regard to risk governance.[30] We will now shortly describe to what extent these regulations indicate a precautionary approach towards CDSS.

Safety of 'machines' in general
There exist a variety of directives that are concerned with risks of the technology and materials that underlie (many) AI systems.[31] When 'precaution' is mentioned in these documents, it seems to be mainly concerned about the specific risks of the technology concerned (for instance that Electromagnetic equipment is accompanied by precautions that must be taken when the apparatus is assembled). In the Machinery Directive, moreover, no mentions seem to be made with regard to the precautionary principle or a precautionary approach.

Medical products and medical devices
EU regulation on medical products and medical devices consist of the Medical Devices Regulation, the Directive on Liability for Defective Products, The Directive On In Vitro Diagnostic Medical Devices, General Product Safety Directive, as well as laws of EudraLex; the collection of rules and regulations governing medicinal products in the European Union.[32] The fact that software and software integrated into devices have to be CE marked can in this sense be viewed as a precautionary measure.

In the case of an AI used in a CDSS in the form of a health app, it may be possible that the General Product Safety Directive is applicable. The General Product Safety Directive states that the precautionary principle can be used under certain conditions. Member States are expected to take measures 'in particular' where products 'could be dangerous' (Art. 8(1)(d)), are 'dangerous' (Art. 8(1)(e)) or where 'dangerous products [are] already on the market' (Art. 8(1)(f)).[33]

Patient or consumer health and safety
Precautionary action towards CDSS can also be inferred from the patient and consumer rights in the EU.[34] The precautionary principle is however not mentioned and the shared responsibilities seem limited. Illustrative in this respect is the following text of the Directive on the application of patients' rights in cross-border healthcare: 'As recognised by the Council (…) there is a set of operating principles that are shared by health systems throughout the Union. Those operating principles are necessary to ensure patients' trust in cross-border healthcare, which is necessary for achieving patient mobility as well as a high level of health protection. In the same statement, the Council recognised that the practical ways in which these values and principles become a reality vary significantly between Member States.'[35]

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30 The GDPR, for instance, does not prescribe rules on data with regard to AI in particular, but speaks about data protection in general (independent of the type of technology that produces the data).

31 such as the Low Voltage Directive, Electromagnetic Compatibility Directive and the Radio Equipment Directives.

32 https://ec.europa.eu/health/documents/eudralex_nl

33 See: WP 1, The effect of the precautionary principle since 2000

34 For instance: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

35 DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, (5), https://www.europarl.europa.eu/ftu/pdf/en/FTU_2.2.1.pdf

On the 12th of February this year, the European Parliament has however adopted a resolution in which it calls for a strong set of rights to protect consumers in the context of artificial intelligence and automated decision-making.[36]

Responsible research and development
Fourthly, precaution can have a place in the R&D of CDSS and the regulatory framework of the EU around it. The notion of Responsible Research and Innovation (RRI) has been associated with the precautionary principle. René von Schomberg mentions the principle as one way to steer technological development in a societally desirable direction (Schomberg 2013). RRI is mentioned as a 'cross-cutting issue' in Horizon 2020, that will be promoted throughout Horizon 2020 objectives.[37]

Regulation on privacy
Finally, risks related to data accumulation are in a sense covered by legislation like the General Data Protection Regulation (GDPR). The GDPR protects citizens' fundamental right to data protection.[38] It is aimed, amongst others, to 'ensure a consistent and high level of protection of natural persons and to remove the obstacles to flows of personal data within the Union, the level of protection of the rights and freedoms of natural persons with regard to the processing of such data should be equivalent in all Member States.'[39]

The GDPR recognizes 'Data concerning health' as a special category of personal data.[40] It explicitly forbids taking decisions which produce legal or similarly significant effects for the individual solely in an automated way[41] and requires that the data subject should receive meaningful information on the logic involved in the process ('right to explanation').[42] This last provision has however not yet been enacted upon through jurisprudence and is questioned in academic literature (Wachter et al. 2017).

The precautionary principle or even the word 'precaution' are not mentioned in the GDPR. However, one could argue in some respects that similar types of reasoning are followed in the GDPR as in environmental legislation in which the precautionary principle is mentioned (Mazur 2019). The GDPR speaks of the implementation of the data protection 'by design and by default'.[43] Moreover, the requirement of a Data Protection Impact

[36] https://www.europarl.europa.eu/news/en/press-room/20200206IPR72015/artificial-intelligence-meps-want-to-ensure-a-fair-and-safe-use-for-consumers
[37] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation
[38] GDPR, (1), 'The protection of natural persons in relation to the processing of personal data is a fundamental right. Article 8(1) of the Charter of Fundamental Rights of the European Union (the 'Charter') and Article 16(1) of the Treaty on the Functioning of the European Union (TFEU) provide that everyone has the right to the protection of personal data concerning him or her.'
[39] GDPR, (10).
[40] GDPR, Article 4 (15). 'Data concerning health' means personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status;'
[41] 'The data subject shall have the right not to be subject to a decision based solely on automated processing, including profiling, which produces legal effects concerning him or her or similarly significantly affects him or her.' GDPR, Article 22 (1). This provision knows a few exceptions though: 'Paragraph 1 shall not apply if the decision: (a) is necessary for entering into, or performance of, a contract between the data subject and a data controller; (b) is authorised by Union or Member State law to which the controller is subject and which also lays down suitable measures to safeguard the data subject's rights and freedoms and legitimate interests; or (c) is based on the data subject's explicit consent.
[42] According to Articles 13(2)f, 14(2)g, and 15(1)h of the GDPR.
[43] GDPR, Article 25.

Assessment (DPIA) is defined in terms of 'Where a type of processing in particular using new technologies, and taking into account the nature, scope, context and purposes of the processing, is likely to result in a high risk to the rights and freedoms of natural persons (….).'[44] The combination of the provisions inside the GDPR to 'ensure a high level of protection of natural persons', 'data protection by design and default', the requirement to perform a DPIA in the case of likely and high risks to the rights and freedoms of natural persons and the scientific uncertainty that is often ascribed to the effects of automated decision-making, seems to indicate to a possible invocation of the precautionary principle, so argues Joanna Mazur (Mazur 2019).

Other regulation
Other EU regulation that also deals with the possible risks of CDSS are rules on intellectual property, cyber security and trade regulation.

Moreover, some safety of CDSS may be covered by industry wide set standards, like from the International Organization for Standardization (ISO)[45] and the European standard (EN).[46] Interoperability of IT systems may for instance reduce some of the risks of CDSS because they make the CDSS more predictable and manageable.

There are also some individual companies that have developed their own ethical guidelines or norms for AI (Rathenau Institute 2019). Alphabet (Google), who recently has also entered the health market, has for instance described their principles on AI.[47] Philips has for instance launched 'Five guiding principles for responsible use of AI in healthcare and healthy living'.[48] It should be noted though that ethical guidelines, codes of conduct or other similar voluntary initiatives are not always very effective for risk governance (Del Castillo 2020).

Finally, there also exist standards, codes of conduct and best practices (like AI impact assessment) used by CDSS-developers, for instance Privacy and Ethics by design, that can reduce some of the risks (for more on this, see section: Effect of the precautionary principle on innovation pathways).

Legal cases
There exist a few legal cases on EU level that are relevant in relation to the risks of CDSS. One relevant court case is that European Court of Justice decided that software can be seen as a medical instrument, even when the software does not have a direct effect on the human body.[49] In this respect, precautionary measures in the context of regulation for medical devices could also be applicable for software-based CDSS.

Another court case that could be influential is the decision of the district court of the Hague, to shut down SyRI – An system Risk Indicator created by the Dutch Ministry of Social Affairs to identify people deemed to be at high risk of committing fraud – by citing the European human rights and data privacy laws. In this case the principles of

[44] GDPR, Article 35 (1) 'Where a type of processing in particular using new technologies, and taking into account the nature, scope, context and purposes of the processing, is likely to result in a high risk to the rights and freedoms of natural persons, the controller shall, prior to the processing, carry out an assessment of the impact of the envisaged processing operations on the protection of personal data. A single assessment may address a set of similar processing operations that present similar high risks.'
[45] The International Organization for Standardization (ISO) is an international standard-setting body. It is composed of representatives from various national standards organizations.
[46] The European standard (EN) is a standard for national standardization bodies of European member states.
[47] Google AI, Artificial Intelligence at Google: Our Principles.
[48] Philips (2020), Five guiding principles for responsible use of AI in healthcare and healthy living.
[49] ECJ, 7 December 2017 (Case C-329/16) 6

proportionality and subsidiarity were also invoked, as it was shown that there are more privacy friendly alternatives that could have fulfilled the same aims.[50]

The European Court of Human Rights and the Court of Justice of the European Union have warned against the impact of surveillance activities from states on privacy rights (Van Est et al., 2017). The European Court has moreover made multiple decisions on data protection.[51]

4.2 Other risk governance dynamics

In this section, we describe how EU risk governance has historically developed. We give an overview of the technological, economic, political and societal dynamics that played a role in how there has been dealt with the risks of CDSS inside the EU. This begins with the first developments and precautionary warnings on AI in the research community (which largely happened outside the EU) and end with forthcoming initiatives of the EU concerned with the use of AI in healthcare.

Early precautionary warnings inside the research community
Many of the main risks of CDSS that are currently discussed in the literature and among policy makers seem to have been voiced for a long time. Precautions were expressed about the fundamental limits of machine decision making, the danger that people would put too much trust in possibilities of the technology and the limits of what decision-making should be attributed to machines in the first place.

Already in the first centuries before Christ did people speculate on the thinking machine and the possible risks they might have (McCorduck 2004). More scientifically grounded assessments about risks of artificial intelligence however only emerged in the beginning of the twentieth century when the theoretical basis and components for constructing a thinking machine were increasingly thought to be in reach. Science fiction writer Isaac Asimov for instance introduced his Three Laws of Robotics in 1942. The first law - 'A robot may not injure a human being or, through inaction, allow a human being to come to harm.' – strongly resembles the medical no harm principle.[52]

The development of AI systems took off in the 1960's when AI research became heavily funded by the US Department of Defence and AI laboratories were established around the world. Criticism on the emerging field was expressed by Mortimer Taube in the book *Computers and Common Sense*. He argued that many AI research was only done on the premise of possible goals, without considering if such possibilities are enough of a justification to spend large amounts of money and time on it.

In the 1970's debates sparked up in the academic community about the (preferable) limits of AI.[53] Hubert Dreyfus argued in 1972 that human thinking could never be captured in formal rules, because it depends on unconscious processes (Dreyfus 1972). Researchers in artificial intelligence confused according to him the rule one is following to do something with the rule that can be used to describe someone doing something (McCorduck, 2004). Though a particular algorithm might perfectly describe someone's behaviour, this does not mean that it accounts for the internal deliberations that motivated the behaviour for example.

In the book Computer Power and Human Reason (1976), computer scientist Joseph Weizenbaum argued that robots should never be used to make important decisions,

[50] https://uitspraken.rechtspraak.nl/inziendocument?id=ECLI:NL:RBDHA:2020:865
[51] https://ec.europa.eu/anti-fraud/sites/antifraud/files/caselaw_2001_2015_en.pdf
[52] This principle is thought to be part of the Hippocratic oath. It is often summarized with the phrase '"First do no harm'.
[53] 'These debates were more academic (in the literal sense) than popular.' McCorduck (2004) Machines Who Think, 443.

because they lack human qualities like compassion and wisdom. He also emphasized that machines would always lack the cultural and social background that play a role when humans make decisions. He stated that 'there are domains where computers ought not to intrude, whether or not it's feasible for them to do so.' And: 'Computers ought not be introduced where the effects can easily be seen to be irreversible and the side effects are not entirely foreseeable.' (McCorduck 2004) These contemplations retroactively show a strong similarity, with the principle of precaution.

Technological precautions taken with regard to the first CDSS

One of the first systems in which AI was used for support in medical decision making, called MYCIN, was developed in the early 70's. MYCIN consisted of approximately 600 rules that were used for making antibiotic treatment recommendations. These rules were based on facts about the patient and results of the antibiotic culture.

Considerations on the risks of such systems for the practice of healthcare professionals seem to be already part of the early development of such systems. Some developers for instance recognized the danger of a CDSS displaying too many messages ('alert fatigue') and the complexity of adjusting a specific expert system to the standards and practices of a specific healthcare system. For instance, the so-called CARE language was developed which allowed non-programmer, clinical experts to flexibly set the if-then-else logic of the alert according to their preferences (McCallie 2016).

Moreover, according to Kenneth W. Goodman the so-called 'Standard View' or standard apporach in computational diagnoses and the leading proponents of CDSS has always been caution. Randolph A. Miller, a 'key figure both in the scientific evolution of computational decision support and in scholarship on correlate ethical issues' has argued: "Limitations in man-machine interfaces, and, more importantly, in automated systems' ability to represent the broad variety of concepts relevant to clinical medicine, will prevent 'human assisted computer diagnosis' from being feasible for decades, if it is at all possible." (Goodman 2007).

The emergence of the first contours of EU risk governance on AI

EU risk governance of artificial intelligence also seems to emerge in the 1980's, in the wake of EU wide collaboration on research and the need for harmonization of IT standards, as well as the emergence of the first EU wide agencies (indirectly) concerned with the risks of technology.

In the 1980's the first EU wide research collaborations that focussed on new technology were started. Under the name ESPRIT (1983) a research programme was initiated to reverse the decline of European competiveness and to ensure global economic and political independence of European Communities in the face of the rise of the US and Japan in this field (Dorst et al. 2016). The programme had to result in better shared European protocols and standards in IT, for instance by financing large scale, long lasting, multi-country projects (a cooperative basis with industry, universities and governments of EC countries). Some of the projects were focused on advanced information processes which overall goal was to develop technological capabilities that underlie machine intelligence (Nilsson 2009).

From the 1980's onward, moreover, a variety of institutes and agencies were established that were concerned with or touched the governance of technology on a European level.[54] The 1980's also gave rise to a variety of ethical debates surrounding new technologies and the institutionalization of technology assessment around Europe (Schot

[54] Examples of such institutes are the Centre for European Policy Studies (1983), European Political Strategy Centre (1989), European Parliament's Panel for the Future of Science and Technology (1987), European Political Strategy Centre (1989), European Parliamentary Technology Assessment Network (1990), The European Institute of Innovation and Technology (2008) and the European Systemic Risk Board (2010)

and Rip 1997). In general, such debates and publications of EU wide agencies seemed first of all concerned with IT and digitization (and therefore only indirectly with AI) and their focus seems to be primarily on ethical, social and juridical aspects and not so much on risks.

In the 1990's the discipline of AI consisted of fragmented competing subfields focused on particular problems or approaches, often under different names (McCorduck 2004). This fragmentation may also partially explain why 'overarching' analyses concerned with risks of AI are hard to find; the development of an AI for a particular problem (like organizing a database) do not bring to mind substantial risks. In the early 2000's, a group of related technological developments promised revolutions with regard to AI capabilities in general[55], which thus again sparked a discussion about substantial and public risks.[56]

An early example of the explicit use of the principle in combination with AI is the report 'The Precautionary Principle in the Information Society Effects of Pervasive Computing on Health and Environment' (2003), by the TA-SWISS and STOA (Hilty et al. 2005). We have not been able to find, however, other analyses of AI, digitization and possible use of the precautionary principle on EU level.

EU risk governance in the wake of the digital single market

The risk governance towards CDSS in the EU significantly changed after the 2010's. In these years 'AI' and the use of AI in medical devices increasingly became an important concern in EU governance. Three developments contributed to the fact that AI and the risks of AI appeared at the forefront of EU policymaking.

First of all, new technological developments – the rise of big data, the growth of sophisticated machine learning techniques and cloud computing – created large expectations with regard to the (business) opportunities of AI.

Secondly, in the wake of the 'AI Revolution' a variety of intellectuals, politicians and societal organizations voiced concerns about the possible future societal risks of AI. Several ethics codes and principles for the development and use of Artificial Intelligence (AI) have subsequently emerged since 2017 from companies, partnerships between science, industry, and NGOs, and from politics and governance (Rathenau Institute 2019).

Thirdly, in the context of the aim to establish a digital single market, the development of AI became of a central economic and societal concern for the EU. Following the Lisbon Strategy, the Digital Agenda for Europe was initiated as one of the seven flagship initiatives of the Europe 2020 strategy.[57] In the context of this strategy, the Digital Single Market strategy sought 'to ensure better access for consumers and business to online goods and services across Europe, for example by removing barriers to cross-border e-commerce and access to online content while increasing consumer protection.'[58] In 2018 the Commission presented an AI strategy as part of the Digital Single Market Strategy. In its approach towards AI the Commission deals with technological, ethical, legal and socio-economic aspects 'to boost EU's research and industrial capacity and to put AI at the service of European citizens and economy.'[59]

[55] The rise of big data, the growth of sophisticated machine learning techniques and cloud computing

[56] In 2015, for instance, a collection of scientists and public intellectuals signed a open letter on which they pleaded caution with regard to the dangers of AI. They warn that 'systems must do what we want them to do.' https://futureoflife.org/ai-open-letter

[57] https://www.europarl.europa.eu/factsheets/en/sheet/64/digital-agenda-for-europe

[58] https://ec.europa.eu/eurostat/cache/infographs/ict/bloc-4.html

[59] https://ec.europa.eu/digital-single-market/en/artificial-intelligence

Recent developments inside the EU

Many of the risks of CDSS are to some extent covered by existing EU regulation and legislation (see section on EU regulation and legislation). More recently, however, a variety of initiatives have emerged that relate specifically towards the risks of AI and the use of AI in healthcare, and therefore risks related to the use of CDSS. It is difficult to give a complete overview of all these initiatives and how they relate to each other. However, a few developments are worth mentioning.

First of all, efforts have been made to reduce ambiguity about the (legal/policy) definition of AI. The implementation of AI-specific legislation has possibly been complicated by the fact that, for a long time, no common understanding existed in the EU on what a robot or an AI system is. Recently, however, the European Parliament has defined what a 'smart robot' is[60] and the High-Level Expert Group on Artificial Intelligence (HLEG) has expanded on a definition of AI from the European Commission.[61]

Secondly, the EU has in collaboration with stakeholders and member states formulated ethical principles for AI and the contours of a specific European human centred approach. Since 2018 a wide variety of EU agencies have published general recommendations on AI (Rathenau Institute, 2019). In April 2018 moreover a declaration was signed by the EU members states in which they agreed to collaborate on the most important issues raised by AI.[62] In December 2018 the EC came with a Coordinated Plan on Artificial Intelligence,[63] in which it sketched out the intention of the EU becoming the world leader in the responsible development and application of AI. An EU high level expert group moreover developed ethical guidelines for AI,[64] an AI assessment list[65] and 'Policy and investment recommendations for trustworthy Artificial Intelligence'.[66] The Expert Group on Liability and New Technologies has moreover published a report about liability for artificial intelligence[67] and a forum - The European AI Alliance – was established for 'a broad and open discussion of all aspects of Artificial Intelligence development and its impacts.'[68]

Thirdly, the EU has implemented specific policies and stimulated collaboration with the specific aim to increase the use of AI in healthcare. There subsequently exist a certain technology push in the EU towards the implementation of CDSS. The European Commission strongly supports an enabling of the digital transformation of health and care in the Digital Single Market.[69] The Commission argues that only by fundamentally rethinking the EU health and care systems, it can be ensured that they remain fit-for-purpose. The Commission mentions ageing, multimorbidity, a growing threat from infectious diseases due to increased resistance to antibiotics and new or re-emerging pathogens, health workforce shortages, and the rising burden of preventable noncommunicable diseases caused by risk factors such as tobacco, alcohol, and obesity,

[60] https://www.europarl.europa.eu/doceo/document/A-8-2017-0005_EN.html
[61] https://ec.europa.eu/digital-single-market/en/news/definition-artificial-intelligence-main-capabilities-and-scientific-disciplines
[62] https://ec.europa.eu/jrc/communities/en/community/digitranscope/document/eu-declaration-cooperation-artificial-intelligence
[63] https://eur-lex.europa.eu/legal-content/NL/TXT/?uri=CELEX:52018DC0795
[64] https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai
[65] https://ec.europa.eu/futurium/en/ai-alliance-consultation/guidelines/2
[66] https://ec.europa.eu/digital-single-market/en/news/policy-and-investment-recommendations-trustworthy-artificial-intelligence
[67] https://ec.europa.eu/newsroom/dae/document.cfm?doc_id=63199
[68] https://ec.europa.eu/digital-single-market/en/european-ai-alliance
[69] https://ec.europa.eu/digital-single-market/en/news/communication-enabling-digital-transformation-health-and-care-digital-single-market-empowering

as some of the main challenges that may need 'digital solutions'.[70] The Commission argues that market fragmentation and lack of interoperability across health systems currently stand in a way of an integrated approach for the EU. Such an approach is difficult because the organisation and delivery of healthcare is the responsibility of the Member States, and in some Members States the financing and provision of healthcare is even the responsibility of regional authorities.

Fourthly, – more recently – the EU has developed a risk-based approach toward some forms of AI. In the White Paper on AI of 2020, the European Commission proposes specific assessment requirements for 'high-risk' AI applications, depending on the sector in which it is deployed and the manner in which it is deployed. Healthcare is mentioned as a high-risk sector, but not all applications are high-risk: 'For example, whilst healthcare generally may well be a relevant sector, a flaw in the appointment scheduling system in a hospital will normally not pose risks of such significance as to justify legislative intervention. The assessment of the level of risk of a given use could be based on the impact on the affected parties.' (European Commission, 2020).

Besides applications that fall under the two criteria, some exceptions could also be considered high-risk, like 'the use of AI applications for the purposes of remote biometric identification and other intrusive surveillance technologies.' The European Commission in this regard mentions pre-marketing conformity assessment requirements, requirements on training data, requirements on record-keeping and data sets, requirements on human oversight, transparency, accuracy and human oversight, monitoring and ex-post controls. The Commission also proposes the establishment of a Code of Conduct for processing personal data in the health sector.

Lastly, the EU has mentioned a variety of forthcoming regulation and revisions of existing legislation with, amongst others, the aim to tackle AI specific risks. The EU does not yet have specific legislation on robotics or AI, but the European Commission is expected to implement (binding) regulatory and policy initiatives in the following years (Molyneux et al. 2017).

The European Parliament has moreover requested to examine legal questions in connection to the development and use of robotics and artificial intelligence foreseeable in the next 10 to 15 years. The Commission has subsequently launched an evaluation of the Directive on Liability for Defective Products, Expert Group on Liability and New Technologies and the Machinery Directive.

In a Resolution on 12 February of this year, the European Parliament has called for a strong set of rights to protect consumers in the context of artificial intelligence and automated decision-making.[71] The Parliament argued that automated decision-making (ADM) technologies should only make use of unbiased data sets and explainable and unbiased algorithms, with review structures set up to remedy mistakes and the possibility of consumers to redress automated decisions. Those systems should only use high-quality and unbiased data sets and "explainable and unbiased algorithms", states the resolution. Review structures should be set up to remedy possible mistakes in automated decisions. It should also be possible for consumers to seek redress for automated decisions that are final and permanent: '"Humans must always be ultimately responsible for, and able to overrule, decisions that are taken in the context of professional services such as the medical, legal and accounting professions, and for the banking sector."

[70] https://ec.europa.eu/digital-single-market/en/news/communication-enabling-digital-transformation-health-and-care-digital-single-market-empowering
[71] https://www.europarl.europa.eu/news/en/press-room/20200206IPR72015/artificial-intelligence-meps-want-to-ensure-a-fair-and-safe-use-for-consumers

5 The precautionary principle and its future

5.1 Reflection on the precautionary principle in the literature

The precautionary principle has not yet been explicitly applied in EU legislation or regulation, in relation to CDSS. It is no surprise, therefore, that explicit reflection on the application of the precautionary principle to CDSS has been limited.

Though criticism on the application of the precautionary principle specifically in relation to CDSS or on the use of AI in healthcare seems scarce, comments have been made on the use of the principle in relation to AI in general. Opponents of the precautionary principle Daniel Castro[72] and Michael McLaughlin[73] argue that it undermines progress in artificial intelligence (Castro and McLaughlin 2019). They refer to a very strong interpretation of the principle: 'The precautionary principle is the idea that if a technological innovation may carry a risk of harming the public or the environment, then those proposing the technology should bear the burden of proving it will not. If they cannot, governments should limit the use of the new technology until proven safe. Those who support the precautionary principle, which call for government intervention even when there is no clear evidence of tangible and imminent threats of harm, adhere to the cliché it is "better to be safe than sorry."' (Castro and McLaughlin 2019).

Castro and McLaughlin state that the application of the precautionary principle in relation to AI leads to slower and more expensive AI development, less innovation, lower-quality AI, less AI adoption, less economic growth, fewer options for consumers, higher prices, inferior consumer experiences, fewer positive social Impacts and Reduced Economic Competitiveness and National Security.

There are also proponents of the precautionary principle. The European Trade Union Institute (ETUI) has called for the precautionary principle and human rights in their Foresight Brief about the need for regulation for workers in the context of AI (Del Castillo 2020). ETUI argues, amongst others, that 'the precautionary principle is an essential principle that must be at the heart of technological development. It can sustain such development, give direction to innovation and, in the case of AI, help to (1) build a governance based on social dialogue and which involves relevant societal actors; (2) provide a framework conducive to the explicability and accountability of algorithmic decision-making; (3) contribute to ensuring that technological innovations are safe for society.' Moreover, the innovation principle is described as '(…) a concept which was invented in 2013 by various CEOs as a lobbying/deregulatory tool and which does not have a legal basis. It is not found in EU treaties, secondary legislation, case law or the national constitutional traditions of any Member State.'

5.2 Effect of the precautionary principle on innovation pathways

The precautionary principle has not explicitly been applied to the use of CDSS, but precautionary thinking has in different examples had an effect on the development of these systems. First, we look at the general (geopolitical) background that influences the innovation pathways of AI development, and thereby the innovation pathways of CDSS. In the second part we examine some of the ways in which other choices are or can be made on the basis of precaution in the development of CDSS.

[72] Daniel Castro is vice president at the Information Technology and Innovation Foundation (ITIF) and director of ITIF's Center for Data Innovation. - https://itif.org/person/daniel-castro

[73] Michael McLaughlin is a research analyst at the Information Technology and Innovation Foundation. - https://itif.org/person/michael-mclaughlin

General (geopolitical) background
The development of AI worldwide is often portrayed as a race, whereby a leading position is deemed essential for national security (Hunter et al. 2018) and/or economic security (McKinsey Global Institute 2018). Because the AI also poses substantial risks – and to attain mitigate such risks as well as assure legal and economic certainty – this has also led to a 'race to AI regulation'. Good regulation could also effectuate a regulatory 'first mover advantage' (Smuha 2019). Besides the EU, also Japan, Canada, Dubai, China, Singapore, the US and Australia have published ethics guidelines for AI (Smuha 2019). Moreover, besides risk-regulation, there exists competition in leading the technological standard-setting processes, which can also have ethical consequences (Beatie, 2019).

Moreover, the potential impact of AI has been subject of wide speculation, from those that characterize it as a fundamental tool for defence or who see it as an inevitable step towards singularity (Creighton 2018), to those that warn for its possibilities of totalitarian control (Helbing et al. 2018). AI is in this sense a 'controversial' technology, a fact that may slow down a steady uptake of the technology.

Another factor that influences the innovation pathways of CDSS is that many of the AI applications that are currently featured in medical literature, are not easily executable at in clinical practice: 'A complex web of ingrained political and economic factors as well as the proximal influence of medical practice norms and commercial interests determine the way healthcare is delivered.' (Panch et al. 2019). Secondly, in many healthcare organizations the necessary data infrastructure to collect data and train an AI, and test for possible biases, is lacking. Besides regulatory uncertainty, a variety of established customs and conservative views and interests may play a role in the innovation path (see also environmental variability section 3.1).

Nevertheless, with these dynamics in the background, different countries follow different strategies with regard to AI. These national strategies set, as it were, the stage within which R&D on AI and CDSS is acted out. In the case of the EU, the background is characterized by the need for harmonization of the regulatory framework of the member states in service of the digital internal market, the conviction that AI can help to solve some of the world's biggest challenges and its human-centric approach to AI (see 3.3.1). In other regions, other political and economic factors play a (more decisive) role. We will shortly look at the strategies of China and the United States.

China
In 2017 the State Council of China released the 'New Generation Artificial Intelligence Development Plan.'[74] China strives to be the leading AI superpower in 2030, largely through state funding and considers the development of AI a national priority. It is part of the state-driven industrial plan 'Made in China 2025'. In May 2019, a multistakeholder coalition consisting of Chinese universities, the Institute of Automation and Institute of Computing Technology in Chinese Academy of Sciences, and firms like Baidu, Alibaba and Tencent, developed the Beijing AI Principles. They are 'proposed as an initiative for the research, development, use, governance and long-term planning of AI, calling for its healthy development to support the construction of a human community with a shared future, and the realization of beneficial AI for humankind and nature.'[75]

The United States
The United States also considers worldwide leadership in AI as a national priority. On February 11 2019 the American AI Initiative was launched. In it is stressed that 'the Federal Government plays an important role not only in facilitating AI R&D, but also in promoting trust, training people for a changing workforce, and protecting national

[74] Future of Life Institute (visited 9 April 2020), AI Policy China, https://futureoflife.org/ai-policy-china/.
[75] Bejing AI Principles, https://www.baai.ac.cn/blog/beijing-ai-principles.

interests, security, and values.' The initiative is guided by five principles: 1. Driving technological breakthroughs, 2. Driving the development of appropriate technical standards, 3. Training workers with the skills to develop and apply AI technologies, 4. Protecting American values including civil liberties and privacy and fostering public trust and confidence in AI technologies, 5. Protecting US technological advantage in AI, while promoting an international environment that supports innovation.

Choices in the design of CDSS

Besides the geopolitical background, the innovation pathways of CDSS are mainly dependent on the specific choices that are made by the developers of these systems. These choices are often determinative for the risks that CDSS pose. The design choices that are made with regard to clinical decision support systems depend naturally on the specific function it serves (for instance the extent to which malfunction would lead to harm). Nevertheless, a few general differences in design choices can be observed.[76]

First of all, choices are made with regard to the data; which data is used, how and where it is stored, shared and processed and who has access to it. The patient data that a CDSS makes use of can for instance be stored at a decentralized location and when it is centrally stored it can be anonymized. Data collection may furthermore be checked for biases and if its algorithms are up to date with contemporary medical knowledge and reasoning.

Secondly, differences exist in how the CDSS comes to conclusions; the technique that is used to reason. This may differ from a machine learning approach that is purely based on data, or a structure that is based on medical knowledge trees (knowledge based vs data based). And in the case of machine learning, a distinction is made between supervised or unsupervised machine learning. In the development of some CDSS, it is monitored by the developers whether the conclusions of the CDSS are in agreement with the conclusions made by real doctors and if their use indeed lead to better results. In various instances CDSS have underwent clinical trials.[77] Accountability of the decision-making can moreover be improved by making use of explainable AI (XAI).

Thirdly, in a variety of ways developers have thought about the layout of CDSS; about how they influence medical decision making in a good way; promoting reflection and calmness. This too may ensure that healthcare professionals stay in control. An example of this are choices in how and how often the alerts are showed to a practitioner (for instance to reduce alert fatigue or stress). The way a message may be presented (coercive, interactive etc) may also be taken into consideration.

Fourthly, choices in the programming language, the software and the hardware that is used may be decisive for the accessibility and flexibility of a CDSS. Some CDSS make use of flexible coding so that healthcare professionals can easily adjust it to their preferences. Interoperability may increase the availability of support and information about particular systems, but it can also lead to the situation where the market is in control of a few companies. This may lead to undesirable dependencies.

Moreover, many of the uncertainties caused by environmental variability of healthcare systems can be reduced by involving stakeholders in the design process of a CDSS. This can ensure that a CDSS is better attuned to the work flow, expectations and requirements of healthcare professionals. This makes the use of the CDSS more predictable for its users, which also diminishes risks. In some instances this might for example prevent a misdiagnosis.

[76] For instance: Zikos, D. and DeLellis, N. (2018) CDSS-RM: A clinical decision support system reference model. BMC Medical Research Methodology. 18. 10.1186/s12874-018-0587-6. See also: 'References' Medicine / Health information technology.

[77] See for instance: Jia P et al. (2016) The Effects of Clinical Decision Support Systems on Medication Safety: An Overview. PloS ONE 11(12).

In this sense, through precautionary approaches or the application of the precautionary principle there are a variety of possibilities in which the innovation pathway of a CDSS can be steered into a more 'risk-free' direction.

5.3 Innovation principle

The innovation principle has not been applied in relation to artificial intelligence, let alone the use of CDSS. As of yet, no policies, laws and regulation on AI can be found that make use of the principle.

There has however been some, but not many, discussions about the innovation principle in relation to AI. In an article, Daniel Castro[78] and Michael McLaughlin[79] advise that the innovation principle instead of the precautionary principle should be applied by policy makers when AI is concerned. 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.' (Castro and McLaughlin 2019).

They 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.' Moreover, they emphasize that the innovation principle – which they define as the principle that '(..) the vast majority of new innovations are beneficial and pose little risk, so government should encourage them' - recognizes 'that market forces, tort law, existing laws and regulations, or light-touch targeted interventions can usually manage the risks new technologies pose.' And that it advocates case-by-case regulation and that, in cases where regulation is needed, it 'stresses the importance of designing regulatory interventions and structuring regulatory enforcement in ways that minimize the harm to innovation, while still achieving the regulatory goals.' Finally, the principle focusses, according to them, 'on ensuring that penalties punish bad actors who cause harm than creating regulations that limit beneficial and benign uses.'

In relation to AI, embracing the innovation principle would, they argue, allow society to experience the benefits of AI 'while adopting the right, limited regulatory frameworks that enable innovation while limiting harms.'

The European Commission has also connected the innovation principle with AI in a communication on AI in 2018. In a footnote the EC writes: 'For any new regulatory proposals that shall be needed to address emerging issues resulting from AI and related technologies, the Commission applies the Innovation Principle, a set of tools and guidelines that was developed to ensure that all Commission initiatives are innovation friendly.' [80]

The European Commission also mentions the innovation principle on its website as a tool 'to help achieve EU policy objectives by ensuring that legislation is designed in a way that creates the best possible conditions for innovation to flourish.'[81] The Commission states that 'the possible effects of emerging technologies on EU rules should be scrutinized early

[78] 'Daniel Castro is vice president at the Information Technology and Innovation Foundation (ITIF) and director of ITIF's Center for Data Innovation.' - https://itif.org/person/daniel-castro
[79] 'Michael McLaughlin is a research analyst at the Information Technology and Innovation Foundation.' - https://itif.org/person/michael-mclaughlin
[80] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2018%3A237%3AFIN
[81] https://ec.europa.eu/info/research-and-innovation/law-and-regulations/innovation-friendly-legislation_en

in the legislative process as part of the Innovation Principle.' AI is mentioned as an example of such an emerging technology. Notably, in this formulation the innovation principle does seem to be in opposition with the precautionary principle.

The Centre for European Policy Studies also mentions AI in its 'study supporting the interim evaluation of the innovation principle'. (Renda and Simonelli 2019). They write that the application of the innovation principle 'would intuitively need to go hand-in-hand with reflecting on and developing experimental regulation' in areas such as artificial intelligence (Renda and Simonelli 2019).

6 Synthesis

The aim of this case study was to better understand the complexities and controversies of applying the precautionary principle to the use of AI in healthcare. We focused on clinical decision support systems (CDSS), because the risks surrounding these systems are exemplary for the general complexities and problems that surround the use of AI in healthcare.

Clinical Decision Support Systems (CDSS) are, in a broad sense (as the name implies) systems that support the decision making of healthcare practitioners. These systems for example provide alerts or reminders, highlight guidelines during care, provide suggested course of action and identify drug-drug interaction. Proponents argue that CDSS provide faster, more accurate decision making with less costs and human errors. In some cases, CDSS might even make new decision-making (on the basis of Big data) possible that could improve the overall efficiency and effectivity in healthcare. It should be noted that there exists considerable uncertainty with regard to many CDSS applications about these possible benefits, especially with regard to long term benefits and the extra costs of, for instance, maintenance.

CDSS replace, augment or supplement decision making processes in healthcare. The use of CDSS is thus accompanied by risks because such decisions can have large impact. A wrong decision in the domain of healthcare can potentially have severe effects on individual health, human rights and – if a CDSS is implemented on a broad scale or if it supports decisions on groups – public health. Although human decision making in healthcare is also accompanied by such risks, CDSS also pose *new* risks to the extent that they transform *how* such decisions are made: their decisions are exclusively based on data, they are based on machine reasoning (and therefore lack human elements), they imply a delegation of control from the patient or healthcare practitioner to a machine, and their use is accompanied by a new division of labour in the healthcare domain.

The risks of CDSS

Taken to its extreme, and if no precautions are taken, the transformation of decision making in a healthcare system by CDSS can have severe consequences. Overconfidence about the capabilities of AI in combination with biased or defective datasets/algorithms, for instance with regard to gender/sex bias in medical data, can cause unnecessary deaths or disease. Moreover, especially data driven CDSS are accompanied by a variety of data related risks, like infringements on the right to privacy and the involvement of unqualified actors into the norm setting of medicine. And, finally, health data that has fallen into the wrong hands can be used against people, like blackmailing, and can be used as a tool to predict and manipulate future behaviour. This primarily has consequences for the distribution of power, equal access to public benefits and the right not to be discriminated.

The use of CDSS can also imply a delegation of control from the healthcare practitioner and the patient. This can endanger the autonomy of these actors and can also lead to

deskilling and accountability gaps. Taking away the human element in the decision making could infringe on the right to healthcare to the extent that care necessitates a person that 'cares for' or is 'involved' your suffering. Finally, the replacement of decision making in healthcare with CDSS, tends to be accompanied by a new division of labour. Other actors, like IT companies and data collection agencies, acquire a (more important) place in the domain of healthcare. This can bring forth new dependencies and therefore new risks, for instance rising costs due to locked ins in suppliers and maintenance, which can have consequences to the affordability of and access to healthcare.

Complexity, ambiguity and uncertainty around the risks of CDSS

The risks mentioned above 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. It can display complex and uncertain behaviour, especially when it makes use of unsupervised machine learning, uncertainty to the extent that small changes in its core code have significant effects and epistemic uncertainty to the extent that its code and connections to other systems are inaccessible and not understandable. Ambiguity may be an issue with regard to understanding 'why' a CDSS has made a particular suggestion.

Secondly, the use of CDSS is characterized by uncertain risks due to the nature of the environment in which it is implemented. Healthcare systems can be complex, unpredictable systems and the role a CDSS fulfils for each of these actors can be ambiguous. For a safe implementation of a CDSS in a healthcare system, for instance a hospital, it has to be attuned to a system that exists of many interacting and unpredictable elements. The CDSS for instance has to be in line with the (changing) expectations, protocols and existing norms and standards of healthcare professionals. A CDSS for instance has to be readable, understandable and helpful in the context of the daily tasks of a doctor, the specific needs of a patient and the oversight of a manager and/or a privacy officer. Some CDSS moreover have to mediate between different aims, standards, inputs and multiple different sets of data or other IT systems. The interaction of CDSS with other systems and actors can lead to feedback loops, especially when it is data driven: it can change according to for instance, the patients that are included in its data, data about the decisions that a doctor has made or updates of its algorithms. This can make them unpredictable. A CDSS moreover has to be attuned to the inherent uncertainty that exists in healthcare when it comes to complex, ethically complex or unknown medical problems.

A third cause for the uncertainty around the risks of CDSS is the variability in the nature of the risks, which makes them difficult to assess. To the extent that 'good' or safe decision making in healthcare consists of many elements, so the risks can be a consequence of multiple elements. A good decision is for instance transparent, explainable, accountable, supported by representative data, sufficient reflection, respect for privacy, autonomy and dignity of the patient. A safe use of a CDSS needs to take into account each of these elements, but these elements are ambiguous.

Scientific uncertainty

The fact that both the technology of CDSS, the environment in which they are used and the assessment of risks are characterized by uncertainty has consequences for the possibility of analysing them scientifically. First of all, because of this the scientific analysis of them is scattered over a wide variety of scientific disciplines. An adequate analysis of the risks of a CDSS has to make use of knowledge from, amongst others, the field of AI, medical professionals, legal scholars, and medical ethicists.

Moreover, it seems to be a challenge to develop uniform criteria to assess the risks of CDSS because each implementation of a CDSS is somewhat unique with regard to the technical characteristics of the system, the environment in which it is used and the precautions that are already taken in this environment. Finally, new developments of

CDSS happen fast and many data driven CDSS are relatively new. All of this seems to contribute that the fact that there does not seem to be a clear scientific consensus or certainty about the risks of CDSS or how they should be assessed.

Risk governance of CDSS
It is difficult to make firm conclusions about the risk governance of CDSS, partially because this seems to be still in process. A few things can be discerned however that are notable in the context of the complexities and controversies in the case.

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. Many of their concerns – for instance with regard to control over AI and the limits of machine reasoning – overlap with the concerns that are still at issue in EU policy debates.

Secondly, precautionary thinking about the specific design of CDSS also seems to have been present early on. Key figures in computational decision argued for precaution and adjustments were developed with regard to programming languages and notification systems.

Thirdly, EU risk governance around CDSS seems to have emerged in the context of a strong economic incentives. The contours of this emerged in the 1980's when the EU began collaborations on AI research to compete with the rise of Japan and the US. In the 2010's AI increasingly became of a central concern in the wake of the establishment of the digital single market.

Fourthly, we showed that the risks of CDSS have been embedded in a complex web of EU legislation. They may be (partially) covered by legislation on safety of machines, medical products, patient or consumer health and safety, regulation on 'responsible' research and development, privacy, intellectual property, cyber security and trade regulation, as well as a few legal cases.

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). In these initiatives the EU distinguishes itself from other geographical areas through cooperation with ethicists, AI researchers, businesses, consumer organizations and other stakeholders and close coordination between the member states. Multiple existing EU legislations are under review to align them with the specificities of AI and multiple ethical guidelines have been published. Notably, these initiatives first of all seem to have an ethical focus. Only in the recent White Paper on AI, published in February this year, did the EU explicitly adopt a risk-based approach in which the use of AI in healthcare was defined as 'high-risk'. As of writing, this paper is up for public review.

The relevance of the precautionary principle and the innovation principle
The precautionary principle seems to be potentially applicable to CDSS, but only on a strict case by case basis: for instance depending on the type of CDSS (especially data driven CDSS), the nature of the decision (for instance: when public health or communicable diseases are concerned), the type of data (for example: biometric data), how it contributes to the decision-making (for example: automatic, in absence of any human reasoning) and the place of the CDSS within a particular health environment (for example: when it is intertwined with a wide variety of processes in a hospital).

In extreme cases the risks of implementing a CDSS meet the criteria of the threshold of damage (public health and human rights). Moreover, scientifically grounded analysis has been done on these risks, but there remains significant scientific uncertainty about both the precise nature of the possible harmful outcomes and the probability of these outcomes are uncertain (See also conclusion).

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 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. However, this too should be examined on a case by case basis.

What can we learn from this case in relation to other RECIPES cases?
An important difference between this case study and the other RECIPES cases is that this case is concerned with if the precautionary principle *might* be applicable, why it has not been applied and to what extent other risk governance has been undertaken. Answers to these questions should primarily follow from the cross-case comparison, but on the basis of this case there are a few possible answers:

1. The precautionary principle has historically mostly been applied to environmental risks (and more recently public health). Though risks regarding CDSS can also be quite severe, they do not relate to the environment. There are, as Joanna Mazur notes (Mazur 2019), nevertheless similarities between the nature of challenges faced in the area of the data protection laws and environmental laws.
2. Many of the most serious risks of CDSS are related to the violation of human rights, like autonomy, equal access to healthcare and privacy. The precautionary principle has been acknowledged by the European Court of Human Rights (EHRM) in relation to human rights.[82] It should be noted though that the application of the principle in relation to human rights does not seems to be an established practice.
3. Problematic applications of CDSS are relatively recent. Only since the 2000's, in the wake of the AI revolution, have questions around (data driven) CDSS become urgent (for the EU). Many of the risks of CDSS are new 'types' of risks. While risks related to public health and the environment have been publicly discussed and institutionalized for a long time, questions concerning autonomy and power asymmetry in relation to big data are newer. Moreover, they are often primary discussed in terms of ethical or philosophical questions and/or difficult to formalize in risk assessment standards. The precautionary principle could be of relevance to these type of risks because a growing body of research indicates that these risks can also be systemic, irreversible and that they are connected with the violation of human rights.
4. In most other RECIPES cases the precautionary principle is applicable because the risks have to do with biological systems. The implications of, for instance, GMO's, are considered to be severe, disruptive and irreversible because they can influence the dynamics of ecological systems. Because these systems are alive, changing and dynamic, such risks are difficult to predict and control. In contrast, 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. If, for instance, a hospital can no longer provide care due to disruptive effects of an AI this may do severe physical, emotional and psychological harm to those who depend on the services of the hospital. This in turn may strain the resilience of the society as a whole.
5. Related to point 4; while the other cases are primarily concerned with risks that arise due to the interaction of humans with the environment (and the long-term

[82] Tătar EHRM 27 januari 2009, ECLI:CE:ECHR:2009:0127JUD006702101 (Tătar/Roemenië).

effects this may have), 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. Subsequently, many of the risks around the implementation of CDSS are, more than in the other cases perhaps, about political and socioeconomical dynamics (and therefore human rights). It is very much about how to balance the different interests and power relations that can be at play in the decision making in healthcare. It is about the humanity, autonomy and privacy that is deemed necessary. The rights of the patient and healthcare practitioner, balanced with, for instance, efficiency, better standards of living, longer life expectancy and economic growth.

7 Conclusion

Our analysis indicates that the precautionary principle is in theory applicable to clinical decision support systems (CDSS), but only in particular cases. A careless implementation of CDSS into healthcare systems can, especially in the case of decisions that affect groups and for systems that are implemented on a large scale, bring significant harm, both with regard to individual health, public health and human rights. The criteria of scientific analysis of these risks, on which it should be decided whether the precautionary principle is relevant for risks associated with CDSS, also seem to be met. Knowledge and empirical findings on the risks of CDSS or similar AI systems, insights on the vulnerability of healthcare systems and health data, as well as examples of problematic usage of AI in decision making processes in healthcare and other sectors, do warrant, in our opinion, invoking the precautionary principle.

Moreover, as our risk analysis shows, the risks of CDSS are in many cases difficult to define, both with regard to their specific outcome or harm, and with regard to their statistical probability. In these cases, the precautionary principle would be more suitable than, for example, the principle of prevention.

It should however also be noted that many of the reasons to invoke the precautionary principle in relation to CDSS are related to very specific circumstances; the risks are highly context specific. Amongst others, they depend on the type of CDSS, its specific technical design, the situation in which it is used and the precautions that already have been taken. For instance, a CDSS that merely gives advice for harmless medical procedures does not seem to be in need of applying the precautionary principle. A CDSS that makes use of a good storage and authorization procedures around data has less need for precaution towards data risks. And, finally, as long as a hospital keeps investing in the education of its personal, deskilling will probably also not be an issue.

In this regard, criteria can be developed by policy makers that point to circumstances in which the precautionary principle is especially relevant in relation to the implementation of a CDSS. This case would suggest criteria based on the type of CDSS (especially data driven CDSS), the nature of the decision (for instance: when public health or communicable diseases are concerned), the type of data (for example: biometric data), how it contributes to the decision-making (for example: automatic, in absence of any human reasoning) and the place of the CDSS within a particular health environment (for example: when it is intertwined with a wide variety of processes in a hospital).

The precautionary principle can be useful in multiple ways. The principle first of all can be instrumental for delineating the limits of the implementation of CDSS. Policy makers, healthcare professionals and companies could ask themselves what the minimal requirements for a safe and good decision-making process in healthcare are. Which decisions should always be taken by a human or in deliberation with the patient? What are the minimal requirements of a decision to make it sufficiently accountable,

transparent, evidence based and uninfluenced by non-medical considerations or interests? Which type of health data or combinations of data should never be used outside of medical practices?

Secondly, the precautionary principle can stimulate reflexivity and awareness of the many uncertainties around the implementations of CDSS. We showed that the risks of CDSS are characterized by many uncertainties, because of the nature of the technology, the properties of healthcare systems and the types of risks that are concerned. To this extent the precautionary principle may encourage anticipation, cocreation and incremental innovation of CDSS.

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9 Appendix

N/A

Microplastics in food products and cosmetics

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Abstract

In the current case study we will analyse if the conceptual core of the precautionary principle, and in particular scientific uncertainty, complexity and ambiguity, is present in the case of microplastics in cosmetics and food. Additionally, we aim to understand the complexities and controversies around the potential application of the precautionary principle in the risk governance of microplastics in cosmetics and foods in the European Union.

Microplastics are synthetic polymers with a size smaller than 5 mm. Cosmetic products contain intentionally added microplastics, which are directly released into wastewater. Additionally, large amounts of microplastics develop in the environment as a side effect of plastic pollution, where they remain for a long time. Via consumption of i.a. molluscs, microplastics end up in food. Scientific evidence on human health effects coming from microplastics is very scarce. This makes it a potential candidate for the precautionary principle.

With this study, we found that the case of microplastics in food and cosmetics does adhere to the key precautionary concepts of complexity, uncertainty and ambiguity. Microplastic is a diverse group of materials, leading to high complexity and difficulties in performing scientific research and defining regulations. This is caused i.a. by a lack of one uniform definition and a lack of standardized measurement tools. Especially scientific evidence for human health effects of microplastics is very thin and its scientific quality is debated. This is particulary important in dealing with microplastics in food products. The presence of intentionally added microplastics in cosmetics is mostly related to environmental issues. In this regard, the mere presence of high amounts of microplastics in the environment is unwanted, regardless of the specific risks caused. Therefore legislation is in the making to ban intentionally added microplastics in cosmetics. This drives innovation in the direction of biodegrable microplastics and natural alternatives with the function to scrub and exfoliate the skin.

Concluding, microplastic has attracted a lot of societal attention and is surrounded with complexities. Lack of a common definition and lack of standardized measurement methods contribute to the complexity and uncertainty on health and environmental effects. Legal actions to reduce microplastics in cosmetics take form via the REACH regulation, which is based on the precautionary principle. Via this route, the Commission and relevant agencies aim to deal with the abundant presence of microplastics in the environment. Health effects due to microplastics in food require more scientific research and are more difficult to regulate. Nevertheless, with the EU Plastic Strategy policy is directed to reduce plastic pollution altogether, including microplastics.

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List of abbreviations

EFSA	European Food Safety Authority
ECHA	European Chemical Agency
EC	European Commission
FAO	Food and Agriculture Organisation of the United Nations
SAM	Scientific Advice Mechanism
SAPEA	Science Advice for Policy by European Academies
SCHEER	Scientific Committee on Health Environmental and Emerging Risks
WHO	World Health Organisation
WWTP	Wastewater treatment plants

1 Introduction

1.1 Introduction

This case study will discuss the potential use of the precautionary principle in regulating the occurrence of microplastics in food products and in cosmetic products throughout the European Union.

Microplastics, mostly defined as polymer particles smaller than 5mm, can be divided into two groups: primary and secondary microplastics. Primary microplastics are intentionally added to products, and are widely applied in cosmetics, such as scrubs, lotions, toothpaste or bath gels (Leslie, 2014). Their function varies among products, e.g. to improve exfoliation, bulking, viscosity control, film formation and skin conditioning (United Nation Environment Programme, 2015). Because many of these products are so-called 'rinse off products', these small plastic particles are directly released into the sewage system. Although part of the microplastic particles do get filtered out of the water in the wastewater treatment plants, some particles are released into the freshwater stream. Another important route for primary microplastics to end up in the environment is by being captured in the sewage sludge. This sludge is often used as a fertilizer on agricultural land (Duis & Coors, 2016). Via this route, cosmetic products contribute to the spread of microplastics in both the aquatic environment and on soil.

The bulk of the microplastics present in the (aquatic) environment is not coming from cosmetics, but is so-called secondary microplastic. Secondary microplastics are not intentionally added, but they breakdown from plastic litter in the environment, under the influence of heat, light and oxygen (Van Wezel, Caris, & Kools, 2016). This process mainly takes place in the oceans, where the bulk of plastic pollution exists. Additionally, washing of synthetic fabrics and wearing down of tyres are important contributors to secondary microplastic pollution in the (aquatic) environment (Boucher & Friot, 2017). Fibres from synthetic fabrics, which are released in the washing process, are even estimated to account for 35% of all microplastics fibres in the oceans (Prata, 2018).

The existence of microplastics in the environment is therefore mostly a consequence of the currently widespread use of plastics in all kinds of applications and the widespread plastic pollution. This plastic pollution, and the question how to deal with plastic debris, has attracted attention of both researchers and the general public over the last years (Schirinzi et al, 2017). In the media, most attention goes to microplastic pollution in the marine environment. This is indeed an important issue, since microplastic is estimated to account for 94% of the number of plastic pieces of the Great Garbage Patch in the Pacific ocean (Lebreton et al, 2018). However, this does not cover the complete microplastic pollution. Also freshwaters, air and soil have shown pollution with primary and secondary microplastics (Koelmans et al, 2019). Since microplastic particles are widespread through the environment, together with their small size and large variation in appearances, they are difficult to be filtered out of the environment. Given their very slow degradation, its pollution is a reason for concern. Potential harmful effects are expected for the environment, but also animal and human health should be carefully considered. The reason for this is as follows: microplastics in the marine environment get eaten by fish and other sea animals. Via this route, also humans get exposed to microplastics, when consuming polluted seafood, such as mussels or oisters. Because these animals are eaten as a whole, including their intestines, the consumption of microplastics by humans is very likely (Santillo, Miller & Johnston, 2017). Other food products that have been reported to contain microplastics are honey, seasalt, water and beer (Koelmans et al, 2019). Additionally, human exposure to microplastics can occur via food packaging, for example plastic water bottles, which can leak small particles into the foods.

Figure 1: Overview of microplastic pollution in the aquatic environment and in food sources, including the main routes of exposure (Westphalen & Abdeirasoul, 2017; Wu, Yang & Criddle, 2017)

Thus far, very little is known on how the human body processes microplastic particles and which health effects might be caused. An important factor to take into account in assessing the human health risk is not only the plastic particles themselves, but also the chemicals that are present on its surface. This often includes endocrine disrupting chemicals, such as bisphenol A, which are added to the plastics to improve certain characteristics such as their flexibility or water resistance (Campanaie, Massarelli, Savino, Locaputo & Uricchio (2020). But also coloring chemicals and fire retardants are often added to the surface of (micro)plastics. While the microplastics stay in the water for a long time, these chemical substances soak off and leak into the water, where they are even more difficult to be measured and removed (Campanale et al, 2020). It is especially problematic when these chemicals are released into the food chain, since scientific literature has suggested associations between endocrine disruptors and a large variation of health effects in humans (Rochester, 2013).

The environmental burden of microplastic pollution is widely recognised as a global problem nowadays (United Nation Environement Programme, 2009). Looking at the large amount of microplastic released in the environment, its very slow degradation and consequently uncertain effects on the environment and animal and human effects on the long term, action is required. Since their specific harmful, long-term effects with regard to the environment and animal and human health are difficult to study because of the variation in materials and the interdisciplinary nature of the subject, this might be a suitable topic for the precautionary principle to be applied.

Many documents have been written to understand the issue of microplastic pollution, potential consequences for the environment, animal and human health and finally to provide policy advice to adequately deal with potential risks. Relevant international bodies with regard to risk assessment and risk management are the European Commission, European Chemical Agency (ECHA), European Food Safety Authority (EFSA), SAPEA (Science Advice for Policy by European Academies) and UNEP (United Nations Environment Programme). Relevant parties in this discussion are also industry

parties like PlasticsEurope and environmental NGO's such as the Plastic Soup Foundation. At the moment, various (policy making) activities are taking place, on national and international level, to reduce the amount of plastic pollution and deal with its potential consequences on the long term. An important document in this regard is the EU Plastic Strategy, which was launched by the European Commission in 2018. This policy to reduce plastic litter in the environment, shows an interesting social as well as political development to work towards a circular economy and thereby reduce plastic waste (European Commission, 2018). The potential, but sometimes uncertain, long-term effects for environment and animal and human health of microplastics played a large role in designing this document. Namely, this uncertainty needs to be balanced with all the benefits that plastic brings to our daily lives and translated into proportionate measures. Although the EU Plastic Strategy concerns plastic pollution in a broad sense, it does specifically address microplastic as a rising problem that needs to be researched and that requires innovation.

Because of the growing public concern worldwide on the magnitude and potential harms caused by the plastic pollution, it would be expected that the release of microplastics into the environment had been regulated already in various legal documents. Examples of relevant European legislation could be the regulation on contaminants in foodstuffs (EC 1881/2006), the regulation on cosmetic products (EC 1223/2009) or the regulation on food contact materials (EC 1935/2004). However, at this moment, none of these EU regulations mention the regulation of microplastics specifically. In the current research we will address the factors that make microplastics a difficult field to regulate, or whether specific regulation is not needed.

Apart from the EU level, several EU Member States, have introduced legislation to ban intentionally added microplastics in cosmetics. France has taken the lead in this, followed by countries like Denmark and Belgium, with a ban on microplastics in rise-off cosmetic products in 2016 (Kentin & Kaarto, 2018). As a response to these national actions, the European Commission has asked the European Chemical Agency (ECHA) to perform a risk assessment and provide advice on how to deal with this issue. ECHA is currently working on a proposal for the European Commission to limit the use of intentionally added microplastics via the REACH regulation. REACH stands for Registration, Evaluation, Authorization and Restriction of Chemicals. This regulation is the founding regulation of ECHA, enacted in 2006, and has the goal to achieve a high level of protection of consumers and the environment. REACH therefore uses the precautionary principle as its guiding principle, to ensure safety on the long term, also in complex and uncertain situations (European Commission, 2006). By restricting the use of intentionally added microplastics via the REACH regulation, it seems to be recognised that a precautionary approach is appropriate to deal with, at least intentionally added, microplastics. However, it should be recognised that intentionally added microplastics are only a small proportion of all the microplastic pollution in the environment. This leaves open the potential regulation of secondary microplastics, which develop from the degradation of larger plastic particles.

Research question

In the current case study we will analyse if the conceptual core of the precautionary principle, and in particular scientific uncertainty, complexity and ambirguity, is present in the case of microplastics in cosmetics and food in relation to human health risks. Additionally, we aim to understand the complexities and controversies around the potential application of the precautionary principle in the risk governance of microplastics in cosmetics and foods in the European Union.

1.2 Key timeline

Political	*Legal*	*Science/risk assessment*	*Public debate*	*Other*

Year	Event	Relevance to case study
1950s	Industrial development led to large scale plastic production	Plastic pollution in the environment started to take problematic forms, leading also to the development of secondary microplastics.
1990s	Cosmetics industry introduced microplastics in their products	Primary microplastics started to get released directly into the wastewater and build up in fresh water and sewage sludge.
2008	EU Marine Strategy Framework Directive (Directive 2008/56/EC) went into force	Goal of this directive is to achieve a Good Environmental Status of the marine environment by 2020. Reducing pollution is one important aspect of this goal.
2013	'Green paper on a European Strategy on plastic waste in the environment' got published by the European Commission	Aim of the green paper is to learn the views of citizens and other stakeholders on how to make plastic products more sustainable, how to reduce generation of plastic waste and how to decrease the impact of any plastic waste that does enter the environment.
2015	Danish Environmental Protection Agency published a report on occurrence, effects and sources of release to the environment of microplastics in Denmark	This report by the Danish authority was one of the first risk assessments by EU countries, on primary and secondary microplastics.
2015	'Opinion of the Committee of the Regions on the better protecting of the marine environment' got published	The Committee of the Regions recognized the long-term impact of microplastic pollution on the (marine) environment.
2015	USA released the Mircobead-Free Water Act	USA is the first country worldwide to ban intentionally added microplastics in cosmetics

2016	France bans intentionally added microplastics in cosmetics	France is the first EU Member State to ban intentionally added microplastics in cosmetics. Reason for this ban is to protect the environment.
2016	'Statement on presence of microplastics and nanoplastics in foods, with particular focus on seafood' was released by EFSA	The EFSA panel on contaminants in the food chain (CONTAM) prepared a statement, based on a scientific assessment, on the presence of microplastics in food. It is concluded that more scientific research is needed.
2018	The European Commission released the European Strategy for Plastics.	EU-wide policy to reduce single-use plastic, together with other actions attempting to limit the formation of secondary microplastics, are based in this strategy
2018	European Parliament called for a ban on intentionally added microplastics in inter alia cosmetic products.	Following the French ban of 2016, the EP is looking into options to ban intentionally added microplastics across the EU.
2019	European Chemical Agency (ECHA) wrote a restriction proposal for intentionally added microplastics via the REACH regulation	Based on a risk assessment, ECHA concludes that intentionally added microplastics should be limited.
2019	Public consultation was opened as a response to ECHA's restriction proposal	A public consultation was held for a period of six months, for the public to respond to ECHA's restriction proposal. In this consultation period, input was mainly provided by industry and environmental NGO's.
Expected June 2020	Final opinions on the restriction proposal by the Risk Assessment Committee and the Socio-Economic Assessment Committee of ECHA	Based on these documents, the European Commission will take a decision on the limitation of intentionally added microplastics in cosmetics.

2 Microplastics

As mentioned previously, microplastics is a name for a collection of synthetic polymers, with a large variety of characteristics but all with a size of smaller than 5 mm. Microplastics have not been developed on purpose, 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. The mass production of synthetic polymers, better known as plastics, has started in the 1950s (Duis & Coors, 2016). 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. This makes plastic suitable for many applications (Thompson, Swan, Moore & vom Saal, 2009). These benefits have resulted in its wide applications and big success all over the world. For example, in cars and planes, the use of plastic reduces the weight of the vehicle, leading to lower CO2 emission and fuel costs. In packaging materials, plastic is a good alternative for other materials such as glass and metals, because of its flexibility and low weight. In clothing and other fabric applications, polymers are used for their high durability and ability to take up dye while being waterresistent. In some of these examples, plastic could actually be seen as a more sustainable alternative to the traditional materials, because of its lower weight and longer life span compared to its traditional alternatives (Andrady & Neal, 2009). However, with the wide application of plastic came not only wealth, but also potential disadvantages and criticism. To a large extent, these downsides are related to the great amount of plastic waste ending up in the environment. This includes spreading of (micro)plastic particles through the air, water and sewage systems. Ultimately these particles pile up in the environment, for example in the Great Garbage Patch, where they stay around for a very long time, due to their very low degradation rate. Given the large amount of plastics used over the years, together with a low attention for correct plastic waste disposal, the pollution of plastic in the environment has become a well-known problem of global proportion (Sun, Dai, Wang, van Loosdrecht, 2019). So interestingly, where the sustainability and longevity of plastic were initially mentioned as a benefitial product characteristic, these characteristics are a disadvantage when it comes to plastic waste ending up in the environment. Over the last years, these downsides of the widespread use of plastics have gained more and more attention in the public debate, also attracting scientific and regulatory attention.

From the widespread plastic pollution develops the issue of secondary microplastics. Secondary microplastics are defined as microplastics particles that have not been intentionally produced as such, but have developed as a breakdown product from other applications of plastics (Branhey, Hallerud, Heim, Hahnenberger, Sukumaran, 2020). A large part of the microplastic particles in the (aquatic) environment develops through this breakdown from bigger pieces of plastic pollution. Additionally, washing of synthetic textiles and wearing of tyres are important contributors to microplastic pollution, via various routes. Washing of synthetic textiles releases many microfibres, which end up in the wastewater and later on in freshwater. Microplastic particles released from tyres spread mostly via the air and pile up in the water stream. Already in the 1970, the occurrence of microplastic as breakdown product from bigger pieces of plastics was recognised as a problem in the aquatic environment (Carpenter, Anderson, Harvey, Miklas & Peck, 1972). In the meantime several regional sea conventions and action plans have been put into place to limit the amount of (micro)plastic pollution. This includes i.a. The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (1989), The UN Open-Ended Informal Consultative Process on Oceans and the Law of the Sea (1999) and the G20 Action Plan on Marine Litter (2017). Most of these actionplans focus on the environmental burden of plastic pollution and appeal to the moral obligation to not polute the oceans any further. Zooming in on the human health effects, these documents recognise that there are many knowledge gaps with regard to specific harmful effects (United Nation Environment Programme, 2016). Therefore, uncertainty with regard to microplastics relates mostly to the health effects for

humans and animals. This provides potential room for the application of the precautionary principle.

Apart from the microplastics that develop from the breakdown of bigger pieces of plastic, there are intentionally added microplastics. This is a more recent development, which started around the 1990's in cosmetic products (Kentin & Kaarto, 2018). Microplastics are added to a wide range of cosmetic products, e.g. shower gels, toothpaste and scrubs. Their role to provide specific product characteristics, such as exfoliating, cleansing, tooth polishing or modifying viscosity of the product (Leslie, 2014). In the past, these functions where performed by natural substances such as sand or sugar. They were replaced by microplastics as cheaper and more constant alternatives (Guerranti, Martellini, Perra, Scopetani & Cincinelli, 2019). Since this mostly concerns wash-off products, the microplastics are directly released into the wastewater system. Although a large part of them are filtered out, they do end up in large scale in sewage sludge and fresh water. Since sewage sludge is used as fertiliser on land, this is an additional route of exposure for microplastics to be spread through the environment (Mahon, O'Connell, Healy, O'Connor, Officer, Nash & Morrison, 2017).

Currently, the exact amount of microplastics present in the environment is still debated. Recent insights, published in May 2020, from the Plymouth Marine Labortory in the UK suggested that the amount of microplastics has been underestimed until now (Lindeque et al, 2020). This underestimation can be seen as an illustration of how difficult it is to adequately measure microplastic particle once they are in the environment. This difficulty relates to the large variation in particles, with regard to its size, shape and materials, and the sensitivity of the measurement tools. Since there is no clear universal definition of a microplastics, different stakeholders advocate a different way of measuring microplastic pollution.

The developing attention for microplastics over the last years could be seen in line with the growing attention for climate change, sustainability and plastic pollution in general. Where in the past the focus was mostly on economic growth and development, the public opinion seems to have shifted in a way that is also focused on long-term effects for the environment. The European Green Deal can be seen as a concrete expression of this development. Consequently, also more and more research funding and research effort has been going to studying the long-term potential harmful effects of microplastics pollution. This can be seen in the increased number of scientific publications over the last ten years.

Although the attention for microplastics is growing in academia as well as in society, regulations to deal with the widespread appearance of microplastics is not yet in place. Dealing with microplastics on EU level is a complex policy area, with many different facets and disciplines involved. Potential consequences take place in the environment, with regard to human and animal health, but also there is an economic and sustainability perspective to the discussion. The perception and explanation of the risks and benefits of microplastics can depend of the specific angle that various stakeholders take. Several of these perspectives will be discussed in this report.

3 Scientific uncertainty about risks

3.1 Risk/threat

3.1.1 Potential risks

From a scientific perspective, the concept of risk constitutes of two parameters; namely, hazard on the one hand and probability of this hazard to happen on the other hand (Stirling, 2008). To gain insight in the potential risks of microplastics, we need knowledge on the hazards potentially caused by microplastic and the likelihood that these hazards happen, looking at the current exposure level in the environment and in the human body. In this paragraph we will discuss the scientific literature on the potential risks of microplastics in cosmetics and food products, by looking at the literature on hazards and exposure.

Both primary and secondary microplastics have a different route of exposure and involve other potential hazards. Where primary microplastics are directly released into the sewage system with the use of cosmetic products, secondary plastics are more present in the marine environment via breakdown of bigger pieces of plastic pollution. All these microplastics can lead to a disruption of the aquatic ecosystem and potential health risks for humans and animals, when being ingested.

Microplastics are known for their very slow degradation and therefore they can stay in the environment for an undefined period of time. This combination of being present in large amount and for such a long time creates a build up of microplastic particles and leads to high exposure of microplastics in the environment. Mere presence of microplastics creates an unpredictable situation for the environment and is generally perceived as undesirable. Determining the exact amount of microplastics present in the environment is however very complicated, due to several reasons. It was already mentioned that no general definition of a microplastic exists, and that a great variety in materials, shapes and sizes is present, which might correspond to different consequences. Additionally, the structure and size of the microplastic particles changes under the influence of high temperature or UV radiation, which is especially likely to happen over such a long exposure time. Depending on the specific polymer, this can include all kinds of changes, making the particles more brittle and vulnerable to breakdown into nanoparticles (World Health Organisation, 2019). These changes make it harder to measure the presence of microplastics, which is necessary to calculate the risks of microplastic exposure in the environment. Additional to the changing *amount* of microplastic particles, the alteration of the structure and composition of the particles might also change their hazardous properties.

Although the exact amount is uncertain, the presence of large amounts of microplastics in the environment has been established conclusively (Mrowiec, 2018). Potential risks resulting from this presence can be found in different directions. Because of their small size and wide spread across the aquatic environment, sea animals can easily consume them. Of course primarily this can lead to consequences for these animals, such as risk of suffocation. These consequences are often depicted in the media, when reporting on plastic pollution (De-La-Torre, 2020). Subsequently, the consumption of microplastics by sea animals, can potentially lead to human risks as well. Namely, via the consumption of seafood, especially when eating whole animals such as mussels, the human intestinal tract gets exposed to microplastics (De-La-Torre, 2020). However, scientific literature on specific human health effects is very slim at the moment. A small research, including only eight participants from various countries, showed the presence of microplastics in human stool samples (Schwabl et al, 2019). Although this research was very small in terms of number of participants, it does provide proof for the hypothesis that humans carry pieces of microplastics in their intestines and is a motivation for future research.

With the growing public attention for (micro)plastic pollution, the research into human health effects is also developing. At this moment it is known that humans get exposed to microplastics via several routes of consumption, coming from sea food, but also from beer, table salt and drinking water and via air (Kosuth, Mason & Wattenberg, 2018). However, the fact that microplastics are found in the intestinal tract does not directly mean that humans necessarily experience harmful effects from this exposure. Namely, as we have described before, the risk arises from the hazard in combination with exposure. At the moment, scientific uncertainty prevails when assessing the potential hazardous consequences of these ingested particles on human health (Koelmans et al, 2019). To get a better understanding of potential health effects, it is important to know whether particles pass through the first cell layer of the intestine and have the ability to enter tissues or cells. This is crucial information to understand where microplastics can interact with cell mechanisms and potentially cause a variety of health problems. At the moment, little is known about the route that microplastics travel inside the human body. Assessments by the European Food Safety Authority (EFSA) and the Food and Agriculture Organisation of the United Nations (FAO) carefully estimated that only a very small percentage of the microplastics consumed by humans are actually absorbed by the intestine (EFSA Panel on Contaminants in the Food Chain, 2016; Lusher, Hollman & Mendoz-Hill, 2017). The majority of the microplastic particles, especially the relatively large particles, are expected to directly pass through the body. In this estimation, it needs to be taken into account that there is large variation in the size of microplastic particles and that the intestinal epithelium (the first cell layer of the intestinal wall) functions as a natural barrier to avert foreign substances (Stock et al, 2019). Therefore, it is expected that only relatively small microplastics can be absorbed in the body and bigger particles will be directly excreted via faeces.

But even when looking past the potential low absorption rate of actual particles, academic literature is not consistent with regard to the hazards caused by microplastic consumption in humans, eventhough associations have been suggested with a variety of health outcomes. A recent review on the human health effects of microplastics mentioned a large number of outcomes potentially being related to microplastic ingestion, including oxidative stress, cytotoxicity, chronic inflammation and increased risk of cancer, neurodegenerative diseases and autoimmune diseases (Prata, Da Costa, Lopes, Duarte & Rocha-Santos, 2019). However, evidence for these health effects has come solely from in vitro studies and animal studies, inter alia in zebra fish and mice (Lu et al, 2016; Furukuma & Kujili, 2016). The level of evidence provided by this methodology cannot directly be translated to the human level and is therefore limited to provide certainty. At this moment, human evidence with regard to long-term health effects on population level is lacking. On a mechanistic level, an explanation for the relationship between microplastics and these health outcomes can partly be found in the increased production of reactive oxygen species and free radicals, which cause damage to cells in the body. Already in the 1990's animal research showed that orally administered pieces of microplastics had the ability to travel from the intestine to the blood stream (Eyles, Alpar, Field, Lewis & Keswick, 1995). Additionally, research has suggested that the health consequences caused by microplastic intake can in theory take contradicting forms. On the one hand, ingestion of microplastics has been linked to deficit of digestive enzymes in fish, which resulted in lower nutrient uptake (Wen et al, 2018). On the other hand, research suggests that ingestion of microplastics might actually lead to more energy intake, by means of increased energy demand, which was demonstrated in mice (Deng, Zhang, Lemos & Ren, 2017). All this information contributes to the situation of uncertainty with regard to animal and human health effects of microplastics.

Apart from the potential risks caused by the pieces of microplastics themselves, microplastic particles carry other chemical substances on their surface or inside the particle. Via degradation, these additives can leak into the intestine and potentially lead to all kinds of problems (Smith, Love, Rochman & Neff, 2018). In this way, also relatively large microplastic particles can still potentially cause harm when they pass through the

body (Toussaint et al, 2019). These chemicals include endocrine disrupting chemicals (EDC), such as bisphenol A and phthalates, but also coloring substances and flame retandants. These substances are frequently applied to plastics for various reasons, such as improving the flexibility of the plastic. Since these chemicals are smaller than the microplastic particles, they are capable to travel through the bloodstream. EDC have been linked to a large variation of different health effects for men and women, although the scientific evidence for specific health effects is still not conclusive (Rochester, 2013; Tsai, 2006). As the name indicates, EDC have the ability to interact with hormone receptors. Potential health risks are therefore mostly related to the hormonal system. In women this exposure might lead for example to breast cancer, whereas for men it has been linked to prostate issues (Lynn, Rech & Samwel-Mantingh, 2017). However, the fact that the link with hormone receptors is possible, does not directly translate in the development of specific health effects. Additional to the potential health effects, EDC also add to the environmental burden of the plastic contamination. Because of the long time that the plastic particles are in the water, it becomes inevitable that the chemical additives leak into the water, where it gets very complex to be detected and removed. In the same way, it has been suggested that pieces of microplastics can carry micro-organisms, such as bacteria and viruses, which have the ability to cause all kind of diseases (Padervand, Lichtfouse, Robert & Wang, 2020). This again leads to uncertain risks for the environment and for animal and human health.

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 hazards are specific for certain groups of people 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. Although no difference in the exposure to microplastics are expected for specific local communities, there is specific concern for future generations (Galloway & Lewis, 2016). Additional to the wide spread of potential health risks that might relate to microplastic pollution, this concern is fed by the fact that microplastic pollution is so widespread and once in the environment, not many options are available to get them removed. The United Nations has even referred to the microplastic pollution as growing concern to a number of human rights, such as the right for future generation to have a clean, healthy and sustainable environmet (Galloway & Lewis, 2016).

3.2 Scientific analysis

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. As described in paragraph 3.1, most available evidence has been collected via animal models and in vitro studies.

Apart from research at universities and research institutes, European agencies and other regulatory bodies have written scientific analyses on microplastics. Aim of these analyses is to map the potential consequences of microplastic pollution for health and the environment. In 2016 the European Food Safety Authority (EFSA) reported a statement on microplastics in food, with a focus on seafood (EFSA Panel on Contaminants in the Food Chain, 2016). This focus on seafood was justified because the highest level of exposure to microplastics is coming from seafoods, since these animals are consumed together with the intestinal tract. Using a conservative scenario, EFSA estimated that consuming a portion of 225 grams of mussels could lead to the ingestion of 900 microplastic particles, which corresponds to approximately 7 micrograms (EFSA Panel on

Contaminants in the Food Chain, 2016). Although EFSA states mussels as the food source that contains the most microplastics per unit, there can be an accumulative effect of multiple food sources. Microplastics have been found in beer, drinking water, table salt and honey. Additionally, fishmeal is often fed to poultry and pigs, and via this route microplastic can end up in non-fish food products as well. With regard to the toxicity of microplastics and consequently the human health effects, EFSA comes to the conclusion that a large knowledge gap exists. No reference methods for sampling or analysing microplastics are available yet, which can explain big differences among studies. Additionally, sampling and analysing harmful effects gets complicated by potential contamination with microplastics coming from the air, clothes or even the measurement tool itself. Ultimately, EFSA concluded that toxicological data on human health effects of microplastics are not available, which makes a human risk assessment not possible at this moment (EFSA Panel on Contaminants in the Food Chain, 2016).

In 2019 'a scientific perspective on microplastics in nature and society' was written by SAPEA (Science Advice for Policy by European Academies) (Koelmans et al, 2019). SAPEA is part of the European Science Advice Mechanism of the European Commission (SAM) and brings together scientific evidence from all kinds of scientific disciplines. In their 2019 report, microplastics are discussed from the perspective of natural science, social science and regulatory science. Interestingly, the report has marked all collected evidence as 'what is known', 'what is partially known' and 'what is unknow', related to the level of uncertainty. This approach increases transparency and makes it well organised for interested readers. SAPEA comes to the conclusion that, although the information on effects of microplastics is growing, it will remain a complex topic. This complexity is explained, inter alia, by its great variability in substances. They also conclude that scientific uncertainty on human health effects remains, as not enough evidence is available to perform a human risk assessment. Different than the EFSA report, SAPEA stresses the high excretion rate in humans. Since most microplastics leave the body directly, SAPEA seems to see less reason for direct concern. As part of that argument, they refer also to the fact that much of the research on toxicological effects has been performed with microplastic concentrations much higher than normally present in the natural situation. This leads to a potential overestimation of the harmful effect and, more important, limits the reliability of the risk assessment (Koelmans et al, 2019).

Additional to SAPEA and EFSA also the European Chemical Agency (ECHA) has performed a risk assessment on intentionally added microplastics in 2019. They have concluded the accumulation of primary microplastics is mostly a problem on the land, where sewage sludge is spread as fertilizer (Corradini, Meza, Eguiluz, Casado, Huerta-Lwanga & Geissen, 2019). Sewage sludge contains a high amount of intentionally microplastics, because the microplastics in cosmetic products are directly released into the wastewater stream, where they pile up in sewage sludge. To limit this spread of microplastics, ECHA has put forward a proposal to restrict the use of intentionally added microplastics (European Chemical Agency, 2019). This proposal focuses is very much on the exposure of microplastics in the environment, instead of the potential hazards, which are both needed to determine the risk. ECHA argues that the long-term presence of microplastics, with unknown hazardous effects for the environment, is undesirable in itself. Intended goal of this restriction is therefore to limit the emission of microplastics by approximately 85% in the next 20 years (European Chemical Agency, 2019). The proposed restriction by ECHA only involves synthetic polymers and specifically excludes biodegrable polymers. Before this proposed restriction can go into force, several steps need to be taken. First, this initial proposal has been subject to a public consultation, with mostly comments of industry and NGO's. Often heard comments relate to the definition of the microplastics. Several comments mentioned that a differentiation should be made between different types, sizes and shapes of microbeads. Other parties argue that the definition of 'microbead' is too specific and should also concider other microplastic particles. At the moment, ECHA's Risk Assessment Committee and the Socio-Economic Assessment Committee are evaluating the ECHA proposal, to come to a conclusion on the

proposed limitation. The outcome of these committees will be forwarded to the European Commission, who has the role of risk manager. Following a comitology procedure, involving the Member States, a final decision will be made on the restriction of intentionally added microplastics.

3.3 Scientific uncertainty

Scientific uncertainty is one of the key components in applying the precautionary principle. To study the level of scientific uncertainty in the case of microplastics in food products and cosmetics in relation to the environment and human health, the current paragraph will assess the strongly linked risk properties of complexity, uncertainty and ambiguity.

3.3.1 Complexity

We use the definition of complexity as provided by Renn, Klinke and Van Asselt (2011): "the difficulty of identifying and quantifying causal links between potential candidates and specific adverse effects" (Renn, Klinke & van Asselt, 2011). To understand the case of microplastic, we can observe complexity on different levels. For example, complexity in relation to its appearance forms, different routes of exposure and potential measurement tools.

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 (Hale, 2018). 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.

As mentioned previously, plastic particles are classified as microplastics if they have a size between 0.001mm and 5 mm, with smaller pieces being referred to as nanoplastics (Koelmans, Nor, Hermsen, Kool, Mintenig & De France, 2019). This size range makes a big difference when it comes to human exposure, the way in which the particles are potentially taken up by the body and consequently the health effects that might be caused. 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 (Frias & Nash, 2019). The type of measurement tool that is available is one of the deciding factors in the quality of the scientific study. Namely, measurement tools can vary greatly in their specificity and validity. A clear illustration of this issue is the measurement of microplastic on a sandy beach or in sewage sludge, which are well-known places for plastic litter to accumulate. Relatively large pieces of microplastics, up to 1 mm, are often visually identified and picked by hand. However, given the context of the sandy beach or sewage sludge, it can be very difficult to correctly distinguish between plastic particles and e.g. sand grains (Duis & Coors, 2016). To identify smaller pieces of microplastics, fine sieves and density separation are often applied techniques. However, the accuracy of the measurement has shown to depend on the type of measurement tool that is used. For example, the specific size of the sieve can lead to an over- or underreporting of the quantity of microplastics, compared to other sieves (Duis & Coors, 2016). 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 (Directorate-General Research and Innovation, 2019).

Another factor contributing to the complexity of microplastics is the fact that there is a wide variety in materials. Most microplastic particles are some kind of synthetic polymer, such as polyethylene, polypropylene, polyvinyl chloride and polyurethane (Koelmans et al, 2019). All these particles have different shapes and characteristics on molecular level. Also, microplastics are available in a variety of forms, such as pellets, fragments, fibres, ropes, foams and film (Frias & Nash, 2019). These variations add to the measuring issue

as described above, since different measurement tool might detect other shapes and materials of microplastic. Additionally, with regard to human health effects due to microplastics in food items, all these variations might lead to different interaction with human cells and tissues and therefore different health outcomes (Weithmann, Moller, Loder, Piehl, Laforsch & Freitag, 2018). Animal research has already shown that the polymer type, size, shape, water solubility and surface charge are crucial in relation to the uptake of microplastics into different body compartments and thereby to the level of toxicity inside the human body (Smith, Love, Rochman & Neff, 2018).

3.3.2 Uncertainty

Apart from the complexity relating to determining the risks of microplastics, there is a lot of uncertainty concerning the potential health and environmental effects of microplastics. Uncertainty can take two directions: uncertainty with regard to the specific hazards and uncertainty with regard to the likelihood of these hazards to happen (European Commission, 2017). A large part of the uncertainty and complexity can be traced back to the lack of consensus on one scientific or regulatory definition of microplastics. This makes that various stakeholders have different understandings of what is a microplastic and thus what are potentially relevant hazards. Interestingly, this variation in definitions is already seen in rules and regulations that are put into place by various countries around the world, in an attempt to lower microplastic pollution. The lack of one clear definition, together with the lack of standardized measument techniques, makes it complicated to do research and make general statements on the potential health effect of microplastics in a general sense. Namely, different materials and different shapes and sizes will lead to other relevant hazards, for example by interacting with certain enzymes and cell structures in the body. Also the exposure to microplastics in humans will vary between different types of microplastics. Therefore, the lack of one clear definition leads to uncertainty when it comes to defining the risk of microplastics as one general outcome.

Reaching consensus on one uniform definition and develop standarized measurement tools for microplastic particles will be an important step in reducing the uncertainty of the microplastics discussion. Setting such standards will help in the collection of scientific evidence and later on in performing a risk analysis. However, when focussing on the potential risk of microplastics for human health, this will not completely solve the scientific uncertainty. The important point that needs to be taken into account in understanding the risk is to know whether the alleged health outcomes are actually caused by exposure to microplastic, and not by other substances. Especially in the case of food intake this is challenging, since many confounding factors, such as other nutritients or physical activity level, can potentially explain health outcomes like inflammation or problems related to metabolism (Willet, 2012). Additionally, it can be argued that it is not ethically acceptable to expose people deliberately to high concentrations of microplastics and its adhesive endocrine disruptors in a randomised controlled trial. Consequently, research on human health effects of microplastics is largely depending on observational research designs.

Finally, uncertainty is caused by an absolute lack of data with regard to the exact hazard and exposure of microplastics (Koelmans et al, 2019). This lack of data can be explained by the previously mentioned complicating factors such as no universal definition, large variety in size, materials and added chemicals. Especially with regard to human health effects, the scientific evidence base is very thin and mostly based on animal studies (Koelmans et al, 2019). Nevertheless, there is a clearly growing research interesting over the last few years, with a rapidly growing number of publications. Potentially this research interest is driven by the overall societal interest for plastic pollution and conversion towards a more sustainable world.

3.3.3 Ambiguity

The third risk property that is relevant for the precautionary principle is ambiguity, which refers to different interpretations of identical assessment results (Renn, Klinke & van Asselt, 2011). 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. Where EFSA sees the lack of human toxicological data as reason to be cautious, SAPEA concludes that, due to the low uptake level in the body, this lack of toxicological data gives no direct reason for concern. Additionally, the risk assessment of microplastic is surrounded by a discussion on different types of bias, which were described previously in chapter 3.2 and will be further discussed on chapter 4. Shortly, it is known for long time that in many research fields, studies with null results (suggesting there is no harmful effect of microplastic on health) are more difficult to publish, giving a skewed presentation of the evidence. Studies reporting positive findings (suggesting there *is* a harmful effect of microplastic on health) are more likely to be published, regardless of their scientific method and quality (Easterbrook et al, 1991). Additionally, researchers have argued that a substantial part of the research has been performed with concentrations of microplastics that are unrealistically high (Koelmans et al, 2017). Both of these issues lead to a misinterpretation of the evidence, potentially resulting in an overestimation of the harmful effect whilst disregarding the harmless outcomes. This is especially complicated, because the amount of unpublished work and the effect sizes found by these studies are not known and cannot be taken into account in establishing the level of misinterpretation.

Additional to interpretative ambiguity, on how to interpret the scientific data, we can also look at normative ambiguity. Normative ambiguity refers to different perspectives on the tolerability of the risk (Johansen & Rausand, 2015). In this regard it is interesting to look at the different perspectives of stakeholders such as industry and environmental NGOs. In the discussion on banning microplastics and reducing its presence in the environment, industry refers often to the differences between microplastics. Because particles are different in i.a. shape, size, polymer composition and water solubility, their potential toxicity for the environment and for human health might be different. Especially since not much scientific evidence is present of its exact harmful effects, industry argues that there is no reason for all microplastic particles to be banned in the same way. Additionally, the plastics branch organisation PlasticsEurope stresses the benefits of plastic product for our current state of welfare and actually mentions it as a contributor for sustainable solutions (PlasticsEurope, 2019). On the other hand, they do recognise the problem of marine litter and stress that action needs to be taken to reduce this (PlasticsEurope, 2018). In terms of a risk-benefits analysis, the high benefits that are attributed to (micro)plastics should put its potential risks in a more tolerable daylight, according to the argumentation of the plastic industry.

On the other hand there are environmental NGO's which have a much lower tolerability to the potential risks caused by microplastic pollution. In November 2019 a group of environmetal NGO has published a position paper to urge the European Commission to ban intentionally added microplastics in cosmetics (European Environmental Bureau et al, 2019). Their view is as follows: although specific hazardous effects for human health are scientifically uncertain at this moment, the mere presence of the large amount of microplastics in the environment is undesired. One of their main arguments in the requested ban is that the function of the microbeads in cosmetic products can be replaced by natural subsitutes. In the past, natural products such as sand, clay or sugar performed the function of microplastics in cosmetics. Therefore the environmental NGOs argue that intentionally added microplastics in cosmetics pose risks to the environment and to human and animal health that are unnecessary and can relatively easily be avoided by going back to these natural alternatives. Looking back at the risk-benefit analysis, the environmental NGOs come to a substantially different conclusion when weighing the potential risks with the benefits of microplastics in cosmetics.

3.4 Relevance of the precautionary principle to the case

The precautionary principle has been defined in different ways by various (international) institutes/organisations. Scientific uncertainty with regard to potential harm is one clear comon denominator in these working definitions. As described in this chapter, the discussion on microplastics is surrounded by scientific uncertainty. Only little scientific evidence on harmful health effects for humans is present and the quality of this evidence is debated. This scientific process is seriously complicated by the lack of a clear definition of what a microplastic is and large variation in the type and shape of microplastic particles. Another aspect that is mentioned in some definitions of the precautionary principle is the irreversibility of the potential harm. This is for example mentioned by the European Environment Bureau and in the Rio declaration on Environment and Development of 1992. Irreversible harm seems to be very much applicable to the case of microplastics and its pollution in the environment. Once microplastic particles are being released into the environment, they will remain there for a long time. In this regard there is is no difference between primary and secondary microplastics. On the other hand, with regard to human health, there might be too little evidence to already speak about irreversible damage. The working definition of the precautionary principle as used by the World Commission of the Ethics of Scientific Knowledge and Technology (COMEST), which is part of UNESCO, mentions not only uncertain risks in the current situation but also uncertain risks for future generations. Given the very long durability of plastic particles, as mentioned in the previous paragraph, future generations are a realistic concern when dealing with microplastics.

We learned that all three characteristics of the precautionary principle, complexity, uncertainty and ambiguity, are applicable to the case of microplastics in food and cosmetics. Uncertainty on potential health risks is mostly caused by a lack of evidence and difficulties with regard to the definition and measurement tools of microplastics. Due to the complexity caused by the types of polymers, their size, added chemicals and other characteristics, it is difficult to make general statements on the potential consequences of microplastic pollution in food. Consequently, it is at this moment not possible to define concrete hazardous effects. Additionally, no long-term studies are available at this moment to assess the effect of microplastics in the human body. Therefore, the likelihood that a harmful effect will occur in a population cannot be determined. On the other hand, the persistence of (micro)plastic particles in the environment is well-known. Although the specific consequences of this presence are not yet known, this persistence in itself is undesired. Therefore, dealing with microplastics might not only be a matter for the precaution, but also a matter of the prevention.

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 amount of scientific evidence available, and its debatable scientific quality, it is not yet possible to set such an acceptable risk level. This is visible in the lack of specific microplastic regulations.

In the end, the precautionary principle is a balancing exercise between the level of risk and the societal risk tolerance. Although the level of risk is not yet clear in this moment, scientific research is currently being conducted to create this knowledge. With this knowledge, it might be feasible to develop an acceptable threshold for the risk, which can be used in regulations. On the other hand there is the societal risk tolerance, which might change over time due to societal developments. In that light, the application of the precautionary principle might change over time, with developments in the tolerance to a risk. This is a very interesting realisation in the case of microplastics in cosmetics and food products. With the growing attention to climate change, sustainability and plastic pollution in the environment, the reduced societal risk tolerance, especially with regard

to microplastics in cosmetic products, might explain the use of the precautionary principle to limit this type of environmental pollution.

4 Risk governance and the precautionary principle

4.1 Political/legal dynamics

When discussing the risk governance of microplastics, it is important to stress once more the difference between primary and secondary microplastics. Since primary microplastics are added intentionally, these will be easier to regulate compared to secondary microplastics, which are not intentionally added but develop as breakdown product of bigger plastic pieces. Expecially determining who is responsible for the plastic pollution and its potential consequences in the long term is a complex issue. 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. The current paragraph describes what these different forms of regulation look like and what is the role of the precautionary principle in these regulations.

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". From this very general description, it would be expexted that microplastics are covered by this regulation. Nevertheless, the regulation does not once refer to microplastics specifically. Potentially this can be explained because the regulation already dates from 2004, and the knowledge concerning microplastics was even more limited back then. However, in the mean time the existence of microplastics in food, especially in seafoods has been clearly proven. The regulation states that, before a substance can be used as food contact material, it needs to be granted community authorisation. To reach this authorisation, it is the task of the applicant to submit a technical dossier, containing all relevant information for the safety assessment, to their national authority. EFSA then reviews this provided information and comes to a conclusion on its safety in an opinion, which can lead to community autorisation. Implicitally, this procedure makes clear that food contact materials always concern materials that are intentionally used. This could be a reasonable explanation for not including secondary microplastics in this regulation. Since the microplastics in food are not intentionally added, this would complicate the enforcement of the regulation. Namely, it can be debated who is responsible for the presence of microplastics in food, e.g. the initial plastic producer, the government who is responsible for the level of plastic pollution or the merchant bringing poluted seafood on the market. Knowing who is responsible is an important decision to enforce the regulation and actually limit the amount of microplastics in food products. Since this cannot be determined, and together with the lack of a clear definition of microplastics and lack of reliable measurement tools, it seems not possible to regulate microplastics in food products via the food contact material regulation.

To develop more suitable regulations to deal with microplastics in cosmetics and food, the European Commission has various committees of scientists and other stakeholders in place to provide advice on the risks surrounding microplastics. One of the main Directorate Generals responsible in this field is DG Research and Innovation. In 2018 an initial statement by the group of Chief Scientific Advisors of the European Commission, who are part of the Scientific Advice Mechanism (SAM), was written with a scientific perspective on microplastic pollution and its impact (Directorate-General Research and Innovation, 2019). After a thorough assessment, including scientific and societal arguments, they have provided several recommendations on how to deal with microplastics on European level. Firstly, they stress the need to not only focus on microplastic pollution in the marine environment, which is often the case in this discussion, but give equal attention to pollution in air, soil and freshwater. With regard to regulating microplastic pollution, it was recommended to explore options within already existing legal instruments before developing new directives and regulations. Focussing on microplastic pollution in the environment, relevant documents can be the Water Framework Directive and directives with regard to wastewater treatment, application of sewage sludge as fertilizer and air quality. Apart from these legal instruments, it is emphasized that also softer voluntary measures, such as economic measures, can be taken to promote more responsible behaviour with regard to the use and waste management of microplastics. These activities stress the *prevention* of further plastic pollution, since it is known with certainty that the presence of microplastic in the environment is undesired. Also in designing these measures it is important to realise that microplastics is a very diverse group of polymers, with large variety in composition, shape and added chemicals. Legal as well as non-legal instruments to limit microplastic pollution in the environment need to be as specific as possible, to make enforcement of the rules possible.

To prevent microplastic pollution most efficiently, it was recommended by the Chief Scientific Advisors to target first specifically high-volume and high-emission sources of microplastics. This could include e.g. stringent standards for washing machines to reduce microplastic pollution from synthetic textiles, which is known to be a big contributor to the pollution. Interestingly, the Chief Scientific Advisors addressed that prevention of microplastic pollution should be politically and socio-economically feasible. E.g. lifecycle assessments, substitution alternatives and cost-benefit analyses should be taken into account when developing legal measures, to avoid the measures to be worse than the problem. It should not be forgotten that plastic also has numerous benefits over its alternatives, such as its flexibility, low weight and long durability. These pros and cons should be weight with respect to environmental issues, but should also include a social, economic and human aspect. In line with this approach, taking action to reduce microplastic pollution should be seen in the light of other environmental issues, such as the use of pesticides and heavy metals. In light of all these environmental issues related to sustainability and the future of the planet, various parties debate the priority that should go to microplastic pollution. Namely, according to the Scientific Committee on Health Environmental and Emerging Risks (SCHEER) of the European Commission, microplastic pollution is indeed one out of fourteen health and environmental risks currently faced by the European Union (Scientific Committee on Health, Environmental and Emerging Risks, 2018). On the other hand, the World Health Organisation requests more research, to get a better idea of the impact of microplastic on the environment and health before placing it as a top priority (World Health Organisation, 2019).

As a final yet very important recommendation, the Chief Scientific Advisors addressed the issue of low quality scientific studies and a lack of standardized measurement tools. This compromises the value of the scientific evidence and actually contributes to the uncertainty, especially regarding the human health consequences after consuming microplastics via food. These methodological issues need to be tackled in order to get to reliable and validated evidence, which is needed to base new policy on (Directorate-General Research and Innovation, 2019).

Zooming in on the legal framework concerning cosmetic products on EU level, it would be relevant to look at the Cosmetics Regulation, which is in place since 2009 (Regulation (EC) 1223/2009). The objective of this regulation is to assure the functioning of the internal market and a high level of protection of human health (article 1). Remarkably, this regulation does not mention intentionally added microplastics. It does refer to the related topic of nanoplastics. However, due to its much smaller size, these have a different way of spreading through the environment and potentially impacting human health. Namely, due to their smaller size, nanoplastics can migrate through the first layer of the intestine into the blood stream and interfere with cell mechanisms. Although the reason for excluding microplastics is not made explicit, this might relate to the idea that microplastics in cosmetics mostly cause issues for the environment and not so much for human health, which is the focus of the regulation. Due to its relatively large size, it is not likely that microplastic particles pass though the skin, in order to cause human health effects (De-La-Torre, 2020). Additionally, not mentioning microplastics in the Cosmetics Regulation can relate to the earlier mentioned issue that, without a clear definition of microplastics, the regulation could not be enforced.

Nevertheless, also without being included in the cosmetics regulation, legal actions are being taken to reduce the presence of intentionally added microplastics in the environment. At this moment, the European Commission is working on the decision to regulate the existence of intentionally added microplastics via the REACH regulation (European Chemical Agency, 2019). This regulation aims to register, evaluate, authorise and restrict chemicals in the EU, with the goal to ensure a high level of human health and the environment. The decision whether or not to include intentionally added microplastics in REACH will largely depend on the advice reports that are currently (summer 2020) being prepared by two ECHA committees, namely the Committee of Risk Assessment and the Committee of Socio-Economic Analysis. This decision might change the current situation in individual EU Member States. According to the REACH regulation, regulating chemicals that potentially pose a risk to the population should be harmonized across the EU, to avoid fragmentation within the European market. This means that once intentionally added microplastics are regulated via REACH, the opportunities for individual Member States to follow their national rules will be limited (Kentin & Kaarto, 2018). This is interesting in the light that several EU Member States and other countries have taken actions to limit the use of intentionally added microplastics in cosmetics in recent years. The United States was the first country worldwide to put a ban on intentionally added microplastics in rinse-off cosmetic products. The basis for this ban was found in the Microbead-Free Water Act. After a brief phase out period, the sale of cosmetic products containing intentionally added microplastics is prohibited since July 2018 (Strifling, 2016). This example was followed by a number of other countries, such as Canada, United Kingdom, Taiwan and South Korea. Since several years also individual Member States within the European Union have taken action to ban intentionally added microplastics. This started with France in 2016 and was followed by Italy, Denmark, Belgium and Sweden. The basis for these national bans is often the Marine Strategy Framework Directive (directive 2008/56/EC). This directive states that all Member States have the obligation to achieve Good Environmental Status, which relates to the marine environment being clean, healthy and productive. Therefore this directive does not only account for intentionally added microplastics, but for limiting plastic litter in the environment altogether. Interestingly, not all countries that have a ban in place apply the same definition of microplastic in their ban. Some countries only use a size restriction, whereas others also specify the shape, excluding soluble particles (Kentin & Kaarto, 2018).

Further analyzing the application of the precautionary principle in dealing with microplastics in cosmetics and food, we will now describe some key element of the principle, namely the threshold of damage, cost effectiveness, reversibility of the measure and the reversibility of the burden of proof.

Threshold of damage

Following from the little amount of scientific evidence, no threshold of damage for human health effects has been established yet. The lacking standard in measuring (the effects of) microplastics leads to large variation between studies and potentially leads to misinterpretation of results and miscommunication between researchers. Also, it is shown that research has been conducted with unrealistically high concentrations of microplastics, which leads to more spectacular results (Koelmans et al, 2017; Lenz, Enders & Nielsen, 2016). Especially when studying microplastics in a laboratory setting, in animals or cell lines, this can easily go undetected. Related to this problem of testing unrealistic exposure levels, is the problem of publication bias. This means that studies that show a harmful effect are more likely to be published compared to studies showing no effect. Since the studies with very high exposure levels are most likely to show harmful effects, compared to studies using a more realistic approach, these unrealistic studies are more likely to be published compared to its more realistic counterparts. In a topic such as microplastics, publication bias is especially problematic. It does not only impact the development of scientific knowledge, but it also impacts the opinion of the general public (Koelmans et al, 2017). By only publishing studies showing harmful health effects, without providing a clear explanation on how the study was conducted, this can easily make the public belief that there is a serious problem, whereas actually scientific uncertainty remains.

Another reason why setting a threshold of damage has not been established yet, has to do with the large variation in microplastic particles. As described before, there is no clear definition on what microplastic is. Microplastics in cosmetics do have some properties in common, for example that they are made from solid particles, insoluble in water and nondegradable (Leslie, 2014). Nevertheless, still much variation exists with regard to the specific polymer structure and the substances that adhere to their surface, such as endocrine disruptors. These variations between microplastic particles may lead to different levels of toxicity (Bhattacharya, 2016). This makes it very complex, to define one threshold of damage that can be applied to microplastics in general. As long as there is not more scientific evidence on the health effects caused by microplastics, it is not possible to set a threshold of damage. These problems could potentially be tackled by making use of more standardized research methods, setting realistic limits for the exposure of microplastics and the use of valid measurement tools and make use of a more critical publication process. Finally, more research is needed before a treshold of damage can be set, which is needed to formulate regulations on microplastics.

Cost effective/proportionality

The second important aspect of the precautionary principle is the measurement needs to be cost effective; the legal measure to prevent potential harmful effects of microplastics needs to be in proportion to the benefits brought by microplastics. When it comes to microplastics in cosmetics, these are added on purpose to enhance certain characteristics of the cosmetics. Prohibiting the use of these primary microplastics is relatively easy, yet can be very expensive for industry (Cosmetics Europe, 2019). 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 (Petsitis, 2018). Additionally, the industry does invest in the development of biodegradable microplastics.

With regard to secondary microplastics, the microplastics that break down from bigger pieces of plastic and end up in the food stream, establishing the cost effectiveness of restrictive measures is more difficult. Secondary microplastics break down from bigger parts of plastics, in all kind of applications, or develop in the washing of synthetic fabrics. More and more policies are put into place to reduce the use of (single-use) plastic and its

waste in the environment. Indirectly, these policies also contribute to the limitation of secondary microplastics in the environment. Proportionality plays a role in these policies, to balance unnecessary plastic waste and environmental pollution with the beneficial aspects of plastics such as its low weight and long lifespan (Koelmans et al, 2019). For example, replacing plastic packaging materials with glass or paper can lead to disadvantages such as higher costs and weight, which also leads to more emission during transportation. In this way, plastic might be favourable, but extra attention is needed for disposing plastic waste. Additionally, plastic is used in many technical and medical applications, which have created also large benefits for society. 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 (Eriksen, Thiel, Prindiville & Kiessling, 2018).

Reversibility of the measure

Another aspect to take into account when applying the precautionary principle is the question whether the measure is reversible. This should allow for new evidence on the potential risks to be collected, for a new risk assessment to come to a different conclusion, which consequently requires different (legal) measures. In the application of the precautionary principle it is therefore often seen that the measures are only put into place for a certain amount of time. After this period of time the newly collected evidence will be reviewed and this allows for a new conclusion on the risk or a prolonging of the precautionary measure. Looking at the proposal for intentionally added microplastics in cosmetics to be taken up in the REACH regulation, there is no end date included. Although the REACH regulation as a whole is based on the precautionary principle, allowing for measures to be changed when new scientific evidence comes to light, the measures concerning microplastics in cosmetics might therefore also be seen as a preventive measure instead of a precautious measure.

Reversibility of the burden of proof

In case the precautionary principle is applied, the reversed burden of proof indicates that a harmful situation exists unless proven otherwise. The burden of proof is therefore on the producer of the product surrounded with uncertainty, to proof that the product does *not* lead to risk for the environment or human health. For intentionally added microplastics in cosmetics, this is a very clear situation. 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. Following the General Food Law, each food producer has the responsibility to make sure the food that is put on the market is safe (Van der Meulen, Van der Velde, Szajkowska & Verbruggen, 2008). However, no measurement tools are available to establish the amount of microplastics in a validated and standardized way. It is therefore not realistic to pose this responsibility on the food producer, or merchant of the seafood. Also putting the burden of proof on the initial producer of the plastic might be difficult, since this producer has no controle over the plastic ending up in the environment and developing into microplastics.

4.2 Other governance dynamics

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 (Henderson & Green, 2020). With regard to intentionally added microplastics, the "beat the microbead" campaign of the Plastic Soup Foundation is a good example of this (Plastic Soup Foundation, 2012). By making use of an app, European consumers were asked to scan barcodes of cosmetics products. In this way, information was collected on a large scale on how many cosmetic products actually contained microplastics. It was found that the percentage of products containing microplastics varies per product group, with the highest percentage in facial cleaners. Moreover, it was found that producers of many of these cosmetic products indicate that they are working on phasing them out (European Commission, 2017). This gives support for the recommendation of the Scientific Advice Mechanism, stating that limitation of microplastics does not rely only on legal standards, but can also be promoted in a more voluntary way. Namely, with this campaign of the Plastic Soup Foundation, awareness for the presence of microplastics in cosmetic products was raised in the general public. Consequently, cosmetic industry will feel more incentives to work on the replacement for microplastics, as the consumer demand for natural alternatives grows.

The growing public attention for the issue of microplastic pollution can be seen in a wider context of public movements. For example, the growing attention for climate change, circular economy, organic food consumption and reduced use of (single-use) plastic come together in the European Green Deal (European Commission, 2019). As part of this societal movement, behaviour of consumers and companies has been shifting towards more sustainable alternatives. A clear example of this can be seen in the reduced use of single-use plastic bags (Angus & Westbrook, 2019).

From a societal point of view, scientific assessment is not the only factor taken into account in adequately dealing with potential risks of microplastics. 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 (Scientific Advice Mechanism, 2019). This is seen to impact the public behaviour, for example in reducing the use of single-use plastics and cosmetic products containing microplastics. Also research has shown, that not many people deny the plastic pollution problem and there is a feeling of co-responsibility in the public with regard to limiting the development of plastic pollution (Koelmans et al, 2019). Of course, only recognising the issue is not sufficient to accomplish behaviour change. When looking at the similar situation of climate change, it is known that not many people deny climate change. However, still the use of cars and planes has not been reduced. Nevertheless, recognising the problem is an important first step in coming to actual behaviour change.

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 (Koelmans et al , 2017; Rist, Almroth, Hartmann & Karlsson, 2018). When microplastics are discussed in the general media, it is often mentioned in relation to 'potential risks', without clear stating of the situation of scientific uncertainty and lack of scientific data. Due to this type of framing, a mismatch might develop between the scientific understanding of the risk and the public perceptio

5 Precautionary principle and its future

5.1 Reflection on the precautionary principle in the literature

In general, the precautionary principle seems relevant to deal with microplastics, given its upcoming regulation via the REACH regulation. The widespread and very long persistence of the microplastics in the water and soil, make microplastics undesired from the environmental perspective, and asks at least for the proportionality principle to be envoked (Verschoor, 2018). Especially the large unknowns with regard to animal and human health and specific environmental consequences on the long-term, ask for a precautious approach.

Although consensus exists on the *abundance* of microplastics in the environment and the complexity and uncertainty with regard to its consequences are widely understood, there is some criticism on the upcoming rules to deal with microplastics in cosmetics. This criticism is specifically coming from the Italian cosmetics industry. They are a large producer of products containing intentionally added microplastics. They mainly 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. Essentially, their criticism refers to the fact that not one definition of microplastics exists and therefore much variation exists between microplastics with regard to their potential effect on human health. Because of the lack of one definition, and because microplastics can change under influence of light and temperature, REACH uses a very broad definition, including all kinds of polymers. The rational behind this, is that all synthetic polymers are non-degrable and stay in the environment for a very long time. The Italian cosmetics industry argues that many differences exists between different types of microplastics and that it is therefore not a correct application of the precautionary principle to cover them as one and the same product in REACH (Chemical Watch, 2019). By being too cautious, industries could have to look for alternatives unnecessarily. Especially for small companies, it is argumented by the Italian cosmetics industry, finding alternatives to the microplastics can be a costly activity. In light of the cost-benefit analysis, the industry argues that the balance between the costs for changing to natural alternatives is not in balance with the potential harmful effects for some of the microplastics (Chemical Watch, 2019).

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 (Plastic Soup Foundation, 2012). This loophole refers mostly to the way the proposed regulation deals with biodegradable microplastics. Namely, biodegradable polymers are excluded from the definition of microplastics and are therefore not subject of the proposed ban (European Chemical Agency, 2019). Although ECHA stresses that biodegradable microplastics are tested for their half-time in the marine environment and sediment, concerns from environmental NGOs remain. Additionally, NGO allegiance Rethink Plastics argues that the transition period, which allows industry to find replacement for intentionally added microplastics, is too long and thereby leads to unnecessary duration of plastic pollution (Chemical Watch, 2019).

5.2 Effect of the precautionary principle on innovation pathways

An interesting tension can be observed when looking at (micro)plastics and innovation. Initially, the development of plastics has actually been an important innovation in itself, which provided many benefits on a global level. It has replaced many products as a cheaper and multifunctional alternative in the i.e. fields of electronics, construction, food preservation and many medical applications (Scientific Advice Mechanism, 2019). Thereby, plastics are a good example of how quickly an innovation can integrate into an essential part of society, given that nowadays plastics are an indispensable part of our modern way of living. Also adding chemicals, such as bisphenol A and phthalates, to plastics was done as an innovation. These substances add certain product characteristics, such as flexibility, to the plastic in order to improve their use and sustainability. For instance in the use of tubes to transport fuel in vehicles or in medical equipment, these characteristics are of crucial importance. Unfortunately, the formation of secondary microplastics is an undesired side-effect of the great amount of plastic used and the lack of an adequate disposal system.

Now that plastic pollution has become a clear issue worldwide, innovation plays again a big role in this discussion. In 2018 the European Commission launched the 'European Strategy for Plastics in a Circular Economy', as one of the initiatives to help reach the Sustainable Development Goals (European Commission, 2018). This strategy aims to reduce the presence of plastic in the environment and contribute to a more circular economy. Thereby, the EU Plastic Strategy can be seen as a precautionary effort to reduce secondary microplastics, in an indirect way. Innovation plays a big role in reaching these goals. According to the press release by the European Commission in 2018 the reduction of plastic use is not seen as a problem, but actually a big business opportunity (European Commission, 2018). The European Commission recognises that the plastic industry is a big driver for European economy. Improving its sustainability will bring forward new business opportunities and accordingly create new jobs, while reducing the plastic pollution that stays around in the environment for a very long time.

Since the regulation under development, following the REACH regulation, focusses on intentionally added microplastics, most innovation is nowadays expected in this area. It is interesting to see that the use of microplastics in cosmetics has actually been introduced quite recently. They have a number of functions, inter alia to improve exfoliation and cleaning properties. In the past, these roles were fulfilled in most cosmetics by more natural products, which did not pollute the environment. Therefore, consumer organisation BEUC described these intentionally added microplastics an example of a 'regrettable innovation' (European Consumer Organisation, 2019).

Since the discussion on microplastics has been going for some years now, the cosmetics industry already took action to find replacement products. In 2015 the branch organisation Cosmetics Europe recommended to discontinue the use of microbeads in wash-off products. CosmeticsEurope phrased this recommendation as part of their responsibility to the environment. However, it is likely that it was already a preparation for the upcoming legal rules and changing societal needs. A survey among their members in 2018 showed that the use of microbeads in these specific wash-off products was already reduced with 97% (Cosmetics Europe, 2019). Potentially pressured by the societal discussion on plastic pollution and climate change and driven by the prospect of EU wide legislation, also other large cosmetic producers such as Unilever have been looking for alternatives for several years (Unilever, 2014).

5.3 Innovation principle

The innovation principle has been suggested by several industry partners, lead by the European Risk Forum, as an alternative to the precautionary principle (Business Europe et al, 2015). They argue that the precautionary principle is often applied in a way that is

too precautious, thereby blocking innovation and reducing the competitiveness of European companies compared to their counterparts in other continents. The innovation principle is derived from the precautionary principle, but with a specific attention for the potential impact on innovation. Although the innovation principle has not been defined as a legal principle, several official documents by the European Commission have made mention of it (Renda &Simonelli, 2019). 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. Implicitely 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.

6 Synthesis

Microplastics is a highly relevant societal and scientific issue that is surrounded with complexity and uncertainty. Plastic litter in the oceans has been a growing problem for approximately the last fifty years (Andrady, 2015). The attention for microplastics has only peaked in the last decade. This growing attention seems to be not solely based in scientific insights, since the harmful effects of microplastics were already known in the 1970s. Although the presence of microplastics has been known for such a long time, academic research into human health effects due to microplastic exposure thrived more recently. Thereby, we can see that development of scientific knowledge does not happen in a complete vacuum, but is driven by societal attention for a subject. The growing attention for microplastic pollution seems therefore to be based in a broader societal development, with growing attention for the environment, climate change and organic food consumption. Especially the abundance of microplastics available in the environment, its very long persistence and the lack of scientific evidence with regard to human health effects, create an undesirable situation. We have found that the lack of knowledge and lack of legislation, especially with regard to microplastics in food and its consequences for human health, can be explained by several factors.

First, performing scientific research and setting a threshold of damage is complicated given that no uniform definition on microplastic exists. There is a great variability of nondegradable polymers and their structure changes in the environment, under the influence of light, water and temperature. Second, no standardized measurement tools for microplastics are available. In terms of scientific research, this makes it difficult to compare results from different studies. With regard to making legislation, valid and reliable measurement tools are needed in order to check for compliance with the rules. Overall, the scientific evidence on potential health effects for humans is very scarce.

Additionally, in the case of microplastics in food, it is very complex to assign who is responsible for the potential risks on human health. This needs to be clearly defined before legislation can be enforced. Looking beyond the microplastics in food, we *do* know with certainty that microplastics are present in large amounts in the environment, in water, air and soil. The combination of their very long durability and the fact that they might leak chemical substances make it an unwanted situation for the environment, even regardless of the potential, consequential risks for animal and human health, now and in the future.

In the current European regulatory framework, microplastics in cosmetic products and in food are not yet specifically regulated. At the moment, efforts are being made by the European Commission to include microplastics in cosmetics in the REACH regulation, which is based on the precautionary principle. In 2019 ECHA published a proposal to restrict intentionally added microplastics, as their presence in the environment is so widespread and persistent over the very long term. Although this restriction is still under consideration with the European Commission, several Member States have already put similar bans in place, with the purpose to pursue a good environmental status. ECHA's proposal to include primary microplastics in REACH is found to be in line with the EU Plastic Strategy, as defined by the European Commission. This strategy is also largely based on the precautionary principle and has the goal to work towards a more circular economy. This strategy can be seen as an indirect attempt to reduce the development and release of secondary microplastics, coming from plastic litter or washing of synthetic textiles. Via this route, also the presence of microplastics in food products, with unknown consequences for human health, should be reduced. ECHA's proposal has been welcomed by various environmental NGO's, such as the European Environmental Bureau and the Rethink Plastic Alliance (European Environmental Bureau et al, 2019). Before the proposed limitation can be installed, the Committee on Risk Assessment and the Committee on Socio-economic Analysis of ECHA are still preparing an advice report for the European Commission. These documents are expected by the end of 2020.

It is interesting to see that the main focus of regulating microplastics is currently on intentionally added microplastics in cosmetic products. This could be expected from the perspective that primary microplastics are directly released into the environment and it is relatively easy to stop this route of pollution. However, primary microplastics account for only a small percentage of the complete worldwide microplastic pollution. Figures differ among countries, but the vast majority of microplastic pollution is not coming from cosmetics, but from other sources such as synthetic textiles, tyres and other plastic pollution. When it comes to secondary microplastics, coming from pollution in the environment, regulating their presence in foodstuff will be more difficult to target. This should be seen in the bigger context of plastic pollution, as secondary microplastics develop as a side-effect thereof. The EU Plastic Strategy is a clear attempt to discourage single-use plastics and work towards a circular economy. Via this route the development of secondary microplastics will be reduced over time, which could lead to a reduction in microplastics in food products. Additionally, as recommended by the Chief Scientific Advisors of the Science Advice Mechanism of the European Commission, microplastic pollution can be integrated in existing legislation regarding (waste)water, soil and air quality.

Looking at the different components of the precautionary principle, the risk characteristics of scientific uncertainty, complexity and ambiguity seem to be met. Zooming in on the legal practice and the key components of the precautionary principle, actually applying and enforcing the principle seems to be rather complicated, especially with regard to microplastics in food.

Learning from the literature and from interviews with high-placed officials at the European agencies dealing with microplastics, it seems that uncertainties and complexities mostly play a role in relation to the environment and human health. Relating to the specific topic of this case study, this uncertainty is expected to be bigger

in relation to seafood in comparison to cosmetic products. Focussing on cosmetic products, it is mostly the *amount* of microplastics ending up in the environment that is the reason for putting in place regulations. In seafood, the presence of microplastics has been shown, but the potential consequences for animal and human health remain highly uncertain, due to different theories and very limited scientific evidence. When envoking the precautionary principle to deal with microplastics in foods, it should however be kept in mind that plastic actually was introduced in the Western world as an innovation that brought great advantages. In many situations (micro)plastics have been used as a replacer of other materials, which will have other disadvantages. 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 the proportionality principle, 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 to act responsibly with regard to the social, economical, environmental and human perspective.

7 Conclusion

We started this report with the aim to understand the complexities and controversies around the potential application of the precautionary principle for the case of microplastics in cosmetics and foods. Additionally we analysed if the conceptual core of the precautionary principle, and in particular scientific uncertainty, is present in the case of microplastics in cosmetics and food in relation to human health risks and how the precautionary principle has been applied in practice.

The discussion on microplastics is surrounded with scientific complexity and uncertainty. Although microplastics are known to be widespread through the environment, they are difficult fields to regulate. Firstly, there is no universal definition of a microplastic. There is a wide variety in materials, shapes and adhering substances, which might lead to different risks for the environment and human health. Secondly, once microplastics are in the environment, their structure and hazardous properties might change under the influence of light, water and temperature. Thirdly, the lack of high quality measurement tools makes it a complex field to study and to regulate. Finally, and crusial to the application of the precautionary principle: only very limited scientific evidence is present on the human health effects caused by microplastics consumed via food products. Although it does not seem likely that microplastic particles are taken up as a whole by the human body, no sufficient quality scientific evidence is present on this. On the other hand, there *is* certainty on the abundant presence of microplastics in the environment. This is the reason why the European Commission is currently working on a proposal to limit the use of microplastics in cosmetic products via the REACH regulation. The REACH regulation is in line with the conceptual core of the precautionary principle, in order to protect the environment from long-term, unknown harms. However, there is only a thin line between precaution and prevention in the regulation of microplastics in cosmetics. Namely, the integration of microplastics in REACH does not have an end date and requires no further data collection. Therefore, this might be more of a prevention measure instead of precautionary measure. Especially given that the abundant presence of microplastics will not be changed with new scientific insights.

When zooming in on microplastics in food, the focus is more on health effects instead of the environmental burden. Thus far, there is no regulation in this field. There is lack of scientific evidence with regard to the hazards and likelihood of these hazards in relation to human health. Based on these findings, the use of the precautionary principle would be justified. However, the lack of a definition, uncertainty on the treshold of damage and difficulty in appointing the party responsible for the microplastic in the food product make it impossible to formulate and enforce specific regulation. Nevertheless, the societal demand is growing to limit the presence of microplastics all through the environment, including in food products. Via the EU Plastic Strategy the use of single-use plastics will be discouraged. Resulting from this policy, over time also the formation of secondary microplastics and the microplastics in food should be reduced. These actions can be seen as more soft implications of the precautionary principle, in order to achieve a Good Environmental Status.

8 References

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