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BTO *Managementsamenvatting*

Streef naar betere interactie met beleidsmakers over (on)zekerheden rond geneesmiddelen in water

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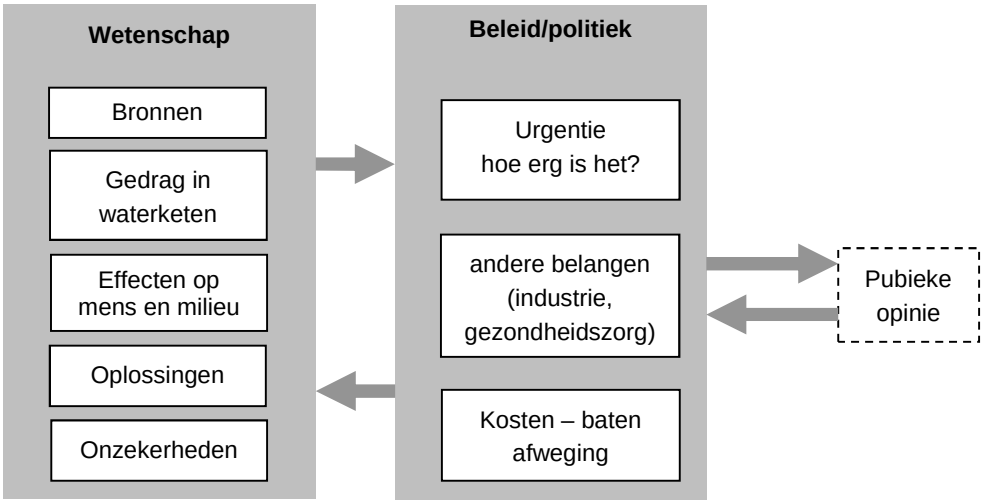
Geneesmiddelen komen voor in de waterketen. Er is veel onderzoek gedaan, maar er zijn niet altijd antwoorden op vragen als “wat is het effect van een levenslange bootstelling aan een complex mengsel van stoffen waaronder geneesmiddelen?” of “hoe groot is het effect van geneesmiddelen op een specifiek ecosysteem?”. Ook met aanvullend onderzoek blijft er een bepaalde mate van onzekerheid over de risico’s van geneesmiddelen in de waterketen. Deze studie gaat in op de onzekerheden in wetenschappelijk onderzoek naar risico’s van geneesmiddelen in de waterketen en hoe wetenschappers en het publiek hier mee omgaan. Vervolgens wordt aan de hand van historische voorbeelden geïllustreerd hoe het beleid omgaat met wetenschappelijke onzekerheden. Betere interactie tussen wetenschap en beleid, waarbij wetenschappers onzekerheden kenbaar maken en beleidsmakers meer kennis nemen van de materie, kan de interactie tussen beleid en wetenschap verbeteren en beleidsvorming bespoedigen. Met dit inzicht kan de watersector zijn kennis effectiever inzetten voor het beschermen van drinkwaterbronnen.



Geneesmiddelen in de waterketen; relatie tussen wetenschap en beleid

Belang: onzekere risico’s van geneesmiddelen maken beleidsvorming rond waterketen complex

Risico’s van geneesmiddelen in de waterketen zijn al lang onderwerp van wetenschappelijk onderzoek en maatschappelijke debatten. Resultaten van wetenschappelijk onderzoek laten zien dat er risico’s voor het ecosysteem bestaan. Publieke debatten laten zien dat het publiek zich zorgen maakt over deze stoffen in de waterketen. De wetenschappelijke resultaten gaan echter gepaard

met onzekerheden; hoe complexer de kwestie, hoe groter de onzekerheden. Beleidsmakers moeten omgaan met de publieke opinie en de onzekerheden van wetenschappelijk onderzoek bij het nemen van beslissingen. Dit heeft grote impact op de toepassing van de wetenschappelijke resultaten in de politieke praktijk. Daarom is onderzocht welke kennis er is over risico's van geneesmiddelen in de waterketen, hoe beleidsmakers omgaan met wetenschappelijke onzekerheden, en wat daaraan kan worden verbeterd.

Aanpak: leren van milieuvraagstukken uit het verleden

De studie bespreekt eerst de wetenschappelijke kennis van risico's van geneesmiddelen in de waterketen en de daaraan verbonden onzekerheden. Dan wordt aan de hand van andere milieuvraagstukken uit het verleden bekeken hoe wetenschappelijke kennis de publieke opinie en politieke besluitvorming heeft beïnvloed, en hoe we de interactie tussen wetenschap en beleid kunnen verbeteren voor de huidige discussies over risico's van geneesmiddelen in de waterketen.

Resultaten: betere afwegingen mogelijk door betere interactie tussen wetenschap en beleid

Bronnen, vóórkomen, effecten en mogelijke technische oplossingen voor geneesmiddelen in de waterketen zijn de afgelopen decennia veelvuldig onderzocht. Wetenschappers schatten dat risico's van humane blootstelling beperkt maar onzeker zijn, terwijl risico's voor het ecosysteem te verwachten zijn. Het voorspellen van effecten van levenslange blootstelling aan mengsels van stoffen is complex. Aanvullend onderzoek zal daarom niet op korte termijn alle onzekerheden wegnemen. Beleidsmakers hebben laten zien dat wetenschappelijke kennis in het verleden het milieubeleid sterk heeft beïnvloed. Naarmate vraagstukken complexer worden, zoals bij de risicobeoordeling van geneesmiddelen in de waterketen, worden onzekerheden groter en blijven tegenstrijdigheden bestaan. Dit maakt beleidsvorming ook veel complexer en kan die zelfs belemmeren. Ons onderzoek laat zien dat als wetenschappers inzicht geven in achterliggende onzekerheden, beleidsmakers de kennis met onzekerheden kunnen gebruiken bij het vormgeven van het beleid. Dit vraagt betere uitleg van wetenschappers en meer kennis van beleidsmakers, maar biedt wel de mogelijkheid om het beleid en discussies te richten op: 'wat is veilig en toelaatbaar' in plaats van op discussies over verschillende interpretaties van resultaten van wetenschappers. Op deze wijze kan het voorzorgsprincipe worden toegepast in het beleid.

Implementatie: gebruik ontwikkelde kennis over risico's effectiever voor bescherming bronnen

De watersector kan het in dit rapport verwoorde inzicht in de effecten van wetenschappelijke onzekerheden op beleidsbeslissingen gebruiken om wetenschappelijke kennis op het gebied van geneesmiddelen, inclusief de daarmee gepaard gaande onzekerheden, effectiever in te zetten voor het beschermen van bronnen van drinkwater.

Rapport

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Summary

Pharmaceuticals are omnipresent in the aqueous environment. Two decades of intensive research has led to a large knowledge base on the sources, occurrence, fate and risks of pharmaceuticals in the urban water cycle. Nevertheless, uncertainties remain, and questions such as “what is the effect of lifelong human exposure a complex mixture of pharmaceuticals at very low concentrations?”, and “what will be the exact effect of the same complex mixture of pharmaceuticals to a specific ecosystem?”, cannot be fully answered by scientists. This study illustrates the current state of knowledge and what is still uncertain, how uncertainties are perceived by the general public and policymakers and how uncertainties complicate implementation of knowledge by policymakers. Subsequently, relations between science and policy are analyzed for historical environmental problems. This analysis suggest that complex environmental problems require better interaction between scientists and policymakers, where scientists explain results with their uncertainties, and policymakers use this knowledge to define what is safe and what precautions are required. Insights on the interaction between science and policy helps the Dutch drinking water sector to apply their knowledge to protect drinking water sources.

Contents

1 State of science

This chapter gives a short overview of the current state of knowledge of pharmaceuticals in the environment with a focus on the water cycle. As this chapter demonstrates, a large amount of data is gathered on the occurrence, fate and risks of pharmaceuticals in the (aqueous) environment. The aim of this overview is to support the further discussions on the uncertainties associated with the gathered knowledge in Chapter 2 and how the knowledge and uncertainties are translated to policy in Chapter 3. A more extensive summary of the state of science considering human pharmaceuticals in the environment is given by Derksen & ter Laak (2013) and Bio Intelligence service (2013).

1.1 Historical perspective of pharmaceuticals as environmental contaminants

The production of chemicals has vastly increased in the 20th century. Since the 1950s growing concern about risks of chemicals and waste produced and used by mankind has led to increased government regulation. Figure 1 illustrates landmarks on knowledge and awareness of contaminants in the (aqueous) environment. A major landmark in concern for (environmental) risks of chemicals was the publication of the book “Silent spring” that documented the detrimental effects on the environment—particularly on birds—of the indiscriminate use of pesticides. The book has led to public awareness on the environmental risks of pesticides, the ban on DDT use, the creation of the U.S. Environmental Protection Agency and the more generic Toxic Substances Control Act in the U.S.A.. European regulation of pesticides and industrial chemicals emerged shortly after that. In the eighties, chemicals were regulated by a number of different regulations and directives. The Council Regulation (EEC) No 793/93, also known as the Existing Substances Regulation (ESR), was one of these. It introduced a comprehensive framework for the evaluation and control of "existing substances" (substances on the market before 1982). This led to a lot of knowledge being developed on the emission, occurrence, fate, and effects of pesticides and industrial chemicals during the seventies and eighties of the twentieth century. At that time, pharmaceuticals were not considered as environmental contaminants that potentially pose a threat to the ecosystems and human health (Daughton & Ternes 1999, Christensen 1998). It was only until the mid-eighties of the twentieth century that pharmaceuticals were discussed as environmental contaminants in scientific literature (Richardson & Bowron 1985) and it took another decade before studies illustrated the omnipresence of these substances and their transformation products in wastewater, wastewater effluents, surface waters, groundwater, manure, soil and drinking water (see Monteiro & Boxall 2010, Evgenidou et al. 2015 and references therein). Pharmaceutical consumption vastly increased over the last decades due to (further) medicalization in developed countries, more access to medication in developing countries. As a consequence, the value of pharmaceutical production has grown four times more rapidly than the world’s income between 1985 to 1999 (WHO 2004). Pharmaceutical production is expected to rise further in future, due to aging populations (van der Aa et al. 2011).

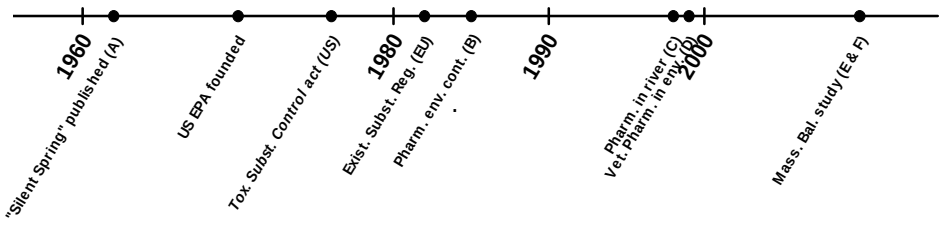


Figure 1: Landmarks on knowledge development on contaminants and specifically pharmaceuticals in the (aqueous) environment. References A: Carson et al. (1962), B: Richardson & Bowron (1985), C: Ternes (1998), D: Boxall (1999), E: Alder et al. (2010), F: ter Laak et al. (2010)

1.2 Where do pharmaceuticals in the environment come from?

Pharmaceuticals can enter the (aqueous) environment via multiple routes. Figure 2 illustrates these routes. The relevance of these routes differs between (classes of) pharmaceuticals as well as regions and countries. In western Europe, most pharmaceuticals enter the environment after being consumed. Direct emissions of pharmaceuticals during production are considered small, since most bulk pharmaceuticals are produced elsewhere (mainly in China and India (WHO 2004, Larsson et al. 2007, Fick et al. 2009). Generally, the volume of pharmaceuticals used in human healthcare exceeds volumes used in veterinary practice which in turn exceeds pharmaceutical use in aquaculture (Montforts et al. 1999). However, ratio's between these applications differ per region and type of pharmaceutical, for example, the use of veterinary antibiotics in the Netherlands exceeds human antibiotics (NETHMAP/MARAN 2012).

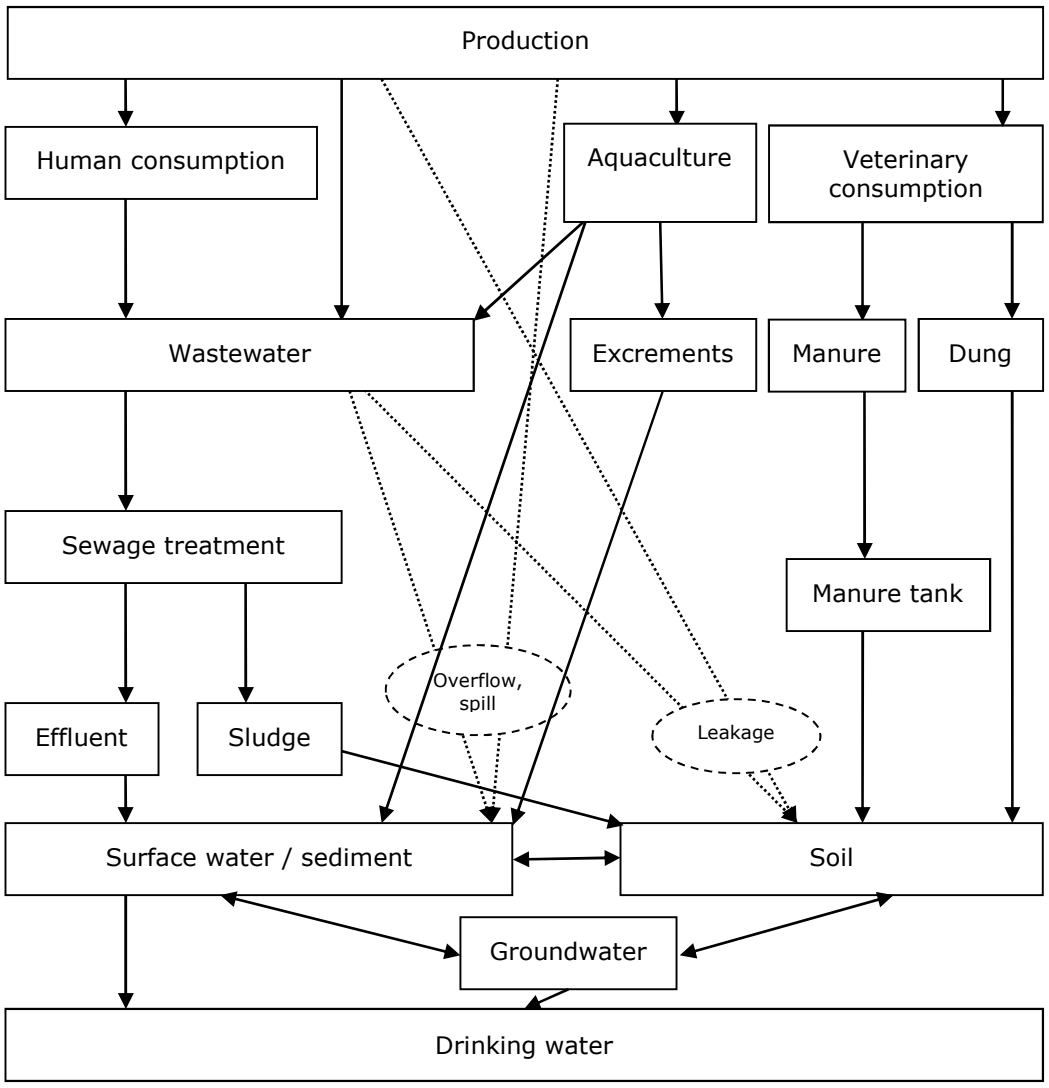


Figure 2: Routes of pharmaceuticals in the environment. Figure adopted and modified from reference (Schmitt et al. in prep).

Veterinary pharmaceuticals are mainly antibiotics and anti-parasitic substances while a more diverse palette of pharmaceuticals such as medication for the gastrointestinal tract, cardiovascular system, central nervous system, against pain and inflamation, musculo-skeletal disorders (etc.) are extensively used in human medicine (van Loenen 2008).

The emission routes of veterinary and human pharmaceuticals also differ. Veterinary manure containing pharmaceuticals is applied to fertilize land, while human pharmaceuticals end up in wastewater and are partially emitted to surface waters via wastewater treatment plants after being excreted by the users. Most pharmaceuticals studied in the water cycle are from human consumption. It is often thought that hospital and care homes emit large amounts of pharmaceuticals via their wastewater. Concentrations of pharmaceuticals in wastewater of hospitals and care homes are indeed higher, but wastewater volumes from these sources are small and generally <10% of the load comes from hospitals and 1-5% from other health care institutions. The major part (~90%) of pharmaceutical are emitted from residential area's (le Corre et al. 2012). However in local situations, the contribution of healthcare institutions can

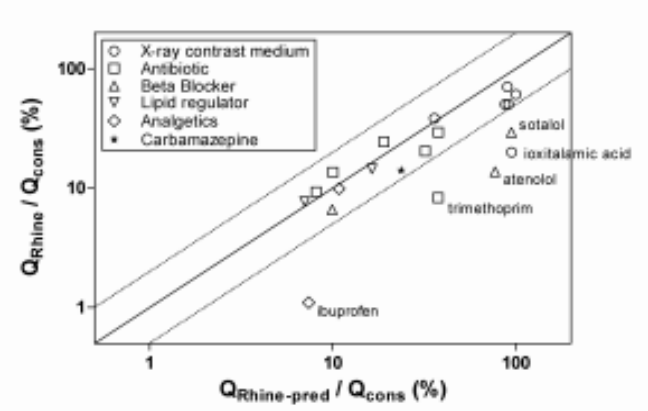
be substantial. Furthermore, pharmaceutical loads stemming from sewer overflows are a small fraction of the total load. For the Netherlands, sewer overflows are estimated account for ~1% of the total wastewater (see Derksen & ter Laak, 2013 and references therein).

Sludge from wastewater treatment plants also contains pharmaceuticals (Martin et al. 2012). The further application of the sludge determines whether pharmaceuticals can enter the environment via this phase. In Europe, approximately 42% of the sludge is recycled (e.g. used to fertilize soil), 27% is incinerated as is the case in the Netherlands, 14% is dumped in landfills and 16 % us used for other purposes. Sludge that is applied to fertilize land or dumped can lead to potential emissions of pharmaceuticals to surface water and groundwater, while full incineration disables further emissions (Samadolada et. al. 2014).

Studies have illustrated that human consumption, excretion and removal during wastewater treatment can predict emissions and environmental loads in rivers rather accurately (ter Laak et al. 2010, Ramil et al. 2010, Alder et al. 2010, ter Laak et al. 2014, Coppens et al 2015). An example of this approach is given in the textbox below. Such relations are not yet obtained for veterinary pharmaceuticals, since use and fate of pharmaceuticals during manure storage, application on land, infiltration and runoff depend on local circumstances (Montforts et al. 1999).

Many pharmaceuticals are transformed during use (metabolism), after being excreted in wastewater treatment plants or manure tanks and the environment. While metabolism and excretion is well studied for therapeutic purposes, knowledge on further transformation in the wastewater treatment plant or manure storage and environment is still rather limited (Massé et al. 2014; Fatta-Kassinos et al. 2011).

Predicting fate of pharmaceuticals from consumption: Prediction of environmental behavior and concentrations of chemicals in the environment is developed in environmental science since the eighties of the last century (Boethling et. al. 2000). Most work in the eighties and nineties of the previous century was done on metals and persistent organic pollutants (POPs) such as industrial chemicals, chlorinated pesticides and combustion byproducts. The focus of this research was to predict the distribution of these chemicals in the environment and the accumulation and subsequent effects in biota. Most paradigms of these POPs do not apply to pharmaceuticals since they are generally more polar and less persistent. However, their continuous consumption and (for human pharmaceuticals) continuous emissions via wastewater treatment plants makes them “pseudo persistent” in surface waters. Consumption and metabolism of pharmaceuticals are well documented. With the aid of removal rates during wastewater treatment, loads in surface waters can be predicted rather accurately. This was for example done for the



Rhine catchment. Ter Laak et. al. (2010) showed that for 15 out of 20 commonly found pharmaceuticals, loads in the Rhine at the Dutch border could be predicted with in a factor two from upstream consumption data (see figure). Similar results were observed at regional and local scales (Alder et. al. 2010, Oosterhuis et. al. 2013, Ter Laak et.al 2014). Such models were subsequently applied to model environmental concentrations under high and low flow conditions in surface waters. It was observed that actual concentrations of pharmaceuticals fell within the modeled concentration window (Coppens et. al. 2015), thereby gaining insight in the loads as well as dynamics of concentrations in surface waters.

1.3 Occurrence of pharmaceuticals in the water cycle

Monitoring and modeling efforts over the past two decades have led to a large body of knowledge on the occurrence of pharmaceuticals in surface water and wastewater. This enabled to validate emission based models such as presented in the textbox above. Furthermore, there are various national and international institutes that collect and manage databases with monitoring data on pharmaceuticals in the aqueous environment (www.riwa.org, www.waterbase.nl, www.norman-network.net, http://www.emissieregistratie.nl/erpubliek/erpub/wsn/default.aspx, http://www.emissieregistratie.nl) Pharmaceuticals have also been observed in sediment, soil, groundwater and drinking water, but there generally is less data available on these matrices (Monteiro & Boxall, 2010).

Concentrations of pharmaceuticals in the water cycle vary in time and space. Generally, concentrations in raw wastewater are highest. Concentrations of numerous common pharmaceuticals such as painkillers, beta-blockers, anti-epileptics, antibiotics, cholesterol regulating agents and X-ray contrast media (a diagnostic aid, not a pharmaceutical) are in the µg/L range in raw wastewater and effluents. There is one exception, metformin, which is found at concentrations over 100 µg/L in raw wastewater and up to tens of µg/L in effluents (Ter Laak & Baken, 2014). Concentrations in larger surface waters are often in the sub-µg/L range. However, waters that are heavily impacted by wastewater treatment plant effluents, i.e. where dilution of the effluents are low, show higher concentrations. Concentrations in groundwater and drinking water are generally lower than in surface waters, often in the ng/L range. Such concentrations are close to current limits of detection for many of these substances. Table 1 illustrates these concentration ranges for a few commonly found pharmaceuticals in the Dutch water cycle. Data are obtained from Derksen & ter Laak (2013)

Table 1: Concentrations of a selection of pharmaceuticals in the water cycle

Pharmaceutical concentrations in µg/L	Wastewater treatment plant effluent (µg/L)	Surface water	Groundwater or riverbank filtrate	Drinking water
Carbamazepine (anti-epileptic)	0.23-1.50	<0.005-0.54	0.01-0.08	<0.01-0.025
Metoprolol (beta blocker)	0.32-3.20	<0.005-1.2	<0.01	<0.006-0.026
Diclofenac (anti-inflamatory, pain killer)	<0.01-0.89	<0.004-0.70	<0.01-0.012	<0.01-0.018
Sulfamethoxazole (antibiotic)	<0.01-0.35	<0.004-0.20	<0.01-0.014	<0.01-0.025
Metformin (antidiabetic)	0.71-27.50	0.07-6.40	<0.05	<0.05
Diatrizoc acid (X ray contrast medium)	<0.05-0.10	<0.01-0.75	<0.01	<0,01-0.09

1.4 Risks and effects

Humans can be exposed to very low concentrations pharmaceuticals and their transformation products via drinking water. Typically, these are those pharmaceuticals with low removal efficiencies by commonly used waste- and drinking- water treatment technologies, and which are used in relatively high quantities. The human health risks associated with the exposure to individual pharmaceuticals in (sources of) drinking water are expected to be negligible. Most toxicological studies show that environmental concentrations are orders of magnitude lower than concentrations in drinking water that could elicit an effect (Versteegh et. al. 2002, Schriks et al. 2010, de Jongh et. al. 2012, Houtman et. al. 2015, Bruce et.al. in press). Nevertheless, information is incomplete since drinking water is not the only exposure route, not all pharmaceuticals in the aqueous environment are monitored, the life-long exposure to a complex mixture of pharmaceuticals and other micro-contaminants is unknown and can't be fully assessed by available toxicity studies. Furthermore, there is currently not much known on the indirect human health risk of antibiotics in the water cycle and soil for antibiotic resistance development. Details on the risk assessment and related uncertainties around the science of assessing risks from information on effects and exposure are given in Chapter 2.

The ecosystem is exposed to residues of pharmaceuticals and transformation products that are emitted via wastewater treatment plants, solid waste and manure. Numerous studies have shown that environmentally relevant surface water concentrations exceed no-effect concentrations or lowest observed effect concentrations for different organisms. This means that organisms in the environment can be affected by the presence of residues of pharmaceuticals. Additionally, exposure of organisms to complex mixtures obtained from the environment have also shown effects (Verlicchi et al. 2012 and references therein, Brodin et al. 2013 & 2014). Nevertheless, as the next chapter will explain, assessing the nature and extent of the impact of continuous exposure of an ecosystem to dynamic concentrations of complex mixtures of pharmaceuticals and other micro-contaminants remains difficult to assess, let alone predict.

1.5 Mitigation

There is currently sufficient knowledge on the sources, emission routes and volumes of pharmaceuticals in the environment. One can distinguish a design, production, application, and waste/disposal stage in the lifecycle of an anthropogenic chemical such as a pharmaceutical. The numerous advanced treatment technologies at the 'end of pipe' have been studied to improve removal from (waste) water (Hofman-Caris et al. 2012, Buthiyappan et al. 2015, Umar et al. 2015, Mehrjouei et al. 2015, Verlicchi et al. 2015). Mitigation measures during earlier lifecycle stages are less studied. Mitigation measures at the end of the lifecycle of a pharmaceutical are generally of technological nature, and can be implemented on local scale. For example by upgrading a sewage treatment plant or drinking water plant to reduce emissions or residues in drinking water, respectively. Mitigation measures at the early stages (development, production and application) are generally of regulatory nature that are effective on an (inter)national scale. Such mitigation measures are for example criteria for properties or applications of substances in order to reduce their potential effects. Such measures are for example applied for pesticides and industrial chemicals (European Commission, 2009, European Chemicals Agency, 2014). The environmental behavior and risk of pharmaceuticals are currently not used to regulate the design and application of pharmaceutical. Recently, there are some initiatives in academia to provide toolboxes for the development of 'environmentally sustainable' pharmaceuticals (Kümmerer, 2015).

2 Uncertainties in risk assessment

Risk and uncertainties feature prominently in studies on pharmaceuticals in the environment, and in the relation between science and policy-making. How risk and uncertainty are defined and approached in society and science, is of major concern. The brief (and incomplete) historical sketch that follows reveals that different interpretations dominated throughout history. Section 2.2 explains how toxicological risk assessment deals with uncertainty, and section 2.3 which issues apply to risk assessment of pharmaceuticals in the environment. Finally, the role of scientific uncertainty in public perception of risk of environmental contaminants is discussed.

2.1 Risk and uncertainty in historical perspective

In 'pre-modern' (western) societies, future events and destiny were perceived as inextricably unknown and mostly feared of. Religion, magic, or divine practices were 'instruments' with which to make sense of this uncertain future and one's destiny. New attitudes towards uncertainty appeared in the late middle ages and at the beginning of the great explorations of kingdoms (circa 16th century). Uncertainty as danger and something to be avoided were replaced by positive views of uncertainty; as something to be further explored, as a chance to improve life, gain fortunes and escape natural or religious 'laws'. Although probabilistic techniques appeared around that time, many were hesitant to use them for forecasting the future and its uncertainties. Rather, in trade ventures, 'risk' involved betting on the future: its 'genuine uncertainty' could be very advantageous or work out disastrously, but this was all part of the game.

These positive attitudes toward risk and uncertainty changed in turn to more reserved ones, driven by major societal transformations like industrialization, modernization and urbanization. Typical of these transformations were the emergence of modern technologies like the steam engine and advanced machinery. These enabled a change from 'traditional' to 'modern' societies, making them more stable and predictable than was hitherto the case. However, such progress did not free society from fear. The one after the other scientific discovery presented great opportunities, but also created new, human-made dangers. Inventions made life and work easier, or solved problems of old, but typically also created new ones that were not foreseen. And these often had ever-greater impact, as evident in railway or mining accidents and steam boiler explosions (see also Bronstein, 2007). A strong feeling of uncertainty as something dangerous, to be avoided rather than to be aspired thus developed. Dangers and uncertainty were to be controlled, so as to minimize surprises and maximize (feelings of) safety and security.

Uncertainties came to be framed as risks in the 'modern' sense, i.e. as quantified uncertainties, and various strategies and institutions emerged to deal with ('manage') these risks. The desire to quantify uncertainty for risk and safety policies in different sectors of society like industry, food and health, speeded up the process of developing new calculating methods and instruments. The insurance system played an important role in this process, as their success depended on measurements of risk and the 'accurate' calculation of uncertainty. The 19th and a good part of the 20th century saw the development and extension of risk calculation techniques and risk awareness in society. Risk assessment, based on probabilistic techniques and statistical understanding of causality, flourished especially in the then emerging field of toxicology, spurred by infamous poison gas attacks

in World War I. Probability Risk Assessments appeared around the same time to measure factors related to safety and reliability of large technical systems.

The continuous search for enhanced methodologies to calculate uncertainty has been successful in the sense that it boosted confidence in abilities to control uncertainty and preventing risk. In fact, coupled with a professionalized insurance system and hence, the idea that damages could be compensated by money, societal actors would not only prevent, but increasingly take the calculated chance of risk. Yet, after World War II, this came to be accompanied with an increased awareness of the perils and dangers associated with more than a century of industrialization and modernization. Whilst these processes boosted economic growth and increased prosperity, they were also detrimental in many social and environmental respects (Disco, 2002; Simissen, 2007). The 1960s and 70s marked a shift in society, as groups came to stand up against the relentless quest for growth for which both people and nature had to give way. Influential publications like 'Silent Spring' (1962) and 'Limits to Growth' (1972) further triggered this.

Perception of risks changed once again, notably through sociological accounts like Ulrich Beck's 'Risk Society' (1992). He indicated the inherent limitations to 'knowing' risk, as well as the recurrence of unintended consequences and side effects of 'new' risks resulting from advancements in fields such as nuclear and aerospace industries, genetic engineering, and (financial) capital markets (Zachman, 2014: 26). The inherent unknowability of future uncertainties, not simply to be compensated by money and best to be avoided or prevented, once more gained ground, although this had various repercussions for the science of risk and uncertainty. It instigated a massive growth and professionalization of risk regulation and risk research. Legislation based on risk assessments took off, all kinds of professional groups and institutions were set-up around the notion of risk and risk analysis, and journals on the topic multiplied. It also became a more multi-disciplinary field of inquiry –albeit disciplines in the natural and social sciences remain largely disconnected- with engineering, health, and environmental related disciplines focusing mainly on quantitative, model and measurement-oriented approaches, and law, sociology, political and economic science focusing on ethical, cultural and political aspects of risk.

In sum, the emergence of and dominant attitudes towards risk and uncertainty changed rather dramatically through time, depending on and following major societal changes. One key feature in these changing perceptions is whether, and to what extent, risk and uncertainty can be known and, relatedly, what that means for human action and intervention. This ranged from perceptions of an unknown future that was either better avoided or seized upon, to supposedly known risks and uncertainties that are better avoided or taken advantage of. The science on risk and uncertainty, and the related field of risk assessment, has nonetheless developed throughout, until this very day. The next chapter will delve deeper into the link between (different perceptions on) risk, uncertainty, and human intervention.

2.2 Toxicological risk assessment

As stated in the previous paragraph, toxicological risk assessment is one of the fields of expertise that gained importance when industrialization and population size increased, which resulted in the ubiquitous presence of potentially harmful anthropogenic substances in the environment. Toxicity studies aim to characterize and quantify the (environmental) health effects of chemical exposure. From these studies, doses that are not expected to result in any adverse health outcome can be derived, which are subsequently converted to safety thresholds that are applied to prevent toxicity. As most other risk assessment

strategies, this procedure requires a multidisciplinary approach that involves chemistry, biology, toxicology, and modeling.

The Dutch Health Council defines risk as the possibility, with a certain degree of probability, of damage to health, environment and goods, in combination with the nature and magnitude of the damage (Gezondheidsraad, 1995). Toxicological risks may thus occur when exposure exceeds established threshold doses. This means that exposure may be high but not relevant with respect to health protection when it concerns a relatively harmless substance with a high safety threshold. The other way around, low exposure to a potent toxicant may very well present a health risk. In toxicological risk assessment of contaminants in the aquatic environment and drinking water, both the level of exposure and the safety thresholds are however surrounded by a certain degree of uncertainty that needs to be dealt with.

2.2.1 Estimation of exposure

Exposure is determined by measuring concentrations of substances in the environment and in drinking water. Environmental concentrations may however not be constant (due to mobility and degradation) and differ per site and compartment. Samples may therefore be a snapshot and only partly representative of the actual dose and duration of environmental exposure. In addition, transformation products of chemicals may be formed in the environment, by microbial, animal or human metabolism, or during drinking water treatment, which exert biological effects as well. Besides, environmental concentrations cannot be linked directly to internal exposure of aquatic organisms, since substances may be adsorbed to soil or sediment and/or poorly absorbed by organisms. Moreover, only a subset of anthropogenic substances in the aquatic environment is monitored, and concentrations of many contaminants are therefore unknown. The same is true for drinking water. The presence of unmonitored substances in drinking water may be predicted based on concentrations in source water, when available, but this requires estimation of removal efficiency during drinking water production, which is another source of uncertainty. Alternatively, in vitro bioassays may be used to demonstrate the presence of biologically active substances in drinking water and its resources. These assays do however yield quantitative results for which the translation to safety thresholds is possible but not regulated yet (Brand et al. 2013, Escher et al. 2015).

2.2.2 Safety thresholds

Safety thresholds are most often based on experimental animal studies, in which exposure conditions are precisely controlled and observed toxicity is compared to effects occurring in an appropriate control group. The sensitivity of test organisms towards the substance under evaluation may however deviate from the sensitivity of organisms that are exposed in practice. Gender and genetic background may affect sensitivity to toxicants as well. Besides, exposed populations may include vulnerable groups such as developing organisms and diseased individuals. Results of toxicity studies are therefore always an estimation of population effects, since adverse health outcomes are not studied in each individual during the entire exposure period. For this reason, uncertainty factors are applied when safety thresholds for lifelong exposure are derived from data from toxicity studies. These factors lower the observed No Observed Effect Level (NOAEL) to correct for inter- and intraspecies differences, the representativeness of the exposure period in the toxicity test for the actual exposure duration, and the quality of the toxicity study (such as population size). In case of genotoxic carcinogens, for which a safe level of exposure cannot be indicated, the acceptable exposure level is set at the dose that correlates to a specified additional cancer risk at lifetime exposure. In some cases, however, the mechanisms of action of a chemical

are not known, and it is not clear whether the threshold or non-threshold approach should be applied.

The above mentioned uncertainty relating to interspecies differences can be avoided by using exposure-effect relations obtained from the population of interest. This means that exposure and adverse effects need to be studied in exposed ecosystems or human populations. Such data are limited, since intentional exposure of these targets to chemicals is obviously not performed for research purposes. Data may be available after accidental exposures (such as spills or disasters), but the duration of exposure will in these instances generally be short and not represent chronic toxicity. For some environmental contaminants, epidemiological studies that correlate exposure levels to human health effects have been performed. Results of such studies are often difficult to interpret, though, since cause and effect relations are uncertain due to a number of reasons. There may be limitations in study design, such as absence of exact information on ingested concentrations, insensitivity due to low dose exposures, insufficient representativeness of the studied group for the general population, and confounding factors such as simultaneous exposure to multiple environmental contaminants, genetics, and lifestyle factors that affect health status as well. Besides, exposure to substances may occur via both environmental contamination and other routes such as diet or occupation exposure. Furthermore, there may be a significant time lag between the moment of exposure and the occurrence of adverse health effects, which troubles the identification of correlations (Villanueva et al. 2014).

Safety thresholds are used to derive health based drinking water guidelines. To this end, estimation of human toxicity after long term exposure to low doses is required. Chronic toxicity, endocrine disruption, and carcinogenicity are relevant health outcomes in this respect. Thus, when only data from acute toxicity or high dose exposure studies are available, this needs to be accounted for by application of uncertainty factors. In some cases, when children have been indicated as a sensitive subpopulation, an additional safety factor is introduced to protect this group of individuals. Furthermore, drinking water guidelines need to be lower than safety standards since other sources than drinking water may contribute to the total chemical exposure as well. Typically, 20% of the total exposure is allocated to drinking water. For substances of which insufficient toxicity data are available to derive drinking water guidelines, which is often the case for new environmental contaminants, the threshold of toxicological concern (TTC) concept may be applied. TTC levels have been derived for groups of compounds with similar chemical structures and mechanisms of action and related toxicity data, and indicate conservative exposure levels beneath which adverse health effects are unlikely to occur. Based on the TTC concept, generic drinking water guidelines of 0.01 µg/l for genotoxic and endocrine disrupting compounds and 0.1 µg/l for other substances with unknown toxicity have been derived (Mons et al. 2013).

2.2.3 Innovative tools

Besides the traditional risk assessment procedure that is outlined above, alternative hazard assessment tools that only define the potential risk of a chemical without including whether humans or the ecosystem are exposed to it. Hazard assessment avoids the need for experimental animal studies or epidemiological data. These tools include the use of in vitro bioassays focusing at toxic events or endpoints in cultured cells or tissues and cellular adverse outcome pathways. Many of the available in vitro toxicity tests are still at the research and development stage. A number of in vitro tests addressing specific endpoints have at present been formally validated and gained regulatory acceptance. A limitation of these tools is that they often poorly resemble their *in vivo* equivalents. One reason for this is the complex interplay between different cell types that occurs *in vivo*. Besides, the toxic outcome of exposure may differ per organ or dose, duration, and timing of exposure. A

single in vitro test is therefore often a too much simplified picture of reality, and ideally, a test battery of complementary in vitro tests should be applied. (Adler et al. 2011; Basketter et al. 2012). The quantitative extrapolation of dose-response data from concentrations of the test substance in *in vitro* models to toxic exposure levels in the whole body is the subject of ongoing research activities (Brand et al. 2013, Punt et al. 2013, Groothuis et al. 2015, Escher et al. 2015).

When inadequate or no toxicity data at all are available, Quantitative Structure Activity Relationships (QSARs) and read-across can be applied. These tools are based on the principle that the biological activity and environmental fate of a chemical can be predicted from its molecular structure and substructure, and inferred from the physicochemical properties and biological effects of similar substances. QSARs are more prevalent for endpoints for which large databases exist, such as ecotoxicity, mutagenicity and carcinogenicity, skin sensitization, and endocrine disruption. Recent developments in computing power, the ability to create extensive databases and the use of the internet to compile, organise and distribute information, have increased the capability to investigate relationships between chemical structure and biological activity. For all the so called *in silico* approaches, however, the size and quality of the underlying databases and availability of physicochemical parameters are critical for reliable predictions. The models are still not overly realistic for complex endpoints since they may ignore essential processes. Similar to *in vitro* tools, increased understanding of mechanisms of toxicity will improve the quality of the predictions made (Combes 2012; ECETOC 2012; Patlewicz et al. 2013).

In vitro and *in silico* tools can be of added value when multiple information sources are systematically combined in integrated testing strategies (ITS). ITS approaches are useful when not all possible outcomes of interest, classes of test substances, or severity classes of effect are covered in a single test. ITS are also valuable when the human predictivity of a single test is not satisfactory. In addition, a tiered ITS approach provides the opportunity to combine existing data with new data, and to filter out certain substances before costly additional testing is performed. By using a 'Weight of Evidence' approach, different pieces of evidence and test data be weighed and combined (Balls et al. 2012).

2.2.4 Mixture toxicity

A significant source of uncertainty in toxicological risk assessment of anthropogenic substances in the aquatic environment is the potential combined health effects of co-occurring individual substances. While safety thresholds and legislation are based predominantly on assessments carried out on individual substances, humans and their environments are exposed to a wide variety of substances simultaneously. Although it has been assumed that safety factors applied to the derivation of safety thresholds protect against the combined action of pollutants, mixture toxicity is not fully understood. Substances with similar modes of action may exert added effects and their toxicity can usually be described by concentration addition. Chemicals from different classes may interact and either increase (potentiation or synergism) or decrease (antagonism) each other's biological activity. The latter effects are considered to be less likely at low exposure levels (SCHER 2012; Cedergreen 2014).

The potential health risk posed by chronic exposure to complex chemical mixtures present at low levels in the environment is a matter of debate. No robust evidence is available that exposure to a mixture of such substances is of health or environmental concern if the individual chemicals are present at or below their zero-effect levels. Three EU Scientific Committees state that in general, the level of concern for mixtures of dissimilarly acting substances should be assumed to be negligible when the intended level of protection is

achieved for each individual substance human health effects, while for ecological effects, the exposure to mixtures of dissimilarly acting substances at low, but potentially relevant concentrations should be considered as a possible concern (SCHER 2012). This is illustrated by an experimental study in which mixtures of pharmaceuticals, pesticides, heavy metals, polyaromatic hydrocarbons, a surfactant, and a plasticizer, each at its safety threshold concentration, were analysed using 35 bioassays. These experiments demonstrated quantifiable ecotoxic effects, indicating that mixture toxicity did occur (Carvalho et al. 2014). An explorative study in which the summative hazard of water contaminants was calculated, on the other hand, indicated that mixture toxicity is unlikely to arise when humans are chronically exposed to anthropogenic substances in drinking water (Van der Aa et al. 2012, Backhaus et al. 2012)).

Uncertainties in the exposure assessment of mixtures include the identity of the chemicals involved, the accuracy of exposure information, and the extent and profile of co-exposure to different chemicals due to varying persistence in the environment and in the body. Uncertainty in the toxicity assessment of mixtures include the adequacy of the toxicological database (in particular the limited number of chemicals for which there is sufficient information on their mode of action), lack of knowledge regarding human relevance, the lack of an agreed definition of criteria for "similar modes of action" and of grouping criteria for chemicals into assessment groups, assumptions on the consequences of the combined effect of co-exposure, in case of concentration addition the similarity in the shape of the dose response curves, and the nature and identification of points of departure for use in combined risk assessments (EFSA 2013; SCHER 2012). For the ecological assessment of mixtures, additional uncertainties refer to the complexity of ecosystems: the sensitivity of exposed biological communities varies; the mode of action of chemicals in different types of organisms (bacteria, plants, invertebrates, vertebrates) differs and is sometimes unknown; toxicological data, when available, are usually limited to a few endpoints on a few indicator organisms; and the effects at the level of population/community, including indirect effects on ecosystem functioning, are complex and largely unknown (SCHER 2012).

2.2.5 Dealing with uncertainty

International expert committees are responsible for a careful evaluation of all available scientific toxicity and exposure data, deciding on the tolerability of the risk, and taking risk reduction measures such as developing guidelines that protect environmental and human health sufficiently. The uncertainties in exposure and effect assessment force risk assessors to use estimations and assumptions for some of the required parameters. In these instances a conservative approach (realistic worst case) is taken, which is represented by the margin between the lowest ineffective dose detected in toxicity tests and the threshold dose for humans that is introduced by safety factors, and between the estimated and actual exposure that is created by assuming maximum dose, duration, and frequency of exposure. For the derivation of drinking water guidelines, it is assumed that each individual consumes 2 liters of water per day containing this concentration level during the entire lifetime.

Besides, health protection is established by application of the precautionary principle, according which in the absence of scientific consensus, the decision-maker must anticipate harm before it occurs and provide some measure of protection (Sandin et al, 1999, van Asselt et al. 2006 & 2011).

2.3 Health risks of pharmaceuticals

During the research and development process of pharmaceuticals, their safety needs to be established using a suite of toxicokinetics and toxicodynamics studies in both animals and humans. The modes of action and potential human toxicity of therapeutic doses of

pharmaceuticals are therefore often well characterized compared to other anthropogenic substances. Relatively little is known, however, about the potential effects of unintended, long-term exposure to low levels of pharmaceuticals in the aquatic environment, in particular with regard to non-target organisms. The active ingredients of pharmaceuticals form an unusual group of chemicals similar to pesticides, in the sense that they are designed to induce specific biological effects, which may be either beneficial or hazardous depending on the circumstances (Snyder 2008). The scientific knowledge necessary for a proper risk assessment is surrounded with uncertainties, which are outlined in the textboxes below.

Effects on the aquatic environment: The targets of human pharmaceuticals are also found in aquatic organisms. In these organisms, pharmaceuticals may show unusual dose-effect relations in which low doses are most effective, which complicates risk assessment. Besides, the information on environmental concentrations, required for risk assessment, is scarce for some environmental compartments, notably for biota in the food web and marine ecosystems. The same is true for information on the environmental hazard, which is often deduced from few acute ecotoxicity studies performed in a very limited number of freshwater species. Moreover, unexpected effects may occur after environmental exposure to pharmaceuticals. In some cases, data from human toxicology studies might help to provide read-across information on the potential effects on vertebrates, but many ecotoxicological modes of action are specific and potential environmental effects cannot therefore always be extrapolated from human studies. The ecotoxicologically relevant modes of action thus need to be better identified. In addition, highly lipid-soluble medicinal products may accumulate in the fat tissues of animals and can thus be introduced into the food chain. Furthermore, transformation products that are more bioactive may be formed in the environment or excreted by users. Information on the environmental occurrence and fate of transformation products is scarce due to knowledge gaps in their behavior in the environment, and/or detection issues (BIO Intelligence Service 2013; Derksen & Ter Laak 2013).

Multiple studies have indicated that uncertainty factors that are applied in traditional toxicological risk assessment may insufficiently protect against environmental effects of pharmaceuticals. For human medicinal products currently consumed, (publicly available) environmental risk assessment studies are available but their results do not have consequences for market authorization. Research results published in peer-reviewed literature show that realistic environmental concentrations of pharmaceuticals are able to induce ecotoxic effects such as immunotoxicity and neurotoxicity. In particular anti-parasiticides, anti-mycotics, antibiotics, and (xeno)estrogens pose environmental risks in specific exposure scenarios, while the environmental risk of other pharmaceuticals can be rather negligible due to low persistence and ecotoxicity of the compounds. In some studies, ecotoxicity has been demonstrated for mixtures of pharmaceuticals. Research in this field has however been limited to specific medicinal products and is difficult to generalize (BIO Intelligence Service 2013; Derksen & Ter Laak 2013).

2.3.1 Water quality guidelines

As yet, no health based regulatory guidelines for pharmaceuticals in drinking water and drinking water resources have been established. RIVM has proposed provisional water quality standards for carbamazepine, metoprolol, and metformin in surface water. For amidotrizoic acid (an X-ray contrast medium), the derivation of environmental quality standards was not possible due to the lack of relevant (accessible) data for this substance. In general, limited access to original study reports hampered the derivation of quality standards. RIVM makes a plea that pharmaceutical companies and competent authorities transparently provide all information needed to derive environmental quality standards (Moermond 2014). However, deriving quality standards for all pharmaceutically active compounds is probably not feasible. Health based provisional guideline values for drinking water have been published for dozens of pharmaceuticals (Versteegh et al. 2003 & 2007; Schriks et al. 2010; Van der Aa et al. 2011a; De Jongh et al. 2012; Houtman et al. 2014). The absence of regulatory guidelines for pharmaceuticals in drinking water and its sources might prevent the constitution of mitigation measures in the design-, production-, consumption-, and emission–stage of the lifecycle of a pharmaceutical.

Effects on humans: For humans, the possible impacts of environmental exposure to pharmaceuticals are less well studied than for the environment, but there are concerns regarding certain types of molecules. Antibiotics, anti-parasiticides, anti-mycotics and anti-cancer drugs are pharmaceutical groups that are especially intended to kill their target organism or target cells and might prove to be the most important pharmaceutical compounds affecting human health via environmental exposure (BIO Intelligence Service 2013). There is however no evidence of short-term or long-term health effects on humans. Available research results indicate that there is a large margin between safe exposure levels, often derived from the minimum therapeutic dose using uncertainty factors, and (lifelong consumption of) concentrations detected in drinking water (resources) (Derksen & Ter Laak 2013; Houtman et al. 2014; WHO 2011; Snyder 2008). A drawback of using the therapeutic dose to determine the acceptable exposure level, is that this dose represents the relatively high level at which pharmacological and in some cases (e.g. for anti-cancer drugs) toxic effects occur in adults after short term exposure, disregarding potentially deviating effects in sensitive subpopulations (such as children) and after chronic exposure to lower doses.

Mixture toxicity has been evaluated using the concentration addition concept, which assumes additive effects of pharmaceuticals with similar modes of action. When summed concentrations of substances were compared to the lowest safety threshold within a group of pharmaceuticals, it was concluded that human health effects of mixtures are not likely to occur (Van der Aa et al., 2011a; De Jongh et al., 2012; Houtman et al. 2014). The potential impact of synergistic effects was not evaluated in these studies.

2.4 Public perception of health risk of pharmaceuticals

The previous sections presented the scientific risk assessment procedure for pharmaceuticals in the aquatic environment and the numerous uncertainties that are encountered during this process. While toxicological risk assessors value risks by experimental observations and calculations, consumer perceptions of risks are to a large

extent affected by intuition, emotions, beliefs, culture, knowledge, experiences, standards and values. It should be acknowledged, therefore, that a perceived risk that is shaped by context and subjective aspects exists (EPA 2009; RIVM 2003). With regard to anthropogenic contaminants, the complex issue of risk and scientific evidence is particularly difficult to translate to the general public. The fact that exposure to pharmaceuticals through environmental contamination is low and human health risks for individual substances seem unlikely, does therefore not imply that the pharmaceuticals in (drinking) water will be regarded as an insignificant threat. This phenomenon is indicated as the 'risk perception gap' (Ropeik 2010).

Factors that influence risk perception in a positive or negative sense either relate to personal characteristics (such as gender, age, level of education, and socio-economic status) or to risk attributes. The latter can roughly be subdivided into attributes that relate to the type of the hazard, the 'knowability' (the extent to which the threat is observable, known, new, and immediately present), the possibility of control, the people involved, and the severity or benefit of the consequences (Breakwell 2007; EPA 2009; Slovic 1987). When these factors are applied to pharmaceuticals in the environment, their chemical nature, omnipresence, involuntary exposure, unclear environmental benefits, potential long-term effects, relatively recent appearance, and limited public and scientific knowledge potentially exert a negative effect on the perceived risk. The Water Research Foundations has evaluated perceptions of consumers in the United Kingdom and U.S.A. towards pharmaceuticals and personal care products in drinking water (WRF 2013). This study showed that overall awareness of pharmaceuticals in drinking water was limited. Nevertheless, the presence of such contaminants in the water supply had extremely negative associations and consumers were convinced that their removal would make tap water safer. A similar level of worry was expressed about these contaminants regardless of where they occurred or whether they affected humans or wildlife. The manmade nature of pharmaceutical contaminants was an important factor in the negative perception among the participants. Besides, scientific discussion and uncertainty on the role of endocrine disrupting substances in adversely affecting the ecosystem and human health and uncertainty about the risks posed by environmental contaminants appeared to be a great cause for frustration for consumers and were associated with 'risk', which had very powerful negative associations. The study also revealed that consumers were driven to recycle or dispose pharmaceutical products responsibly by experienced responsibility for environmental contamination.

The human health risks of pharmaceuticals in drinking water may thus be perceived as more serious than toxicological risk assessment for single compounds indicate. This may partly be explained by the complexity and uncertainty of the topic, resulting in limited information or incorrect assumptions among the general public, but is also caused by the societal and moral aspects that affect risk perception of the general public. In spite of attention for this matter, there may be a tendency in risk research to view consumer perceptions as deficient, uneducated, or wrong when compared to expert views (RIVM 2003; Roeser 2011; WRR 2011). However, other studies emphasize that risk perception of the general public is important in how a society and regulators deal with this issue (Lahr et al. 2010, Hage et al. 2010). This illustrates that no universal measure for quantification of risks exists, though, and both views may add in defining the most appropriate approach to deal with pharmaceuticals in the aquatic environment.

3 Translating science to policy: past, present & future

The previous two chapters gave an overview of the state of (toxicological) science on pharmaceuticals in the environment and how knowledge is produced on this topic, with a focus on (the assessment of) risks and uncertainty. This final chapter links these concepts and debates to regulation and policy-making on pharmaceuticals and more generally, micro-contaminants, in the environment. The main focus is on the role of science and knowledge in policy-making on and regulation of substances (specifically pharmaceuticals) in the environment, but to clarify the arguments made in this chapter, it also turns to examples in other, related scientific fields.

The chapter is structured in three parts. The first part sketches the changing role of science in regulating substances from roughly the 19th century onwards. The second briefly discusses where we stand now with regard to the role of science in society in general and with assessing environmental risks in particular. It also briefly highlights the role of science in two fields of current interest, climate change and nuclear energy. How some of the issues raised in these two parts can be dealt with in the future is discussed in the third part.

3.1 Science & regulating substances in the environment: a historical overview

One section in chapter two situated the concepts of risk and uncertainty in a historical context, to better understand their origins, their different understandings over time and how we have arrived at current interpretations of risk and uncertainty. A similar exercise will follow for the link between science/knowledge and policy-making/regulation on substances [1], focusing on the 'Western' context (i.e. Europe and United States). Its aim is to provide a background and understanding of certain historical patterns and antecedents to current ways of regulating substances, and the role of science herein.

3.1.1 Initial regulatory systems

A vast increase in the production of knowledge and the making of policies and regulation on environmental health problems in Europe date back to the 19th century, in response to processes of industrialization and its many and major impacts on society and the environment. Scientific expertise and knowledge came to play an important role in these early regulatory systems and this would only grow stronger during later regulatory transformations. Science helped regulating the dangers associated with industrialization, such as pollution and the health consequences of increasing amounts of pesticides, medicines, cosmetics, etc. in the environment, for instance by delivering chemical analyses, contributing to building a hygienist paradigm, developing the field of toxicology and setting or raising safety standards.

This however, could not prevent the ongoing occurrence of environmental and health impact events. Most of the early regulatory policies in place were the result of negotiated compromises; they were not in the first place aimed at improving science on the environmental and health effects of contaminants, but rather revolved around the question of what is acceptable by industry. This bias towards industry, in turn, had all to do with the primary objective of most Western states, namely industry-led economic development (Boudia & Jas, 2014: 5; Shapiro, 2014).

[1] Based on Boudia & Jas (2014), unless otherwise stated.

While repeated scandals gave rise to transformations of regulatory systems in the inter-war period, the renewed regulations were ill-prepared for the massive change of scale in problems posed by contaminants following World War II. Industries such as the petrochemistry, synthetic chemistry and nuclear industries only grew faster and more powerful, whilst science could not keep up tracing and investigating the numerous new substances brought to market. Most of these (new) substances were thus not evaluated or regulated, and increasingly, their traces started to be found in the environment, including water.

3.1.2 Environmentalism and the rising importance of science

Boudia & Jas (2014) emphasize that in particular the period 1960–1980 is essential to understanding the way in which the regulation of substances is currently structured and functioning. As also indicated elsewhere in this report, it was during this period that both policy-makers and the public at large became more and more concerned with environmental (health) issues. Air- and chemical pollution, water- and food contamination were among the issues that featured more prominently on (political) agendas. Awareness grew that pollution was both local and global and that it would not only threaten health, but also the ecosystem at large. This created all sorts of new questions for experts, policy-makers and politicians. This period therefore saw the establishment of many more environmental agencies such as the Environmental Protection Agency in the USA, the United Nations Environmental Programme (UNEP) as well as environmental regulation on a European scale, in the then European Economic Community.

Science and the production of knowledge on contaminants in the environment also changed considerably during this period. While science has since long informed policy-making and regulation, with the rise of 'environmentalism' (heightened environmental awareness), it obtained a much more central place, both in society at large and in regulatory issues. Scientific experts were better able to show the effects of all sorts of chemical substances in the environment on health and the mechanisms behind it. Hence, the volume of scientific work expanded, with researchers beginning to systematically screen dangerous substances, developing new testing and screening methods and classifying chemicals substances effect. New subfields of inquiry emerged, such as carcinogenesis, ecotoxicology and environmental mutagenesis. Regulations were adapted after new scientific findings, such as 'toxicity tests' and following work on the categorization of dangerous substances (e.g. the CMR category: Carcinogens, Mutagens, Reproductive substances).

3.1.3 Alternative knowledge production and regulation

More and progressed science and knowledge did not, however, take away public concerns. More sophisticated regulatory systems based on enhanced science did not translate into significant decreases of the number and quantities of (potentially) toxic substances in the environment and their negative effects. Scientific approaches and regulation based on those were also itself increasingly scrutinized and questioned. For instance, criticism increased on the threshold paradigm, and hence, on the regulatory systems based on threshold values. This critique was based on the argument that substances might have health and environmental effects with chronic exposure to levels below set threshold values.

To cope with this, framing changed from doses of substances deemed safe to 'socially acceptable' levels of risk, thereby acknowledging that exposure norms were not only a matter of expert judgment based on "sound" science, but involved a great deal of uncertainty and economic and political dimensions as well. This in turn triggered a distinction between

'risk assessment' and 'risk management', based on the idea that the two can be kept apart, with the former (risk assessment) done in a value-free manner and the latter (risk management) involving decision-making based on the former.

The numerous activist and environmentalist groups that were established during the 1970s and 1980s addressed these issues and began producing 'alternative' scientific knowledge and 'counter-expertise' on these topics. They did so in various ways of which two are mentioned here. A first one is by involving established scientists who, based on their work on the effects of toxicants called for the implementation of (stronger) environmental and/or health policies. The appearance of alternative forms of knowledge production, especially from the 1990s onwards, also emerged out of (perceived) limits of science to identify and investigate the potential perils of the many (new) contaminants found in the environment, as well as a lack of democracy in the way decisions on how to regulate those were made. Therefore, new modes of governing were called for, often organized around labels such as "participation" and "transparency". In particular, questions around scientific uncertainty and biased decision-making by experts led to calls for the inclusion of "lay people", whose interests, concerns and knowledge were seen as worth considering in policy-making and regulatory issues. Knowledge production, in short, had to become more democratic.

3.1.4 Regulation of and policy-making on pharmaceuticals

How does this brief historical sketch link specifically with regulating pharmaceuticals? Figures indicate that between the 1960s and 1980s prescription drug sales hardly changed, but tripled thereafter to nearly $400 billion worldwide in 2002 and continued to grow thereafter, but not as fast as between the 1980s and 2002 (Abraham, 2010: 607; Bell & Figert, 2012; WHO 2014 & 2011). Particular pharmaceutical markets expanded rapidly, such as Ritalin and Prozac (Abraham, 2010). Such trends in 'medicalization' and 'pharmaceuticalization' are explained by many as illustrative of the progress in medical science. New discoveries in and increased prescription of medicines enable a better life for many people. But they also produce substantive volumes of wastes in the environment, which presents serious challenges (Agamuthu & Fauziah, 2011). Regulating pharmaceuticals in the environment is thus an important issue, which has increasingly been recognized within the EU. Pharmaceuticals must thus go through an authorization process, on the basis of environmental risk assessment (Küster & Adler, 2014), Large challenges remain in regulating pharmaceuticals, however, not least those related to the strong influence of the pharmaceutical industry on regulatory agencies (Permanand & Altenstetter, 2004).

Most European countries have no specific regulations to affect production, use emissions and further spreading in the environment and drinking water. However, in Sweden, pharmaceutical producers and health care professionals have developed a system for environmental classification of risks and hazards of human pharmaceutical substances. This provides an instrument for doctors and patients to choose the environmentally friendly alternative of medically equivalent pharmaceuticals. It is assumed that the prescriber and user's access to environmental classification induces a shift in market preference which stimulates producers to develop sustainable pharmaceuticals in future. In the end this is intended to lead to lower consumption of hazardous pharmaceuticals thereby reducing emissions and residues in the water cycle. Furthermore, Switzerland decided to upgrade all large wastewater treatment plants with additional advanced treatment steps to reduce emissions of pharmaceuticals and other micro-contaminants in wastewater effluents with ~80%. Similar approaches are adopted on regional scales in Germany. This illustrates that policies in different countries cope differently with the uncertainties associated with the risks of pharmaceuticals in the environment.

All in all, regulatory systems and institutions in the USA and Europe grew parallel to the growing numbers and volumes of contaminants in the environment since industrialization kicked off. Such systems and institutions are backed up by the vast increase of scientific knowledge. This scientific grounding could not, however, take away uncertainty and (public) concerns regarding the health and environmental effects resulting from substances in the environment. This then raised numerous questions, especially during the 1960s and 1980s, many of which loom large even today. In essence, these revolve around the notion that scientific expertise alone, however advanced and sophisticated, will not solve these issues (Shapiro, 2014). Not only because there is always uncertainty involved in this field of science, but also given the interplay of other, political and economic processes and concerns. Since then there have been multiple calls for alternative ways of producing knowledge on this subject, as well as regulating substances differently.

3.2 Current debates and examples on the role of science in environmental issues

Various techno-scientific and environmental issues have recently led to a wider debate about the role of science in understanding and tackling the regulation of substances. This part will highlight two of these concrete examples, briefly recalls the ensuing debate on science's role afterwards and lastly, returns to the peculiarities involved in the specific field this report is concerned with, i.e. assessing pharmaceuticals in the environment.

Science, regulation & nuclear energy: the case of Fukushima

On 11 March 2011, a major earthquake caused a tsunami that hit a nuclear power plant at Fukushima in the northeast of Japan. This resulted in a nuclear meltdown of some of the reactors, followed by a mass discharge of radioactive material into the environment. The official report of the "Fukushima Nuclear Accident Independent Investigation Commission" (The National Diet of Japan, 2012: 16) makes it very clear that this has been a man-made, not a 'natural' disaster:

The TEPCO Fukushima Nuclear Power Plant accident was the result of collusion between the government, the regulators and TEPCO [Tokyo Electric Power Company], and the lack of governance by said parties. They effectively betrayed the nation's right to be safe from nuclear accidents. Therefore, we conclude that the accident was clearly "manmade." We believe that the root causes were the organizational and regulatory systems that supported faulty rationales for decisions and actions, rather than issues relating to the competency of any specific individual.

This largest nuclear disaster after Chernobyl in 1986 and its investigation makes a number of points clear related to regulation and knowledge in major 'techno-scientific' operations. Foremost it shows that "even in one of the richest and safest countries in the world –and one of the most economically and technologically developed ones- in a high-tech sector that mobilizes a large community of experts and is subject to a whole range of very strict international regulations, and in spite of decades of experience, the management of technoscientfic risks –particularly environmental contamination by dangerous chemical substances- is still a major scientific, technological, social and political problem" (Boudia & Jas, 2013: 1). In Japan, nuclear regulation involved a dense 'web of connections' between politicians and government officials, nuclear companies, and regulators that came to be known as "the nuclear village". This likeminded community had its eyes set on the growth of nuclear

power and tried to do away with proposals or regulations that stood in the way of this goal. The investigation report calls this "regulatory capture", to indicate that despite regulation seemingly based on 'state-of-the-art' scientific knowledge and involving the best experts, power relations and (everyday) politics (e.g. marginalizing whistleblowers) are imperative in the understanding of how such major disasters are made.

3.2.1 Distrust in science?

As the examples above and below make clear, the role of science, knowledge claims and experts is subject of discussion not only in the (expert) field of substances in the environment, but in many other fields as well. In fact, a broader debate on trust in science and experts has recently held sway. Reports from The Royal Netherlands Academy of Arts and Sciences (KNAW, 2013) and from the Scientific Council for Government Policy (WRR) and the Rathenau Institute (Tiemeijer & De Jonge, 2013) deal with an alleged distrust of society in science, following examples like those given in the chapter. In general, they found little evidence for the claim that the legitimacy of science is waning. What seems more plausible is that trust in the ideal of science and science itself is still very high –which might explain the popularity of TV programmes on science– but that (established) scientific institutions are looked upon with (various degrees of) suspicion (Achterberg, 2015).

Factors that might influence trust in science are potentially manifold. Still, some influencing factors indicated in the abovementioned reports include:

- the ease with which the public can nowadays inform themselves using modern (ICT) technologies and the Internet
- a general distrust in authorities that may 'spill over' to scientific institutions, high expectations from the public of science that cannot (always) be met, due to inherent uncertainty about problems and solutions
- educational level and acquaintance with the nature of science and the scientific system
- an increased interconnectedness of science with political, public and private entities
- integrity and the way science is financed and reviewed (KNAW, 2013; Tiemeijer & De Jonge, 2013).

Thinking about potential influencing factors is one thing, examining causality between such factors and trust in science is quite another, and no easy task. Nevertheless, this debate is a reminder to remain critical about the ways in which knowledge is produced and under what conditions in specific fields of science. The remainder of this report will do so for the field of substances in the environmental.

Science & climate change: the IPCC

Fifty-five renowned scientists in the Netherlands published an open letter in 2010, claiming that mistakes in the 2007 report of the Intergovernmental Panel on Climate Change (IPCC) were used by some to bring the entire climate science into discredit (see here). The then Dutch Minister of the Environment Cramer was also deeply troubled, since, she said, her policies were based on 'sound' science. These reactions followed public concerns raised on the objectivity of science on climate change after the discovery of the two errors in the 2007 IPCC report. One such error concerned the projected date of the melting of Himalayan glaciers that was wrongly set on 2035, another in which the proportion of

the Netherlands under sea level was said to be 55%, whilst in fact this number should have been 26%. Mike Hulme, in his book "Why we disagree about climate change" (2009), says that disagreement with science has not so much to do with evidence upon which scientific statements are based, rather because of different understandings of what we perceive as the 'truth', the legitimate role of knowledge in policy-making and the way risk and uncertainty are related. He argues that we need to recognize the limits to scientific knowledge about complex, 'wicked' problems like climate change, and in particular three such limits, namely that [1] scientific knowledge on climate change is and always will be incomplete and uncertain, [2] knowledge production is inevitably related to the 'politics' of climate change and should thus not be treated separately and [3] that we must be honest and transparent about what science can tell us and what it can't (Hulme, 2009: 105-107).

3.2.2 Risk assessments as "post-normal" science

We come across the message on the limits of science when returning to the exercise of risk assessment with which chapter two was concerned, only now cloaked in the concept of "post-normal" science. Enick & Moore (2007: 715) argue that environmental risk assessment of pharmaceutically-active compounds (PhAC) fits the nature of "post-normal" science, which means that "…uncontested legitimization of a substantive problem structuring cannot be achieved". In other words, the problem at hand is complex and multidimensional to such an extent that uncertainty and disagreement will remain about the nature of the problem (and hence, the 'best' solution), despite the best efforts to come to a consensus. This comes with a number of observations. One is on the uncertain nature of 'facts' produced. Such uncertainty remains, given the impossibility to "provide unequivocal data for every chemical, every chemical combination and every specific situation". Facts are thus not 'waiting' for risk assessors to be discovered and unveiled. Rather, as Latour and Woolgar (1979) have demonstrated long ago in their seminal study on 'laboratory life', facts are constructed.

This relates to a second observation, namely the inherent subjective nature of risk assessments (Enick & Moore, 2007; Richardson, 2005). From hazard identification and dose-response assessments to risk characterization, the various stages of risk assessments requires addressing conflicting needs and values. Such values can be epistemic or non-epistemic. Epistemic values relate to the goals to be achieved in science, including coherence with accepted hypothesis, whereas non-epistemic values relate to restrictions based on social or personal values as well as the use (or non-use) of particular methods, based on practical, financial or ethical concerns. Depending on the social and policy context in which risk assessments are carried out, researchers may hold a specific 'risk window', "that only allows those risks that have been pre-defined as relevant to a social value, to be visible" (Enick & Moore, 2007: 717). Furthermore, risk assessors are often faced with a rather short time frame in which risk assessment decisions need to be made and even in the face of inconclusive data, need to come up with 'scientifically sound' conclusions.

How to cope with such features underpinning risk assessments? The next section will briefly tackle this question.

3.3 What role for science in policy-making?

As outlined, science has been an important pillar upon which regulation and policy-making on substances in the environment is based. For this to continue in the future, it is recommended to proactively reveal and deal with (rather than conceal) some of its major

limitations, some of which have also been described in this and the other chapters. This part provides some suggestions.

3.3.1 RIVM: broaden conceptions of risk vis-à-vis policy-making

The Dutch National Institute for Public Health and the Environment (RIVM) has published several reports over the years that deals with the issue of science, risk and environmental regulation in the Netherlands (RIVM, 2003; 2014). The 2003 report 'Coping rationally with risk' opened up and broadened the discussion on the concept of 'risk', beyond the 'conventional' interpretation of risk as 'probability times impact' that was hitherto customary, and the 2014 report partly followed up on this. These reports advised or observed changes in policy-making on environmental risks, notably a departure from the technical, 'classical approach'. In this approach scientists and experts deal with risk assessment. Supposedly value-free, they quantify possible damage, loss, costs etc., after which policy-makers decide on the social acceptability of risk or to what extent risks should be reduced. Based on this, the cost-effectiveness of policy measures could be estimated quite well. This approach has been fairly successful for 'well-known' risks, e.g. familiar substances of which much and fairly robust knowledge was available regarding their origin, dispersion, behavior, exposure and effects.

But the number, diversity and magnitude of substances in the environment grew and parallel to that developed the concept of 'risk'. Risk could no longer be seen, the reports indicate, solely as a technical construct. Increasingly it came to be seen as a 'social construct'. This implied that risks related to environmental health issues involved all sorts of issues that could not be quantified or 'objectified', such as differing values, preferences, experiences and the distribution of 'joys' and 'burdens'. Coupled with the insight that risk assessments are not 'neutral', value-free exercises either, but based on assumptions and values that are inherently (inter-)subjective, the reports recommend to broaden up the treatment of risks by professionals and policy-makers, depending on the 'risk type'.

They distinguish, based on Klinke & Renn (2002), four types of dominant risk types. One concerns 'simple' risks whose complexity and uncertainty is limited. In this case, traditional risk assessments by experts suffice. A second are 'complex risks', whereby it is much more difficult to establish causal links. Increasing the knowledge base and involving a more diverse range of experts is called for and policy-makers need to weigh the effectiveness of different policy responses. The third and fourth risk types relate to uncertainty and ambiguity, for instance when the available knowledge can and will not provide a definitive basis for assigning probabilities or that different, all legitimate interpretations on the issue at hand, exist. In these cases, involving only experts could in itself be a risk in terms of generating misunderstanding and irritation, and so it is recommended to also involve societal actors including citizens.

3.3.2 Towards (policy-making based on) deeper understandings of 'incomplete knowledge'

Some of the parts in the RIVM reports are based on the work of Andy Stirling, who has for long investigated questions on risk, precaution and science-based policy. He goes a bit further than the RIVM though; he argues for a move away from "a narrow focus on risk to broader and deeper understandings of incomplete knowledge" (Stirling, 2010: 1030). However, he continues, a tendency of policy-makers and experts is often that of 'closing down' rather than 'opening up' understandings of incomplete knowledge, ultimately ending up assessing and judging risks in the same, technical style manner (Stirling, 2009). This final section will elaborate on these arguments.

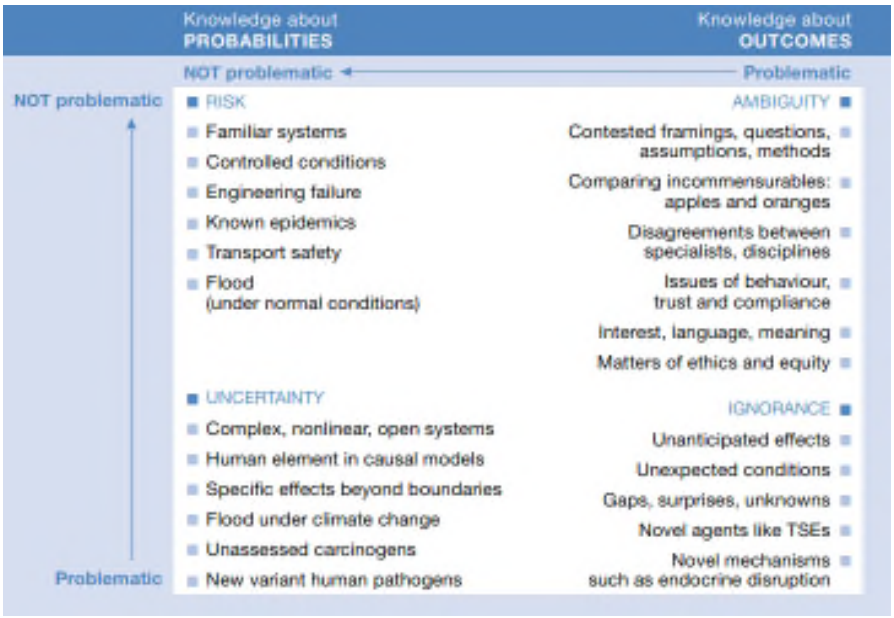


Figure 3.1 Contrasting states of incomplete knowledge
(Source: Stirling, 2007: 319)

Stirling intentionally distinguishes risk from uncertainty, ambiguity and ignorance and does not reduce these latter three types of conditions to 'risk-types'. Risk, to him, presupposes an unproblematic attitude towards possibilities and probabilities, making those suitable to probabilistic assessments. Risk as quantified uncertainty thus, as the historical overview on the concepts of risk and uncertainty showed in chapter two. Surely, in some cases, such as the epidemiology of familiar diseases, such methods can still yield important information for policy. But even in the most familiar processes -let alone in others we know much less about- there are unforeseen possibilities, which can undermine policy decisions based on these methods. We therefore need not only search for answers within the paradigm of risk, like Christensen et al. (2003) propose, but also explore concepts and policy options beyond the concept of risk.

Many environmental issues that confront us now meet one or more of the characteristics pertaining to uncertainty, ambiguity or ignorance (i.e. 'we don't know what we don't know') listed in figure 3.1. If this assumption is accepted, and this could well be the case for pharmaceuticals (Enick & Moore, 2007), then it is useful to also broaden up the 'toolbox' and embrace methods, tools and approaches that are more suitable to exploring conditions of uncertainty, ambiguity or ignorance than traditional risk assessment techniques, examples of which are given in a similar matrix, depicted in figure 3.2. This has consequences for policy advice based on science as well. Instead of experts spending hours negotiating 'consensus' advice and come up with a 'single definitive interpretation', under conditions of uncertainty, ambiguity or ignorance it would be more useful and rigorous to make explicit and transparent contrasting views and recommendations and explain their differences. Equally, instead of concealing important regulatory questions deriving from research, they could better be highlighted, such as what is safe or tolerable?

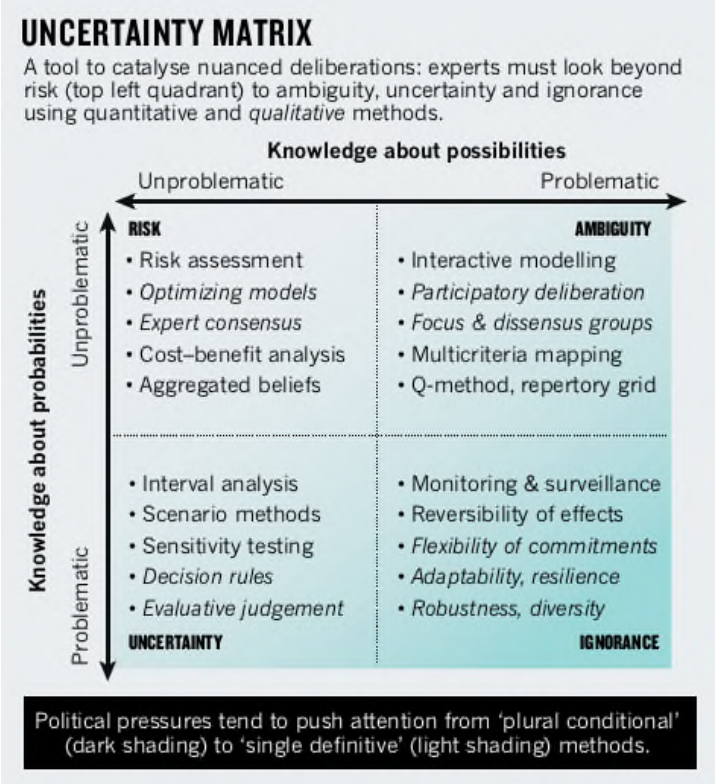


Figure 3.2 Plural methods for different types of conditions (Source: Stirling, 2010: 1030)

Doing so has potential to acknowledge (rather than doing away with) the role of power and politics in expert and policy-making processes. A single definitive interpretation, Stirling states, is often most vulnerable to political manipulation, whilst 'alternatives' that may prove very useful are 'crowded out'. More plural approaches opens up possibilities for argument, deliberation and hence, democratic accountability. It also provides a more comprehensive basis for operationalizing the precautionary principle, a central tenet of environmental policies in the European Union. This principle implies that even in the face of (scientific) uncertainty, measures need to be taken to prevent environmental damage. The principle is not a circumscribed measure, rather a guideline and motivation to deliberately and openly discuss environmental issues at hand. The toolbox proposed by Stirling offers ways to systematically organize such debates. And not only in risk *management*, but also in the production of knowledge, including, but not restricted to risk assessments (Bro-Rasmussen, 2003; Stirling, 2007; Stirling & Scoones, 2007).

For this to happen, tendencies, (political) pressures and convictions (such as on the nature of 'sound' science) need to be overcome to prevent pushing plural, conditional advice towards a single interpretative recommendation, or, as depicted in figure 3.2, "to move understandings of knowledge away from the lower right hand quadrant and towards the upper left" (Stirling, 2007; 2009; 2010).

4 Conclusions

All in all, we have seen that a lot of research is conducted on the sources, occurrence, fate and effects of pharmaceuticals in the environment. This research has shown that the major source of pharmaceuticals in (Western European) surface waters originated from human consumption. Loads and concentrations in wastewater, wastewater effluents and surface waters can be related and even predicted from consumption patterns. Observed concentrations are not expected to be of human health concern since concentrations in (drinking) water are orders of magnitude lower than concentrations that have potential effects. Nevertheless, current research cannot fully assess the integrated effects of the complex mixtures of pharmaceuticals and other micro-contaminants over the course of a human life. So although studies indicate no human health risks, a 100% certainty will not, and probably never be obtained.

Contrastingly, ecological effects of environmental concentrations of pharmaceuticals are evident, as many studies have shown subtle and less subtle effects of environmental concentrations. However, the integrated chronic effect of dynamic concentrations of all pharmaceuticals and other chemicals on the full ecosystem and its functions is not fully known. The mere complexity of the ecosystem makes the nature and magnitude of effects difficult to assess, let alone predict. So, although it is clear that there can be effects on the ecosystem, uncertainty remains on the nature and magnitude of these effects. Again 100% certainty will probably never be obtained.

Scientists cope with these uncertainties pragmatically by introducing risk factors that are either based on for example distributions of sensitivity within a species or between different species. The more there is known on the exposure and effects of a chemical or a mixture of chemicals the smaller these risk factors can become. This generally results in higher thresholds and larger margins between (low) environmental concentrations and these thresholds. Nevertheless, knowing ‘everything’ is not feasible so a certain margin of uncertainty will always remain. Factors that influence risk perception of the general public differ from science. Besides personal characteristics such as gender, age, level of education, and socio-economic status of the general public, the ‘knowability’ and ‘controllability’ of the risk play an important role in the perception of the risk. When these factors are applied to pharmaceuticals in the environment, their chemical nature, omnipresence, involuntary exposure, potential long-term effects, relatively recent appearance (in media), and limited public and scientific knowledge potentially exert a negative effect on the perceived risk. So the perception of the risk of the general public might be larger than the risk perception of scientists.

Surely, this also has repercussions for the link between science and knowledge production and regulation and policy-making. From a historical perspective, science and knowledge production have been highly important for regulation and policy-making related to contaminants in the environment. However, the use of science in policy-making is not able “solve” or take away all uncertainty. Placing the topic of substances in the environment in a historical perspective or describing other complex and/or techno-scientific problems (e.g. climate change or nuclear disaster) revealed this; despite ‘state-of-the-art’ knowledge which feeds into ever more stringent regulation and environmental awareness, disasters happen, surprises occur or competing interpretations remain. This has to do with questions of

politics on the one hand, e.g. whose priorities dominate, by what mechanisms of power are priorities set, who gets to negotiate with policy-makers or politicians and who regulates whom? On the other hand, it has to do with the production of knowledge itself; narrow conceptions of 'risks', their quantitative assessment by experts, leading to one-sided advice based on single interpretations may suffice for those substances and pharmaceuticals of which much is known and little uncertain, but less so for (complex mixtures of) substances that are surrounded by conditions of uncertainty, ambiguity (whereby different or contrasting views remain on a topic, which are all valid) and ignorance (i.e. 'unknown unknowns', a situation in which we don't know what we don't know).

Risk assessments have played and continue to play an important role in the assessment of pharmaceuticals and in informing policy-making processes. However, one message of this report is to broaden up the 'toolbox' with which to investigate and assess pharmaceuticals in the environment, Next to 'traditional' risk assessments, there are other methods that can support the assessment of pharmaceuticals, many of which are more suitable to cope with conditions of uncertainty, ambiguity and ignorance. Such a broader and enhanced toolbox should generate policy advice that reveals, rather than conceals the uncertainty (or ambiguity or ignorance) underpinning the scientific assessment of pharmaceuticals. This in turn might provide a basis for a more comprehensive operationalization of the precautionary principle in policy-making and regulation, where policy-makers focus on what is safe and acceptable. This may lead to more democratic decision-making regarding the regulation of substances than has often been the case.

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