KWR Waterwijs
KWRW 2025.040 | April 2025

Protecting drinking water through different regulations

Differences and similarities of avoidable and unavoidable risks

KWR | waterwijs

KWR | waterwijs

Impact through drinking water research

Colophon

Protecting drinking water through different regulations

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Samenvatting

Bescherming van drinkwater door middel van verschillende beleidskaders: Verschillen en overeenkomsten tussen vermijdbare en onvermijdelijke risico's

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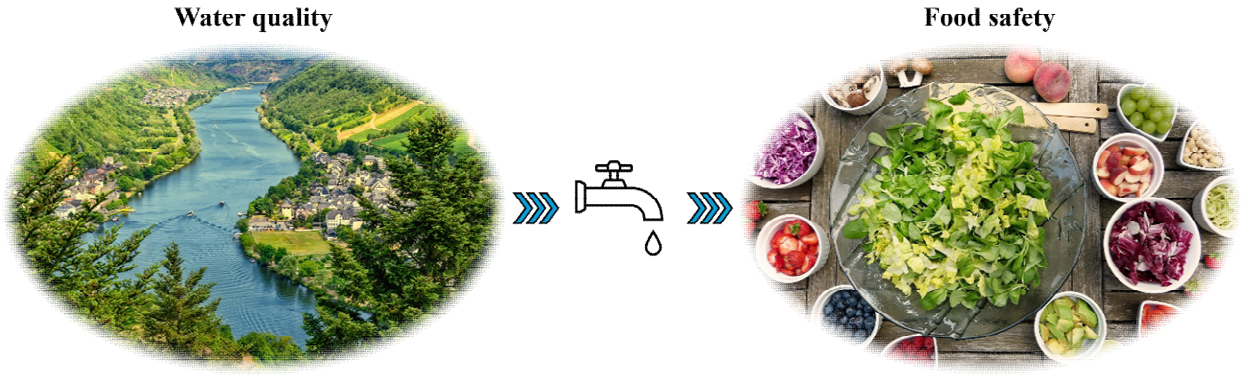


Aanleiding:
Water en voedsel zijn intrinsiek met elkaar verbonden. Water speelt vaak een cruciale rol in de vroege stadia van voedselproductie. De alomtegenwoordige watervervuiling en debatten over alternatieve bronnen voor drinkwater leiden tot striktere regelgeving, zoals strengere normen voor waterkwaliteit. De basis voor wetgeving rond drinkwater rust op goed ingeburgerde principes en hulpmiddelen voor risicobeoordeling, maar biedt die basis voor wet- en regelgeving ook voldoende bescherming tegen toekomstige uitdagingen door chemische verontreinigingen en complexe mengsels daarvan? Kunnen risicoprincipes en -benaderingen uit andere wetenschappelijke en regelgevende kaders, zoals voedselveiligheid, worden aangepast voor het domein van drinkwater? Worden de eisen voor waterkwaliteit strenger vanwege zulke nieuwe benaderingen? En hoe kunnen drinkwaterbedrijven vermijdbare en niet-vermijdbare verontreinigingen effectief beheersen? Het integreren van waterkwaliteit en voedselveiligheid is een uitdaging vanwege de verschillende gehanteerde benaderingen voor risicobeoordeling en -beheer. Drinkwaterbedrijven zouden voordeel kunnen hebben van het toepassen van de nieuwste wetenschappelijke methoden uit zowel de water als de voedingsmiddelensector bij het evalueren van risico's, het beheersen van verontreinigingen en het vaststellen van veiligheidsdrempels.

Aanpak:
Om de ontwikkelingen rond de wettelijke risicobeoordeling in de voedsel- en drinkwatersector te evalueren is een semi-systematische review gedaan van wetenschappelijke literatuur en documentatie over regelgeving in beide domeinen. Daarvoor zijn de huidige wetenschappelijke en wettelijke grondslagen van waterkwaliteitsnormen vastgelegd en zijn onderzoeksvragen geïntroduceerd om het onderzoek naar alternatieve principes voor risicobeoordeling te sturen. De analyse omvat ook inzichten van samenwerkende experts. Via speciaal opgezette discussies deelden zij hun ervaringen en geleerde lessen rond uitdagingen met betrekking tot de kwaliteit van drinkwater, zoals niet-vermijdbare blootstellingen en onzekere wettelijke vereisten. Door gevestigde methodologieën te vergelijken met innovatieve, zoals het hergebruiken van toxicologische concepten uit voedselveiligheid, het integreren van diervrije New Approach Methodologies (NAM's) en het aanpakken van de complexiteit van chemische mengsels, is kritisch onderzocht hoe deze alternatieve kaders de vaststelling van waterkwaliteitsnormen en risicobeheerpraktijken zouden kunnen hervormen.

Resultaten:
Deskundigen op het gebied van waterkwaliteit en voedselveiligheid passen vaak verschillende methoden voor risicobeoordeling toe, met name op het gebied van risicomanagement. Beide groepen hebben echter hetzelfde doel: het waarborgen van water en voedsel van hoge kwaliteit. Door juist de overeenkomsten tussen beide groepen te erkennen, wordt het mogelijk de beste kennis uit beide vakgebieden te combineren. Onderzoek suggereert dat, net als bij voedsel, sommige resten van verontreinigende stoffen in drinkwater onvermijdelijk zijn. Ondanks strikte naleving van de regelgeving wordt verwacht dat niet-gereguleerde verontreinigende stoffen zoveel mogelijk worden geminimaliseerd. Dit daagt waterleveranciers en regelgevers uit om actie te ondernemen, bijvoorbeeld via (strengere) regelgeving, hogere investeringen in behandeling en productie, en meer samenwerking om vroeg in de keten verontreiniging aan te pakken. De geleidelijke invoering van alternatieve risicoprincipes en NAM's biedt een veelbelovende route naar verbetering van de beoordeling van chemische waterveiligheid en op wetenschappelijk bewijs gebaseerde waterkwaliteitslimieten. Door de afhankelijkheid van dierproeven te verminderen en het voorkomen en de toxiciteit van nieuwe verontreinigende stoffen beter te voorspellen, kunnen deze benaderingen de risicobeoordeling verbeteren. Investeren in domeinoverstijgend onderzoek en het versterken van domeinoverstijgende partnerschappenzal waterbedrijven helpen met de aanwezigheid van microverontreinigingen om te gaan.

Vervolg:
Interactie en kennisuitwisseling tussen drinkwaterexperts en experts op het gebied van voedselveiligheid draagt bij aan de beoordeling van alternatieve strategieën voor risicobeoordeling en -beheer. In beide domeinen worden verschillende strategieën en methoden toegepast om verontreinigingen te beheersen en de volksgezondheid te beschermen, zoals Margin of Exposure (MOE) en Disability-Adjusted Life Year (DALY) om op basis van blootstellingsrisico's voor de lange termijn te bepalen welke verontreinigingen prioriteit moeten krijgen bij de aanpak ervan. Waterkwaliteitslimieten, die zijn gebaseerd op de effecten van verontreinigingen op het menselijk lichaam, kunnen evolueren naarmate regelgevers zich steeds meer gaan richten op de nieuwe generatie risicobeoordelingsbenaderingen, zoals Adverse Outcome Pathways (AOP's). Bovendien kunnen diervrije NAM's voor het testen van water- en voedselverontreinigingen (bijv. gastro-intestinale organoïde-modellen) waardevolle inzichten bieden in het gedrag van opkomende stoffen. Door trends in de toepassing van dit soort modellen en de daarbij horende ontwikkelingen in waterkwaliteitsnormen te bestuderen kunnen bedrijven veranderingen in de regelgeving voor stoffen voorblijven.

Implementatie:
Verschillende belanghebbenden hebben vaak verschillende standpunten over huidige en toekomstige drinkwaternormen, de potentiële impact van de nieuwe generatie risicobeoordeling en de overgang naar dierproefvrije en NAM-gebaseerde drinkwaternormen. Duidelijke communicatie over de mogelijkheden en onmogelijkheden van huidige risicobeoordelingen van waterverontreinigingen kan het vertrouwen in NAM’s vergroten. Samenwerken in verschillende domeinen – door experts, bedrijven en beleidsmakers te betrekken bij gezamenlijke discussies – zal helpen kennis te delen en consistente risicobeoordelingen te creëren. KWR zou bijvoorbeeld een forum voor kennisuitwisseling kunnen faciliteren tussen water- en voedselexperts via jaarlijkse bijeenkomsten die voortbouwen op de in dit project gevoerde discussies over de toekomst van voedselveiligheid en waterkwaliteit. Daarnaast zal investeren in onderzoek naar mengselblootstellingen, NAM's en wetgeving ten aanzien van chemische verontreinigingen waterbedrijven helpen zich voor te bereiden op ontwikkelingen in waterkwaliteitsnormen.

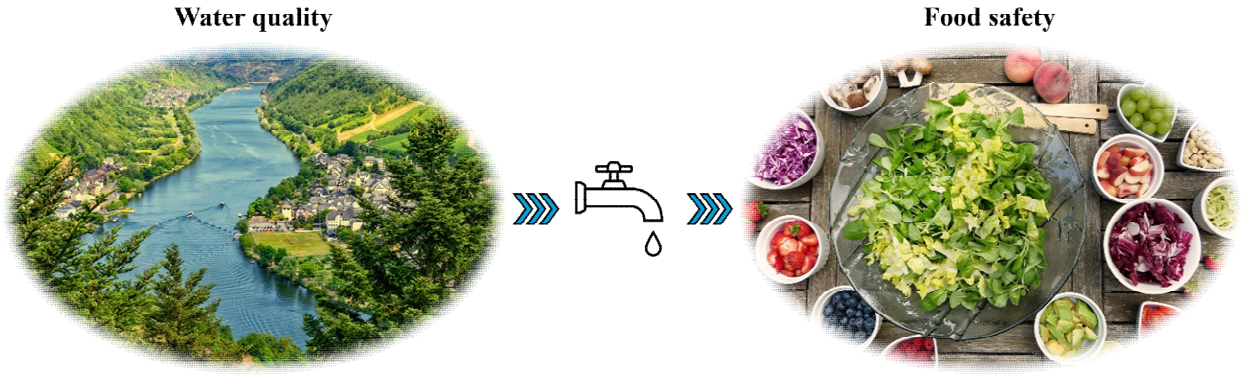
Maatschappelijke impact:
Waterbedrijven kunnen een proactievere rol aannemen binnen het bredere netwerk van stakeholders die van waarde zijn voor water. Dit netwerk omvat alle actoren en entiteiten die aan water waarde toevoegen of afnemen, waaronder sectoren die vervuilende stoffen uitstoten, waterschappen, gemeenten, handhavingsinstanties, academische experts en zowel publieke als private organisaties. Er kan bijvoorbeeld een jaarlijks forum voor kennisuitwisseling tussen

wetenschap, beleid en maatschappij worden georganiseerd om een geïntegreerd begrip van de toekomst van voedselveiligheid en waterkwaliteit te vergroten en op te bouwen. Een sterkere betrokkenheid van upstream-actoren (zoals de landbouw- en industriële sectoren) kan helpen de indirecte overdracht van verontreinigingskosten te beperken. Transparante communicatie over beperkingen en risico's van het afzonderlijk beoordelen en beheren van de waterkwaliteit en voedselveiligheid, samen met experts en andere belanghebbenden, zal het publieke vertrouwen vergroten en de algehele waterveiligheid versterken. Gezamenlijk zorgen deze maatregelen niet alleen voor veiliger drinkwater, maar positioneren ze waterbedrijven ook als proactieve leiders op het gebied van volksgezondheid en samenwerking tussen sectoren.

Summary

Protecting drinking water through different regulations: Differences and similarities of avoidable and unavoidable risks

Authors: Daniel João Duarte, Sanah Majid Shaikh, Inge van Driezum, Astrid Reus



Context:
Water and food are intrinsically connected, with water playing a critical role in the early stages of food production. Pervasive water pollution and debates about alternative sources of drinking water are prompting stronger regulatory actions, including stricter water quality standards. Well-established risk assessment principles and tools underpin drinking water legislation. However, will these withstand future challenges posed by chemical contaminants and their complex mixtures? Could risk principles and approaches from other scientific and regulatory frameworks, such as from food safety, be adapted for the drinking water domain? Will water quality requirements become more stringent due to upcoming new approaches? And how can drinking water companies effectively manage avoidable and unavoidable contaminants? Integrating water quality and food safety is challenging due to differences in risk assessment and management approaches. However, drinking water companies may benefit from adopting the latest scientific methods for evaluating risks, managing contaminants, and setting safety thresholds across both sectors.

Approach:
The study employs a semi-systematic review of scientific and regulatory literature to evaluate developments in regulatory risk assessment across the food and drinking water sectors. It establishes the current scientific and regulatory foundations of water quality standards and introduces research questions that guide further inquiry into alternative risk assessment principles. The analysis also incorporates insights from collaborating experts and dedicated discussions were held to learn from their experiences and share lessons learnt from challenges related to drinking water quality, such as unavoidable exposures and uncertain regulatory requirements. By comparing established methodologies with innovative ones, such as repurposing toxicological concepts from food safety, integrating animal-free New Approach Methodologies (NAMs), and addressing the complexity of chemical mixtures, the report critically examines how these alternative frameworks might reshape water quality standard setting and risk management practices.

Results:
Water quality and food safety experts often apply different risk assessment methods, particularly in risk management. However, both share the goal of ensuring high-quality water and food. Recognizing their commonalities and

integrating the best knowledge from both fields seems crucial to improve public health. Research suggests that, like food, some contaminant residues in drinking water may be unavoidable. Despite strong regulatory compliance, contaminants (regulated or not) are expected to be minimized as much as possible. This challenges water suppliers and regulators to act, e.g. by (stricter) regulations, higher treatment costs, and increased collaboration to address contamination of source materials. The gradual adoption of alternative risk principles and NAMs offers a promising path for improving chemical safety assessment and evidence-based water quality limits. By reducing reliance on animal testing and better predicting the occurrence and toxicity of emerging contaminants, these approaches enhance risk assessment. Investing in cross-domain research and strengthening cross-domain partnerships will help water companies to navigate practical constraints related to the presence of micropollutants.

Follow-up:
Interaction and knowledge exchange between drinking water experts and food safety experts contributes to the evaluation of alternative strategies in risk assessment and management. In both domains, various strategies are used to manage contaminants and protect public health by using methods such as the Margin of Exposure (MOE) and Disability-Adjusted Life Year (DALY) to prioritize which contaminants to control based on concerns of long-term exposure risks. Water quality limits, grounded in the causal effects of contaminants on the human body, might evolve as regulators will increasingly focus on new generation risk assessment approaches such as Adverse Outcome Pathways (AOPs). In addition, animal-free NAMs for testing water and food contaminants (e.g., gastrointestinal organoid models) can provide valuable insights into the effects of consumed chemicals of emerging concern. By studying trends in the application of these approaches and associated developments in water quality standards, drinking water companies can stay ahead of changes in chemical regulation.

Implementation:
Different stakeholders often hold different viewpoints on current and future drinking water standards, the potential impact of next-generation risk assessment, and the transition to animal-free and NAM-based drinking water standards. Clear communication about the possibilities and impossibilities of current water contaminant risk assessments can build trust in the use of NAMs. Working together across different domains – by involving experts, companies, and policymakers in joint discussions – will help share knowledge and create consistent risk evaluations. For example, a knowledge exchange forum may be facilitated by KWR together between water and food experts via annual meetings that expand on the discussions within this project about the future of food safety and water quality. Additionally, investing in research on mixture exposures, NAMs and chemical regulation will help companies prepare for developments in water quality standards.

Social impact:
Water companies may consider to assume a more proactive role within the broader stakeholder network of the water value chain. This network includes agents that add to or subtract from the value of water intended for human consumption, such as pollutant-emitting sectors, water boards, municipalities, local enforcement agencies, academic experts, regulators and both public and private organizations. For example, an annual science-policy-society knowledge exchange forum may be facilitated to order to expand and build an integrated understanding about the future of food safety and water quality. Stronger engagement with upstream actors (such as the agricultural and industrial sectors) could help mitigate the indirect transfer of contamination costs to society. Transparent communication regarding the limitations and risks of assessing and managing water quality and food safety separately, along with greater interaction among stakeholders, will build public trust and strengthen overall water safety. Collectively, these measures not only ensure safer drinking water but also position water companies as proactive leaders in public health and cross-industry collaboration.

Content

Reading guide

The present report is the result of a comprehensive study on recent developments in (inter)national regulatory risk assessment across domains, with a focus on food and drinking water quality, and an evaluation of the potential impact of adopting alternative risk assessment principles on water quality standard setting and risk management. The reader is encouraged to select the most relevant (sub)chapters based on their specific interests, as these may offer valuable insights to various experts in the water sector and beyond. Chapter 1, introduces the subject matter of the present report by laying regulatory and scientific foundations of how water quality and water quality standards are established at the international and national level. Chapter 2 lays in simple terms the main aim of the report, i.e., to examine recent developments in regulatory risk assessment across domains, focusing on food and drinking water quality. The main research questions are also presented in this chapter. It also evaluates how adopting alternative risk assessment principles, uncommon or not yet established in drinking water practices, might influence water quality standards and risk management. Chapter 3 explains and explores how foundational principles in water and food quality standard setting are established for different types of contaminants causing adverse effects. It also highlights key differences in relevant terminology in water quality and food safety. Chapter 4 explores how toxicological and risk assessment concepts from the food safety domain may be repurposed as alternatives for risk assessment by the water sector. Importantly, it reflects on how to address unavoidable water contamination and risks. In Chapter 5, the potential changes in water quality limits and health-based guidance values, whether they remain the same or become more or less stringent, are discussed in light of the need for capable tools to assess chemical risks while aligning with ethical ambitions in the use of innovative (animal-free) approach methodologies (NAMs). Chapter 6 breaks down the similarities and differences in risk assessment across the water quality and food domains. Examples of food contaminants are used to help elaborate on how one conceives and balances the risks and benefits, while appreciating the rationale that lead to risk mitigation measures. Furthermore, the added complexity of mixtures risk assessment is currently being discussed in the scientific literature and how it relates to the interconnectedness of a diverse legislative landscape. Chapter 7 highlights the key challenges and opportunities in integrating the insights from previous chapters to help the water sector adapt to evolving regulatory requirements. Challenges lay ahead in the water sector's ability to cope with pressure over the pollution or contamination of sources of water for human consumption, posing a problem of achievability while balancing risks and benefits of potentially contaminated drinking water. Chapter 8 provides an outlook on the future of water quality standard setting. In Chapter 9 the main outcomes of the present research are compiled and formulated according to the key question underlying this work "What does the future have in store for the processes of water quality limit derivation, compliance, and risk assessment?". Finally, Chapter 10 concludes the report with overarching reflections on the findings of the study and insights about the differences and similarities of avoidable and unavoidable risks with the ultimate goal of protecting drinking water under different regulations.

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1 Introduction

In October 2020, the European Commission adopted its new chemicals strategy geared towards a toxic-free environment as part of the European Green Deal. This initiative includes protecting aquatic environment and, consequently, drinking water sources. However, many challenges remain in curbing the degradation of the environmental water quality. The Netherlands has been reported to have the lowest water quality in the EU, with only 1% of waters classified as 'good', according to the Water Framework Directive (WFD) (van den Brink, 2022). This carries implications and challenges the ability to retain and keep water accessible for use (quantity), but also in guaranteeing the accessibility to safe drinking water (quality). The WFD was adopted shortly after the Drinking Water Directive (DWD) requiring the protection of bodies of water, including those used for drinking water abstraction, supporting the compliance of DWD requirements (Box 1).

Box 1. *Provision on water used for the abstraction of drinking under the Water Framework Directive of the European Union (Directive 2000/60/EC).*

Article 7

Waters used for the abstraction of drinking water

1. Member States shall identify, within each river basin district:
— **all bodies of water** used for the abstraction of water intended for human consumption providing more than 10 m^3 a day as an average or serving more than 50 persons, and
— those bodies of water intended for such **future use**.
Member States shall **monitor**, in accordance with Annex V, those bodies of water which according to Annex V, provide more than 100 m^3 a day as an average.
2. (...)
3. Member States shall ensure the **necessary protection** for the bodies of water identified with the aim of avoiding deterioration in their quality in order to reduce the level of purification treatment required in the production of drinking water. Member States may establish safeguard zones for those bodies of water.

In some European countries, such as the Netherlands, tap water quality is assured by means of source protection and the treatment as well as the maintenance of the distribution system. This is an important aspect because, although the directive is colloquially referred to as 'Drinking Water' Directive, its official name does not include the term, nor does it provide a specific definition. Instead, the subject matter is water intended for human consumption (Box 2). Thus, it is noteworthy to remind that for the purposes of the DWD, the definition of 'water intended for human consumption' applies.

Box 2. *Definition of water intended for human consumption for the purposes of the Drinking Water Directive of the European Union (Directive (EU) 2020/2184).*

Article 2
Definitions

(a) **all water**, either in its original state or after treatment, **intended** for drinking, cooking, food preparation or other domestic purposes in both public and private premises, **regardless** of its origin and whether it is supplied from a distribution network, supplied from a tanker or put into bottles or containers, including spring waters;

(b) **all water** used in **any food business** for the manufacture, processing, preservation or marketing of products or substances intended for human consumption.

In 1980 the EU adopted the Drinking Water Directive (Directive 80/778/EEC), followed by its replacement in 1998 (Directive 98/83/EC), and again replaced in 2020 (Directive 2020/2184), regulating the quality of water intended for human consumption. To help manage and keep drinking water contaminants at acceptable levels, water quality standards are established. As countries and territories often review their legislation and values, specifications of values for drinking-water and its water sources are constantly subjected to change. This is explicitly established in Article 5 of the DWD (**Box 3**).

Box 3. *Article 5 of the Drinking Water Directive of the European Union (Directive (EU) 2020/2184).*

Article 5
Quality standards

1. Member States shall set values applicable to water intended for human consumption for the parameters set out in Annex I.

2. The parametric values set pursuant to paragraph 1 of this Article shall not be less stringent than those set out in Parts A, B, C and D of Annex I. As regards the parameters set out in Part C of Annex I, the values shall be set only for monitoring purposes and for the sake of ensuring that the requirements set out in Article 14 are met.

3. A Member State shall set values for additional parameters not included in Annex I, where the protection of human health within its national territory or part of it so requires. The values set shall, as a minimum, satisfy the requirements of point (a) of Article 4(1).

Several legislative frameworks are in force to safeguard water quality in the European Union besides the DWD, the WFD. These include the Environmental Quality Standards Directive (EQS), the Ground Water Directive (GWD), the Marine Strategy Framework Directive (MSFD), Bathing Water Quality Directive (BWQD), the minimum requirements for water reuse Regulation, and Urban Wastewater Treatment Directive (UWWT). For drinking water and its abstraction, the most important laws are the WFD (Directive 2000/60/EC) and the DWD (Directive (EU) 2020/2184). The WFD strives for good qualitative and quantitative health of water bodies by setting monitoring requirements and refers to its daughter directives, the GWD (Directive 2006/118/EC) and EQS (Directive 2008/105/EC). Good qualitative and quantitative health of water bodies, such as groundwater and surface water, is key for the abstraction of source water in good condition for the production of drinking water.

EU Directives require transposition into national law. However, Member States have the freedom on how to devise their national laws to reach the Directive's goal. Implementation of more stringent parameters is the Member States' choice. For example, the Netherlands has seven parameters with more stringent limits implemented in its national law (Table 1).

Table 1. Difference in minimum requirement chemical values for quality assessment of water intended for human consumption in 2024. Substances with the same statutory values are not included.

Substance	WHO (4th Ed.)	European Union's Drinking Water Directive (µg/L)	Dutch Drinking Water Decree (µg/L)
Bromate	10	10	1
Fluoride	1500	1500	1000
Nitrite	3000	500	100
N- nitrosodimethylamine (NDMA)	0.1	–	0.0012
PFAS total	–	0.5	–
Polychlorinated biphenyls (PCBs) (individual)	–	–	0.1
PCBs (sum)	–	–	0.5
Trihalomethanes total	–	100	–
Trihalomethanes (sum)		–	25
Trihalomethane - Chloroform	300		
Trihalomethane - Bromoform	100		
Trihalomethane - Dibromochloromethane	100		
Trihalomethane - Bromodichloromethane	60		
Vinyl chloride	0.3	0.5	0.1

The World Health Organisation (WHO) has issued guidelines for numerous drinking water contaminants, however, these are not legal or enforceable standards, as WHO is not a regulatory body (Levin et al., 2024). Since the first edition of the Guidelines for Drinking Water Quality (GDWQ) in 1958, the guidelines have followed a risk-benefit philosophy and has remained advisory in nature. Notably, the term "international standards" were abandoned. Interestingly, the parameters and values set in the DWD are generally underpinned by WHO derivations (WHO, 2017b). In fact, in a comprehensive analysis by the WHO on worldwide national regulations and standards for drinking-water quality, it was found that the GDWQ was referenced by more than half of the countries and territories, either directly or indirectly by referencing other countries. Furthermore, it is likely that this number is higher as full value standard was not always available. Since the local context is highly relevant and these standards are applied differently (i.e., mandatory, recommended and/or risk-based), a direct comparison is difficult and should be done with caution (WHO, 2021).

The DWD takes a preventive approach favouring actions to reduce pollution at source by introducing the risk-based approach. However, the drinking water sector needs to guarantee water quality being serviced, even if it requires improving water treatment operations to cope with ever increasing polluted waterways. In justified circumstances, Member States may provide derogations so long as these do not constitute a potential danger to human health.

In the Netherlands, the main players in standard setting are the Directorate for Environmental Safety and Environmental Risks of the Ministry of Infrastructure and Water Management (IenW), and the National Institute for Public Health and the Environment (RIVM). RIVM receives requests from IenW policy departments and competent authorities to derive risk limits for air, water and drinking water. Ultimately, IenW decides whether or not standards ought to be established, while RIVM is responsible for providing advice and the scientific basis (TAUW, 2023). The formal procedure to establishing these standards is depicted in **Figure 1** (Waterstaat, 2022).

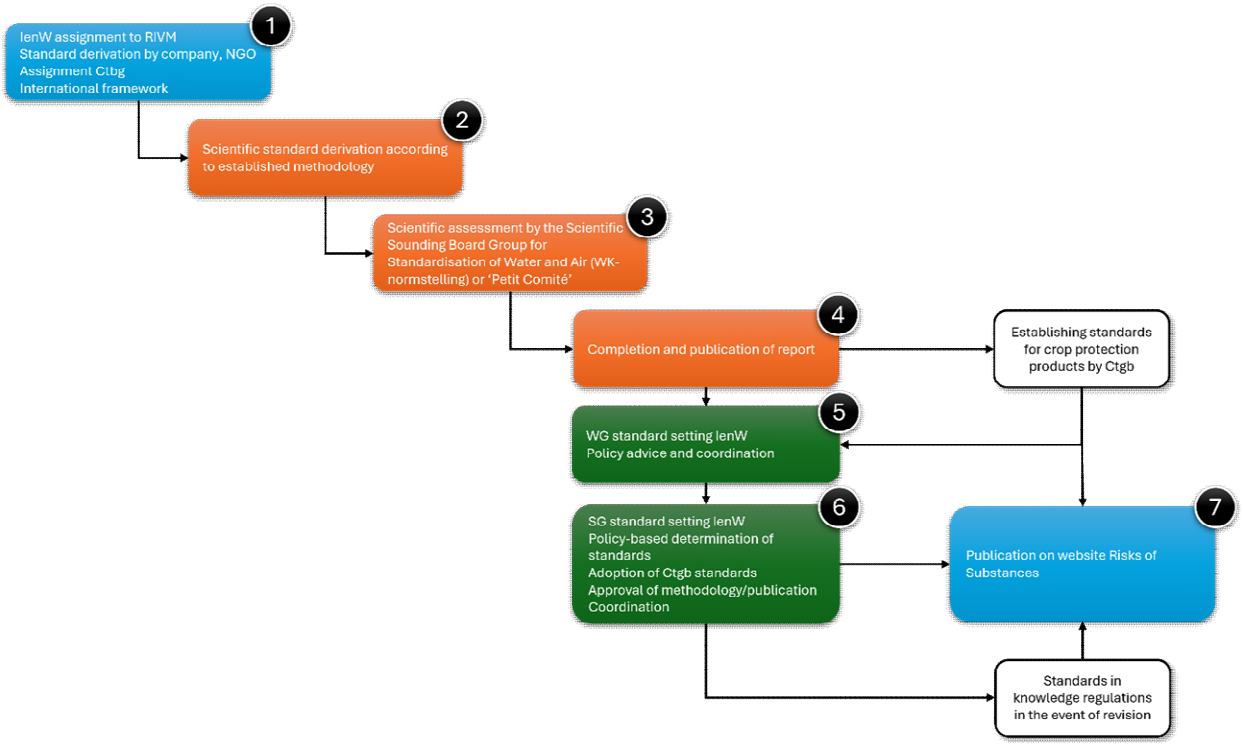


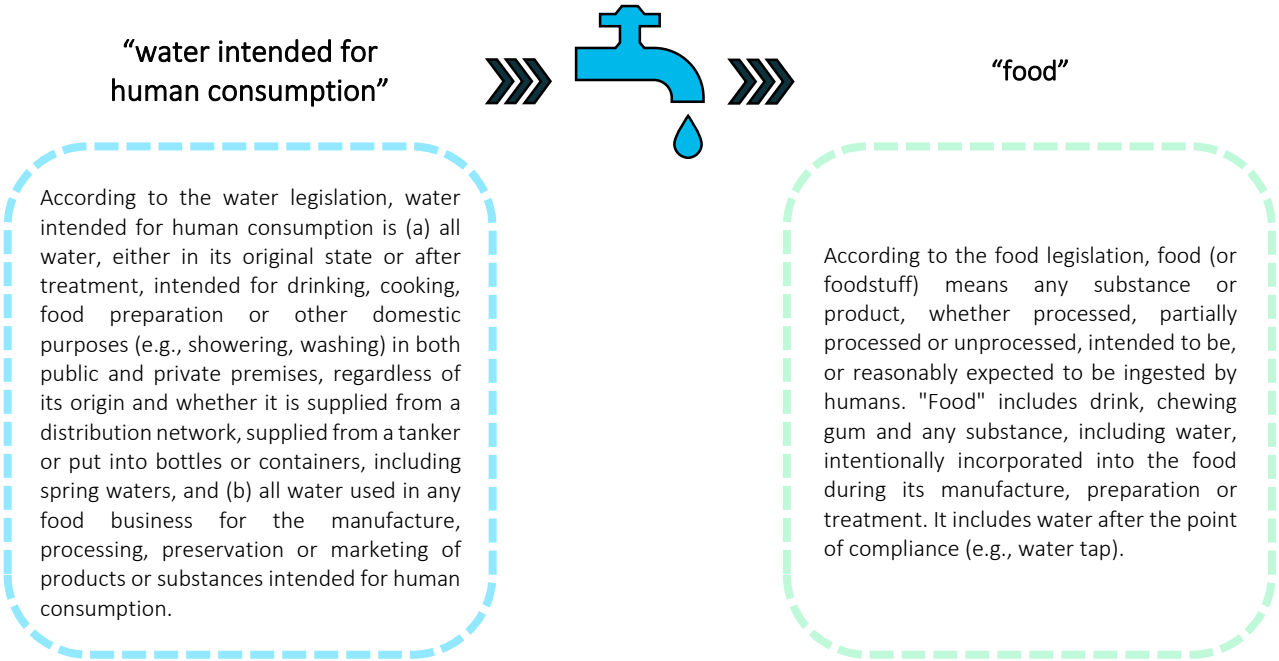
***Figure 1**. Water quality standard setting procedure in the Netherlands. Based on: Waterstaat (2022)*

The drinking water sector in the Netherlands is strictly regulated, often acting beyond recommendations and regulatory obligations. It operates within a well-coordinated governance framework, where drinking water companies collaborate closely with stakeholders such as water boards and national authorities. Traditionally, the drinking water domain is managed by its own niche of experts, practitioners and regulators. However, drinking water is increasingly becoming a broader matter, not confined to a particular set of stakeholders but instead being expanded as a transdisciplinary matter. This shift is especially essential for adapting to growing demands and emerging challenges in the sector.

Water is ingested directly or indirectly like through other foods, thereby contributing to the overall exposure of a person to ingested substances. Therefore, it does not come as surprise that 'food' includes water that is intentionally incorporated into the food during its manufacturing, preparation or treatment (EC, 2022b). This is laid down in the water legislation (see **Box 2**), where this refers to all water intended for cooking and food preparation, or used in any food business. According to food law, after the 'point of compliance', for example the water tap, water is to be considered as food if it is intended or reasonably expected to be, ingested by humans (EC, 2002b). Unlike food, feed (i.e., animal food) does not include water. However, feed businesses must ensure that water used is of suitable quality and meets hygiene requirements (EC, 2005). Note that natural mineral waters are excluded from the scope of the DWD. As shown in **Figure 2**, the water and food sectors are intrinsically connected with water playing a critical role in the early steps of food production. Therefore, Dutch, Belgium and other EU member state industries that use high

quantities of water, such as the food and drink industry, can generally rely on drinking water supplies and do not need to install their own extensive treatment facilities (EC, 2016). Another example of the intricate relation of water and food is also reflected in legislation, for example, in the creation of positive lists for materials in contact with drinking water developed on the basis of substances authorized for use in food contact materials (ECHA, 2025). The Dutch Commodities Act is yet another example of water-food connection, where the ruling applies to all products used by consumers, both food and non-food (NL, 2025). Here the producer is responsible for the safety of the product and information about the product (including potential risks). Thus, it makes sense to evaluate the relatedness of water and food, and better understand the similarities between the water and food risk assessment. Furthermore, with increasing technical abilities to detect contamination in both water and food, it is becoming increasingly challenging to ascertain which risks are associated with particular contaminant groups, and achieve a good understanding of which risks are avoidable or unavoidable.

***Figure 2**. Water as referred to in the Drinking Water Directive and the Food Regulation.*



2 Aim

The aim of this project is to study recent developments in (inter)national regulatory risk assessment across domains, in particular food and drinking water quality, and evaluate the potential impact of the adoption of alternative risk assessment principles on water quality standard setting and risk management. In the context of the study, the term 'alternative' refers to principles and approaches that are not presently, commonly applied, or established in drinking water legislation and practice. The following key questions will be attempted to be answered:

- ‘Does current knowledge and estimates in the food and water domain have impact on the acknowledgement that contaminant residues in drinking water are sometimes unavoidable?’
- ‘What impacts may drinking water companies expect on water quality requirements due to developments in risk assessment and management?’
- ‘Could other risk principles and NAMs become an increasingly acceptable idea to adopt in the drinking water domain?’
- ‘How can drinking water companies influence future costs of (un)avoidable risks posed by water contaminants?’

Additionally, other ancillary questions which emerged throughout the current work have been addressed.

3 Principles in quality standard setting

3.1 Health-based guidance values (HBGV)

Health-based guidance values (HBGV) are a key concept in human health risk assessment and in establishing water quality and food safety standards. These values are typically derived from modelling dose-response relationships drawn from *in vivo* studies or observational epidemiological studies. HBGVs establish a safe level of human intake of chemicals and are typically expressed in µg/kg bw/day applying to the general population. A guidance value may also be described as the concentration of a constituent that does not exceed tolerable risk to the health of the consumer, typically over a lifetime of consumption (WHO, 2011, 2022). The process for the establishment of the HBGV includes the selection of a dose that can be used as a starting point for risk assessment as the 'Reference Point' (RP), also named 'Point of Departure' (POD), followed by the selection of uncertainty factors (UFs) or safety factors, which are applied to the RP to ensure a sufficient level of protection for humans (Baken, 2018).

The POD forms a basis to establish HBGV and two main approaches are generally used to derive it: no-observed-adverse-effect level (NOAEL) approach and benchmark dose (BMD) approach. The NOAEL is the highest level of a test substance that does not cause any observed and statistically significant adverse effect in animals compared with the controls, and remains the most frequently used POD. In certain cases, the lowest-observed-adverse-effect level (LOAEL) may also be used. The BMD approach is however scientifically more advanced and, at this stage, broadly recognized as the preferred option for deriving HBGV when possible (EFSA Scientific Committee, 2012a).

Health-based guideline values for drinking water are calculated using the following formula:

$$HBGV = \frac{POD}{UF}$$

Where UF is the uncertainty factor and POD is the lower bound of the BMD confidence interval (BMDL), NOAEL or LOAEL. The UF is intended to provide adequate margin of safety for the consumer, including sensitive subpopulations (e.g., infants and children). A default value of 100 is often used due to the lack of quantitative species-specific toxicokinetic or toxicodynamic information. This value is used to convert the POD from an experimental animal study into an HGBV for human exposure. Additional uncertainty factors may be used according to experts' judgement on the reliability of the data. The appropriate choice and use of UF for HGBV derivation date back to basic principles laid down since 1990 by the International Programme on Chemical Safety (IPCS) and WHO. It must be kept in mind that PODs should be based on effects linked to adverse responses in humans, and the POD for the most critical endpoint is used for deriving the HBGV. After a HBGV is established and combined with exposure data, risk managers are equipped with quantitative information to support their decisions concerning the protection of human health.

3.1.1 Water domain

The Drinking Water Directive establishes that EU member states are obligated to guarantee that water designated for human consumption is '*wholesome and clean*' – a key precept guiding drinking water quality setting (EC, 2021a). As minimum legal requirements, this entails being devoid of any microorganisms, parasites, or substances that, in numbers or concentrations, pose a potential risk to human health. In the Netherlands, the Drinking Water Decree absorbs these requirements and in some cases the regulatory requirements are even more stringent then the EU DWD (Table 1).

In the Netherlands, the drinking water guideline value is a human-toxicological risk limit that is used to assess the risks to drinking water if the 'signalling parameter' of 1 µg/L for anthropogenic substances is exceeded. The value also becomes used for weighing the risks to drinking water quality when drawing up discharge permits and deriving surface

water quality standards for drinking water intake points (water sources used for the preparation of drinking water). In addition it is up to the government to decide whether a drinking water guideline value should be derived based on the risk potential of a substance (Waterstaat, 2022). Although there is no EU guidance for the derivation of drinking water guideline values, the Netherlands and other countries base these derivations from other European and international guidance, most notably from WHO GWDQG and $EQS_{hh,dw}$. (Environmental Quality Standard for human health via consumption of drinking water). For the derivation of drinking water (DW) guideline values, the Netherlands uses the guidance developed by RIVM (RIVM, 2024a; van der Aa et al., 2017).

3.1.2 Food domain

Base European food law recognizes that securing "*safe and wholesome*" food is an essential aspect of the internal market and contributes significantly to the health and well-being of citizens (EC, 2014). In the food domain, HBGV are determined by the European Food Safety Authority (EFSA) by extrapolating toxicity data (obtained with laboratory animal experiments) and using safety factors. HBGVs, along with aspects of their derivation, such as the selection of uncertainty factors, are not established in legislation but are instead outlined in guidance documents and official statements. HBGV can be based on acute or chronic exposure. In acute-based HBGV, the term acute reference dose (ARfD) is often used which indicates the maximum amount of a substance in food or drinking water (bottled) that can be ingested within a 24-hour period without any appreciable health risk. In chronic-based HBGV, several terms can be applied depending on the type of substance and data availability.

Acceptable daily intake (ADI) is applied to permitted substances, such as plant protection products (PPPs), veterinary medicinal products, and food additives, that occur as residues in food for necessary technological purposes or plant protection reasons. The tolerable daily intake (TDI) is applied to substances introduced unintentionally, such as process contaminants and environmental contaminants. If ADI or TDI values cannot be derived due to lack of data, another measure called Margin of Exposure (MOE) can be used. MOE is based on PODs, such as BMDL and NOAEL, and its application supports the conclusion about the safety of products. The MOE considers the margin between the POD and the estimated exposure (human dietary consumption) (EFSA, 2023), see details in Chapter 4.2). In essence, these all indicate the amount of a substance that can be ingested daily over a lifetime without any appreciable health risk.

Policy frameworks other than those on (drinking) water sometimes use a different approach and terminology in the process of setting standards for chemical contaminants. For example, in the case of food, one does not speak of standards but of (product) limits (maximum levels, ML) and in the case of food contact materials (e.g. food packaging) one speaks of specific migration limits (SML). For MLs, this means that a limit is determined for different substance-product combinations, for instance a ML for Pb in green salad is different from the ML for Pb in milk. MLs for contaminants in food are included in Regulation EU 1881/2006 (now replaced by Regulation 2023/915) and are directly applicable in all EU Member States. For some contaminants for which no European MLs are available, legal limits have been set in the Dutch Commodities Act.

Food product limits can also be derived for permitted substances, which are legally established under the terms Maximum Residue Limit (MRL) or maximum use levels for intentionally introduced food additives (Chen et al., 2022). For some contaminants for which no European MLs are available, legal limits have been set in the Dutch Commodities Act. For all Plant Protection Products (PPP), veterinary medicinal products, and food additives, MRL's and maximum use levels are determined, otherwise a default value is established.

The MRL and ML are then compared with HBGV to determine whether foods and other products are allowed on the market. If MLs or MRLs are exceeded, the products are not allowed on the market. For example, in regards to PPPs, once the amount of substance in foods is determined (MRL and ML) based on Good Agricultural Practices (GAP), these are used to estimate the intake of the substance and compared to HBGV. If the MRL is below HBGV, a PPP may be authorized for marketing in the EU. If the MRL exceeds HBGV, authorization is not granted. In the case of veterinary medicinal products, the MRL is based on ADI under the assumption of standard daily 'worst case' consumption of products of animal origin. In the case of unintentionally introduced substances (contaminants), the ML is based on the As Low As Reasonably Achievable (ALARA; Chapter 4.5) principle. Food product standards are summarized in Table . In terms of enforcement, the focus is on whether the ML or MRL has been exceeded, determining compliance or

non-compliance. The actions taken after an exceedance can be risk-based and may include a warning to the producer, a public warning, a retail recall, or even a consumer-level recall.

Table 2. *Toxicological basis of chronic safety thresholds for permitted and unintendedly introduced substances in foods.*

	Permitted substances (Maximum Residue Limit, MRL)		Unintended introduced substances (Maximum Limit, ML)
	Plant Protection Products	Veterinary medicinal products	Environmental and process contaminants
Based on	GAP	ADI	ALARA
Toxicological limit	No	Yes	No
Exceeding limit	Can be a risk	Risk	Can be a risk
Below limit	No risk	No risk	Can be a risk

GAP: Good Agricultural Practices, ADI: Acceptable Daily Intake, ALARA: As Low As Reasonably Achievable.

From a drinking water perspective, **Table 2** provides interesting insights to further discuss and evaluate parallelism about the principles on how water safety and quality limits are founded and estimated. In food safety, substances are said to be allowed, i.e., permitted substances, for PPPs, veterinary products and additives, whereas environmental contaminants are not permitted substances even when the maximum limit is not exceeded. In this case, the concentration is often said to be tolerated. Similarly to food safety, there are substances which are permitted in drinking water, intentionally or unintentionally introduced (see **Chapter 6.1.** and **7.6.4.**). Permitted substances are for example the ones listed in **Table S1**, as long as the concentrations do not exceed (legal) limits. If the concentrations exceed the permitted limits, action must be taken to remove the substance. Permissibility does not imply water contaminants are allowed; rather, it is an implicit recognition that unintended introduction may occur. To address this, a statutory limit is established to enable regulatory compliance and enforcement. Another example of permissibility, although implicitly, are all other substances which are not listed (i.e., regulated) or occur below the 'signalling parameter' value of 1 µg/L (or 0.1 µg/L if a pesticide metabolite) (NL, 2024). This is not to say that reducing the presence of these substances should not be sought in the pursuit of "*clean and wholesome water*", but it leaves room for these substances to be present without enforceable risk mitigation or reduction measures. This may be a contentious discussion since the absence of a listing of non-permitted substances does not imply that these should be allowed. Interestingly, there seems to exist a careful choice of terminology. One could expect that the opposite of permitted substances would also be formalized, i.e., limits established for non-permitted substances. However, instead it is acknowledged that in the production of food, intentionally added substances (e.g., colorants, flavourings, pesticides) may or may not pose a risk to health, whereas for unintended introduced substances (i.e., contaminants) risks cannot be discarded. Note that substances exceeding MRL are not allowed in food, in order to prevent risks. However, when for PPPs the MRL is exceeded, it is possible that there is no risk. To help understand this and how it relates to water contamination, it is important to understand if a substance can illicit an adverse effect after a particular exposure level or at any level (threshold and non-threshold). Also, it is relevant to understand which approaches are used to handle each kind (e.g., ALARA).

3.2 Terminology in water and food safety

An often overlooked matter, yet of critical relevance, is the one of terminology. In Article 1 of DWD, important key terms are evoked such as, 'contamination', 'adverse effect', 'wholesome' and 'clean'. Some of these can be found in other regulatory documentation. However, these terms are often associated with vague concepts or interpreted differently. In interdisciplinary activities, such as the one in the present report, a common yet overlooked challenge by experts is that terminology may carry different meanings across scientific disciplines and legislation (Hrudey, 2024).

For example, the terms 'contaminant' and 'adverse effect' are of particular relevance in refining one's understanding about the underlying assumptions in safe guidance values and the (un)avoidable health risks posed by certain substances. The terms are explained below, particularly from water quality and food safety perspectives.

3.2.1 Contaminant

In the water quality domain, specifically the DWD, several mentions are made regarding the protection of human health against *any contamination* in water intended for human consumption. Yet, a definition of contaminant is not provided. In the DWD's predecessor document (CE, 1998), a definition is also not offered. This means that an interpretation of this term can be made in its broader sense. However, it may also lead to conflicting understandings by stakeholders and intractable in practice. Furthermore, just like it is missing in the DWD, no explicit definition of contaminant (e.g., *verontreiniging*) is offered in the Dutch Drinking Water Decree (NL, 2024).

In food safety, a contaminant can be simply defined as any substance not intentionally added to foodstuffs (EFSA, 2024b). In fact, this means that contaminants can be present in food as a result of the production, manufacture, processing, preparation, treatment, packaging, transport or holding of such food, or as a result of environmental contamination. If one inspects the term further, the definition becomes narrower according to the regulatory framework for food contaminants (CE, 1993), as it states that it does not apply to contaminants which are the subject of more specific EU rules (e.g., plant protection products, veterinary drugs, food contact materials). For example, the term does not include contamination from insects or rodents, whereas contaminants may be veterinary medicines used in animals that unintentionally make their way into food during production. Additionally, human medicines may also be covered by this definition if entering the food chain through environmental pollution.

A key objective of the DWD is "*to protect human health from the adverse effects of any contamination of water intended for human consumption by ensuring that it is wholesome and clean*". It is worth explaining this sentence. The sentence emphasizes protecting human health from the adverse effects of water contamination. It explicitly ties the prohibition or regulation of water contaminants to their potential for adverse effects. Therefore, if no adverse effects exist, one could interpret this to mean that the presence of contaminants is implicitly permissible, as the criterion for concern, i.e., adverse effects, is not met. However, this reasoning hinges on the broader regulatory or legal framework that the sentence operates within. In many water quality standards, there are often additional stipulations that prohibit certain contaminants outright, even if adverse effects are not currently known, to account for precautionary principles or unknown long-term risks. An example of this is the inclusion of per- and polyfluoroalkyl substances (PFAS) in ANNEX I of the DWD. In the DWD, one can still find that contamination is permissible for example in Article 11 (1b), stating that materials in contact with water intended for human consumption "*do not leach contaminants into the water at levels that are higher than necessary in view of the intended purpose of the material*". Here again, the criterion of concern is the quantity of leached contaminant, not its presence. Similar provisions are made for treatment chemicals and filter media.

This concept seems to indicate that water and food domains have much in common. In both domains, contaminant presence is not understood as being inadmissible per se. Yet, in the food domain, there seems to exist a more widespread explicit recognition and acceptance that contamination cannot be entirely avoided nor, sometimes, the risks of food contaminants to human health (for example, see Chapter 6.1.1. on acrylamide). On the other hand, this recognition is often not explicitly made in water legislation and by water management, despite the in principle very restrictive regulations. At high contaminant concentrations, certain foods (e.g., dioxin-contaminated fish from the Baltic Sea) can be consumed less frequently or even avoided altogether. However, such selective avoidance is less feasible for drinking water.

In food safety, the definition offered by EFSA may be seen as applicable also to the water intended for human consumption. Adjusting the definition would be that a water contaminant is any substance occurring in water intended for human consumption that was not added intentionally. The topic of *intentionality* is a hard one to tackle, particularly if the interpretation is not equivalent across stakeholders. For example, certain constituents of materials in contact with water for human consumption possess hazardous properties (e.g., in water production, water distribution) (KWR, 2025). These serve important functions that allow the materials to have desirable properties for their end use and the products are certified as to guarantee their safe use. However, if these migrate to water, this phenomena is not intended by the manufacturers or water managers. Yet, it is understood that this is a possibility

and may happen even if in very small amounts, for example due to aging of the material, material constituent composition or damage. In short, in the food safety domain, contamination is permissible so long as the amount is considered acceptable, whereas in the water quality domain contamination is only permissible if it does not lead to adverse effects (Table 3). This means that both domains adopt a risk-based approach, as they account for hazard and exposure when determining permissibility, although the descriptions used may differ slightly.

Table 3. Differences and similarities in the permissibility of contamination and associated adverse effects, in the water quality and food safety domains (EC, 2014, 2020b).

	Water quality	Food Safety
Contamination	Permissible (contingent on absent adverse effects)	Permissible
Adverse effects	Not permissible	Permissible (contingent on contamination)

3.2.2 Adverse effects

Numerous legislations, including DWD, evoke "adverse effect", yet its definition is often missing, implicitly conveyed or cross-referenced to other sources. According to an old reference (Sherwin, 1983), an adverse health effect is defined as "*the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality produced has the potential of lowering the quality of life, contributing to a disabling illness, or leading to a premature death*." In the food domain, according to EFSA, an adverse effect is a "*change in the health, growth, behaviour or development of an organism that impairs its ability to develop or survive*" (EFSA glossary). According to OECD GD 116 (OECD, 2014), it is a "*change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences*".

The differences in terms can be very subtle (e.g., one definition explicitly mentions survivability whereas another does not), yet these can make a substantial difference, and have large implications in practice, depending on the context as well. Sharing a common understanding between stakeholders of what key concepts mean and related is not a main focus of the present report but it is deserving more careful consideration. For example, in large cross-discipline projects such as the VHP4Safety project (VHP4Safety, 2021), it became very clear among experts that ontology is critical for enabling all stakeholders and actors to communicate effectively and coherently combine chemical safety data, for example. While ontology and terminology are not the same, they are important related concepts. This is of particular relevance in establishing which effects fall within the definition of adverse effects for the purposes of deriving safe thresholds and, ultimately, deriving guidance values in the water, food or other domains.

3.3 Threshold and non-threshold substances

The derivation of guideline values is typically done by considering a distinction between non-carcinogenic (non-cancerous) and carcinogenic (cancerous) chemicals (see Chapter 3.1.). Non-cancerous chemicals, also known as "threshold substances", are considered to have a definable threshold exposure level below which it is considered "safe". For example, a substance for which a HBGV could be defined, for example ADI, this is considered a threshold substance. The prevention of effects from such substances is achievable by restricting exposure to low values so that no threshold dose is reached, even under chronic exposure (e.g., person's lifetime). However, the effects for some substances are not as deterministic, but instead their effects are stochastic, for example cancerous chemicals (ICRP,

1977). Cancerous chemicals, considered “non-threshold substances”, are (mostly genotoxic) carcinogens for which no definable dose is considered “safe” (no definable threshold), meaning a risk of biological effects cannot be excluded. Exceptionally, (non-genotoxic) carcinogens may be treated as a contaminant with a threshold if credible evidence exists, normally based on an understanding of the mechanism of action (MOA). For threshold and non-threshold substances distinct assumptions and methods are thus used, although there is increasing discussion questioning the oversimplification of this dual categorization. In food, if concern for genotoxicity remains, derivation of a HBGV is not considered appropriate (IPCS, 2020). The water legal framework establishes that human health must be protected from adverse effects of any contamination of water intended for human consumption (EC, 2020b).

In drinking water, guideline values established for non-threshold substances correspond to the concentration associated with an upper-bound (95% confidence interval) excess lifetime cancer risk of 1 additional case of cancer per 1 000 000 individuals (10^{-6}). This concentration is derived under the default assumption of exposure via the consumption of 2 litres of water per day, during 70 years. For risk assessment in food, a MOE of 10 000 or higher for genotoxic and carcinogenic substances is generally considered of low concern, if based on 95% confidence on the lowest dose causing a 10% increase in tumour incidence ($BMDL_{10}$) from an animal carcinogenicity study (EFSA Scientific Committee, 2012b).

In food safety, the *in vitro* micronucleus assay (MN) is one of the most widely used methods for evaluating the genotoxicity of chemical and physical factors (EFSA guidance, 2021). For food safety regulators, the *in vitro* MN assay often constitutes the strongest line of evidence for chemical genotoxicity which, if positive, should then be followed by an *in vivo* mammalian erythrocyte MN test. For water quality assessment a micronucleus protocol specific for water quality assessment is available as ISO standard (ISO, 2006). Although, in current practice in the Netherlands, genotoxicity is most often assessed using the Ames fluctuation test (modified version of classical Ames test) or p53 CALUX. However, it has been recommended to use multiple mechanisms of genotoxicity rather than one, such as a combination of Ames and p53 CALUX (Reus, 2023).

In the case of threshold substances the approaches on how to handle them revolves around efforts in reducing its presence below derived limits (e.g., ADI, TDI, …). However, in the case of non-threshold substances for which there is no such limits bounding their riskiness due to their stochastic nature, the efforts default to attempts at reducing exposure as much as possible. Since there is no toxicological limit, i.e. upper limit (above which concentration until adverse effects?) nor lower limit (no concentration below which adverse effects can be expected), risk management becomes more complex. In this instance, what may have been before secondary factors used in risk management deliberations, now became key elements in decision making regarding on how to best manage highly uncertain risks. The main goal becomes lowering the exposure to the hazardous substances as much as reasonably achievable.

4 Alternative risk approaches and principles for the water sector

HBGVs are a central piece in safekeeping the quality of drinking water and for regulatory compliance. So much so, that the first EU repository of HBGV is currently being built to supplant the inconsistencies and dispersed information underlying their derivation (Pieczyk et al., 2023). However, in the absence of *in vitro* or *in vivo* equivalent adverse effects data, classical HBGV will increasingly be replaced by *in vitro* PODs, which provide an indication of probability of adversity, often approximating *in vivo* outcomes (Niemann et al., 2023). POD have been traditionally established using measures such as ADI and TDI, which depends on dose selection and dose spacing in the toxicological studies. BMD has been increasingly endorsed as an advanced and preferred alternative to establish PODs (Baken, 2018).

It is interesting to note that the use of a handful of approaches in establishing HBGV is already envisioned in the context of chemical exposure via food and drinking water intake (IPCS, 2020). In situations when adverse effects cannot be established, such as for non-threshold, unintended or unavoidable substances, the advanced BMD framework is no longer applicable. Therefore, as laid in Tier 3, in Figure S1, it is advised to use margin of exposure (MOE) or another approach outside the BMD framework when (1) biologically relevant Benchmark Response (BMR), i.e., a level of change that is considered adverse, does not yet exist for the end-point considered and (2) an expert decision for an adversity-based BMR cannot be made. This also means that values estimated using MOE or other, should not be used for establishing an HBGV. In the food domain, if a HBGV is not needed for the risk characterisation, other alternative approaches are proposed such as MOE, comparative approaches in which the regulated product under evaluation is considered “as safe as” already authorised products, or estimations based on the relative contribution to the total dietary intake (Table S2).

In this section, contaminants as well as risk approaches will be discussed from a food safety and water quality perspective. From a food safety assessment point of view, three main approaches used in the derivation of HBGV are LOAEL, NOAEL (both derived from a single observed dose in animal toxicity studies), and BMD (derived from statistically modelling the complete dose-response) (EFSA Scientific Committee, More, Bampidis, Benford, et al., 2021). However, when an HBGV or threshold cannot be established, most notably for non-threshold substances, alternative approaches are used such as the threshold of toxicological concern (TTC) and margin of exposure (MOE). An important test which often holds a strong scientific and regulatory validity is the micronucleus (MN) assay for evaluating aneugenicity (EFSA Scientific Committee, More, Bampidis, Bragard, et al., 2021). It can support early risk management decisions, such as restricting the marketing of genotoxic food ingredients, and may provide a basis for foregoing threshold-based HBGVs. In water quality research, micronucleus assays continues to be a topic of discussion and were recently adopted by the German Environmental Agency (UBA) in its ToxBox strategy for water quality assessment (Grummt Tamara; Braunbeck, 2020). The MN assay could be further considered in the Dutch context, where it is not routinely used. However, there is no business case for implementation at this stage, as it is not included in the standard bioassay sets in the Netherlands. Without regulatory requirements or official guidance recommending its use, there is currently no demand from drinking water companies to perform micronucleus testing (Reus, 2024).

The TTC and MOE are approaches that are sufficiently flexible as risk assessment approaches, particularly in conditions of limited toxicological and exposure information. Therefore, these are discussed in dedicated sections (Chapter 4.1 and 4.3.) The TTC approach borrows from the idea that a chemical may be classified into groups based on their toxicological properties. Besides TTC and MOE other supporting risk approaches are highlighted. Since contaminants often occur simultaneously, particularly in water, the concept on chemical grouping is further explained in Chapter 4.3. while considering its relevance in mixture toxicology. One important prioritization tool which may deserve further attention and adoption in water quality practice is the Disability-Adjusted Life Year (DALY) (Chapter 4.4.), as it offers a way to contextualize the impact of certain chronic exposure to a population and support in decision-making of more effective risk reducing measures. Following on how risks ought to be ultimately handled, in Chapter 4.5., a key foundational concept of ALARA is revisited and reevaluated from a food safety and water quality viewpoints. The present chapter, closes with a reflection on how these risk assessments approaches and principles may offer alternative paths to deal with (un)avoidable contamination and risks and be further integrated into drinking water quality practices.

4.1 Threshold of Toxicological Concern (TTC)

The TTC approach was first proposed by Cramer and others (1978) stemming from the major challenge of assessing the toxic threat of a staggering number of chemicals with limited toxicological evidence and resources. They developed a tiered scheme which allows the classification of chemicals into three classes of concern (Class I, II, and III). Later, Munro (1990, 2008) extended the concept to accommodate health risks from food additives and refined it for health risk assessment. The TTC approach was later reviewed and incorporated into guidance documents (EFSA & WHO, 2016). A TTC value is calculated from the distribution of 2941 conservative NOAELs associated with 613 chemicals, from a broad range of uses (agricultural, food, industrial, pharmaceuticals, consumer products, environmental). Cramer Classes I, II and II, were thus built based on 137, 28 and 448 chemicals (EFSA Scientific Committee, More, Bampidis, Benford, Bragard, et al., 2019).

Although originally based on carcinogenicity data, the TTC is not a tool only for genotoxic compounds; it's also used for many other compounds that are now detectable and found in food in low concentrations (EFSA Scientific Committee, More, Bampidis, Benford, Bragard, et al., 2019). It is nearly impossible to have sufficient and adequate toxicological information for all individual hundreds of thousands of substances people are exposed to. And so therefore, the threshold of toxicological concern gives a pragmatic option to assess the potential health significance of previously undetectable trace substances. It is important to note that the approach can be used when the chemical structure of the substance is known, limited chemical-specific toxicity data is available, and the exposure can be estimated. For example, TTC-based acceptable intake was developed for any unstudied mutagenic impurities in pharmaceuticals to limit potential carcinogenic risk (ICH, 2023). It has also recently been recommended the further investigation of the applicability of the TTC approach to aneugens (EFSA Scientific Committee, More, Bampidis, Bragard, et al., 2021).

The TTC approach has also been excluded for a number of categories of substances, namely high potency mutagenic carcinogens (i.e., aflatoxin-like, alkyl-azoxy- or N-nitroso compounds), inorganic substances, metals, organometallics, proteins, steroids, substances that are known or predicted to bioaccumulate, nanomaterials, radioactive materials, and mixtures of substances containing both known and unknown chemical structures. From a theoretical perspective, this limitation can significantly hinder the ability of water professionals to use TTC as an all-purpose tool since several water contaminants fall within the examples abovementioned, which are also often the ones that may escape current water treatment processes. Nonetheless, from a practical perspective it may at occasion provide a much needed alternative to assess risks under very limited data and resource conditions. For example, for substances with a structural alert for genotoxicity, i.e., the potential to be DNA-reactive, mutagens, and/or carcinogens based on the weight of evidence, the relevant toxicological threshold of concern is 0.15 µg/person/day or 2.5 ng/kg bw/day (EFSA & WHO, 2016). In a study by Baken & Sjerps (2016) , it was shown that drinking water threshold levels using TTC were sufficiently preventive of health risks from contaminants (Baken, 2016). However, these could not be taken as to represent acceptable intake for all drinking water contaminants. Despite inherent uncertainties, this approach can facilitate discussions about potential risks of certain water contaminants and offer a pragmatic low-effort attempt at setting water quality target values in case of limited toxicological information, because the drinking water target values derived by higher TTC values would not match with current standards for e.g. pesticides in drinking water (Mons et al., 2013). In Chapter 6.2, the concept of TTC is further explored in the context of mixture risk assessment.

4.2 Margin of Exposure (MOE)

From a risk management point of view, the MOE approach is generally used for contaminants in foods. The use of MOE is reserved for substances which are both genotoxic and carcinogenic. By genotoxic agents it is meant substances that are toxic via a DNA-reactive mechanism (non-thresholded dose-response), such as gene mutation and clastogenicity, or via non-DNA-reactive mechanism (thresholded dose-response), such as aneugenicity (EFSA Scientific Committee, More, Bampidis, Bragard, et al., 2021). The MOE is the ratio of a defined POD on the dose response curve to an estimated human exposure intake. Similarly to TTC, MOE is also an assessment prioritization tool but used for cases where it is impossible or inappropriate to derive a health based guidance value (EFSA Scientific Committee,

More, Bampidis, Benford, Bennekou, et al., 2019). MOE is a tool used by risk assessors to consider possible safety concerns arising from the presence in food and feed of chemical substances when they deem it inappropriate or unfeasible to establish a HBGV, such as ADI or TDI. Generally, MOE is applied when (1) assessing presumed DNA-reactive mutagenic carcinogens, (2) there are insufficient data for deriving HBGV and (3) for additives used in infant formula (IPCS, 2020). It is important to highlight that the MOE is not a HBGV, i.e., it is not a safety threshold below which risk assessors conclude that the daily intake is safe. MOE only indicates if harm is likely (small MOE) or not (large MOE). Instead, the Margin of Safety (MoS), as the name suggests, provides an indication of the degree of safe exposure. The MoS is the ratio between HBGV, such as an ADI, and the actual or estimated exposure.

For genotoxic carcinogens, the use of the $BMDL_{10}$ (benchmark dose lower confidence limit 10%) is recommended/preferable to obtain the MOE. In general, a MOE of 10 000 or higher, if based on the BMDL10 from an animal study, would be of low concern from a public health point of view and might be considered as a low priority action in risk management. So, the larger the MOE the lower the concern. A high MOE does not mean there is no risk, instead it provides an indication to risk managers if actions on the chemical should be prioritized over other chemicals and more lenient risk management strategies. It is important to note that even in cases of MOEs lower than 10 000, compounds can still become regulated because health concerns cannot be discarded. MOE is used as a prioritization tool by providing a measure of concern to risk managers.

MOE approach is well accepted (almost 20 years in regulatory use by EFSA) for substances that are genotoxic and carcinogenic, based on carcinogenic potency. An analogous MOE approach based on genotoxicity potency would provide a valuable tool for risk assessors and regulators. However, some issues with MOE are the adequate selection of relevant data and that BMR is used for continuous data (not incidence data) carrying issues in defining a relevant BMR for genotoxicity data. Additionally, how to interpret MOE results, with scientific justification for defining a MOE of low concern, is posing a challenge to risk managers. For example, what is an appropriate MOE where sufficient exposure data are available?

4.3 Chemical Grouping

Dutch drinking water companies play a crucial role in safeguarding and assessing source water quality, particularly concerning alternatives to hazardous chemicals (e.g., EDCs, PMT, vPvM), which can sometimes evade regulatory scrutiny (Giglioli et al., 2023). For drinking water suppliers, it is especially relevant to investigate whether chemical variants of emerging contaminants and their marketable substitutes within the same chemical group are being released into aquatic environments. To address this, an increasingly championed approach is to proactively adopt a pragmatic “chemical grouping” approach (Chirsir et al., 2024). This strategy helps prioritize mitigation measures for data-poor contaminants rather than waiting for comprehensive toxicological data to become available and regardless of perceived mechanisms (EFSA et al., 2021; Kortenkamp, 2022). This approach has been contested by some authors (Natsch et al., 2023). However, it appears to be particularly useful for contaminants whose risks are increasingly recognized as unavoidable. Another important consideration is the manner in which mitigation measures against alternatives to toxic substances with poor-data are handled (*regrettable substitution trap*), and most of all the urgent need to understand the effects after metabolic transformation (Mhaouty-Kodja et al., 2024). This calls for more guidance on the determination of relevance of metabolites (EC, 2021b).

In recent regulatory developments, the Cumulative Assessment Groups (CAGs) and Mixture Assessment Factors (MAFs), have emerged as important tools to address the risks associated with chemical mixtures (Backhaus, 2023; EFSA et al., 2019). The EFSA has introduced the CAG approach, grouping chemicals with common mechanisms of action or similar toxicological effects to allow cumulative risk assessments, particularly concerning pesticide residues (EFSA et al., 2019). In addition to CAGs, the concept of MAFs is gaining attention under the EU REACH regulation, as a precautionary measure to address potential cumulative risks from multiple chemicals (Backhaus, 2023). Recent advancements in determining sufficient similarity of whole complex mixtures to determine ‘thresholds of similarity’ are also a topic of increasing interest, where non-targeted screening and bioassay approaches are explored (Rager & Rider, 2023). Chemical producers argue that the grouping criteria are too vague and lack precision. They advocate for the inclusion of additional criteria, such as similar risk profiles, hazard profiles, and exposure routes, to avoid overly restrictive limitations on the use of potentially safe alternatives (CEFIC, 2021; Natsch et al., 2023). Nonetheless, in light of the overwhelming challenge to perform risk assessments for all (un)known water contaminants and the

ambitions to further integrate mixture toxicity tools and requirements into regulation, it is expected that chemical grouping will eventually become widely used for prioritization and influence water quality safe threshold derivation. In fact, grouping of chemicals based on their structural similarity, constitutes a foundational justification of the broad restriction proposal to ban the many uses of thousands of PFAS in the EU (ECHA, 2023b). Therefore, the water sector will likely benefit from being an early adopter of not only precautionary approaches but also pragmatic ones while remaining an active stakeholder in these discussions as they evolve.

4.4 Disability-Adjusted Life Year (DALY)

One important consideration in food safety and nutrition is the evaluation whether the benefits of a certain food, outweigh the risks of its consumption (e.g., due to contaminants), i.e., a risk-benefit assessment. To some extent the risks involved in the exposure to hazardous substances via food may be known, yet the implications of withdrawing from its consumption and all the nutritional benefits in brings may not be justified from a broader public health perspective. This falls within the space of risk management were compromises are made and certain outcomes prioritized over others. It is worth to highlight that risk-benefit assessments often rely on quantitative as well as qualitative considerations. Examples of this include the risk-benefit of raw milk vs. pasteurized milk, the substitution of red and processed meat by fish, the proof of efficacy of pesticides against pests, and bisphenol A (BPA)-like derivatives and alternatives vs. BPA (Verhagen et al., 2021).

One useful metric for burden of disease to help establish public health priorities is the Disability-Adjusted Life Year (DALY) indicator (Kim et al., 2022). DALY considers a set of factors (incl. life expectancy, disease incidence, prevalence, duration, severity). In simple terms, one DALY corresponds to one healthy year of life lost. Besides being used in food safety, DALY has also been proposed and used in water quality domain to varying degrees of success (Havelaar, 2003; van den Brand, 2023). DALY follows the introduction of the Burden of Disease in 1990s, and has since been adopted by the RIVM in national studies, the first of which published in 1997 (Hilderink et al., 2020). In 2003, the DALY approach was used to assess the public health impact of microbial and chemical contaminants in drinking water. Bromate was estimated to pose a disease burden to the Dutch population of 10 910 DALYs per 1000 related cases renal cell cancer cases (Havelaar, 2003).

There are many challenges in calculating DALY values particularly due to the difficulty in collecting sufficient relevant and reliable data, yet the burden of disease, expressed in DALYs, has for long been considered of great value to understand Dutch population health trends and to support better public health management and policies (Havelaar et al., 2000; Hilderink et al., 2020). DALY's are also strongly dependent on expert judgment, which may lead to variation between estimates. In the context of drinking water, DALY may be used as a complementary risk assessment tool for the water sector because it may help better understand the impact of permanent consumption of regional serviced water to the its population health (van den Brand, 2023). DALY may also be used as a potential warning sign about which water contaminants may become under public scrutiny and potential stricter water quality regulation. Further research is needed to refine the application of the DALY concept into water quality assessment, particularly in developing standardized methods and defining the necessary data for an effective and meaningful interpretation and implementation.

4.5 As Low As Reasonably Achievable (ALARA)

In 1977 the International Commission on Radiologic Protection (ICRP) introduced the "as low as reasonably achievable" (ALARA) principle, founded on an older rationale about minimizing exposure to ionizing radiation to the lowest possible level in so far as that the benefits of that exposure are justifiable (ICRP, 1977). This means the risks and benefits of using radiation, for example, diagnostics, had to be balanced. The ICRP laid down three principles for radiation protection back in 1977 (Box 4). The ALARA principle was born from radiation physics, protection and safety in the mostly clinical domain has since permeated the risk assessment and management discourse in other fields.

Box 4. *The main features of the system of dose limitation as recommended by the ICRP (1977), sustaining the ALARA principle.*

> (a) no practice shall be adopted unless its introduction produces a positive net benefit;
>
> (b) all exposures shall be kept as low as reasonably achievable, economic and social factors being taken into account; and
>
> (c) the dose equivalent to individuals shall not exceed the limits recommended for the appropriate circumstances by the Commission.

In the context of food safety, this concept is well ingrained when dealing with contaminants, for which no toxicological limit is derived. This has required the acknowledgement and acceptance that some substances unintentionally end up in foodstuffs or are unavoidably present as part of the process of producing food products. For example, the ALARA principle constitutes the basis for establishing MLs (for unintended introduce substances). Instead of toxicologically based, the ML is based on the 95th percentile of data collated across the EU (via EFSA) of a particular substance in a particular food type (e.g., the ML for arsenic in rice waffles is 0.3 mg/kg).

In the context of water contamination, many substances remain to be quantified or detected even thought their presence is suspected or cannot be dismissed entirely due to lack of evidence. Furthermore, water contaminants can lack safe limits, i.e., are non-threshold substances. This means that a discussion surrounding the application of principles like ALARA, borrowed from radiation protection, become interesting to consider in terms of water quality (Yeung, 2019).

The term ALARA, and other similar terms such as ALAP and ALARP, are vague terms. When a given exposure to a drinking water contaminant is 'practical', 'achievable' or 'attainable', may be strictly interpreted as whenever its reduction is technically possible, regardless of what the costs may be (Hansson, 2013). However, achievability is intrinsically associated with the "*ability to*", thus it often implies and expands beyond technical possibility to accommodate socio-economic considerations (Box 4 (b)).

In the DWD, "*as low as reasonably practical*" is mentioned in relation to lead (Pb), according to WHO's recommendations (Provision 6). More interestingly, another variation to ALARA is introduced in the Directive, "as low as possible" (Article 9, 1(d)). This concept is only explicitly associated and expected to be applied to treatment chemicals and disinfection by-products. This means that the '*as low as possible'* or other equivalent, such as ALARA, principle under this Directive does not seem to be enforceable to other water contaminants challenging the water sector.

The ALARA principle offers a versatile way of integrating uncertainties into risk assessment methods. More than ever, the water sector is under increasing pressure due to its obligations to provide wholesome and clean water, while the quality of sources of water for human consumption are increasingly under pressure due to persistent pollution by threshold and non-threshold substances. Also, how to handle these substances' risks in terms of these being avoidable or unavoidable is a challenging discussion. Alternative approaches on how to handle the risks of these substances is of great importance, be those older approaches applied to novel substances (e.g., should the ALARA principle be applied to PFAS?) or novel approaches applied to old substances (e.g., animal free new approach methodologies on nitrate, Chapter 6.1.2.). Up until 2005, the ALARA principle was generally advised by risk managers when dealing with unavoidable contaminants and impurities. However, this principle alone does not allow setting priorities for risk management action according to the potency of the carcinogenic substances. Therefore, the MOE approach was

developed and is routinely used by bodies such as the Joint FAO/WHO Expert Committee on Food Additives (EFSA, 2023). For more information on MOE, see Chapter 4.2.

4.6 Dealing with unavoidable contamination and risk

The overall principle in the risk management approach to contaminants is that contaminant levels should be kept as low as reasonably achievable by following good practices at all stages of the production chain, known as the ALARA principle. Maximum Limits (ML) for unintended introduced substances and temporary Maximum Residue Limits (MRL) for permitted substances are established for food or feed products, in line with the ALARA principle (EC, 2020a). The ALARA principle is not typically applied to permitted substances unless under temporary extraordinary conditions (e.g., chlorate, see Chapter 6.1.4). As discussed in Chapters 3.3 and 4.5, this principle is particularly relevant for genotoxic carcinogens or genotoxic substances. In the DWD, wording such as *'as low as possible*' alludes to the ALARA principle. Although not explicitly embedded in several water quality documents, the ALARA principle, as seen in the food domain, is suggested as a potentially desirable approach for drinking water, while emphasizing the need to continue minimizing contaminants. For example, EFSA sometimes proposes temporary (lower) action limits to obligate producers to take measures to diminish concentration of a substance in food. Despite differences in regulation, the water and food domains are closely related and could benefit from a more integrated approach. In fact, the present project is a prime example of the desire from both the water and food sectors to increase dialogue and cooperation. At the European level, this integration is also evident in agencies (EFSA, European Chemicals Agency (ECHA) and European Medicines Agency (EMA)) and other bodies that are increasingly involved in activities related to the DWD. For example, the health-based parametric value for BPA, derived by EFSA (2.5 µg/L), was later added to the DWD. Another example, the DWD introduced minimum requirements for materials that are in contact with water meant for human consumption throughout the EU, for which ECHA is responsible for facilitating the implementation of the adopted European lists of allowed substances (i.e., positive list) (ECHA, 2025).

Contaminants can be unavoidably present in food due to their natural occurrence (plant toxins), toxicogenic fungi (mycotoxins), environmental pollution, or unintended consequences of cooling or other manufacturing processes. What about contaminants in drinking water? An interesting parallel can be drawn with drinking water because food contaminants are seen as unavoidable and not subject to market approval, whereas drinking water is not subjected to market approval. For example, only in 2022 was the first watch list of substances and compounds of concern for water intended for human consumption adopted at the European level (EC, 2022a). This means that drinking water across the EU must be closely monitored for two endocrine-disrupting compounds (β-estradiol and nonylphenol) throughout the entire water supply chain. The applicability of widely used concepts and tools from the food safety domain in the water quality domain are presented in Table 4.

In Chapter 3.2 and Chapter 4.5, the semantic difficulties inherent to the use of critical terms in toxicology and risk assessment have been highlighted. The ALARA principle too is hard to implement as it requires a minimum degree of consensus among risk managers and regulators. Nonetheless, the same flexibility and nuance that defines it allows for compromise to be found among a diverse set of stakeholders. This means that operationalizing ALARA or even the setting of HBGV, sits on the actors involved in the process of intelligently and empathically reducing risks to human health and the environment. In effect, this seems to also imply that today's HBGVs may be decreased, increased or rejected, as policy-making increasingly shifts towards evidence-based values. In a study by Sprong et al. (2023), risk managers are advised to revise maximum limits of metals for food and for drinking water, or consider additional maximum limits on metals in foods not included in the EU regulation on maximum levels for certain contaminants in food (Sprong et al., 2023).

Table 4. *Applicability of widely used concepts and tools from the food safety domain in the water quality domain.*

Concepts and tools	Applicability in food domain	Applicability in water domain	Overview
Threshold of Toxicological Concern (TTC)	Yes (with limitations)	Yes (with limitations)	• Focus: easy categorization of mutagenic chemicals • Not applicable to certain chemicals (e.g., high-potency carcinogens, inorganics, metals, nanomaterials, radioactive materials, mixtures) • Low-resource demanding to assess health risks • Particularly useful when toxicological data is scarce but exposure and chemical structure is known
Margin of Exposure (MOE)	Yes	Yes	• Focus: minimizing exposure through prioritization • Supports risk managers to develop strategies to minimize exposure (e.g., impurities) as an indicator of risk prioritization • Alternative for when the derivation of a HBGV (e.g., ADI) is not feasible (genotoxics and carcinogenics) • Exposure must not be known, instead can be estimated
Chemical Grouping	Yes	Yes	• Focus: rapid risk assessment and management • Allows to circumvent issues related to, e.g., regrettable substitution • Accelerates risk management action based on prevention
Disability-Adjusted Life Year (DALY)	Yes	Yes	• Focus: estimate loss of livelihood due to chemically-induced disability • Data intensive but important tool to help prioritize measures based on risk-benefit balance strongly based on expert judgment
As Low As Reasonably Achievable (ALARA)	Yes	Yes	• Not sufficient to set priorities (complement with MOE, for example) • Orients action sustained on the precautionary principle • Not strictly depended on full evidence • Flexible applicability but presumes stakeholder consensual understanding

5 New Approach Methodologies in risk threshold setting

A risk threshold refers to a predefined level of exposure to a chemical or substance below which there is no appreciable risk to human health or to the environment (Connors et al., 2019). This concept is fundamental in establishing safety standards for chemicals, including in the assessment of drinking water quality. Regulatory authorities rely on these risk thresholds to ensure the protection of human health and the environment from potential hazards associated with chemical contaminants. In the context of drinking water, risk thresholds comprise the health-based targets that are established on the basis of evidence indicating a level of no-adverse effect or negligible risk level often derived by regulatory bodies from exposure levels that result in adverse effects in experimental animals (Dingemans et al., 2018; WHO, 2022). Traditionally, animal testing has played a significant role in establishing risk thresholds, particularly in situations where research on humans is restricted due to unknown health risks and ethical concerns (Karmaus et al., 2022; Nagendrababu et al., 2021; van der Zalm et al., 2022). However, despite their historical significance and widespread use, animal studies have a number of limitations, including inherent variability and uncertainty, poor extrapolation to humans, ethical considerations, time and resource constraints, and inflexible regulatory frameworks (Schmeisser et al., 2023). In recent years, the adoption and slow integration of new approach methodologies (NAMs) has improved the process of risk assessment by offering alternative approaches to conventional toxicological studies, often reducing or eliminating reliance on animal testing while providing robust toxicity and exposure data as well as human-relevant testing strategies (Niemann et al., 2023; Schmeisser et al., 2023).

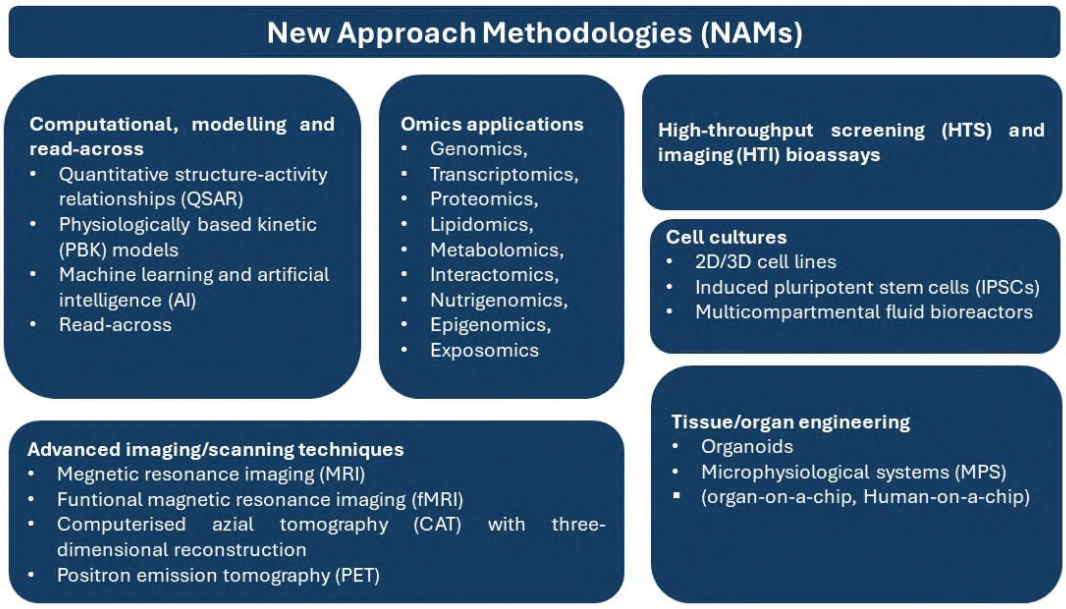


Figure 3. List of methods, techniques, tools, applications and systems commonly encompassed under the umbrella of NAMs (adapted from: Schmeisser et al. (2023))

NAMs is a recent and broad encompassing term with no formal nor legal definition, which refers to a varied number of methods and approaches. According to ECHA, in short, "*NAMs denote alternatives to traditional toxicity methods that typically involve animal testing*" (ECHA, 2023a). These methods focus on mechanistic data rather than solely relying on apical endpoint data (for setting point-of-departure) (Reddy et al., 2023) and include a range of approaches (see Figure. 3) (De Castelbajac et al., 2023; ECHA, 2016; Schmeisser et al., 2023; Stucki et al., 2022; USEPA, 2018). It

is important to emphasise that NAMs are as such not necessarily newly developed methods (Baumgartl-Simons, 2019), but their application for regulatory decision making or as a replacement for traditional testing requirements is relatively new (Stucki et al., 2022). It should be noted that NAMs may include new (refined) animal studies. Therefore, it is often important to specify whether one is referring to animal-based or non-animal NAMs.

Currently, NAMs are gaining increased attention for chemical safety assessment and have the potential to become a major component of regulatory risk assessment (De Castelbajac et al., 2023; Paul Friedman et al., 2019). The European Commission will publish a roadmap in the beginning of 2026 on the phasing out of animal studies for chemical safety testing, and thus phasing in of NAMs, covering 15 different regulatory areas (including water and food). This is also illustrated in an exploratory exercise where we observed that many regulatory and supporting documents explicitly mention or allude to NAMs. However, these are referred to in a wide range specificity, applicability and requirements (Table 5).

Table 5. *New approach methodologies (NAMs) in national and international regulatory and supporting documentation. The validation of NAMs is complex, particularly in the regulatory context. The mentioning of NAMs in these documents does not imply that these NAMs have been accepted or implemented.*

Region	NAMs mentioned?	Yes	No
World Health Organization	Guidelines for Drinking Water Quality	X	
European Union	BPR & Guidance	X	
	Chemical Agents Directive		X
	CLP & Guidance	X	
	Cosmetic Products	X	
	Drinking Water Directive	X	
	EFSA Guidances	X	
	Food Law		X
	Groundwater Directive		X
	Medicinal products for human use	X	
	Minimum requirement for water reuse		X
	MRL & guidance		X
	PPP & Guidance	X	
	Procedures for contaminants in food		X
	REACH	X	
	Urban Wastewater Treatment Directive		X
	WFD & EQS		X
The Netherlands	Drinking Water Decree		X

NAMs such as high-throughput screening and omics technologies including (toxico)genomics, transcriptomics, proteomics, and metabolomics, hold the promise of generating new data helpful for chemical risk assessment. While some NAMs may still involve the use of animals, these methods are continuously refined to minimize animal usage and provide valuable mechanistic insights alongside dose-response data. Furthermore, the mechanistic insights provided by NAMs contributes to a deeper understanding of the toxicity mechanisms of individual chemicals or mixtures and are often more relevant to humans compared to conventional animal-based toxicity tests (Health Canada, 2023). For example, the use of cell- and organ-based methods allows the use of human tissue, making the

toxicity data obtained from these NAMs more relevant for the assessment of risks to human health. This shift towards human-relevant data is particularly significant in light of the limitations associated with traditional animal testing, which may not always accurately predict human responses to chemical exposures. As a result, NAMs are increasingly being explored and successfully applied in certain regulatory settings, either mostly as part of a weight-of-evidence (WoE) approach to address specific endpoints (see Table 6) or for prioritizing chemicals for further study. However, this prioritization may carry the risk of also requiring additional animal studies or necessitating the proof of harm of a substance via *in vitro* studies.

Table 6. *Overview of some selected NAMs based test methods for regulatory chemical safety assessment. The greatest developments in NAMs have been observed in the cosmetic sector due to the ban of animal testing of cosmetics. This illustrates that enforcement of non-animal NAMs through legislation can work.*

End point	Test method	Source
Skin Irritation/Corrosion	OECD TG 439: *In vitro* Skin Irritation Test (RhE model)	*OECD Test No. 439*
Skin Sensitization	OECD TG 442E: h-CLAT (Human Cell Line Activation Test)	*OECD Test No. 442E.*
Skin Corrosion	OECD TG 431: Reconstructed human epidermis (RHE) Test	*OECD Test No. 431*
Eye Irritation/Corrosion	OECD TG 492 and 492B: 3D RhCE Test Method	*OECD Test No. 492*
Eye Damage	OECD 438: Isolated Chicken Eye Test	*OECD Test No. 438*
Skin absorption	OECD TG 428: Skin Absorption (*in vitro* method)	*OECD Test No. 428*
Genotoxicity	OECD TG 471: Bacterial Reverse Mutation Test	*OECD Test No. 471*
	OECD TG 487: Mammalian Cell Micronucleus Test	*OECD Test No. 487*
	OECD TG 476: Mammalian Cell Gene Mutation	*OECD Test No. 476*
Immunotoxicity	OECD TG 444A: *In vitro* immunotoxicity	*OECD Test No. 444A*
Neurotoxicity	Developmental Neurotoxicity (DNT) *In vitro* Testing Battery	*OECD 2023*

OECD: Organisation for Economic Co-operation and Development, OECD TG: OECD Guidelines for the Testing of Chemicals, RHE: Reconstructed Human Epidermis, RhCE: Reconstructed Human Cornea-like Epithelium

The Cosmetic Ingredient Review (CIR) Expert Panel, for example, has emphasized the importance of using alternative methods for safety assessments, particularly in light of the regulatory bans (Manful et al., 2024; Vinardell & Mitjans, 2017). The Organisation for Economic Co-operation and Development (OECD) has been instrumental in developing guidelines for chemical testing, which have evolved significantly since their inception. Initially, the OECD established its Test Guidelines Programme in the early 1980s (OECD, 2024). These guidelines primarily focused on traditional animal testing methods for assessing chemical safety. However, as scientific understanding advanced and ethical considerations regarding animal testing gained prominence, the need for alternative methodologies became increasingly apparent. The incorporation of NAMs into OECD guidelines began to take shape in the 2000s, with a significant shift towards integrating *in vitro* and *in silico* methods. For instance, the OECD has developed guidelines that specifically address the use of *in vitro* methods for various endpoints (see Table 6). However, despite the advancements offered by NAMs, they have not yet fully replaced traditional methods for setting risk thresholds (Chang et al., 2022; Manful et al., 2024; Niemann et al., 2023; van der Zalm et al., 2022; Vinardell & Mitjans, 2017). For example, *in silico* methods, such as, structure-activity relationships (QSARs) and read-across have gained recognition in regulatory domains worldwide for chemical safety assessment (Rovida et al., 2020). Predictions based on QSAR are used to prioritize chemicals for further testing to assess their potential risks to human health and the environment, and inform regulatory decisions on chemical safety and management (Pery et al., 2009; Politi et al., 2014; Roy et al., 2018). Recently, Organisation for Economic Co-operation and Development (OECD) published the framework for assessing QSARs (OECD, 2023). The framework was developed by the expert group led by European Chemical Agency (ECHA) and the Italian National Institute of Health (OECD, 2023). It includes guidance and a checklist for assessing models, predictions and results derived from multiple predictions, to provide clarity, consistency, and

transparency in the QSAR result assessment. Recently, OECD initiatives on Integrated Approaches to Testing and Assessment (IATA) and Adverse Outcome Pathways (AOP) have also used WoE approaches for integrating traditional and alternative data for hazard assessment (OECD, 2019).

The implementation of NAMs is a stepwise process involving different phases and stakeholders, (RIVM, 2022; Svingen, 2022). In the EU, the phases that a new NAM is required to follow are shown in Figure 4 (RIVM, 2022). The phases from validation to incorporation into legislation/regulation take place at international level and involve several (international) organisations and advisory bodies. In the Netherlands, experts are actively involved in these committees to contribute to the process (RIVM, 2022). Despite the potential benefits of NAMs, there are still some challenges in the implementation of NAMs related to methodological decision-making, adaptation across various research domains, lack of experience and lack of regulatory acceptance (Botha, 2022; Reddy et al., 2023; Svingen, 2022). The decision-making process can be complex for researchers due to the array of methodologies available, the lack of established guidelines and the lack of confidence/trust in these new methods. In regulatory frameworks, a general principle is that, the greater the toxicity of a chemical substance and/or higher the market volume is, the more extensive the information required (Kienhuis, 2020). Therefore, there is a growing need for increased reliance on data from NAMs to supplant animal toxicity studies, but the availability of such quality data is also one of the major challenges (Svingen, 2022). In addition, the established endpoints of toxicological assessments often cannot be gauged by a single NAM and usually require a combination of methods (Niemann et al., 2023). To address these challenges several initiatives are underway in Europe (Zuang, 2023). For example, the European Partnership for the Assessment of Risks from Chemicals (PARC) established in 2022 aims to address many of the challenges related to adoption of NAMs and also to advance research and knowledge exchange in the field of chemical risk assessment, thereby supporting the European Union´s Chemicals Strategy for Sustainability and “zero pollution” ambition of the European Green Deal (COM/2019/640 final) (De Castelbajac et al., 2023; Marx-Stoelting et al., 2023), and the EC’s roadmap to phasing out animal studies for chemical safety testing.

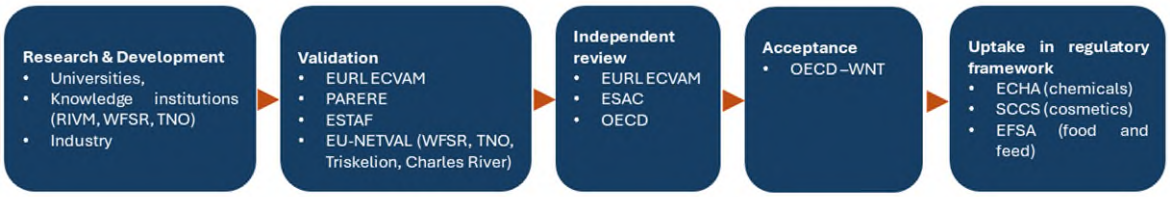


Figure 4. *Phases that a new NAM has to move through from research to uptake in regulatory frameworks in the EU (adapted from: (RIVM, 2022).*

There is an ongoing societal and regulatory concern to ensure the safety of both food and drinking water through setting lower risk thresholds for chemicals. This aligns with the “Chemical Strategy for Sustainability”: One Substance-One Assessment (see: Chemicals Strategy for Sustainability - ECHA (europa.eu) strategy outlined by the European Commission to promote the safe and sustainable use of chemicals (Doak et al., 2022). This concern arises from several factors, including the desire to protect public health, zero pollution goal, promotion of safer and more sustainable chemicals as well as a more integrated and holistic assessment of chemicals (ECHA, 2020). By applying "One Substance, One Assessment" principle, regulators can ensure that each substance is evaluated based on its unique properties and potential hazards, irrespective of the regulatory domain it falls in, leading to more targeted risk management strategies.

To establish scientific confidence in NAMs for regulatory use, essential elements such as fitness for purpose, biological relevance, technical characterization, data integrity, transparency, and independent review need to be addressed (Rivetti & Campos, 2023). The latest report from the ECHA highlights the widespread use of read-across in REACH registration dossiers, especially for human health data endpoints. Alternative methods were employed in approximately 34% of dossiers for lower tier toxicological endpoints (local and acute endpoints) and nearly 84% for higher tier endpoints (repeated dose toxicity, and reproductive and developmental toxicity). However, the evaluations

by ECHA revealed poor quality information in many dossiers, leading to low acceptance rates (Rovida et al., 2020). This assessment was supported by findings from the German Federal Institute for Risk Assessment (BfR) (BfR, 2018). Registrants often failed to provide important details, such as explaining structural differences between chemicals or justifying the inclusion/exclusion of group members. Despite these shortcomings, read-across remains a direct approach for adapting standard information requirements when executed correctly.

Currently, the food industry, has not extensively adopted NAMs, largely for lack of a receptive regulatory framework and the inherent challenges of these new models to accurately predict systemic toxicity and often fail to replicate the complexity of the *in vivo* system (Reddy et al., 2023). In our knowledge, the same holds true for the drinking water sector. A strong belief has persisted that animal studies are necessary, even though in recent decades complex *in vivo* animal models have often proven to be poor predictors of human outcomes (Godlee, 2014). Nevertheless, the use of NAMs in toxicity testing can significantly influence the derivation of risk thresholds for both food and drinking water relevant contaminants. In the context of drinking water, the impact of NAMs such as *in vitro* methods holds a substantial potential to provide a more accurate, mechanistic and high-throughput data for toxicity assessment (Zhang et al., 2018). As mentioned above, drinking water guideline values have traditionally relied on animal studies, which may have inherent limitations in terms of interspecies differences, extrapolation to human health risks and ethical considerations (Karmaus et al., 2022; Nagendrababu et al., 2021; van der Zalm et al., 2022). In this regard, effect-based trigger (EBT) values serve as a complementary approach to support risk assessment through the application of NAMs. EBT values are threshold levels derived from bioassay responses, indicating concentrations at which biological effects may raise concern (Been et al., 2021). By incorporating *in vitro* testing, a deeper understanding of toxicity mechanisms can be gained, improving the prediction of adverse health effects even at lower exposure levels. This improved sensitivity and mechanistic insight can refine the determination of risk thresholds for contaminants in drinking water, and consequently support evidence-based decision making for setting safe exposure limits, which can potentially lead to lower guideline values that are more protective of public health. However, the impact of lower risk thresholds may pose significant challenges for the water sector. Compliance with these new regulations could necessitate infrastructure upgrades, modifications in treatment processes, and increased monitoring efforts. These changes may however be essential for achieving the overarching goals of the "Chemicals Strategy for Sustainability," which prioritizes human health and the promotion of safer and more sustainable chemicals throughout their life cycle (Reddy et al., 2023). Taken together, the use of NAMs in standard setting in both drinking water and food safety assessment is a promising approach to improve risk assessment and protect public health. However, overcoming long-lasting challenges and gaining acceptance by authorities are important steps to realize the full potential of these methods to ensure the safety of drinking water and food.

6 Risk assessment in different domains

Risk assessment is composed of four basic steps: hazard identification, hazard characterization, exposure assessment and risk characterization (IPCS, 2008). In the process of hazard characterization there is a key step for establishing HBGVs, generally termed dose-response assessment. Dose-response assessments determines if a dose-response is present or absent, and establishes relationships between exposure and the adverse health outcomes. These relationships are subsequently used in the process of calculating a HBGV. Dose-response relationships are derived from experimental or observational data. In terms of 'dose' there are three types: external dose (or administered), internal dose (or absorbed), and tissue dose (or target dose). External dose can be expressed in a variety of metrics, namely simple single dose (e.g., mg/kg bw) or a daily intake or daily exposure (mg/kg bw/day). The former is used when establishing an HBGV for acute exposure whereas the latter for chronic exposure. When a chemical is administered via food or drinking-water, concentrations are the original dose metric, in which case it has to be converted to external dose.

6.1 Risk assessment of single substances

Previous chapters explain that the DWD has been influenced by advancing knowledge from other domains before, however often regarding individual substances (Schriks et al., 2010). For example, in 2015 EFSA published an opinion on the risk to public health related to the presence of BPA (EFSA Panel on Food Contact Materials & Aids, 2015). Based on this opinion, a health-based parametric value (PV) of 2.5 µg/L was adopted in the DWD (EC, 2020b). Also, risk assessments in the food and drinking water domain share multiple similarities, both assessing lifelong oral exposure to (frequently the same) contaminants and acute toxicity. In addition, ADI and TDI reference values for chemical contaminants derived in the food domain are also used in the development of guideline values for drinking water quality (WHO, 2022). Harmonized risk assessment across EU legislation would contribute to the 'One Substance, One Assessment' ambition, which is one of the key deliverables of the Chemical Strategy for Sustainability. Predictable processes, shortening the gap between identification, possible risk and necessary regulatory action fall within this aim (EC, 2023). To highlight some of the differences between the risk assessment in the food and water domains, four substances relevant to both water quality and food safety are further discussed below: acrylamide, nitrate, arsenic and chlorate. In summary, these case substances help us stress the important nuances in our understanding of the sources, risks, and regulatory approaches to managing contaminants in both food and drinking water, despite sharing the common goal of safeguarding human health.

6.1.1 Acrylamide

Acrylamide is a chemical that forms in starchy food containing sugars and amino acids, particularly asparagine, during every-day high-temperature cooking, such as frying, baking, and roasting. According to the DWD, acrylamide must not exceed 0.10 µg/L in drinking water. In the Netherlands, this value is currently the same. However, from a food safety perspective it has been considered to be inappropriate to establish a health-based guidance value (e.g., tolerable daily intake [TDI]), justifying the estimation of a lower limit of the dose range within which acrylamide is likely to cause measurable adverse effects (e.g., neoplastic), which is subsequently use in the MOE approach (EFSA, Benford, et al., 2022).

In 2005, in the food safety domain, EFSA agreed with the United Nations Joint FAO/WHO Expert Committee on Food Additives (JECFA) that dietary exposure levels to acrylamide may indicate a human health concern. Ten years later, acrylamide was first fully assessed by EFSA in 2015 based on new scientific evidence, which concluded it to be potentially cancerogenic to individuals of all ages, with children as the most exposed group (on body-weight basis) (EFSA, 2024a). More recently, in 2022, it was concluded that there is substantial evidence for the genotoxicity of acrylamide mediated by the formation of its active metabolite glycidamide, in addition to a potential contribution of non-genotoxic effects towards acrylamide's carcinogenicity (EFSA, Benford, et al., 2022). This conclusion follows on

results from *in vitro* and *in vivo* (oral) exposure of mice and rats, resulting in dose-dependent increases in DNA adduct formation.

No maximum level is stablished for food safety, therefore a mitigation approach is used, meaning that when benchmark levels are exceeded, food business operators shall review without delay the mitigation measures applied and adjust processes and controls with an aim to achieve levels of acrylamide as low as reasonably achievable/possible (ALARA) (EC, 2018). This also means that the 'benchmark levels' are used as performance indicators of mitigation measures and cannot be used as reference to evaluate if a product can be placed on the market or not. For example, the benchmark level for ready-to-eat French fries is 500 µg/kg (EC, 2017). For baby foods, processed cereal based foods for infant and young children (excluding biscuits and rusks), the benchmark level is 40 µg/kg. If one takes the approximate equivalence to water (i.e., density water of ~ 1 kg/L), this would translate to 40 µg/L. In contrast, the water quality limit for acrylamide in the EU and The Netherlands is 0.1 µg/L. This highlights the extent to which risk managers may allow the presence of an unintended substance in food due to challenges in finding a more feasible alternative. Similarly, water risk managers may face comparable dilemmas with unintended water contaminants, where complete removal may not be practically achievable.

6.1.2 Nitrate

Currently, the European legal limit of nitrate in drinking water is 50 mg/L. In 2020, RIVM has for the first time estimated the combined intake of nitrate and nitrite via food and drinking water for the Dutch population. It was estimated that drinking water may contribute up to 19% of nitrate (and nitrite) exposure. Estimates indicate a possible higher than desirable combined exposure but unable to determine how high due to lack of data. In this report, without making mention of the ALARA principle, it does hint at the existing options to keep the intake of nitrate and nitrite as low as possible (Sprong, 2020). It reads, "*Given the finding that high nitrate concentrations in drinking water, even below the legal limit for nitrate in drinking water, resulted in a relevant contribution to the combined exposure to nitrate and nitrite, it is important to keep levels of nitrate in drinking water and its sources, as low as possible*". Another recent study resulted in a successful epidemiological research on drinking water distribution. This time in Denmark, the health effects found in the study due to nitrate in drinking water informed a discussion on drinking water standards internationally (Stayner et al., 2022).

Guideline values for water quality, as established by WHO, are set to be protective of the general population over a lifetime. There are a few exceptions, such as lead and nitrate, which values are set to be protective for susceptible subpopulations (WHO, 2011). On the other hand, food standards are often set to be protective of subsets of a population (e.g., children). According to WHO (4th Ed), the nitrate drinking water guideline value of 50 mg/L (as nitrate ion) protects the most sensitive group, bottle-fed infants, from adverse health effects like methaemoglobinaemia and thyroid issues. Unlike most guideline values based on animal studies, this value is based on epidemiological studies showing no harm below this level and is also protective for long-term effects and other population groups, including older children and adults.

6.1.3 Arsenic

Arsenic, a genotoxic carcinogen, occurs naturally in the environment in various oxidized forms, particularly soil and groundwater. The most notable form is inorganic arsenic due to its range of serious adverse health effects, including cancers and neurodevelopment disorders. Despite being a non-threshold substance, on the basis of practical considerations such as achievable removal (WHO, 2022), a standard of 10 µg/L is established according to the DWD as well as in the Dutch Drinking Water Decree.

In terms of inorganic exposure via food, a recent risk assessment established a conservative reference point of 0.06 µg/kg bw/day based on a case-control study on skin cancer (Chain et al., 2024), a value approximately 10 times lower than the previous reference point (0.3-8 µg/kg bw/day in 2009). This is a conservative estimate of the lowest dose that could be associated with increased induction of skin cancer after exposure to inorganic arsenic. The ML for total arsenic in natural mineral waters in the EU is 10 µg/kg. According to emission data, arsenic is the third with most entries in the emission database ZZS (*Zeer Zorgwekkende Stoffen*, i.e. substances of very high concern) in the Dutch

Emissions Registration database (Bodar, 2023; RIVM, 2024c). Furthermore, it is possible that the standard will lower in the future. Dutch drinking water companies aim to produce drinking water with <1 µg/L As (Ahmad et al., 2020).

6.1.4 Chlorate

An interesting case is chlorate, as an example for which no specific limits were set until recently, despite existing knowledge of its occurrence in drinking water. In a 2015 scientific opinion, EFSA derived a toxicological reference value for chlorate and revealed the existence of chronic health risks on the thyroid on infants and children (Chain, 2015). In this assessment it determined that the main contributing food source is drinking water, accounting for 40-60% of the total chlorate exposure (EC, 2016). In 2020, the European food regulation was amended to accommodate temporary MRL for chlorate according to the ALARA principle, and based on the 95th percentile of the occurrence data. According to the DWD, the limit of 0.25 mg/L will be enforced from January 2026 onwards. In the Netherlands, a health-based exposure limit in drinking water of 0.07 mg/L was derived, but is not laid down in legislation and is based solely on targeted measurements (BuRO, 2021).

6.2 Risk assessment of mixtures

An increasing number of chemicals from anthropogenic sources is reflected in the complex mixtures found in environmental water bodies, which complicates the characterisation and interpretation of water quality information (RIVM, 2024b). It must be noted that despite the prevailing misunderstanding, HBGV do not protect against chemical mixtures. In a regulatory context, possible human health risks resulting from exposures to mixtures are generally not assessed. Nevertheless, there is a broad understanding of a need to move beyond single-chemical assessment by developing more ambitious frameworks to assess mixture toxicity. Currently, there is no 'regulatory-applicable' accepted methodology for carrying out risk assessments for chemical mixtures in source water and drinking-water (WHO, 2017a). Interestingly, in the food domain, in determining whether any food is injurious to health, it establishes that regard shall be had to the probable cumulative toxic effect of substances (EC, 2002b). It is also mentioned for risk assessment that the EFSA shall promote and coordinate the development of uniform risk assessment methodologies in the fields falling within its mission (EC, 2002a), but no direct reference to guidance/methodologies is present. This again seems to indicate that food safety regulators make things more explicit in regards to joint toxicological effects (Verhagen et al., 2021). Nonetheless, due to the relevance and width of mixture toxicity and risk assessment from a water drinking water perspective, a dedicated study was performed within the context of the present project (see also (Steenhof, 2024).

To explore how current human health risk approaches from different (inter)national legislative frameworks could potentially improve mixture risk assessment in a drinking water context, a comparative analysis between regulatory frameworks was conducted to identify differences and similarities in legislative requirements and risk assessment approaches (Chapter 3.2.1). Two frameworks were selected as potentially applicable in a drinking water context, one published by the WHO and the other by EFSA (EFSA Scientific Committee, More, Bampidis, Benford, Bennekou, et al., 2019; WHO, 2022). Both frameworks recommend a tiered approach for mixture risk assessment. The first tier (Tier 0) is a Hazard Index approach based on reference values. In case the outcome of the HI is lower than 1, the risk from combined mixture components is considered acceptable. A difference between the frameworks in Tier 0 is how data-poor substances are dealt with. If reference values are not available, the WHO framework recommends conducting a TTC concept for substances missing an ADI, whereas the EFSA framework recommends using the lowest available reference value in the mixture as reference value for substances lacking one.

6.2.1 Interconnectedness of the legislative landscape

Regulatory permeation, meaning legislative domains influencing the drinking water domain or vice versa, may influence future adoptions of regulatory (mixture) risk assessment approaches. The results from the comparative analysis of selected legal documents (Table S2) highlight the legislative embedding for consideration of mixture effects in the food and chemical domain whilst pointing out their unspecific requirements and the necessity for developed and approved methods by the authorities. Although drinking water legislation has its own specific requirements, the

visualization of interconnections between legislative and guidance documents revealed strong links to other legislation, particularly regarding the common contaminants they regulate (**Figure 5**).

The graphical display of the legislative landscape provides a useful tool helping understand the interconnectedness and dependence between relevant legal documents (**Figure 5**). **Figure 5A** shows the found references in the context of 'substance' term definition. The Medicines Products for Human Use Directive (MPH) receives relatively many references in the category ´excluding substance as defined in´ (see green dotted line in **Figure 5**). This indicates that these substances are not expected to be subjected to the same rulings under other legislation. These seem to be exempt from other regulations, based on how substances are legally defined. The DWD relies on the 'substance' definition laid in the WFD, the GWD and the PPP (see black line in **Figure 5A**) which implies a strong form of dependence. Also, the chemical domain is clustered, since relatively many references are incoming and outcoming. This suggests a high regulation regarding the definition of substances in the chemical domain. **Figure 5B** shows regulatory dependency. Interestingly, the water domain seems to be predominantly regulated by Directives. This suggests a less strict regulation when comparing to in the food and chemical domains, which are predominantly regulated by Regulations. This regulatory freedom with Directives might possibly be one of the reasons the WFD goals are not met by the Netherlands (van Kats et al., 2022). However, for a deeper and accurate understanding of this complex regulatory web and its effect, a more comprehensive study together with legal scholars could yield crucial yet missing insights. Only in the CLP guidance, relevant stakeholders are explicitly asked to use data from other documents, namely the Biocidal Products Registration (BPR) and PPP regulations. This suggests limited active mentioning of (re)use of data generated under different pieces of legislation. In the chemical legislative domain, the BPR regulation is a central piece when comparing the amount of references to other legislations. This suggests a high dependency on the BPR regulation. Overall, the selected legislation refers often to each other, even though within different legal contexts, confirming the intricate and integrated nature of EU legislative network to which Dutch law is subjected to (La Cava, 2022).

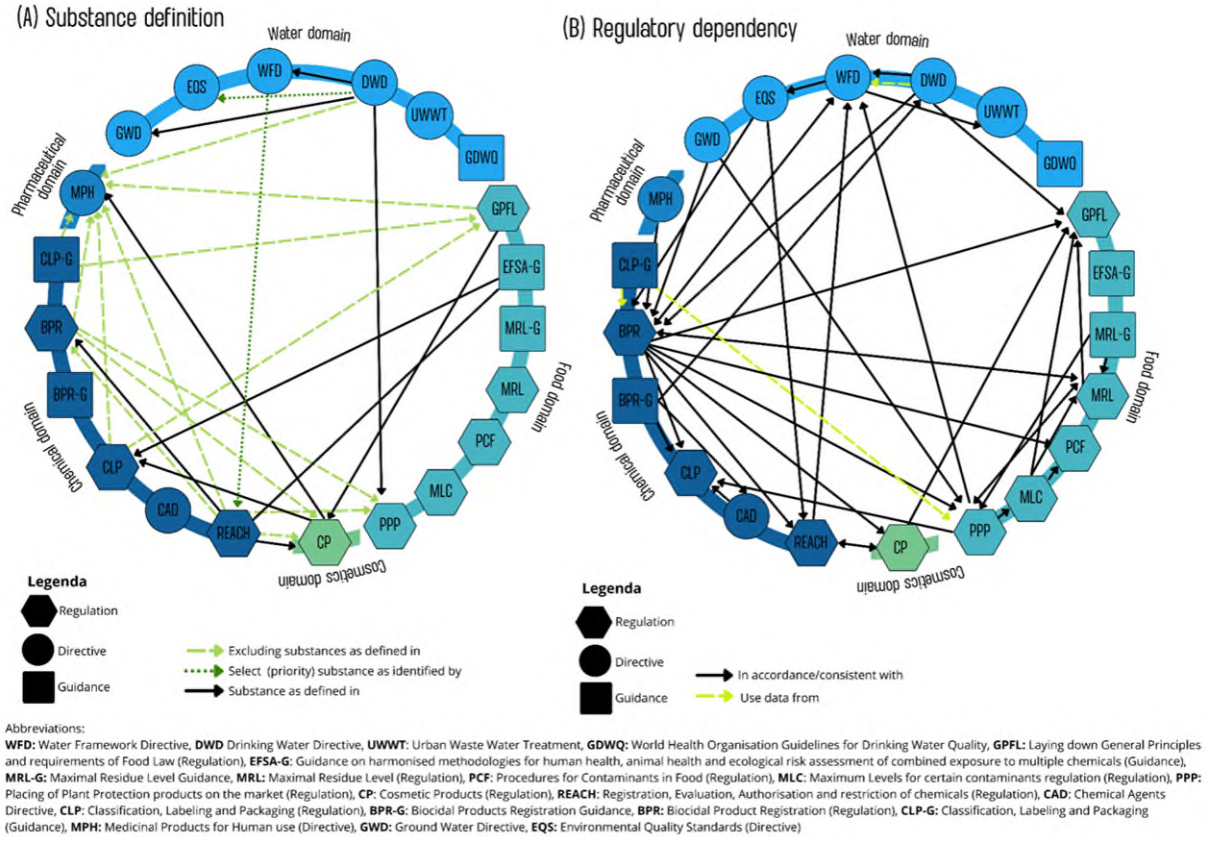


Figure 5. *Interrelatedness of European Union legislative and guidance documents. The water domain is predominantly regulated by Directives, while other domains contain more regulations. (**A**) shows high regulation*

*in the context of substance definitions, especially in the chemical domain. (**B**) shows clustering in the chemical domain and high dependencies on BPR and PPP legislation in the context of regulatory dependency. The arrows display the directionality of referencing. Credit: Tessa Steenhof.*

6.2.2 Alternatives in hazard indexing

Risk quotients of multiple compounds may be summed to obtain a total measure of a mixtures' risk, referred to as the Hazard Index (HI). Guidances propose different approaches to include data-poor substances in HI assessment using the TTC approach as proposed in the WHO guidance (water domain) (WHO, 2022), or the lowest available reference value approach as proposed in the EFSA guidance (food domain) (EFSA Scientific Committee, More, Bampidis, Benford, Bennekou, et al., 2019). This likely leads to overestimation due to added uncertainty of each TTC value and the presence of many low TTC values. However, the TTC value could serve as a guide for prioritization for inclusion of water contaminants in risk characterization since these values are based on the potential for toxicological risk. Using the lowest available reference value is pragmatic and not health or structured-based. Thus for risk-based decisions in regulation, this approach would be less applicable. Additionally, it is highly dependent on a single substance in the mixture without further mixture considerations and weights all mixture components equally regardless of potency. This makes the risk index conversely driven by exposure concentrations.

7 Challenges and opportunities in drinking water risk assessment

In the European Union, that tap water achieves a compliance level of 99% or better with EU standards (Tosun et al., 2020). In the Netherlands, the regulatory compliance is an impressive 99.9% (RIVM, 2018). However, these levels can be misinterpreted, leading to overconfidence in the meaning of such figures and overlooking what the monitoring results fail to show, particularly regarding the large number of unregulated contaminants (Rizak & Hrudey, 2006). It is important to recognize that the impressive high compliance rates pertain only to regulated substances (i.e., those expected to occur), while unregulated substances, or those for which little to no knowledge exists, demands reasonable questions about the current state of water quality (Ferraro & Prasse, 2021; Rosenblum et al., 2024).

A crucial distinction must always be made between regulatory compliance and regulatory suitability in light of changing pressures. There have been instances in the past where certain parameters, once deemed essential to meet quality standards, were later determined to be less relevant than previously assumed (EC, 2016). Even when water quality standards are fully met, unknown risks and uncertainties unaccounted for may remain due to knowledge gaps. Also, mistakes can occur in the calculation of non-binding HBGVs by WHO, such as for boron, which are later adopted as binding values in the EU (Frisbie et al., 2015), supporting the need to uphold precautious measures. Legislation is a tool for achieving minimum requirements by enforceability, but it can be misunderstood to be a waiver of effort beyond full regulatory compliance or may give the false impression that hazardous substances are safe simply because these no longer occur in drinking water (EC, 2016).

7.1 Challenges in risk assessment and regulation

The water domain is predominantly regulated via Directives, allowing Member States to meet legal requirements more flexible. This suggests a less strict regulation when comparing to the food and chemical domains, which are predominantly regulated by Regulations. Nonetheless, challenges in risk assessment across these domains persist. The difficulty in handling chemical risk assessments and ensure regulatory compliance is well expressed in the delays in the regulatory processing of toxicity files and calls for expedition by the EU Ombudsman (EO, 2016). Regulatory quality requirements are based on the best available evidence but are also constrained by biased expert opinions and the ability of regulatory systems to keep them relevant and enforceable. This, in a way, explains the tendency for protective standards to strengthen, even if it occurs decades later (e.g., Amand-Eeckhout (2024)). Exceptions to this trend include boron and selenium, whose standards have increased from 1000 to 1500 and 10 to 20 µg/L, respectively (CE, 1998; EC, 2020b). Furthermore, the challenges of aligning new scientific evidence, regulatory expediency, and adequate, timely public health protection are once again highlighted by the emergence of PFAS in the public eye (Reinikainen et al., 2024). For example, different agencies involved in exposure science and risk assessment may rely on varying methodologies, datasets, and assumptions for the same exposure route and when combining exposure routes in an aggregate exposure assessment (Paulović et al., 2022).

7.2 Advances and bottlenecks in deriving HBGV

In the present study, we aim to reconcile the domains of water and food from a safety perspective, which ultimately falls under the responsibility of risk managers and public officials. Risk assessment involves diverse considerations that vary depending on the specific domain. For example, consider the dispute between EMA and EFSA regarding BPA (EFSA & EMA, 2023). We believe there is great potential in establishing scientific agreement on hazard identification and characterization across different domains. However, risk assessment processes differ between fields. For instance, in the pharmaceutical domain, hazards can be weighed through a benefit-risk evaluation, whereas in the food domain, the primary goal is the absence of, or minimal, risk (see Chapter 3).

The derivation of drinking water HBGV is under continuous revision by international and national organizations. These are a continuous effort to provide risk management with the best possible estimates of risk. Despite some advancements in risk assessment, traditional paradigms and dominant approaches remain in use. For example, the partition of the chemical universe into threshold and non-threshold chemicals overlooks increasing evidence of chemicals not fitting into either category (Futran Fuhrman et al., 2015). For example, EDCs are not necessarily carcinogenic, yet most cannot be assigned a practical safe threshold due to their low dose effects (< ng/L) and temporal considerations (e.g., critical window of exposure, latency). This may mean that HBGV may eventually be lowered because EDCs have identifiable low-dose effects while potentially having no safe threshold level. Similar to EDCs, the complex long-term or delayed adverse effects of immunotoxicants and neurotoxicants may soon undergo scientific and regulatory re-evaluation to determine whether thresholds can be established. This is in alignment with similar debates regarding genotoxic carcinogens, for example, the number of DNA mutations or adducts to be increasingly associated with apical effects. A further parameter that adds to this complexity is the growing evidence that genomic instability of epigenetic events can drive cancer independently of genetic mutations (Singh et al., 2024). In fact, there is growing consensus that genotoxic agents may exhibit a threshold (or non-linear) dose-responses, via non-DNA-reactive mechanisms (EFSA Scientific Committee, More, Bampidis, Bragard, et al., 2021). This opens up the discussion on the use of HBGVs based on PODs for aneugenicity, as well as the potential for further investigating tests such as *in vitro* micronucleus (MN) assays in conjunction with BMD modelling or MOE for water quality risk assessment and management. The further implementation of NAMs and complementation of existing data may soon shift the way in which HBGV are derived and may carry several implications to drinking water quality compliance. However, these developments are sometimes met with great resistance and it remains unclear how these will translate into practice (Baumgartl-Simons, 2019).

7.3 Ahead of regulation and innovative alternatives

If current water quality standards are not exceeded, there is a lower incentive to prioritize measures to reduce ongoing emissions or to mitigate potential risks. However, if new drinking water and drinking water sources standards are established or reduced, this will compel the water utilities to react potentially less efficiently if not enough transition time was envisioned. For persistent substances this may be particularly concerning since these prevail in the environment even after retrospective measures have been taken (Hans Peter H. Arp, 2023). This advances the argument in favour of proactive regulation which will be preceded by innovative approaches (e.g., NAM-based guidance values) and may be followed by stricter water quality standards for individual substances or, arguably more critically, for groups of substances. For example, through case studies, Rager and Rider (2024) provide an interesting exploration of the concept of “sufficient similarity” in whole mixture risk assessment, highlighting the significance of comparing complex mixtures using non-targeted chemical analysis and NAMs to help establish thresholds of similarity (Rager & Rider, 2023).

7.4 The achievability problem

What is desirable in terms of risk control is not always achievable. For example, for the genotoxic carcinogen acrylamide, MOEs of 50, 283, and 89 have been calculated assuming different conditions. More recently, these were confirmed by EFSA, following earlier doubts about whether acrylamide was indeed a genotoxic carcinogen or if a health-based guidance value could be established. EFSA has reaffirmed that no health-based guidance values can be set for acrylamide. When it comes to risk management measures, MLs have not yet been established. Instead, mitigation approach has been adopted, aiming to reduce acrylamide levels as much as reasonably achievable (ALARA principle in practice). However, achieving a MOE of more than 10 000 (commonly accepted standard) for acrylamide is practically unreasonable unless, for example, the consumption of products such as breakfast cereals, coffee, or French fries is heavily restricted. Socioeconomically this is not currently an acceptable option, just like consumers do not accept drinking water with unfamiliar colour, odour, taste or turbidity. It would therefore be beneficial to receive guidance on what constitutes a real risk and what thresholds are realistic. This would help determine when the industry must implement specific measures due to genuine health concerns. Additional guidance from risk assessments would be invaluable in this context.

Regulators, when managing contaminants, do not rely solely on assessments performed by official agencies, like EFSA. They must also consider the feasibility and achievability of applying good practices (e.g., Good Agricultural Practices, see Table 2, Chapter 3.1.2), which poses its own challenges. For example, with aflatoxins, regulators are seeing increased prevalence and higher detection frequencies in cereals. This raises the possibility that current MLs, particularly for maize produced within the EU, may no longer be achievable. What can be done in such cases? Should permissible levels be increased, or is that not an acceptable option? This presents a significant challenge since risk managers and policymakers may feel compelled to take lenient measures despite the risks. These same challenges are progressively coming to the forefront of discussions among experts in the (drinking) water domain, with the increasing number of contaminants detected and with unknown long-term impact on human health.

A more robust assessment to determine the extent to which levels could be increased without jeopardizing public health would be extremely helpful, especially given the anticipated effects of climate change. In the drinking water domain, similar challenges exist under more stringent conditions, as the variety of food products generally provides more flexible choices, whereas people are bound to the drinking water serviced in the region they inhabit. Balancing the risks posed by contaminants against the benefits of consuming certain foods or waters (tap, bottled, other) is critical – so called, risk-benefit assessment. A more precise health risk-benefit assessment, particularly for the most challenging compounds such as genotoxic and carcinogenic compounds, would allow to quantitatively and qualitatively compare risks with benefits. Such an approach encourages risk mitigation action even under uncertainty (inconclusive risks) by providing more clarity and support better decision-making in this complex area. Interestingly, in the neighbouring country of Germany, Health-Related Indicator Values (HRIV; in German: *Gesundheitlicher Orientierungswert* (GOW)) are used as precautionary trigger values (between 0.01 and 3 µg/L) for drinking water, if insufficient toxicological data is available to establish a guideline value. When a guideline value is derived, the HRIV is (most often) superseded (Grummt Tamara; Braunbeck, 2020).

Despite all of this, these dilemmas are not entirely novel to the water sector. Take bromate as an example. Bromate is a carcinogenic substance which may be formed as a by-product of ozone disinfection step during drinking water production. Despite its properties and presence, the net benefit to public health has been deemed greater by reducing the burden of disability due to disease caused by pathogens, thus outweighing the disadvantages of additional cancer risk (1 in 1 000 000 cases, life time based) and maximum permissible cancer risk (1 in 10 000 cases, lifetime based), according to Dutch standards for lifetime cancer risk for genotoxic carcinogens (Havelaar et al., 2000; Versteegh, 1995). For cancer risks associated with drinking water contaminants, established guideline levels may in essence be viewed as being 'below an arbitrarily defined probability'. For example, the WHO sets guideline values for genotoxic carcinogens consistent with an upper-bound estimate of an excess lifetime cancer risk of 1 in 100 000 (i.e. one additional cancer per 100 000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years) (Sinclair et al., 2014; WHO, 2009). In context, 1 in 2 persons in the Netherlands is expected to be diagnosed with cancer over the course of their lifetime (Puts, 2023).

The ALARA principle dictates that risks must be kept as low as reasonably achievable, attempting to find the best compromise between safety and consensual achievability. In the food safety literature, this principle is evoked more frequently than in the water quality literature. Instead, in the water quality domain high aspirational language is used (e.g., "*wholesome and clean*"). However, the challenge remains the operationalization of ALARA into ethical decision-making in public policy (Hansson, 2013). As illustrated above, the risks posed by certain food and water contaminants can be difficult to quantify, probabilistic in nature, or even unavoidable to some extent. Under these circumstances, the priorities and goals set by stakeholders (e.g., reducing exposure by a factor of 10 000) are intricately tied to the complex discussion surrounding their achievability (e.g., the removal of PFAS from water and soil) (A. A. Ling, Hans Peter; Aubert, Raphaëlle; Bersi, Eurydice, 2024).

7.5 Balancing risks and socioeconomics

Water managers are generally successful at keeping drinking water and sources clean according to quality requirements. However, problematic substances continue to lurk in (sources of) drinking water and throughout the aquatic environment in the Netherlands and Europe. For example, substances classified as (potentially) being of very high concern (SVHC) (e.g., aldrin) or a candidate for substitution (CfS) under the pesticide and biocide frameworks, continue to be found in environmental waters (e.g., diflufenican). This may be due to illegal or legal use. Interestingly, regarding the latter, despite the hazardousness of these substances, these may still be authorized in the market under

specific circumstance due to socio-economic benefits been deemed to outweigh the substances risks (van Dijk et al., 2021). In principle, this cost-benefit analysis accounts for the impacts of the products and their ingredients throughout their lifecycle. However, this may not be the case for all substances in the market, which may unintendedly downstream responsibility and forego necessary risk mitigation measures. This downstreaming of responsibility places drinking water companies under additional stress due to increased efforts required for quality compliance.

One interesting implication of integrating risks across product domains is the implementation of 'risk allocation' following the concept of 'extended producer responsibility'. According to particular exposure routes this could lead to discussions about the allocation of costs and responsibilities to food products and drinking water producers. These active discussion can already be witnessed, for example, under the current developments related to the recast of the Urban Wastewater Treatment Directive, where pharmaceutical and cosmetic sectors are objecting the current 92% allocation (Bio Innovation Service, 2022). Therefore, a similar discussion may soon expand to the drinking water sector when posing equivalent questions such as "*What is the extended responsibility of drinking water producers?*" or "*How much the risk associated with a food and water contaminant be allocated to a particular sector?*" (see example in Chapter 6.1.2.). An open collaborative dialogue will become necessary early on between water experts, food experts, risk assessors, risk managers and others, with the highest interest of safekeeping human health.

7.6 Bridging water and food regulatory domains

HBGVs derived by the WHO are widely adopted in Europe. Occasionally, equivalents are taken from the USA, and individual EU member states very often derive their own values to meet their particular circumstances. This is particular the case for HBGV for drinking water. However, in regards to national legal food safety standards (MLs) in countries like the Netherlands, this exercise is often outsourced and heavily relies on the derivations made by EFSA. One reason for this is that there is no equivalent single entity at the EU level dedicated to water quality. Instead, mandates covering the water legal and scientific landscape is dispersed across national and international organizations (e.g., WHO, European Environment Agency (EEA), RIVM). However, with the recast of the DWD, entities like ECHA have seen their mandate expand to also include parts of the water regulation (e.g., Article 11 on the minimum requirements for materials in contact with drinking water).

7.6.1 Differences between food and water

The development of standards for drinking water and food is similar in that it shares significant underlying principles (e.g., Chapter 3.2.1., Chapter 4.5.) but also notable differences. The process of establishing safe levels for contaminants, such as TDI or ADI, is fundamentally comparable for both. In food, standards are primarily designed as benchmarks to prevent substances from reaching levels in food that would cause the ADI (permitted substances) or TDI (unintended substances) to be exceeded through dietary intake. Examples include MRLs for pesticides and migration limits for food packaging materials. For other environmental contaminants, such as metals in shellfish, there are MLs above which the product cannot be sold. However, it is often argued that the risks associated with food consumption are more manageable due to the variety of product alternatives available. The benefits of a particular food can often be found in other equivalent options, and this flexibility extends to choosing safer products when the risks are deemed unacceptable. On the other hand, consumers and drinking water suppliers are considerably more constrained, as fewer options are available for tap water, which is often single-sourced (e.g., groundwater or surface water) or geographically limited. For example, a drinking water supplier is constrained to the quality of the water source and the allowed production processes in place (WHO, 2017b). Therefore, activities such as agriculture may affect the quality of source waters for drinking water. In fact, the impact pesticides can have in water sources is the main reason why pesticides have assigned limit values under the Drinking Water Directive and the Dutch Drinking Water Decree. This has led to a stringent approach to contaminants in water quality. However, how stringent is stringent enough seems to remain a topic of great debate among food safety and drinking water experts.

7.6.2 Drinking water as food

Once the drinking water flows out of the tap (formally, the 'point of compliance'), it no longer falls under the DWD, but instead it enters the legal domain of food safety (EC, 2002b). This comes to emphasize that drinking water from the tap intended for human consumption is, ultimately, regulated as food, and it gets to be legally dealt differently in practice by regulators and risk assessors. It was highlighted that drinking water regulations include extensive monitoring (EC, 2020b; NL, 2009), with utilities regularly testing for over 1 000 compounds and taking mitigation actions when necessary. There was a consensus that drinking water utilities often maintain stricter standards than the established regulations, but the expected increasing stringency of these standards poses challenges. It must be noted that nowadays there is little option for choosing the source of water. Also, as opposed to food safety, drinking water must be devoid from any contamination causing adverse effects (with exceptions, like bromate), whereas in food this is expected and allowed (due to unavoidable use of pesticides, for example). With the current tools it is hard to make the water cleaner than it already is, unless greater low-waste socioeconomic shifts take place or great monetary costs are incurred (A. L. Ling, 2024; van der Borst, 2025). However, there are concerns over aspects like "regrettable substitution", i.e. replacing a banned or disputable substance by another potentially more hazardous substance, which will continue to challenge, which may lead to a false sense of progress towards a zero-pollution environment. To advance towards a zero-pollution environment, regulatory frameworks must not only prevent damaging actions, such as regrettable substitution and drinking water source contamination, but also ensure coherence across different domains, avoiding contradictions that could undermine public trust and health protection efforts. A key research and regulatory need is to establish PODs for drinking water which are coherent an in agreement between food and drinking water. In the water domain, the presence of any contaminants is strictly regulated, whereas food safety legislation does not explicitly include this precondition, perhaps because it is acknowledged that complete absence of contaminants in food is unrealistic. Future research should explore how these differences impact risk assessment and regulatory alignment, ensuring a scientifically sound basis for setting equivalent safety thresholds across both domains.

7.6.3 MOE and ALARA in water

In the EU food safety legislation, the approach of risk management approach to genotoxic compounds, there is a considerable difference in approach between substances and the residues requiring authorization before their use in or on food, i.e., regulated substances, and contaminants. For regulated products, which are indeed a substance to be authorized, that have been identified to be genotoxic, no safe dose can be established and indeed no authorization and also no use in food. So that is very straightforward. However, during the production of food, impurities may be added unintentionally that are genotoxic or genotoxic carcinogens. In 2012, EFSA issued a statement addressing this issue. While the substance itself may not be genotoxic, if impurities are present that are genotoxic or genotoxic carcinogens, a MOE approach can be used to determine if the impurity levels are acceptable from a public health perspective. This approach indicates a level of concern but does not quantify the risk. EFSA may conclude that the MOE is of high concern, low concern, or unlikely to be a health concern. If EFSA concludes that the MOE is of high concern, the substance (due to the impurity) would not be authorized. If the concern is low or unlikely to be a health concern, the substance may be authorized. This presents challenges, especially in the case of smoke flavourings, which are mixtures of different compounds. These compounds are not impurities but components of the mixture. Some compounds, such as 2(5H)-Furanone and benzenediol, are genotoxic. EFSA concluded that the health concern could not be excluded and, as a result, risk management measures need to be taken. The practical use of the MOE is evident for substances that, despite being harmful (e.g., genotoxic carcinogens), are not banned from food. Although undesirable, these substances are sometimes unavoidable. In such cases, MOE can help support risk managers in proposing actions that aim to keep exposure as low as possible. This approach builds on the foundational concept of ALARA (see Chapter 4.4). This approach could be rethought in the context of drinking water quality since unintentionally added contamination may also occur during the production of drinking water.

7.6.4 Harmonization across food and water

In water regulation, water managers and authorities must comply to certain requirements according to the Dutch water decree, as do drinking water companies. This applies to 'known substances' (e.g., pesticides) and 'unknown substances'. An analogy may be drawn with food regulation, where the quality requirements for 'known substances'

equates to MRLs (for permitted substances) and 'unknown substances' equates to MLs (unintended substances) (Table 7).

Table 7. Analogs between water and food regulation in terms of water quality requirements and food safety requirements, for known and unknown substances.

Water Regulation			Food regulation
	Water manager/authority	Drinking water company	
Known substances (e.g., pesticides) *[Quality requirements]*	0,1 µg/L (0,5 µg/L sum)	0,1 µg/L (0,5 µg/L sum) 1 µg/L: non-relevant metabolites	Permitted substances [Maximum Residue Limits (MRL)]
(Un)known substances *[Signalling value, precaution]*	0,1 µg/L: "early warning" signalling structural problem substances (years)	1 µg/L: signalling acute problem substances (days)	Unintended substances [Maximum Limits (ML)]

The number of chemical contaminants in food for which no regulatory levels exist is increasing due to the diversification of the food supply and the advanced analytical capabilities (lower detection and quantification limits). Therefore, there is a need for alternatives by, for example, adopting cut-off values or prioritization tools, to assess low levels of chemicals exposures and whether further data is required to assess human health risks. This is exactly what the WHO Food and Agriculture Organization of the United Nations (FAO) proposes in situations demanding a pragmatic-risk-based approach (FAO & WHO, 2019) by suggesting the use of 1 µg/kg as cut-off value, or the TTC approach. This is equivalent to the 'signalling parameter' of 1 µg/L used in the Netherlands to assess the risks to drinking water when a drinking water guideline value has not been yet established. If a substance falls withing the 'Other anthropogenic substances' category as a 'Indicator - Signalling parameter', meaning that as soon as a maximum value of 1 µg/L, i.e., 1000 ng/L is measured, further investigation needs to take place as it could be indicative of contamination at the source and/or potential health risks.

For processed foods, contamination levels can be minimized by changing the production methods or advising dietary alternatives. However, for environmental contaminants, this is more challenging. For drinking water, similar discussions are ongoing about how to decrease contaminants' concentrations, but it is a technical and economical challenge to identify and implement the most effective measures. An option for some businesses may be to change water source, but changing a drinking water source is not straightforward due to practical and financial implications. Additionally, differences in legislation between food and water may further complicate the issue. Mixture toxicity is another major concern due to the complexity in assessing the combined effects of multiple contaminants in drinking water and food. NAMs may provide some solutions, or at least significantly improve our ability to evaluate these mixtures, since it is impractical to empirically study all possible chemical combinations. At the moment, it remains unclear how to translate NAM-based results, such as those from QSAR models and bioassays, into risk measures due to varying uncertainty. Although water holds a unique status among consumable goods, it is conceivable that water intended for human consumption will eventually become partially regulated under food legislation. At the very least, a shift towards a more harmonized regulatory framework across water quality, food safety, and potentially other

domains appears to be an opportunity. However, whether this shift is desirable and justified remains an open question.

7.6.5 Towards integration to better serve consumers

Regulations are essential governing tools but can be challenging to apply effectively, much like natural language. Indeed, drinking water and food safety experts need to improve their ability to map the gaps in our toxicological knowledge at the edge of science and regulation, which is, in itself, a form of knowledge generation – an uncomfortable exercise in asking, 'What do we not know?' Hopefully, this will further emphasize that evidence is crucial to guide policy, while the temporary lack of it should not prevent the drinking water sector from taking precautionary action nor a more holistic view (e.g., 'One Health', 'One substance, one assessment'). This knowledge integration and dialogue is becoming increasingly a necessity, as exemplified by joint decisions by EU multiagency regulatory joint positions (EFSA et al., 2025). Creating standards for different parameters (chemical, microbial) and domains (water, food) does not consider the totality of an individual's exposure. One interesting attempt to guide evidence-based prioritization of policy action was made by Hartman et al. (2022) through the development of an model for calculating drinking water risk scores for emerging chemical and microbial contaminants (Hartmann et al., 2021). Sociopolitical ambition of the 'One Health' concept and the recognition of the need for an integrated and cross-sectoral collaboration in the animals-plants-environment axis, may eventually lead to increasing coalescence of the drinking water and food safety domains, followed by better harmonization of standard-setting processes between policy frameworks in the future.

7.6.6 Future perspectives and open questions

There is increasing discussion about how safe thresholds are derived, including for (drinking) water quality limit setting, which is generating debate amidst confusion and, as more lightly termed by sociologists, some *chaos*. This term has been used in relation to transition or transformative events, where chaos can be seen as a sign of an eminent major change or turning point – hopefully for the better. The manner in which safe thresholds and risk management choices are made based on non-animals based NAMs and Next Generation Risk Assessment (NGRA) may be accelerating this process. The drinking water sector is also undergoing a transition due to various factors, such as climate change and societal pressures (Brouwer, 2018; EC, 2024). These challenges are compounded by contamination issues, which bring a host of problems together. There is, undeniably, a sense of disruption at present. Planning for future drinking water production is becoming increasingly challenging.

Bisphenol A is an interesting example bringing water quality experts to face the need to reflect on the developments and risk considerations made by food safety experts. At the start of the present project in January 2024, a European BPA ban from food or drink contact products was likely. Later that year, in December, the ban was adopted due to its potential harmful health impacts. However, BPA is also used in water contact materials. This type of developments outside of the water domain, forces water experts and risk assessors to reflect on the implication of such decisions (see Chapter 5.6). Current human exposure to BPA occurs mainly through food with less than 2.8% via drinking water (Arnold et al., 2013). A default exposure allocation in the derivation of drinking water guideline values, is that of 20% for drinking water. It is sometimes argued that lowering a drinking water standard for BPA would only achieve a maximum reduction in 3% of total exposure. The follow-up rational is that setting standards for BPA thus becomes only effective if exposure through food (and other exposure routes) is also regulated. However, this may have to be reconsidered because 20% is not necessarily a realistic percentage adjusted to a particular context, the concentration allocation may vary across the multiple exposure routes (food, water, air, soil, …), and in the derivation of a guideline value in the effect assessment module assumptions of exposure allocation should not be considered but instead reserved solely to the exposure assessment module. Ultimately, what matters is how much of a chemical contaminant enters the body and effectively targets the vulnerable receptors, regardless of the exposure routes. The drinking water sector is not responsible for such holistic considerations on multiple chemical exposure routes. The sector is responsible to uphold its duty to guarantee that quality requirements are met. Yet, as the present report illustrates, it wishes to develop a broader view by touching bases with the knowledge and understanding from related domains like food safety. This ought to be also facilitated and encouraged by other private and public national organizations.

There are growing efforts by experts and decision-makers to dispel the often isolated water-focused and food-focused mindsets. For example, in 2019, RIVM conducted the first study on combined dietary exposure assessment of nitrate and nitrite, where exposure via both food and water were assessed (van den Brand et al., 2020). From our observations and consultations with experts in the food safety and water quality domains, most agree that these two fields should become increasingly interdependent, not just in theory but in practice. Furthermore, recognizing that expert opinions can be biased, an increased focus on whole-evidence synthesis is necessary for strong evidence-based policy, something many experts are willing to accept. In food safety, drinking water is sometimes considered in the calculation of risks posed by food contaminants. However, this perspective is also gaining recognition among drinking water experts (see Chapter 6.1.2.).

8 Outlook

Drinking water companies act within the constraints of legitimacy, consistent with their commitment to deliver safe and high quality drinking water to the public. The voluntary willingness to stay ahead of regulatory obligations and minimum legal requirements, as to avoid implications to the public health far into the future appears to be of critical importance for the institutional integrity of the sector, in an era when Europeans are increasingly concerned about environmental pollution and their health. Over half of Europeans consider that the actual level of protection of human health and the environment from hazardous chemicals is too low and should be increased (EC, 2024). Yet, it remains a significant challenge among risk assessors from different domains to establish a common understanding of how risks should be determined and ultimately handled. Stakeholders often hold a different viewpoint on current and future drinking water standards, on the potential impact of next generation risk assessment, and on the transition to animal-free and NAM-based drinking water standards. These viewpoints are further explored below.

8.1 On current drinking water standards

Most of the eleven experts and managers involved in this project, including those in food safety, water quality, animal science, toxicology, regulation, scientific research, and risk assessment, are of the opinion that current drinking water quality standards may be insufficiently protective. A similar concern has been voiced by the Dutch Inspectorate of Human, Environment and Transport by raising concerns about the quality of national water sources and the insufficient ability of current regulation to protect water quality (Jonker, 2024). If water quality is compromised, food safety may be as well, leading to an exacerbated exposure to the same contaminant(s) or cumulative exposure to multiple contaminants. In the context of environmental chemical pollutants, studies have already demonstrated that individual environmental quality standard (EQS) values do not necessarily provide sufficient protection against combined adverse effects of chemical mixtures (Carvalho et al., 2014). In regards to drinking water, RIVM scientists have recently highlighted that a combined exposure assessment, spanning different regulatory frameworks (water and food) and using different scenarios for drinking water, provides a better option (van den Brand et al., 2020).

In the Netherlands and Belgium, the public believes that the main threat linked to water is pollution (24%), in line with the average European (21%) (EC, 2024). Also, in the Netherlands, 84% of people think that the EU should propose additional measures to address water problems in Europe. However, it was not evaluated if this position is in the belief that EU should do more to match the stricter standards held in the Netherlands and Belgium, or instead a reflection of the wish to have more measures than the current ones being applied at the national level. Freshwater is a shared and finite resource, and effectively managing it requires a shift in perspective. Businesses must move beyond the boundaries of their own operations and consider their impact at the broader water catchment or basin level, particularly regarding transboundary sources of drinking water downstream, as this may affect another region's ability to comply with drinking water standards. This means addressing the unique challenges and risks of the specific water systems they rely on, rather than focusing solely on internal operational issues. For leaders, this shift entails adopting a basin- or system-centric approach, prioritizing collaboration over isolated efforts (De Kervenoael, 2024). In deriving of drinking water quality standards, it is implicit that a level of zero risk cannot be achieved, leaving risk assessors and risk managers to acknowledge certain risks as being 'tolerable' or 'acceptable' (Sinclair et al., 2014), also in regards to their unavoidability in water (see Chapter 4.6). Food standards are often more stringent but less frequently monitored than water standards, which may lead to greater suspicion regarding their adherence. On the other hand, there are particularities, such as considering sub-populations in standard derivation. In food safety risk assessment, a 60 kg body weight (BW) is used as the default, complemented with sensitive groups-specific parameters such as children, while the default of 70 kg BW on water safety risk assessment is typically used without detailed regional or national population considerations.

8.2 On future drinking water standards

Risk assessment ought to be scientifically and evidence-based, with consideration of public health and precaution (under uncertain information). The revised DWD has brought many welcomed improvements for consumers (Dettori et al., 2022). Nonetheless, it may be interesting to further explore the interplay between the precautionary principle and the ALARA principle from a drinking water perspective. The former seeks to prioritize minimizing risks regardless of the level of scientific certainty. The latter is more accommodating of factors which affect the feasibility of taking certain implementable exposure reduction measures over others. In this regard, it may be interesting to explore Best Available Techniques frameworks from a value chain perspective to assess the best sectoral activities and methods of operation in water installations for preventing drinking water contamination (OECD, 2022). Most of the eleven experts and managers involved in this project, including those in food safety, water quality, animal science, toxicology, regulation, scientific research, and risk assessment, expect that drinking water quality standards decrease in the future, and that the adoption of a thoughtful combination of alternative and NAMs for toxicity and risk assessment approaches may influence this.

NAMs could be particularly useful for high-throughput screening of groundwater samples or establishing low substance concentration ranges based on subtle biological effects (EEA & ECHA, 2024). This is because substances are often found at lower concentrations in groundwater compared to more polluted surface waters. In certain cases, the higher sensitivity of animal-free NAMs (e.g., effect-based bioassays) in detecting the presence of toxicological active agents may be preferred over conventional analytical methods. In addition, experimental NAMs could be useful in testing these lower concentration ranges, particularly for those pollutants for which no risk assessment has yet been possible to finalise due to lack of toxicological information (EFSA, Alvarez, et al., 2022; EFSA et al., 2018).

8.3 On Next Generation Risk Assessment

All relevant techniques along with established toxicity endpoint assays are generally included in OECD technical guidelines. Qualitative studies are very useful, yet quantitative evaluation of data supported by statistical tools seems as an increasing necessity for improving evidence-based risk management decisions. To assist in the interpretation and reduction of animal use, NGRA is the incorporation of information from NAMs (e.g., *in vitro*, PBTK/IVIVE) and human data (e.g., epidemiological and biomarkers) to make informed choices on PoD and MoE. One of the main primary goals of NGRA is to estimate the lowest concentrations which give rise to a measurable toxic effect (point of departure, POD). Subsequently an *in vitro* to *in vivo* extrapolation (IVIVE) allows to estimate what the intake (external dose) would be required to achieve the corresponding concentration at the site of relevance (e.g., cell or tissue) and the corresponding toxic effect in a human. It is widely recognized that such strategies for quantitative interpretation of toxic compounds is needed. For example, one approach is to develop a harmonized hazard characterization (i.e., following the EU's Green Deal 'One substance, one assessment' approach) and then draw different conclusions depending on the regulatory context. This could enable the collection and provision of scientifically-sound advice to risk managers by considering all relevant data, irrespective of the particular regulatory framework it originated from. Unfortunately, limitations and uncertainties underlying testing and risk assessment, make it hard to overcome the large differences regarding data requirements and risk assessment currently triggering different outcomes, namely differences in water quality limits derived from different actors (Table 2, Chapter 3.1.2; Table 3, Chapter 3.2.1). For example, the use of PODs over HBGV provides important advantages such as modularity, flexibility and technological openness. Yet, using NAMs-based PODs for regulatory purposes pose substantial technical and communication challenges (Niemann et al., 2023).

8.4 On the transition to animal-free drinking water sector

The transition to animal-free and evidence-based NAMs for chemical risk assessment seems inevitable given the practically impossible challenge to test all available chemicals and mixtures by animal testing alone (Rovida et al., 2023) (Figure 8). NAMs seem the most realistic opportunity to overcome such lack of capacity to safely assess chemicals if concrete steps are taken (Hansell, 2024). Most importantly, the use of NAMs solves the "translational failure" of animal testing, namely the poor predictive value of animal testing results in assessing human responses to chemical exposure (Leenaars et al., 2019), which needs to be considered when assessing the strength of the evidence

underlying safe levels of human intake of water contaminants. Fortunately, efforts are being made at the national and international level. For example, in the Netherlands, the National Growth Fund reserved 125 million EUR for a new Center for Animal-Free Biomedical Translation to accelerate the transition to animal-free research over the next ten years. The unique initiative VHP4Safety (2021), of which KWR is a partner, constitutes another example of a collective committed to build a platform for safety assessment of chemicals and pharmaceuticals by replacing animal testing and improve the translation from NAMs to human outcomes (Duarte, 2024). The first ever commitment from the Dutch government was expressed in the Transition Programme for Innovation without the use of animals (TPI).

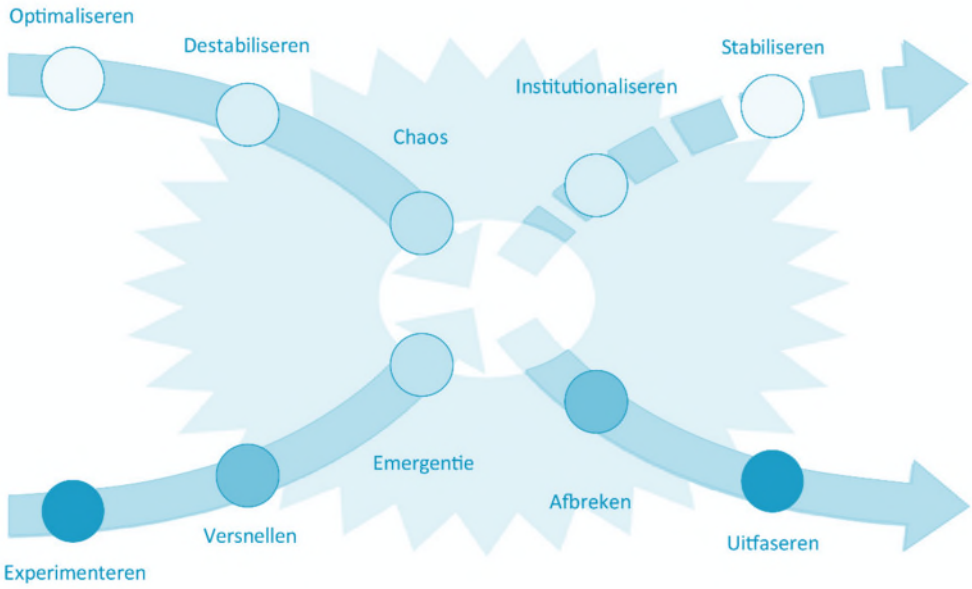


Figure 8. *Indication of the state of transition from animal to non-animal studies on the x-curve. Source: Bode (2019)*

In the EU, a roadmap towards phasing out animal testing for chemical safety assessments is expected soon. Leading the way is the PARC consortium, in which KWR is also a partner, the largest ever in Europe dedicated to address current, emerging and novel chemical safety challenges and enabling the transition to NGRA (KWR, 2022; PARC, 2022). A report by RIVM highlighted for example that legislation ought to be better aligned (e.g., with Classification, Labelling and Packaging (CLP)), global harmonization and regulatory acceptance ought to be quickly seeked, and a bigger focus should be put on mechanistic understanding (adverse outcome pathways, AOP) and weight of evidence approaches (RIVM, 2022). For example, an analysis by Heusinkveld et al. (2020) demonstrated that a limited set of mode of action networks is underlying nongenotoxic carcinogenicity of agrochemicals, strengthening the plausible transition to mechanism-based methods for animal-free risk assessment (Heusinkveld et al., 2020). We may be already witnessing the initial phases of a transition period where NAMs will become ever-more relevant and impact the way toxicological limits underlying legal safe thresholds are derived (Niemann et al., 2023). The discussions held during the expert meetings associated with the present project and in interactions with various stakeholders for the production of the present report, is a demonstration of a potential acceleration towards a convoluted period when chemical risk assessments reforms (**Figure 8**). So far, these changes have been very slow. Take for example the validation of the Monocyte Activation Test on human blood to replace Rabbit Pyrogen test which took 25-30 years to become incorporated in the European Pharmacopoeia (EDQM, 2024). Yet, these are all signs that we are already in a transition curve and potentially at an accelerating pace.

8.5 On NAM-based drinking water standards

Only 500 out of 100 000 chemicals on the EU market are well characterized for their risk and hazard (EEA, 2019). Ultimately, the widespread adoption of non-animal NAMs could lead to substantial changes in HBGV and toxicological safe limits, meaning that what is today deemed as acceptable concentrations of water contaminants or compliant with water quality standards, may change in the future. For example, in a recent EFSA study, an integrated testing strategy using NAMs was successfully implemented to explore the immunotoxicity of PFAS, resulting in good agreement with evidence from human epidemiological studies (Corsini et al., 2024). For example, selected PFAS affected the total release of antibodies at very low concentrations (0.001 µg/mL or 1 µg/L). This is higher than the legal water quality limits, yet it demonstrates how NAMs may soon play a role in risk assessment and standard setting. The Dutch water sector under the Joint Research Program Waterwijs (Hummelen, 2025), continues to explore the future integration of NAMs in the field of water quality (e.g. Shaikh (2024)). The acceptance of non-animal approaches under REACH is low, and many regulators consider NAMs yet unable to provide quantitative data for HBGV derivation (Macmillan et al., 2024). Therefore, there seems to be a shift in focus towards using NAMs in a protective way, rather than requiring them to be predictive of a specific toxicity endpoint (Schmeisser et al., 2023). This shift aligns well with the water sector's priorities in guaranteeing consumer protection, for example, by improving its understanding of key toxicological initiating events or modes of action, rather than focusing on a full account of intermediary toxicological mechanisms and pathways (see Chapter 8.4). The EU Reference Laboratory for alternatives to animal testing (EURL ECVAM), has recently proposed a new regulatory framework for chemicals – Chemicals 2.0 (Zuang, 2023). This new classification system does not consider the measurable adverse effects but instead focuses on essential toxicodynamic and toxicokinetic mechanisms leading to said effects, foregoing complex predictions. The microbial and chemical standards as well as monitoring, sampling and risk-assessment procedures must be reviewed every five years, until the DWD will be reevaluated in January 2025. Setting NAM-based regulatory guidance values may in the meantime become increasingly adopted, perhaps replacing the long-established approaches to derive HBGV and MRLs (Niemann et al., 2023). Therefore, it is essential for the water sector to continue to follow these developments and proactively identify potential implementation strategies tailored to its specific needs.

9 Outcomes

Reconciling the domains of water and food safety remains challenging but crucial, as risk assessment considerations vary between fields. In the present report, the authors address the need for water companies to **(1)** better understand the latest risk assessment advancements and NAM-based limit derivation from a food and drinking water sector perspective, **(2)** increase their adaptability and preparedness for potentially important regulatory developments and requirements and **(3)** strengthen the position of drinking water companies and KWR as engaged and trustworthy actors in the public health debate with key-stakeholders across regulatory domains about (drinking) water quality limit setting, including for contaminants of emerging concern (Hummelen, 2025).

Key questions have emerged as important considerations in achieving the main objectives of the project. These include the following:

- **Does current knowledge and estimates in the food and water domain have impact on the acknowledgement that contaminant residues in drinking water are sometimes unavoidable?** The DWD is an important factor in risk assessment, consumer safety and informative communication. However, current knowledge and estimates indicate that contaminant residues in drinking water may sometimes be unavoidable, compelling drinking water suppliers and regulators to acknowledge this reality. This acknowledgment is grounded in the understanding that even with stringent treatment processes and regulatory frameworks, trace amounts of contaminants may persist due to various factors, such as limitations in current technology and the pervasive nature of certain pollutants.

- **What impacts may drinking water companies expect on water quality requirements due to developments in risk assessment and management?** Drinking water companies should anticipate several impacts due to the continuing revision of regulatory limits on contaminant residues. If limits decrease, companies may face greater regulatory and societal pressure to adopt more advanced water treatment technologies. These upgrades often come with significant costs, which may need to be passed on to consumers unless alternative funding mechanisms are implemented. Additionally, water companies may need to assume a more proactive role within the broader stakeholder network of the water value chain. This network comprises the agents and entities that add to or subtract value from water intended for human consumption, such as pollutant-emitting sectors, water boards, municipalities, local enforcement agencies, academic experts, and both public and private organizations or individuals. This could involve stronger engagement with upstream actors, such as agricultural and industrial sectors, to mitigate the indirect transfer of contamination costs.

- **Could other risk principles and NAMs become an increasingly acceptable idea to adopt in the drinking water domain?** Some NAMs are already in use for hazard assessment in the evaluation of (drinking) water contaminants. The adoption of alternative risk principles and New Approach Methodologies (NAMs) for water quality standard setting in the drinking water sector is slowly but steadily becoming an increasingly acceptable idea. Currently, drinking water quality HBGV are mainly based on toxicological evidence originated from animal testing. These principles and methodologies, which include advanced risk assessment tools and innovative monitoring techniques, offer the potential to enhance the safety and quality of drinking water. In a sense, chemical safety and water quality activities in the water sector may ultimately depend on the extent to which NAMs developed in other domains (e.g., industrial chemicals, cosmetics, food safety) are accepted. Expert opinion can be very biased, thus requiring a move towards evidence synthesis and systematic review. Therefore, by further integrating NAMs in hazard and risk assessment, the sector can more efficiently predict and mitigate risks associated with emerging contaminants and evolving environmental conditions.

- How can drinking water companies influence future costs of (un)avoidable risks posed by water contaminants? To avoid 'avoidable' future costs, drinking water companies have some options. They can focus research and development investments to stay ahead of regulatory changes and emerging contaminants. Collaboration with other sectors and stakeholders to implement preventative measures upstream can also be effective, such as reduced industrial and urban wastewater emissions, as long as a long-term strategic plan is devised. Moreover, the current proactive approach to infrastructure upgrades and maintenance can help mitigate future risks and associated costs. Of course, practical constraints such as financial limitations, regulatory hurdles, and organizational priorities may influence the extent to which these measures are implemented. Finally, in order to retain its adaptability and preparedness to new scientific and regulatory developments affecting its operations, the water sector must remain at the forefront of research on toxicology, analytical chemistry, risk assessment and management.

10 Final remarks and recommendations

Building on the conclusions and the comprehensive information laid throughout the present report, the following closing remarks and recommendation can be made:

10.1 Final remarks on enhancing drinking water protection through cross-domain insights

- Theoretical overlap vs. practice in risk assessment: There is substantial theoretical overlap between the food safety and water quality domains in terms of risk assessment. However, these principles are often applied differently in practice, both scientifically and regulatorily, such as the foundational principle that exposure should be as low as reasonably achievable (ALARA). For instance, in food safety, some contaminants are explicitly permitted, whereas in water quality, no contaminants causing adverse effects are allowed.

- Distinct underlying evidence in food and water safety limits: Water quality and food safety limits are sometimes derived from distinct underlying evidence, safety assessment factors, and timelines for updates. For example, aminopyralid has an ADI of 0.26 mg/kg body weight/day (EFSA) based on rabbit developmental toxicity, while the WHO/JMPR assigns it an ADI of 0.9 mg/kg body weight/day based on histological gastric changes in dogs. A coherent approach to deriving drinking water limits, preferably based on mechanisms of action (AOP), is becoming increasingly advocated for, particularly in the context of EU's Green Deal "One substance, one assessment" ambition.

- (Animal-free) New Approach Methodologies (NAMs) for standard setting: Increasing pressure to adopt risk mitigation measures for an intractable number of pollutants based on robust evidence is pushing scientist and regulators to rely on NAMs, particularly animal-free methods, for assessing chemical safety. Following successful implementation of NAMs in other regulatory domains (e.g., cosmetics), water quality limits may increasingly be updated using animal-free NAMs. At the present time it remains unclear whether future regulatory accepted NAMs will provide evidence leading to the raise or lowering of human health-based guidance values for drinking water.

- Emerging contaminants: As new and unknown substances continue to be found in the water system, these are developments that the drinking water sector ought to remain particularly attentive to, e.g. by supporting research on the developments on AOPs in particular water contaminants able to cause adverse neurotoxic, immunotoxic and endocrine effects.

- Integration of expertise: Experts in food safety and drinking water quality generally agree that greater efforts are needed to integrate knowledge between the two fields. However, collaboration remains limited and opposing views may apply. Water and food experts alike may benefit from avoiding the division of water as either an object of water law or food law. Instead, they should recognize that water can serve as a conduit for contaminants to food and that both water and food share risks of contamination, aligning with the European "*one substance, one assessment*" ambition.

- Risk reduction and feasibility: What is desirable in terms of risk reduction is not always immediately achievable. A common argument for difference in risk assessment and management in the food and water domains is that individuals have greater control over the foods they consume (e.g., different products, different manufacturers; more replaceability) but less control over which drinking water to consume (e.g., single serviced water, single drinking water company; less replaceability). Furthermore, the impact of environmental contamination on drinking water sources may be unavoidable in addition to lack of toxicological evidence. Finding a balance between economic stress and public service demands may become

increasingly hard to achieve, requiring sustainable socioeconomic and governance strategies, strong cross-regulatory frameworks, and ongoing investment in innovative NGRA and IATA.

- Improve cross-sectoral understanding and connections: Actors in the drinking water and food sectors stand to benefit significantly from increasing and strengthening their connections, given the unifying element of water. There should be greater permeability and collaboration between these domains and an increased effort to follow-up on the developments and particular challenges each face because alternative solutions may be already available.

- Advancements in mixture toxicology: Advancements in mixture toxicology and new approaches are expected to play an increasingly important role in risk assessments in both fields. Foreseeable increasing regulatory obligations to incorporate mixture effects in quality requirements. However, these are likely to be implemented under other legal frameworks, a main reason why the drinking water sector ought to follow the discussion and advancements in other regulatory domains (e.g., cosmetics, chemicals, food). The water sector may soon be faced with obligations to shift their focus from single chemical occurrence and reduction to combinations of prohibitive co-occurring chemicals (RIVM, 2024b).

10.2 Recommendations and follow-up

Drinking water companies are encouraged to adopt a comprehensive and forward-thinking approach to managing the risks posed by contaminants, ensuring both public health safety and regulatory compliance. This includes exploring and understanding how risk assessors and managers address contaminants, particularly by examining methodologies such as the Margin of Exposure (MOE) and Disability-Adjusted Life Year (DALY), while upholding the ALARA (As Low As Reasonably Achievable) principle. For example, repurposing the MOE to water contaminants may provide a complementary measure of concern for prioritization based on estimated long-term exposure, and an effort to calculate DALYs based on regional and provincial differences would also support prioritizing the removal of specific contaminants which may exacerbate the disabilities in consumer cohorts. Companies should prioritize a coherent approach to deriving drinking water limits, ideally grounded in mechanisms of action like Adverse Outcome Pathways (AOPs), by supporting cross-sector research and staying informed about emerging regulatory trends.

Investing in and collaborating with research efforts focused on animal-free New Approach Methodologies (NAMs), especially those aligned with AOPs, will further strengthen the evidence base. For example, gastrointestinal organoid-based NAMs are particularly promising because they mimic the human gastrointestinal system, a critical exposure route, and can provide insights into the toxicokinetics of water contaminants. This approach would facilitate IVIVE studies relevant to drinking water, enable the exploration of acute-to-chronic effects, and possibly support risk assessments tailored to local demographics. Building internal expertise through pilot studies and supporting multidisciplinary research projects with external experts will enable companies to address risks proactively and innovate solutions.

By proactively monitoring the developments in water-relevant NAMs and NAM-based water quality standard setting, the water sector will be better equipped to meet future regulatory requirements. For example, evaluating historical trends in water quality standard and analysing potential future projections (e.g., 2030, 2040, 2050) can provide valuable insights into what to expect under various probabilistic scenarios. Transparent communication about the limitations in establishing risks for water contaminants, paired with efforts to prioritize high-risk contaminants, will enhance public trust. Cross-sector collaboration, particularly through participation in science-policy-society forums that include stakeholders from sectors directly and indirectly involved in water use, will also be key to harmonizing efforts. For example, the KWR Water Research Institute, in partnership with drinking water companies and external experts, could coordinate annual cross-disciplinary meetings to build upon the discussions on food safety and water quality initiated in the present project, thereby playing a central role in facilitating the exchange of expertise and

promoting consistent risk assessment across domains. Additionally, allocating resources to mixture toxicology research will help companies anticipate and adapt to potential new water quality requirements. Collectively, these measures will not only ensure safer drinking water but will also position drinking water companies as proactive leaders in public health and cross-sector collaboration.

Supplementary

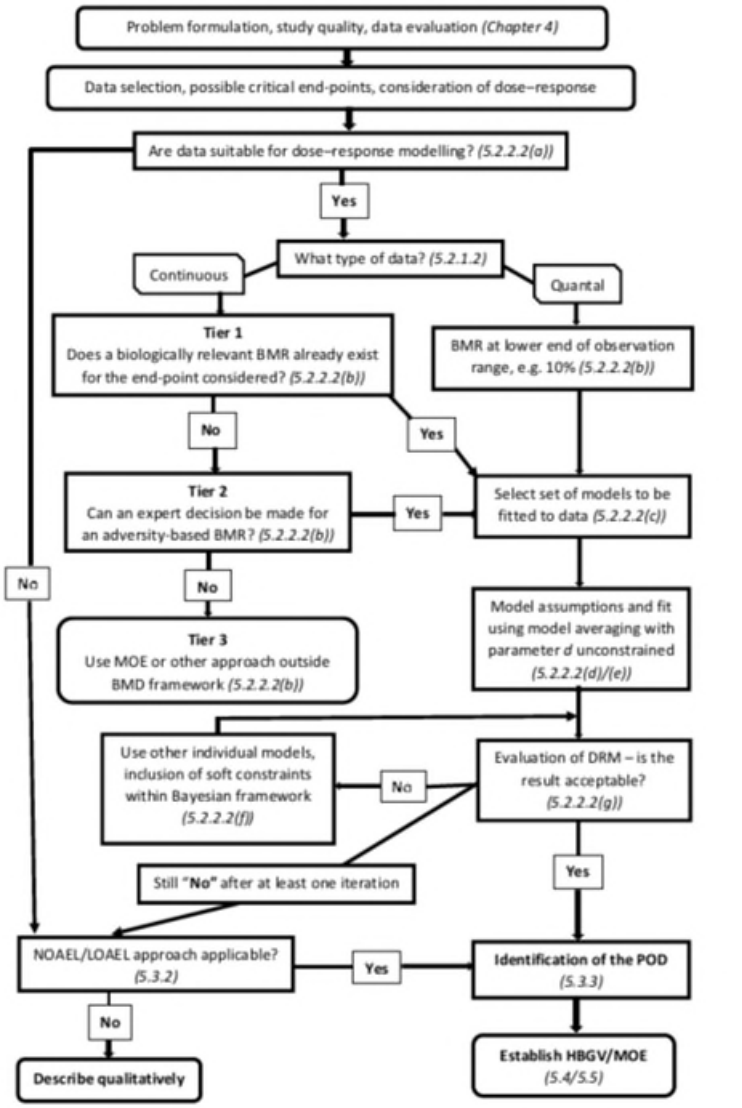
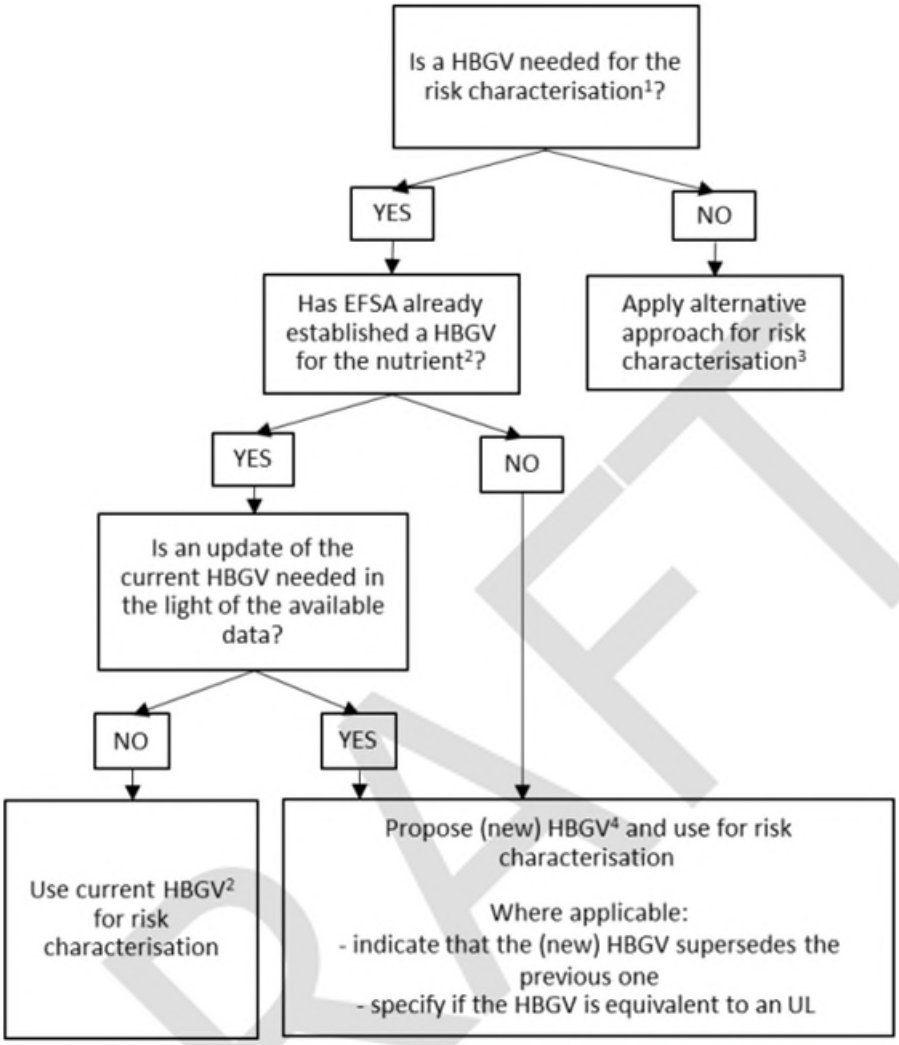


Figure S1. *Flow chart for the dose-response assessment processes used to develop risk assessment advice described in Chapter 5 'Dose-response assessment and derivation of health-based guidance values' of IPCS (2020) . The process may be used to develop risk assessment advice based on the BMD approach or NOAEL approach. Source: IPCS (2020).*



[1] The need for establishing a HBGV should be established according to the sectoral legislation.
[2] This includes ULs established by the SCF/NDA Panel or other HBGVs for nutrients (e.g. ADI) established by other Panels in the context of previous assessments. Indications from the SCF/NDA Panel on the highest level of intake where there was reasonable confidence in data on the absence of adverse effects may also be considered.
[3] Examples of alternative approaches include, for example, the application of a margin of exposure (MoE); comparative approaches in which the regulated product under evaluation can be considered "as safe as" already authorised products; or estimations based on the relative contribution of the use as regulated product to total dietary intake.
[4] When data are insufficient for establishing a HBGV, an indication on the highest level of intake where there is reasonable confidence in data on the absence of adverse effects may be provided.

Figure S2. *Decision tree for risk characterisation step of EFSA's assessments of regulated products, which are also nutrients. Source: EFSA Scientific Committee, More, Bampidis, Benford, et al. (2021).*

Table S1. *Water and food standards for substances listed in the WHO GWQD, EU Drinking Water Directive, Dutch Drinking Water Decree, and FAO CODEX. Bold fonts depict substances for which different standards currently apply between EU and Dutch standards.*

Substance	WHO (µg/L)	EU (µg/L)	NL (µg/L)	FAO CODEX food contaminants (MLs) (natural mineral waters) (µg/L)
Acrylamide	0.5	0,1	0,1	-
Antimony	20	10	10	-
Arsenic	10	10	10	10
Benzene	10	1	1	-
Benzo(a)pyrene	0,7	0,01	0,01	-
Bisphenol A	-	2,5	2,5	-
Boron	2400	1500	1500	-
Bromate	**10**	**10**	**1**	**-**
Cadmium	3	5	5	3
Chlorate	700	250	250	-
Chlorite	700	250	250	-
Chromium	50	25	25	-
Copper	2000	2000	2000	-
Cyanide	-	50	50	-
1,2-dichloroethane	30	3	3	-
Epichlorohydrin	0,4	0,1	0,1	-
Fluoride	**1500**	**1500**	**1000**	**-**
Haloacetic acids (HAAs)	-	60	60	-
Lead	10	5	5	10
Mercury	6	1	1	1
Microcystin-LR	1	1	1	-
Nickel	70	20	20	-
Nitrate	50000	50000	50000	-
Nitrite	**3000**	**500**	**100**	**-**
Pesticides	-	0,1	0,1	--
Pesticides total	-	0,5	0,5	-
N- nitrosodimethylamine (NDMA)	**0,1**	**-**	**0,0012**	**-**
PFAS total	**-**	**0,5**	**-**	**-**
Sum of PFAS	-	0,1	0,1	-
Polycyclic aromatic hydrocarbons		0,1	0,1	-
Polychlorinated biphenyls (PCBs) (individual)		**-**	**0,1**	**-**
PCBs (sum)		**-**	**0,5**	**-**
Selenium	40	20	20	-
Tetrachloroethene	100	10	10	-
Trichloroethene	8	10	10	-
Trihalomethanes total	**-**	**100**	**-**	**-**
Trihalomethanes (sum)	**-**	**-**	**25**	**-**
Uranium	30	30	30	-
Vinyl chloride	**0,3**	**0,5**	**0,1**	**-**

Table S2. Similarities and distinctions across legal documents in regards to chemical mixtures, risk assessment, new approach methodologies, standard limit setting and drinking water. Credit: Steenhof (2024).

	Water EU	Water EU	Water EU	Water EU	Water Global		Food EU	Food EU	Food EU	Food EU	Chemicals EU	Chemicals EU	Chemicals EU	Chemicals EU	Cosmetics EU	Pharmaceuticals EU
	DWD	GWD	EQS	UWWT	WHO GDWQ	Annex mixtures	MRL	PPP	GPFL	EFSA guidance	CLP	CLP guidance	REACH	BPR	CP	MPH
Mixtures in a human health context:																
Mixtures/interactions mentioned?	×	×	×	×	✓	✓	✓	✓	×	✓	✓	✓	✓	×	✓	✓
Aggregate/synergistic/cumulative effects mentioned?	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×
Unintentional mixtures mentioned?	×	×	×	×	✓	✓	×	×	×	✓	×	×	×	×	×	×
Assumption of additive behaviour?	×	×	×	×	✓	✓	×	×	×	✓	✓	×	×	×	×	×
Approach for compound-based risk assessment/hazard classification?	×	×	×	×	✓	✓	×	×	×	✓	✓	✓	✓	×	×	×
Regultion of unknown compounds in mixtures?	×	×	×	×	×	✓	×	×	×	×	✓	✓	✓	×	×	×
Distinction between similar and dissimilar achting chemicals?	×	×	×	×	×	✓	×	×	×	✓	×	✓	×	×	×	×
Similar chemicals: hazard index mentioned as screening approach?	×	×	×	×	✓	✓	×	×	×	✓	×	×	×	×	×	×
Approach for bridging data gap of mixtures?	×	×	×	×	×	✓	×	×	×	✓	×	✓	×	×	×	×
Development for methods to account for cumulative/aggregate/synergisitic effects?	×	×	×	×	×	×	✓	×	×	✓	×	×	×	×	×	×
Chronic toxicity reviewed?	×	×	×	×	✓	✓	✓	✓	×	✓	×	×	✓	×	×	✓
New Approah Methodologies (NAM's)																
Development of alternative methods for hazard assessment promoted?	×	×	×	×	×	×	×	✓	×	✓	✓	×	✓	×	✓	×
In silico approaches and softwares mentioned?	×	×	×	×	×	×	×	×	×	✓	×	×	×	×	×	×
Animal testing prohibited?	×	×	×	×	×	×	×	×	×	×	×	×	×	×	✓	×
List of validated alternative methods to animal testing?	×	×	×	×	×	×	×	×	×	×	×	×	×	×	✓	×
Validated read-across/QSAR/in vitro testing allowed?	×	×	×	×	✓	✓	×	×	×	✓	✓	✓	✓	×	✓	✓
Limit setting																
Specific limits for individual substances?	✓	✓	✓	×	✓	×	✓	×	×	×	✓	×	×	✓	×	×
Specific limits for sum parameters?	✓	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×
Substances prioritized?	✓	×	✓	×	✓	✓	×	×	×	×	✓	×	✓	×	×	×
Drinking water																
Drinking water mentioned?	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	×	×	×	×
Specific parameters for drinking water?	✓	×	×	×	✓	×	×	×	×	×	×	×	×	×	×	×

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