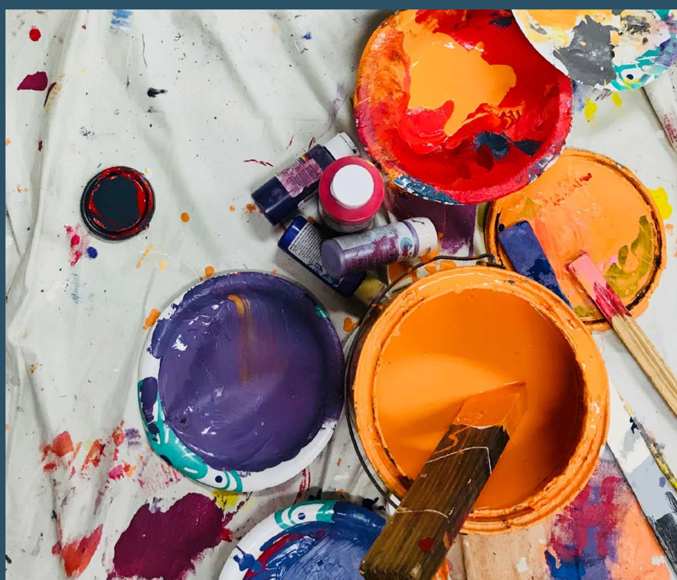
CHEMICAL COCKTAILS

CHEM Trust
Protecting humans and wildlife from harmful chemicals

The neglected threat of toxic mixtures and how to fix it

A CHEM Trust report
March 2022



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EXECUTIVE SUMMARY

The EU should urgently address the risks of exposure to chemical cocktails

We, our children, wildlife and the wider environment are constantly exposed to a complex cocktail of known and suspected harmful chemicals through air, water, food, consumer products and other routes. Decades of research have demonstrated that combined exposure to several chemicals can result in toxic cocktail effects [1,2,3]. Yet most chemical safety regulations ignore this fact and assess chemicals one by one, in isolation [3,4]. **We are not properly protected from the impacts on our health of real-life exposure to cocktails of chemicals - neither is the wider environment.**

The EU's Chemical Strategy for Sustainability in 2020 recognised that exposure to harmful chemicals is "a threat to human health" and that chemical pollution is "one of the key drivers putting the Earth at risk, impacting and amplifying planetary crises such as climate change, degradation of ecosystems and loss of biodiversity" [5]. As global chemical production grows [6] and the number of chemicals in use around the world multiplies [7] we face enormous challenges to our ability to keep humans and the wider environment safe from the impacts of exposure to cocktails of harmful chemicals.

The EU should act urgently. In CHEM Trust's analysis there are workable and effective policy solutions available to address this complex problem, and the EU should now adopt them.

We are all exposed to mixtures of chemicals

A huge range of currently-used chemicals are detected in humans, wildlife and the environment, including flame retardants, pesticides, water repellents, plasticisers, as well as persistent residues of highly toxic chemicals banned decades ago. Scientists have measured dozens to hundreds of chemical pollutants in our bodies and the environment, e.g. in rivers [8], the dust in our houses [9], our bodies [10] and those of new-born babies [11].

The chemicals that have been detected are the tip of the iceberg as studies of chemicals in humans and environmental samples are always restricted to a limited selection of chemicals. **The true chemical burden on our bodies and the environment is therefore unknown, so we have no idea about the full composition of the chemical mixture we are exposed to daily.**

Mixtures matter

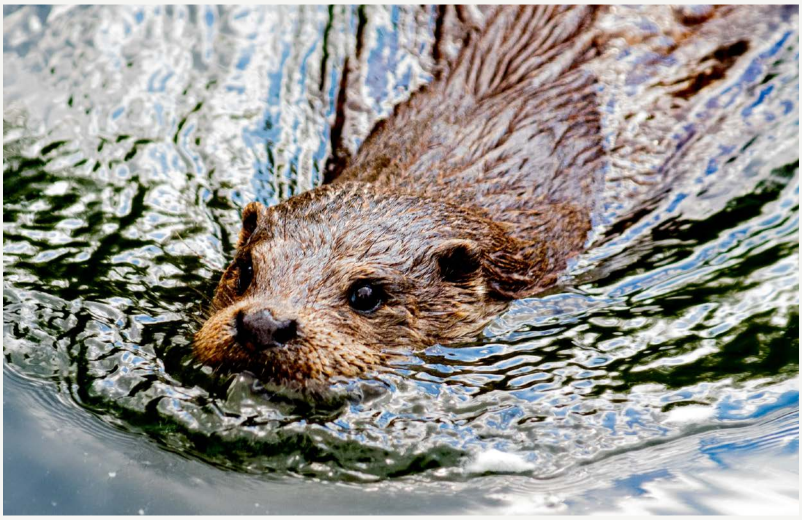
Many of the chemical substances we are exposed to are individually known to cause harm to human health, wildlife and the environment. But in reality we are not exposed to individual chemicals one at a time, and **there is now clear evidence from decades of research that these chemical exposures can add together, reinforcing their negative impacts** [1,2,3].

Studies show that chemical mixtures present in the environment ('real-life mixtures') can affect a range of biological processes – from the hormonal and neurological systems of children [12] to the immune systems of marine mammals [13]. Crucially, adverse impacts can be observed in cases where the individual chemicals in the mixture are present at or below the level considered safe [3]. The effect(s) of the combined exposure to multiple chemicals from multiple routes can be called the ***cocktail effect***, ***combination effect***, or ***mixture effect***.

Mixture toxicity means that risks are underestimated

EU regulators have spent decades developing assessment processes for individual chemical substances in isolation, and it is accepted that these processes still need improvement. However the reality is that people and wildlife are exposed to multiple chemicals at the same time. A few regulatory processes assess exposure from a combination of chemicals, but this is usually limited to chemicals from the same regulatory silo, for example, pesticides. **This ignores the fact that a person or a fish will be exposed to pesticides and other chemicals.**

The true risks resulting from combined exposure to numerous chemicals, even at low levels, are being vastly underestimated. **This means we lack proper protection from our real-life exposure to a large number of different chemicals.**



Trying to predict mixture toxicity

Scientists have developed models to estimate the toxicity of mixtures of known composition [14,15]. When all chemicals present are known, as well as their concentration and effects, it is then possible to estimate the toxicity of the mixture and predict the risk in various exposure scenarios.

However, with thousands of chemicals currently in use and many unidentified substances present in the environment and our bodies, predicting the risk from exposure to real-life mixtures presents an extraordinary challenge. **In the words of the Chemicals Strategy for Sustainability, it is "not realistic nor economically feasible to specifically assess and regulate an almost infinite number of possible combinations of chemicals" [5].**

A pragmatic solution: the Mixture Assessment Factor (MAF)

Because of the difficulty in assessing combination effects in detail, scientists have developed simpler and more general solutions, with the **Mixture Assessment Factor (MAF)** now seen by many scientists and regulators as the only feasible approach for controlling risks from chemical mixtures [16].

Put simply, the 'safe' level of exposure that is determined for an individual chemical is then divided by an extra uncertainty factor, the Mixture Assessment Factor. The MAF acts as a safety net to account for the mixture toxicity that would result from combined exposure to this chemical with other known and unknown chemical substances. **In CHEM Trust's view, the MAF is a pragmatic and effective way to manage the reality of mixture exposure.**

There is a debate about the best value for the MAF, and **in CHEM Trust's view, the factor must be high enough to truly increase the level of protection of human health, wildlife and the environment from real-life chemical cocktail exposures.**

According to our analysis, considering 1) the vast number of chemicals from various sources found in wildlife and people, 2) their respective contribution to mixture effects, 3) the uncertainties related to the contribution of unknown chemicals, **we consider the MAF should be 100.**

Time for the EU to act

The science is clear – people and the environment are exposed to mixtures of chemicals and the impacts from the combined exposures have been underestimated until now.

EU chemicals regulation must protect human health and the wider environment from the harmful impacts of combined exposures to multiple chemicals, whether they are pesticides, pharmaceuticals or industrial chemicals. This is not the case at the moment and this gap in protection must be closed now to act on the scientific warnings and to deliver the promises of the EU to work towards a "toxic free environment" as laid out in the 2019 European Green Deal [17].

What is at stake is the health of current and future generations. Tackling chemical cocktails is also part of the challenge of addressing the biodiversity crisis.

CHEM Trust's recommendations for EU chemicals policy on mixtures

Our analysis is that the following policy measures are the minimum the EU should be doing to address these risks:

1. Incorporating mixture assessment into all EU chemical regulations

- **A Mixture Assessment Factor (MAF) should be incorporated in all chemical assessments.** We assess that a factor of 100 would be optimal to cover the contributions of different chemicals to mixture toxicity, the different sources of exposure, and additional uncertainties related to unknown chemicals.

  This MAF should be introduced to the main EU industrial chemical law REACH as soon as possible, as part of implementation of the Chemicals Strategy for Sustainability.

- **A legal requirement for mixture assessments should be integrated into other EU chemicals laws during upcoming revisions, including those stipulated by the Chemicals Strategy for Sustainability.** It is essential to integrate approaches to address mixture toxicity in all relevant EU laws and in many cases the best option will be a MAF approach. Where targeted mixture assessments are used they must be improved, e.g. by widening the number and scope of substances covered and by introducing more transparency about inherent uncertainties and limitations.

2. Identify and control the use of the most hazardous chemicals, to reduce the quantity of hazardous chemicals we are exposed to

- **There should be more resources put into biomonitoring and environmental monitoring programmes in the EU, and harmful chemicals found in humans and the wider environment should be prioritised for regulatory action.** It is particularly important to reduce exposure to persistent chemicals and endocrine (hormone) disrupting chemicals.

- **Regulatory processes for controlling the use of chemicals must become faster and more protective. One way to do this is through grouping of chemicals for regulatory measures.** Chemicals from a group (e.g. bisphenols, phthalates, PFAS, brominated flame retardants) should be regulated together under REACH, and in other chemical-related laws to speed up substitution with safer alternatives.

2
INTRODUCTION

2.1 Addressing the risk from chemical mixtures

We're used to hearing about a small number of toxic chemicals such as bisphenol A, lead and glyphosate. But we are exposed to hundreds of chemicals every day – whether from air pollution, food additives, personal care products or many other consumer products - and so are wildlife and the wider environment. Dozens to hundreds of chemical pollutants are detected in samples ranging from river water to umbilical cord bloods.

This vast cocktail of chemicals permeates our lives. There is increasingly robust evidence that mixtures – not just the few well-known hazardous chemicals – put our health at risk. As a 2020 progress report from the European Commission explains, "exposure to a mixture can give rise to adverse health and environmental effects, even at levels of exposure which are considered 'safe' for the individual chemicals on their own." [3]

This perturbing fact challenges the assumptions that underlie our chemical regulatory system. Except in a few instances, in the EU, safety assessment for chemical exposure is usually conducted on an individual chemical. European research projects have clearly shown that current EU policies are systematically underestimating the risks from chemical mixtures.

> **"safety of chemicals in the EU is usually assessed through the evaluation of single substances, or in some cases of mixtures intentionally added for particular uses, without considering the combined exposure to multiple chemicals from different sources and over time."** European Commission's Chemicals Strategy for Sustainability, 2020 [5]

2.2 EU promises more protection against mixture toxicity

Attention to mixture toxicity in recent years has led to its explicit recognition in the European Green Deal. As one aspect of the "zero pollution ambition for a toxic-free environment", regulatory systems must address the risks posed by "combination effects of different chemicals" [17]. This goal was fleshed out in the EU Chemicals Strategy for Sustainability, which recognised that "scientific consensus is emerging that the effect of chemical mixtures needs to be taken into account" and that, to accomplish this, "legal requirements need to be consistently in place to ensure that risks from simultaneous exposure to multiple chemicals are effectively and systematically taken into account across chemicals-related policy areas" [5].

The Chemicals Strategy for Sustainability recognises that this is not simply an issue for industrial chemicals, or biocides, or food packaging: **because we are exposed to so many chemicals through so many different routes, addressing the problem of chemical mixtures will require action in many different policy domains.**

2.3 Policy must include latest science

Global chemical production is growing fast: it doubled between 2000 and 2017 and is projected to double again by 2030 [6]. More than 350,000 chemical substances have been registered on the global market [7].

As our chemical universe continues to grow and diversify, it becomes more important that our regulations address not merely the hazards of a handful of bad actors – but the combination effects of the chemical soup in which we live and breathe. There is growing public concern about the effects on health and the environment of our daily use of chemicals.

For over a decade CHEM Trust has been calling for more attention to cumulative risk assessment. (This is the formal name for the process of understanding risks from exposure to multiple chemicals from numerous sources [18]). For example, we have shown that children are at risk from exposure to many chemicals that are capable of affecting brain development [19].

Starting with a reality check of modern-day chemical exposure, this report provides examples that show why the impacts of chemical mixtures are a real concern for human health, wildlife and environmental protection. It then highlights the regulatory challenges of addressing combined exposure to multiple chemicals from various sources. Finally, we make recommendations for changes in EU legislation, including implementation and the necessary magnitude of a Mixture Assessment Factor.

84%

of Europeans are worried about the impact of chemicals on their health

90%

of Europeans are worried about the impact of chemicals on the environment

European Commission's Chemicals Strategy for Sustainability, 2020 [5]

Guide 1 – Key definitions

Chemical mixture or **mixture** or **chemical cocktail:** A combination of chemical substances present in media (e.g. water) and/or a product (e.g. cosmetic) to which people and/or wildlife might be exposed. A chemical mixture of a known composition in a product such as a cosmetic or pharmaceutical is referred to as an **intentional mixture**. A mixture present in environmental media such as water, air, and soil, or present in an organism, is referred to as an **unintentional mixture** or **coincidental mixture**. An unintentional mixture is made of synthetic and naturally-occurring chemicals and their degradation products, as well as known and unknown chemicals.

Combined exposure or **cumulative exposure** or **co-exposure:** Exposure to multiple chemical substances from one or multiple sources.

Mixture effect or **cocktail effect** or **combination effect** or **cumulative effect:** Toxic effect on an organism resulting from the combined exposure to multiple chemical substances from multiple sources.

Mixture risk assessment or **cumulative risk assessment**: Estimation of the risk for given exposure scenarios, taking into account the combined exposures to multiple chemicals from multiple sources.

Mixture Assessment Factor or **Mixture Allocation Factor** or **MAF**: Additional uncertainty factor that can be applied in the assessment of single chemicals. This factor acts as a safety net to account for the mixture toxicity that would result from the combined exposure to this chemical and other known and unknown chemical substances.

Concentration addition model or **dose addition model**: Model used to estimate the toxicity of a mixture of known composition, based on the toxicity and concentration of the individual chemical substances.

3

REALITY CHECK

3.1 There is a vast number of chemicals in use ...

350,000+

chemicals and technical mixtures of chemicals have been registered for production and use on the global market

22,000+

chemical substances have been registered for production and use in the EU

In 2020 a study estimated that over 350,000 chemicals and technical mixtures of chemicals have been registered for production and use on the global market. This is three times as many as previously estimated [7].

REACH is the main EU chemical law covering manufacture and use of industrial chemicals. Since 2008 more than 22,500 chemical substances have been registered for production and use in the EU in quantities of >1 tonne per year under REACH. A recent EU restriction on chemicals in tattoo inks covered more than 4,000 chemical substances [20]. Around 8,000 chemical substances for use in different types of food contact articles are listed in the EU and EU member state regulations [21]. And the widely-used class of fluorochemicals known as PFAS – in products from non-stick pans, bicycle grease, water-repellent outerwear to cookie bags – is thought to consist of at least 4,700 separate chemicals [22].

There are numerous other types of chemical substances such as pharmaceuticals, biocides and pesticides which are not covered by REACH. For example, more than 400 active substances are approved for pesticide use in the EU [23].

3.2 ... and we are exposed to many chemicals all the time

We are exposed to this chemical cocktail in countless ways. Whether via ingredients in care products applied to our skin, flame retardants in furniture and electronics that leach out and we inhale, or additives in plastic packaging leaching into our food, we encounter many hundreds or thousands of chemicals every day (Figure 1). We are exposed to many more through the environment: from hundreds of pollutants in the air we breathe, to pharmaceutical residues in rivers and streams used for drinking water, and pesticides residues in our food.

3.3 Some chemicals accumulate in our bodies (the body burden) …

Traces of this myriad of chemicals are found in our bodies, as shown by human biomonitoring studies such as those conducted and evaluated under the EU research programme HBM4EU[1] [24]. Some substances, referred to as bioaccumulative, can accumulate in fatty tissues and remain in the body for decades. Others are easily excreted but still found in body fluids as a result of constant daily exposure.

In recent years investigations in the general population have highlighted widespread exposure to chemicals which have known or suspected harmful properties. The German environmental survey detected many chemicals that are currently in use, including chemicals used as replacements for harmful chemicals that have been banned [25]. They range from anti-oxidants [26] to fragrances [27,28], solvents [29] and plasticisers [30,31]. As certain harmful chemicals are being banned and replaced with a variety of new substances, exposure to high levels of some chemicals is decreasing, yet the complexity of mixtures is increasing. This means that more substances at low and medium concentrations become part of the unintentional mixtures that represent our body burden [25].

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[1] https://www.hbm4eu.eu/

Chemical pollutants in the home

Within our homes and our daily lives we are exposed to hundreds of chemicals from multiple sources, such as flame retardants in soft furnishings, phthalates in plastic food packaging, or PFAS in cosmetics. Yet most chemical safety regulations completely ignore the fact that we are being simultaneously exposed to a cocktail of hundreds of substances from a diversity of sources.

1. PFAS chemicals in waterproof clothing
2. Siloxanes, parabens, and many others in shampoo, shaving foam, deodorants
3. Oxybenzone UV filter in sunscreens
4. Phthalates, parabens, many others in makeup
5. PFAS in nonstick cookware e.g. frying pans
6. Triclosan in antibacterial handwash
7. BPA in some plastic water bottles and food can linings
8. Pesticide residues in foods
9. PCBs, dioxins, PAHs found in disposal nappies
10. Phthalates, flame retardants and bisphenols in children's toys
11. Flame retardants in virtually all electronics
12. Phthalates, and thousands of secret compounds, in fragrances found in air fresheners, cleaning products, cosmetics, soaps
13. Pharmaceuticals and other contaminants in drinking water
14. Tattoo inks can contain a mixture of thousands of harmful chemicals
15. Flame retardants in furniture and mattresses
16. Unknown and unwanted chemicals in recycled products
17. Bisphenols in till receipts
18. Phthalates and many other plastics additives in food packaging
19. PFAS in microwave popcorn bags, bakery bags and compostable food packaging
20. Phthalates, flame retardants and volatile organic compounds in vinyl flooring

Figure 1 - Chemical pollutants in the home

"Human biomonitoring studies in the EU point to a growing number of different hazardous chemicals in human blood and body tissue, including certain pesticides, biocides, pharmaceuticals, heavy metals, plasticisers and flame retardants. Combined prenatal exposure to several chemicals has led to reduced foetal growth and lower birth rates." European Commission's Chemicals Strategy for Sustainability, 2020 [5]

Children are particularly sensitive to impacts from chemicals. There are developmental periods when the endocrine, reproductive, immune, visual, and nervous systems are particularly sensitive to certain chemicals. These periods are referred to as windows of vulnerability. Chemicals can also be transferred from a mother to her unborn child during pregnancy. Exposure to endocrine disrupting chemicals[2] during this time can lead to serious and irreversible effects later in life because the foetus is unable to protect itself: compensatory and detoxification mechanisms present in the adult are not yet in operation [32].

This is why it is very concerning that mixtures of known and suspected harmful chemicals are present in umbilical cord blood and placentas, as the examples below show. A whole range of chemicals including pesticides, PCBs, PFAS have also been found in breast milk [33,34]. (Even though breast milk is one route by which bioaccumulative chemicals are transferred from mother to baby, breast-feeding is still acknowledged to be the best option for babies' health [35]).

Example 1: In the EU research project EDC-MixRisk[3] Swedish scientists tested the blood and urine of pregnant women for 54 potentially hazardous chemicals. In more than half of the 2,300 maternal samples they identified 41 chemicals – including a number of bisphenols, phthalates and PFAS – that are associated with reproductive disorders [12,36].

41

different chemicals found in thousands of pregnant Swedish women

Example 2: In another study 22 persistent organic pollutants (POPs) – synthetic chemicals that degrade very slowly and accumulate in people's body – were analysed in maternal serum, placenta and foetuses from a Swedish cohort of pregnancies that ended in stillbirth. All samples contained at least 15 different chemicals, showing that the foetuses were exposed to mixtures of industrial chemicals [37,38].

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2 https://chemtrust.org/hormone-disrupting-chemicals-edcs-faq/
3 https://edcmixrisk.ki.se/
4 https://cordis.europa.eu/project/id/101036631

Progress in analytical chemistry is allowing screening for an increasing range of potential contaminants. Starting from a list of over 3,500 known industrial chemicals, a 2021 US study was able to identify 55 chemicals, previously unreported in the literature, in mothers and their babies [39].

A new EU research project PANORAMIX4, which started in 2021, is investigating possible combination effects of chemicals in the womb.

3.4 ... and some chemicals accumulate in the environment and wildlife (the environmental burden)

Many of the chemicals that society uses find their way into the natural environment, whether via sewage, leaching out of landfill, direct emissions from factories, runoff from fields and parking lots, or deposits from the air. Chemical pollutants accumulate in soils, rivers, the deep ocean and the remote Arctic, exposing wildlife to cocktails of hundreds of chemicals (Figure 2).

The UK saw shocking headlines in 2020 when its Environment Agency reported that only 16% of England's 4,600 rivers, lakes or estuaries achieved "good" ecological health by 2019 – and not a single river achieved a "good" rating for chemical pollution [40]. The situation for the rest of Europe is hardly better: only 40% of Europe's surface waters achieved "good" or "high" ecological status by 2015 [41]. Among the main pressures identified by the European Environment Agency is chemical pollution including from urban wastewater and agriculture. To give one example of a chemical cocktail found in wastewater, a 2020 study identified over 300 contaminants in effluent waters from wastewater treatment plants in Athens, Greece. The synthetic chemicals detected included 66 pesticides, 215 drugs, 10 PFAS and 31 industrial chemicals [42].

315
chemicals detected in 24h in effluent wastewater in Athens, Greece

149
chemicals detected in seabirds' eggs from Norwegian remote colonies

A broad cocktail of chemical pollutants is found at every level of the food chain, from invertebrates in the Danube River [43] to fish in remote Alpine lakes [44] and killer whales in the North Sea [45]. A 2015 study detected 149 chemical substances in eggs of three seabird species from remote colonies in Norway [46]. Concentrations of pollutants such as PFAS, organophosphates, and alkylphenols, were similar to or higher than the legacy persistent organic pollutants such as PCBs banned decades ago.

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[4] https://cordis.europa.eu/project/id/101036631

Chemical pollutants in the environment

Chemical pollutants related to human activities find their way into the natural environment via many routes: effluents from wastewater treatment plants connected to households, hospitals, and businesses; runoff from fields, roads, and airports; air and water emissions from factories and waste treatment sites. Chemical pollutants accumulate in soils, rivers and the deep ocean, exposing wildlife throughout the food chain to a cocktail of hundreds of substances.

1. Everyday chemicals from clothes, detergents, cosmetics etc. emitted in sewage water from households
2. Pharmaceuticals emitted in sewage water from hospitals
3. Chemical contaminants discharged into rivers and the sea from wastewater treatment plants
4. Pesticides, fertilisers and biosolids contaminate soil, rivers, and groundwater from agriculture
5. Veterinary drugs and rodenticides used in farms contaminate soil, water, and fauna
6. Car tire leachates contaminate soil and rivers from road runoff
7. Industrial chemicals emitted into the air and wastewater from industrial sites
8. PFAS contaminates soil and water from firefighting foam used at airfields
9. Synthetic chemicals contaminate soil and water from landfill leachates
10. Chemical pollutants emitted into the air from incinerators
11. Pesticides and veterinary drugs contaminate the sea from aquaculture farms
12. Process chemicals, such as lubricants, contaminate the sea from oil rigs
13. Chemical contaminants, such as surfactants and biocides, are released into the sea from shipping

Figure 2 - Chemical pollutants in the environment

3.5 The true chemical burden is unknown

The examples above show the scale of chemical exposure in Europe. However, the true chemical burden on our bodies and the environment is unknown. This is in part owing to the limited scope of monitoring programmes, which focus on a small number of priority substances, and to the limitations of analytical chemistry. There are no procedures by which scientists can simply read out a list of chemicals present in a sample. Only targeted chemicals for which an analytical method has been developed can be quantified, and this is limited by the availability of reference standards[4] [47]. As a consequence **many of the chemical contaminants and their transformation products that are burdening our bodies and the environment remain unknown.**

To give a sense of the scale of the knowledge gap we can take the example of PFAS – the family of thousands of fluorinated substances. Fewer than 100 of the known PFAS can be measured and identified by chemical analysis. When scientists analyse organic fluorine – a proxy for the total PFAS load – large proportions of the PFAS concentration cannot be accounted for: for instance, 84-99% of the organic fluorine extracted from surface water samples, sediment and fish from Norway was of unidentified origin [48]. In human samples from Austria, on average between nine and 51% of extractable organic fluorine remained unidentified [49].

[5] A reference standard is the chemical substance in its pure form.

4
THE MIXTURE EFFECT

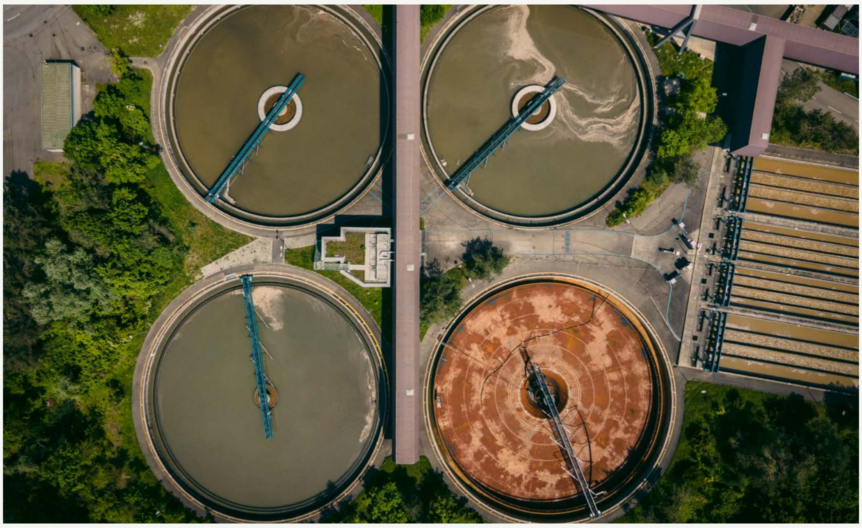
4.1 What do we mean by mixture effect?

People and wildlife are constantly exposed to a complex mixture of known and unknown chemicals. Among these mixtures, many chemicals have diverse toxicological properties such as acute toxicity, hormone disruption, carcinogenicity, immunotoxicity, neurotoxicity, reprotoxicity etc., which may lead to serious health effects. Toxicological tests allow us to determine what level of exposure to a given chemical can trigger a specific adverse effect. These tests are usually performed on single chemicals.

We're all aware of the danger of mixing various medicines. A doctor will usually ask about our current medications before prescribing, in order to avoid potentially adverse pharmaceutical interactions. Science has shown that when several chemicals contributing towards the same adverse effect are combined in a mixture, their toxicity can add up or interact to produce a *combined effect* or *mixture effect* [1].

Usually, the toxicity of a mixture will follow a simple additive model of the toxicity and concentration of the individual chemicals present in the mixture. The combined effect in this case is best predicted by a *concentration addition model*[6] [3].

In some cases, the combined effect can be greater than what would be expected on the basis of the toxicity of individual chemicals in the mixture. This is known as *synergism*. In other cases the resulting effect can be weaker, and this is known as *antagonism*. These more complex interactions have been reported less frequently [15].



[6] The way a chemical exerts its toxicological effect on an organism is called mode of action. Usually, for chemicals with similar modes of toxic action, the resulting toxicity of the mixture will follow a simple additive model of the toxicity and concentrations of the chemicals present in the mixture. This is called the concentration addition model.

4.2 Assessing mixture toxicity

The toxicity of a mixture can be assessed either directly or indirectly. A whole mixture, such as a water sample (unintentional mixture with unknown compounds) or a paint (intentional mixture with known compounds) can be tested directly. Alternatively, a prediction of the combined toxicity can be made, based on the concentration and toxicity of each chemical present in the mixture – which is an indirect assessment.

The concentration addition model is considered the most relevant to predicting the toxicity of mixtures. It can be extended to mixtures with any number of chemicals and has been validated by many studies. A review sponsored by the EU Joint Research Centre of over 1,200 mixture experiments [15] confirmed that "the concentration addition concept can be applied as default for predictive assessment of chemical mixtures." [3]

However, one major drawback in the assessment is the lack of knowledge of the chemicals and their concentrations in real-life mixtures (unintentional mixtures). Chemical analysis detects only those chemicals we are looking for - i.e. those that are targeted, for which the analysis is well-defined and where analytical standards are available. By design, analysis of a sample ignores the many possible non-target chemicals that are also likely to be present. Therefore, the number of chemicals detected in any sample is always an underrepresentation of the real number in a sample.

4.3 "Something from nothing"

In recent decades scientists have begun to conduct robust studies into the effects of chemical mixtures, in particular of endocrine disrupting chemicals (EDCs). **A growing body of evidence indicates that these mixtures can have important adverse effects on health and the environment – even at extremely low concentration when the amount of individual chemicals is considered too small to be of concern [3,50] (Figure 3).** This was referred to as "something from nothing" by Silva, Rajapakse and Kortenkamp in a 2002 seminal study [51]. The scientists tested the total estrogenic effect of model mixtures made of eight synthetic chemicals with estrogenic properties (including bisphenol A and paraben). When creating the mixtures they added each chemical at a concentration below their no-observed-effect-concentrations (NOECs) and close to what can be found in environmental samples. Their results show that the chemicals were able to act together to produce significant effects when combined at the low concentrations considered safe for the individual chemical. The resulting mixture effect observed in the study was perfectly predicted by a concentration addition model, in which "every mixture component contributes to the overall combination effect in proportion to its concentration, even below zero effect levels".

Something from nothing - mixture toxicity matters

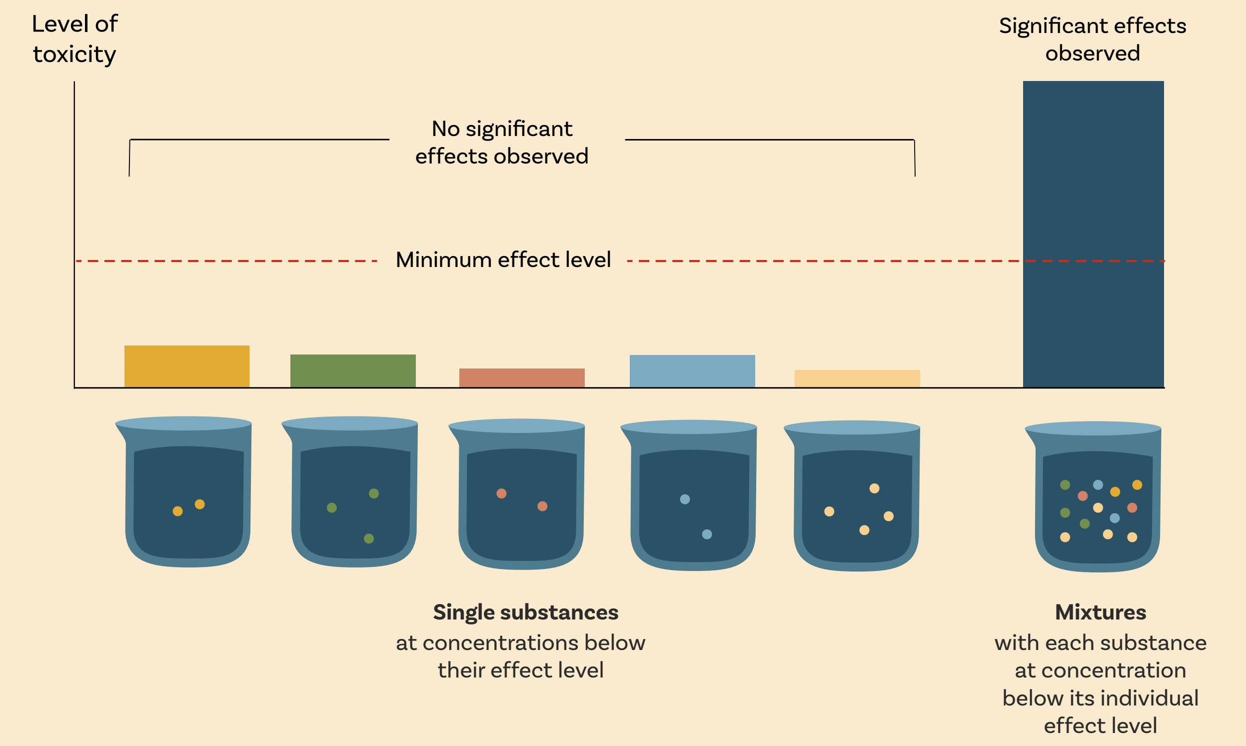


Figure 3 - Something from nothing

This is of great concern for people and wildlife because the chemical regulation system is overwhelmingly based on risk assessment performed on individual chemical substances, not in their combination, which is the real-life scenario. **So the true risk resulting from combined exposure to numerous chemicals, even at low levels, is being vastly underestimated. In other words people and wildlife are inadequately protected from real-life exposure to chemical mixtures.**

For example, the EU Water Framework Directive aims to achieve good ecological status in member states' water bodies; it sets Environmental Quality Standards (EQS) for priority chemicals of concern to protect the aquatic environment from chemical risks. In 2014 researchers from the European Commission's Joint Research Centre tested whether the current EQS were protecting the aquatic environment against mixture effects [52]. They tested the combined toxicity of two mixtures of 14 or 19 common environmental contaminants, including pesticides, pharmaceuticals and industrial chemicals. Each chemical in the mixture was present at its EQS level. **They found that although the chemicals were present at concentrations considered safe, clear adverse effects were demonstrated for the tested mixtures. This shows that the current EQS are failing to properly protect aquatic wildlife and ecosystems from combined exposure to multiple contaminants.**

Case study #1 - Muddled reproduction

In the past half century we've witnessed a decline of about 60% in sperm counts in western countries. We've also seen an increase in the incidence of testis cancer and malformations of the reproductive organs in new-born boys [59]. Experiments have demonstrated serious and irreversible reproductive effects in animals after exposure to endocrine disrupting chemicals (EDCs). There is more and more evidence that this also happens in humans and wildlife [60].

Sexual development is a sensitive process controlled by the hormone system. Estrogens are a group of hormones critical to female sexual development; and androgens are a group of hormones, including testosterone, critical for male sexual development. The hormonal balance in our body is maintained by a sophisticated feedback mechanism, but this mechanism is not fully developed in foetal life. Therefore, the foetus is extremely sensitive to the mother's hormonal balance.

Many synthetic chemicals have the potential to interfere with the function of these hormones and are known as endocrine disrupting chemicals (EDCs). Environmental contaminants such as phthalates, bisphenol A and other bisphenols, and many pesticides, have been shown to be EDCs and to disturb male sexual development. **This may lead to male reproductive disorders at birth, decreased semen quality, and development of testicular cancer in later life; all of which have great impact on male reproductive ability.**

In the EDC-MixRisk[7] research project (see also case study #3) researchers began by identifying chemicals in the blood and urine of more than 2,300 pregnant Swedish women, and correlating these with sexual effects observed in the children [12,36]. They then tested these chemical mixtures in animals and cell cultures to see if the same effects could be confirmed under controlled conditions. **The researchers identified a number of boys with clinical signs of disturbed sexual development.** Four phthalates, all of which are known to reduce the production of testosterone, were present in the boys' mothers. **Following further investigations, the data provided strong evidence that this mixture was responsible for the impacts seen [12,36].**

[7] https://edcmixrisk.ki.se/

Case study #1 - continued

Time trends of phthalate exposure in Germany have been studied based on human biomonitoring data [53]. In many people the level of exposure back in the 1990s exceeded the acceptable level for the individual phthalates. Following the introduction of EU restrictions on some of the most-used phthalates in the early 2000s, the situation improved. More importantly, however, **the combined exposure to phthalates still exceeded acceptable levels from 2006 onwards.**

Both of the above examples focus on phthalates; but hundreds of other chemical substances are known to disrupt or suspected of disrupting the action of androgenic hormones. These include painkillers such as paracetamol and ibuprofen, numerous pesticides and common pharmaceuticals used to treat fungal infections, high cholesterol, and hair loss [61].

To protect human reproduction, the combined exposure to all endocrine disrupting chemicals from all sources should be taken into account when assessing risks from exposure to chemical substances.

4.4 Concerns about serious impacts on people and wildlife

Numerous studies demonstrate that the combination of chemicals found in body fluids of people and in environmental media result in increased risk compared to the exposure to individual chemical substances. Studies also show that mixtures are a cause of concern at real-life exposure levels. A 2016 report from the Commission's Joint Research Centre reviewed 21 case studies [14]. The review highlighted the need to address mixture effects across all chemical classes and different pieces of legislation.

The following section summarises some examples that demonstrate increased risk to human health and ecosystems from combined exposures to multiple chemicals.

Estimated mixture effect based on real-life exposure scenarios

A 2020 study of nearly 30 years' worth of data on phthalate exposures in Germany provides a vivid example of the importance of assessing combination exposures [53]. From 2006-2010 **"no study participant experienced exposures above acceptable levels for a single phthalate"** yet the estimated combination effects often exceeded acceptable limits. Moreover, the authors point out that the estimated combination effects encompass only the small set of chemicals under study, ignoring all the other similar chemical substances to which subjects may have been exposed.

The Danish Environmental Protection Agency has shown an increased risk of adverse health effects related to combined exposure to multiple chemical substances in everyday situations. Two studies [54,55] used estimated daily exposure scenarios and data from biomonitoring studies to examine whether pregnant women, the unborn child and children under 3 years of age are at increased risk owing to combined exposure to endocrine disrupting chemicals (EDCs) and neurotoxic chemicals. A limited number of chemical substances were included in these studies (35 EDCs in 2012, and 37 EDCs and 39 neurotoxic substances in 2017). **Yet it was clearly shown that the risk of endocrine disrupting effects and neurotoxic effects increased to an unacceptable level when the combined exposure to several chemicals was taken into account.**

A 2017 study of Swedish streams found mixtures of as many as 53 pesticides in river water samples [56]. The researchers used Swedish water quality indicators to calculate the total effect of each of these mixtures. In over 70% of samples the estimated environmental risk exceeded acceptable levels – even though analytical limitations led to a significant underestimation of mixture risks. **While the mixture effects were often driven by only a few important chemicals, these chemicals varied from sample to sample. "Single substance risk mitigation," the authors noted, "will not lower mixture risks to acceptable levels."**

Case study #2 - Immunotoxic cocktail in marine mammals

Marine mammals are long-lived in the wild; up to 30 years for seals and polar bears, 60 years for killer whales (orcas) and 200 years for bowhead whales. Being at the top of the food web and having a long life means a high concentration of contaminants can build up in their bodies through decades of exposure to trace contaminants in the ocean. Especially bioaccumulative chemicals that are stored in fatty tissues, such as persistent organic pollutants (POPs), can become more concentrated at each level of the food chain.

Lulu, a 20-year-old female killer whale found dead on the cost of Scotland in 2016, had one of the highest levels of polychlorinated biphenyls (PCBs) ever recorded in a wild animal [62]. PCBs, a group of industrial chemicals widely used in the past century, were globally banned in 2001 but are still polluting the environment because of their high persistence. It is not just legacy PCBs that marine mammals are exposed to, however. **Hundreds of different chemical pollutants have been reported in marine wildlife [63]**, including dozens of per- and polyfluoroalkyl substances (PFAS), and flame retardants, phthalates, chlorinated paraffins, pesticides and synthetic chemicals derived from personal care products to name a few.

In 2017 an international team of **scientists evaluated the effects of realistic contaminant mixtures on the immune functions of marine mammals [13]**. A deterioration of the immune system can have dire consequences for marine mammals by making them more susceptible to infectious disease and pathogens.

The scientists extracted complex contaminant cocktails from the blubber of dead polar bears and killer whales. They then performed in vitro experiments on immune cells from various species of cetaceans, seals and polar bears.

The results show that the extracted chemical mixtures induced immunotoxic effects on all of the species tested. **Crucially, the effects were observed at lower concentrations than for single chemicals.** The authors concluded that the results of this study “confirm the immunotoxic risk marine mammals face from exposure to complex mixtures of environmental contaminants”. They added: “Our results showing lower effect levels for complex mixtures relative to single compounds suggest that previous risk assessments underestimate the effects of real world contaminant exposure on immunity.”

Testing the toxicity of real-life mixtures

Case studies #1 and #3 highlight results from the EU Horizon 2020 EDC-MixRisk project[8] [12,36]. In this project the toxicity of model mixtures of endocrine disrupting chemicals (EDCs) was tested. The model mixtures were designed to match the nature and concentration of EDCs found in blood or urine of pregnant women in Sweden. The project concluded that current regulation of chemicals – based on individual chemical substances – systematically underestimates the health risks associated with combined exposures to EDCs.

An alternative to testing real-life mixture toxicity by creating model mixtures is to test chemical mixtures extracted from an organism or environmental media. The advantage of such a method is that it will take into account both known and unknown chemicals present in the mixture.

As part of the Human Biomonitoring for Europe (HBM4EU[9]) Project a team of scientists examined the combined biological effect of chemical mixtures extracted from the placentas of pregnant Spanish women at full-term [57]. The results of the screening study show that most mixtures triggered estrogenic activities and a clear inhibition of the thyroid activity.

A similar approach is presented in case study #2 where real-life chemical mixtures extracted from marine mammals have been tested for their immunotoxicity.

Applied to environmental media, a classic approach is to test the toxicity of natural water samples. For example, a 2017 study tested the toxicity of water samples from the river Rhine [58]. The original water samples exhibited mutagenic effects in in vitro tests. Scientists identified and tested 21 environmental contaminants (including pharmaceuticals, industrial chemicals and pesticides as well as natural alkaloids) potentially responsible for the mutagenic effects[10] observed. **They found that none of the chemicals showed a mutagenic effect individually, even at a concentration 1,000 times higher than in the original river sample. When mixed together, however, the mixtures exhibited mutagenic effects.**

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[8] https://edcmixrisk.ki.se/
[9] https://www.hbm4eu.eu/
[10] Mutagenic effects refer to induced mutation in the genetic material of organisms.

Case study #3 – Disordered brain development

The thyroid hormone system is essential for the health of humans and wildlife. It directs a number of important body processes such as growth, reproduction, sexual and neurological development, and – not least – brain development. Thus, disruption of this complex hormonal system may lead to serious health effects. It is well known that low maternal levels of thyroid hormones during pregnancy affect children's IQ; and there are indications that even minor variations in maternal levels of thyroid hormones in general may affect brain development [64].

Many environmental contaminants are known to interfere with the thyroid hormone system, potentially leading to impaired foetal and child brain development [19]. A striking and worrying example of daily-life exposure to neurodevelopmental toxicants comes from flame retardants called polybrominated diphenylethers (PBDEs). These chemicals were used extensively until their global ban in 2009. Because of their high persistence and bioaccumulation they are still widely found in the environment and in our bodies, particularly in breastmilk [65].

A human risk assessment for neurodevelopmental toxicity [66] suggested that exposure to combinations of PBDEs may exceed acceptable levels in breastfed 0-3-month-old infants and in small children, even for moderate exposure scenarios. Small children had the highest combined exposures, with some estimated body burdens at levels known to cause neurotoxicity in animal experiments. Acceptable levels of combined PBDEs can also be exceeded in adults whose diets are high in fish.

Case study #3 – continued

Looking at a wider range of neurotoxicants, the EDC-MixRisk[11] project (see also case study #1) looked at real-life chemical mixtures that had impacts on children's neurological development and metabolism/growth [12,36]. Neurological impacts identified in the children's cohort studied were language delay aged 30 months and impaired cognitive functions aged 7 years, particularly among boys [67]. Impacts on metabolism/growth were identified by low birth weight and reduced growth at age 5 1/2 [68].

The researchers designed experimental chemical mixtures based on neurotoxic chemicals identified in the blood and urine of the mothers. When these mixtures were tested experimentally in animal and cell models they caused effects and dysfunctions, including on the thyroid hormone system, at exposure levels similar to those measured in the mothers. **This shows that real-life chemical mixtures have the potential to affect the brain development of children [12,36].**

Given 1) the importance of the thyroid hormone system and the wide variety of chemicals that can interfere with it, and 2) that we are also exposed to other chemicals that may harm brain development by other mechanisms, **it cannot be overemphasised how important it is to include the combined exposure to all neurotoxic chemicals in chemical safety assessments**

[11] https://edcmixrisk.ki.se/

5
REGULATORY CHALLENGES

5.1 Authorities usually assess a single chemical at a time ...

The staggering complexity of our daily chemical exposures stands in sharp contrast to the simple assumptions made by regulatory agencies and chemical companies. The general process of risk assessment used in REACH, and in most other regulatory controls of chemicals, relies on single-chemical toxicological studies to identify a safe (or 'acceptable') level of exposure for a chemical of concern[12]. If available, data from human epidemiological studies and/or environmental field studies are also used to complement the single-chemical assessment. This in itself is a challenge, because of the diversity of effects that may be relevant – from carcinogenicity to endocrine disruption to immunotoxicity – and the challenges of measuring those impacts.

In the majority of cases each chemical is assessed as if it is the only one we are exposed to, as if hazardous chemicals are emitted into a pristine environment or human body. The small amount of 'acceptable' risk is sometimes envisioned as a cup which can hold a certain amount of risk but must not be overfilled (Figure 5). As long as the real-life exposure is lower than this amount – as long as the *risk cup* does not overflow – the chemical exposure is considered acceptable. This approach has an obvious flaw: it assumes that the risk cup contains only that one exposure. This means our current regulations permit each and every chemical of concern to completely fill the risk cup, regardless of what other chemicals might be in it. Another important caveat is the assumption that a threshold of 'safe' exposure exists – which is not the case for chemicals with persistent, genotoxic or hormone disrupting properties (see also Guide 4).

[12] The safe or acceptable level of exposure is derived from information related to the health/environmental effect regarded as the most relevant and sensitive at that time.

Guide 2 – Data gaps are the big limitation in all chemicals assessments

It is well recognised that the European Union's chemicals regulations cannot keep up with evaluations even of single chemicals. Although REACH was successful in closing some of the knowledge gaps on environment and human health properties for over 23,000 chemical substances, the data are often far from adequate even to evaluate the hazards of single chemicals [69].

Compliance checks by ECHA in 2020 found that 88% of the registration dossiers for chemical substances required additional information [70]. The authorities' substance evaluation proceeds at a glacial pace: in 2020 evaluations were published for only 30 chemicals, nearly half of which were recommended for additional risk-management measures [71]. Since REACH came into force in 2007 only about 50 of the most problematic chemicals – the Substances of Very High Concern (SVHC) – have been moved to the REACH authorisation list (Annex XIV). Nearly 200 others are waiting on the Candidate List. Yet the Substitute It Now (SIN) List, maintained by the Swedish NGO ChemSec, lists more than 1,000 which should be designated as SVHCs under REACH and replaced by safer alternatives.

Another example of the data gap is the lack of information on chemicals used in food contact materials. A recent overview compiled a database of 12,285 substances that could possibly be used worldwide to manufacture food contact materials [72]. For over a quarter of them no hazard information could be found. This hampers prioritisation for further assessment and exposure reduction.

More needs to be done to speed up the management of risks from **single chemicals** and prevent the use of chemicals of concern in wide dispersive and consumer uses. For **mixtures** these knowledge gaps will hamper the quality of assessments [3]. Closing these knowledge gaps will take time; meanwhile people and wildlife are being exposed. This is why restriction of the most hazardous chemicals from consumer products, as promised in the EU Chemicals Strategy for Sustainability, will have to be implemented as part of the upcoming REACH revision in order to reduce overall chemical exposure [73].

5.2 … and authorities have failed to properly consider mixture effects for years

Scientists have been studying mixtures for several decades but it was not until the 1990s that calls to incorporate cumulative assessment in chemical regulation became louder (Figure 4). The 2001 Commission White Paper for a new EU Chemicals System (REACH) mentioned the need for more research on the combined effects of multiple chemical exposures. Then, over several years, a growing number of publications demonstrated that real-life mixtures can have unexpected effects. In 2007, an international workshop was arranged by WHO and the International Programme on Chemical Safety (IPCS) with the aim of initiating risk assessment of combined exposure [74]. Finally in the EU, in 2009, DG Environment commissioned a comprehensive review of chemical mixtures [1]. The report concluded that there was already "a consensus in the field of mixture toxicology that the customary chemical-by-chemical approach to risk assessment might be too simplistic." It added: "It is in danger of underestimating the risk of chemicals to human health and to the environment." The report prompted several research activities to consider in detail how the problem of mixtures might be added to REACH and other regulatory frameworks. In 2014 a German Environment Agency report provided recommendations for better consideration of environmental assessment of mixtures for the actors under REACH [75]. It also highlighted the options for authorities to assess mixture risks, e.g. during substance evaluation or in the context of restriction and authorisation.

Many years later, despite substantial progress in the science of chemical mixtures, almost no regulatory action has been taken. A 2019 report by the Swedish government concluded that "the last ten years have been a phase of confirmation and consolidation of knowledge about mixture risks"; but on the specific details of implementation, the report continued, "progress is slow" [2]. It notes that little progress has been made on the specific legal bases for mixture risk assessments, a need highlighted by the 2009 review.

Decades of inaction on mixture toxicity

1980s

Additivity effects demonstrated in fish and other aquatic organisms

2007

International WHO/IPCS work-shop on combined exposures of multiple chemicals

2009

•Nordic Council Workshop on combination effects.
•EU Council conclusions “Combination effects of chemicals”

2010

EU Commission Report “State of the art of mixture toxicity”

2012

Commission Communication on “The combination effects of chemicals”

2013

EU 7th Environment Action Plan promises to address combination effects of chemicals

2015

Swedish chemicals Agency KEMI proposes the use of a mixture assessment factor (MAF)

2018

EU Commission announces ban on four phthalate chemicals due to their combination effects

2019

Joint statement from global researchers recommend the application of a MAF as a way to decrease the total burden of exposure to chemical mixtures

2019

The European Food Safety Authority (EFSA) develops a framework when evaluating the potential "combined effects" of chemical mixtures in food and feed

2020

EU Chemical Strategy for Sustainability recommends assessment of inclusion of MAF in REACH and provisions to address mixtures in other laws

Figure 4 - Decades of inaction on mixture toxicity

5.3 EU approaches on mixture assessments fall short ...

A handful of policies in the EU explicitly mention the consideration of mixture effects. However, they mostly refer to intentional mixtures under a specific regulation. Several laws do include some provision for the assessment of a certain product for market approval (e.g. for a formulation where the mixture composition is known). And an assessment of cumulative and synergistic effects is required for biocides and pesticides, as well as pesticide residues in food [4]. But an overarching approach – one that covers the risks from combined exposure to all chemicals co-occurring in the environment or human tissues, i.e. unintentional mixtures – is missing.

The mixture assessments in EU laws are partial in that they are limited to the chemical substances covered by their specific regulations (e.g. cosmetic ingredients or pesticides or biocides) [76]. In other words, they are done in silos, as if the same person could not be using cosmetics and be exposed to pesticides.

A 2016 report from the Commission's Joint Research Centre pointed out that "even though methodologies for assessing/estimating the combination effects of chemicals are being developed and used by scientists and regulators in specific circumstances... so far there is no systematic, comprehensive and integrated approach across different pieces of legislation." [14]

Based on this, the Commission Staff working document from 2020 concluded that "requirements on the assessment of unintentional mixtures are broadly absent" and recommended additional efforts to introduce and strengthen provisions in EU legislation.

The following examples illustrate how combined exposures to similarly-acting chemicals have been assessed for a group of PFAS, for pesticides and a group of plasticisers. These assessments are steps forward but remain limited.

Example 1: Mixture considerations in food safety

The European Food Safety Authority (EFSA) has initiated several assessments of mixture toxicity over the years [77] and in 2019 published guidance on different risk assessment methods for combined exposure to multiple chemicals that fall under EFSA's remit [78]. EFSA used this guidance to set recommendations for the tolerable intake for the sum of four PFAS which have been found in food and are co-occurring in humans [79]. While it is a very important step in the right direction this approach should be broadened to consider and act on overall exposure to other chemicals from all sources (see Guide 6).

For over a decade EU law has required cumulative and synergistic effects of pesticides to be addressed in the regulation of maximum residue levels for pesticides in food. However, this has not yet been implemented and regulators continue to carry out safety assessments as if humans were exposed to only one pesticide [80]. EFSA's more recent work included two cumulative risk assessments of pesticides causing effects on the nervous system and thyroid hormone system [81,82]. The studies took into account only pesticides that were authorised at the time of the assessment, even though some banned pesticides are still detected in EU food [83]. The reports concluded that dietary exposure to pesticide mixtures is below the threshold which would trigger further regulatory action. CHEM Trust and others have criticised these approaches as being too narrow and for concluding safety despite data limitations and large uncertainties [84]. For instance, a child is exposed to chemicals which affect the nervous system from a variety of sources. The cumulative risk assessment should therefore address all neurotoxicants present including those in indoor air, dust and food contact materials etc.

Example 2: Restriction of four phthalates under REACH

REACH mainly focuses on individual chemical substances[13]. One rare example of risk management based on cumulative assessment is the 2018 restriction of four phthalates [85]. Using biomonitoring data it was shown that these substances pose an unacceptable risk to human health when present in any plasticised material at a concentration – individually or in any combination – above 0.1 %. This very important restriction has been long overdue and shows that the REACH restriction process can and should be used to address combined effects from multiple chemicals. However, it required a large amount of data on the hazards and exposures to these four phthalates, which is usually not available for most substances. Moreover, decisions based on (human) biomonitoring data are retrospective; meaning that exposure has taken place and impacts will probably already have happened. Therefore, restriction processes need to be complemented with a more prospective[14] one to enhance protection against combined exposure to chemicals.

5.4 Why a mixture assessment factor (MAF) is a solution

A full assessment of all combinations of chemical contaminants to which people and wildlife are being exposed is impossible – and so, therefore, is estimating the true toxic effect of these daily cocktails. Even if all combinations were identified, estimating the effect of these mixtures would require detailed understanding of the effects of each chemical, as well as the amount, timing and route of each exposure. This is an extraordinary challenge – it is simply impossible to test all potential real-life exposure scenarios.

While highlighting the near-impossibility of comprehensive specific mixture risk assessments for different mixture scenarios, however, scientists point out that "intermediate" approaches can be applied to the problem immediately. A Nordic Council workshop in 2010 on combination effects of endocrine disrupting chemicals agreed to the idea of applying a Mixture Assessment Factor (MAF) (see Guide 3 and Figure 5). In 2015 the EU's Joint Research Centre described the MAF as one of the scientific tools available to address risks from combined exposures [86]. In 2020 researchers from five major EU research projects – HBM4EU[15], SOLUTIONS[16], EDC-MixRisk[17], EU-ToxRisk[18] and EuroMix[19], as well as CHEM Trust – supported the MAF as a concrete step forward [87].

[13] REACH also includes special considerations for multi-constituent substances (MCS) and so-called UVCBs (substances of unknown or variable composition).
[14] 'Prospective' as opposed to 'retrospective': a retrospective assessment analyses the cause of a damage which is already done (e.g. polluted river). A prospective assessment tries to predict the potential damage, ideally before putting a chemical on the market.
[15] https://www.hbm4eu.eu/
[16] https://www.solutions-project.eu/
[17] https://edcmixrisk.ki.se/
[18] https://www.eu-toxrisk.eu/
[19] https://www.euromixproject.eu/

Guide 3 - What is the MAF?

The MAF – Mixture Assessment Factor or Mixture Allocation Factor – is a factor applied to a single chemical's evaluation to lower the 'safe' or permitted level of exposure to a chemical. **The MAF acts as a safety net to account for the mixture toxicity that would result from the combined exposure to one given chemical, and other known and unknown chemical substances.** It is a tool that can be applied to the established chemical risk assessment process done on single substances.

The MAF builds on the *uncertainty factor* approach. When conducting risk assessments on single chemicals to derive 'safe' levels of exposures, it is common to apply *uncertainty factors* (sometimes called *safety factors*). These factors acknowledge the uncertainties inherent in the estimation process [3]. As an example, let's take the extrapolation of safe exposure levels derived from animal studies to humans. In this case an uncertainty factor of 100 will be applied; and the value of the no observed adverse effect level (NOAEL) derived from animal studies will be divided by 100 to set a safe level for humans[20]. **The MAF is an additional factor applied to account for the total risk of mixture exposure. (Figure 5)**

The MAF is practical because it considers the contribution of every chemical to mixture toxicity in a systematic way, without requiring knowledge of the chemicals present, their concentrations or hazard profile. **It is a good tool for compensating for data gaps and can help create a straightforward, protective system for managing the unknown.**

The advantage of a generic MAF is that it operates within the existing chemical-by-chemical regulatory process, avoiding the need to develop novel mixture-assessment processes for each possible chemical combination. Its application means, effectively, building a default mixture-assessment into the regulatory 'safe' dose for each substance and/or group of substances.

The MAF approach is simple, protective (if set at a high enough value) and based on well-understood scientific models of combination effects. It provides a clear path to incorporate mixtures assessment into the existing regulatory process in a science-based, yet precautionary way.

Using a MAF in scientific assessment would end the practice of 1) assessing chemicals in isolation regardless of the real-life cocktail of exposures; and 2) ignoring the reality of environmental contamination and our body burden of chemicals.

[20] The result of the subsequent risk characterisation will obviously depend on the (eco) toxicological endpoint investigated, on the exposure estimations and several other implicit assumptions. This is why many controversies in chemical regulation evolve around the question of 'safe levels' - as these will determine the protection - or lack thereof.

What is a Mixture Assessment Factor or MAF?

1 Let’s start with a cup. This cup holds the maximum amount of acceptable risk from exposure to chemicals. **We call it the ‘risk cup’.**

2 Classic chemical risk assessment assumes that risks only occur when the cup overflows.

3 Currently, chemical risk assessment usually considers only one chemical - each chemical is allowed to fill one cup.

4 But in reality, we are exposed to several chemicals at once and the ‘risk cup’ overflows – **we are not protected from the combined exposure to chemicals.**

5 The solution is to reduce by a factor – **the MAF** – the space every chemical gets to contribute to the overall combined risk in the cup.

6 Like this, there is room for all chemicals and **we are better protected from real life exposure**

The ‘risk cup’ should be able to hold hundreds of chemicals and also leave extra room for the unknown.
All worrisome substances with no safe level of exposure, e.g. endocrine disrupting chemicals, should be substituted wherever possible.

Figure 5 - MAF

6
THE WAY FORWARD FOR EU POLICY

Two major shortcomings in the current chemical regulatory framework lead to systematic underestimation of the risks from real-life mixtures exposure:

1. The assessment and management of chemicals mostly in isolation; and
2. The assessment and management of chemicals within regulatory silos (e.g. REACH, pesticide legislation, food contact material law etc.)

We must also consider that we are not dealing with a few novel chemicals being examined before being placed on the EU market. We are addressing the thousands of chemicals already in use, as well as banned legacy chemicals that persist – and we are potentially exposed to all of these. This means that **time spent on further research, analysis, or debating regulatory approaches leads to continued exposures and therefore increased risks of adverse impacts. It is therefore imperative to apply precautionary approaches to protect against current combined exposures to chemicals.** We have enough evidence of risks from combined exposures (see Chapter 4) and should not lose more time waiting for more data and resources for complex mixture assessments.

In recent years research has delivered more tools for dealing with the risks from mixtures [88]. Now it is time for policymakers to act to close the protection gap.

> **"Mixture risk assessment is needed for better protection of humans and the environment. Scientifically justifiable tools are available and ready for use in risk-assessment practice."** Kortenkamp and Faust, Science, 2018 [88]

In a significant step the European Commission in its 2020 Chemicals Strategy for Sustainability has committed to protecting people and the environment from the combination effect of chemical mixtures. It recognises, however, that "it is currently not realistic nor economically feasible to specifically assess and regulate an almost infinite number of possible combinations of chemicals" [5].

The Commission's main commitments are therefore to:

1. "assess how to best introduce in REACH (a) **mixture assessment factor(s)** for the chemical safety assessment of substances";
2. "introduce or reinforce provisions to take account of the **combination effects in other relevant legislation**, such as legislation on water, food additives, toys, food contact material, detergents and cosmetics".

EU chemical-related policies are now being revised in the wake of the Chemicals Strategy publication. This provides a window of opportunity to include provisions that address mixture toxicity.

This section presents CHEM Trust's recommendations on the introduction of a MAF, and on how to integrate mixture assessment in all relevant legislations. Finally, it lists immediate actions to reduce mixture toxicity by lowering overall chemical exposure.

Guide 4 – FAQ on MAF

Will the MAF enhance protection?

Yes, if large enough. The MAF is a pragmatic first step to increase protection. It is a useful tool to manage unknowns, i.e. daily-life exposure to the hundreds of chemicals. The level of protection will depend on the magnitude of the MAF (see Guide 5), which is still under discussion.

Does the MAF apply to non-threshold substances?

No. The MAF is not intended to deal with non-threshold substances – those for which no safe level of exposure can be assumed owing to high uncertainties in the risk assessment. For non-threshold substances – such as genotoxicants, persistent chemicals and endocrine disrupters – emissions and exposures should be minimised. This means stringent risk-management measures, including restrictions. REACH foresees the eventual replacement of all Substances of Very High Concern with safer alternatives.

Aren't mixture effects already covered by the uncertainty factors normally used in risk assessment?

No. The uncertainty factors currently used cover protection of vulnerable individuals and conversion of animal data to predict the effects in humans, not mixture effects [90,94]. An additional factor is needed to account for the reality of combined exposure to multiple chemicals from multiple sources.

Why is a MAF needed if all risks from all single chemical substances are controlled (i.e. chemical exposure is below the individual risk levels)?

Science has shown that exposure to a chemical mixture can lead to adverse effects on health and the environment, even if the concentrations of all the individual chemicals – from different sources and uses – are below their individual thresholds for what is considered 'safe'. So, while ensuring better compliance with current laws is urgently needed to prevent risks for health and the environment, on its own this will not address the additional risk from mixture toxicity.

Guide 4 – continued

Why can't we just identify the key toxicants, given that usually a few chemicals are driving mixture toxicity?

Research has found that the toxicity of many mixtures is often driven by five to 10 substances [95]. The problem is that these chemicals are not always the same. They vary with time and location for different exposure situations (e.g. in rivers or indoor air), as do their concentrations. Therefore, if the overall risk needs to be addressed, gathering data only on a few priority chemicals will not suffice.

If sufficient data are available it is possible to calculate the risk from combined exposures. So why do we need the MAF?

Targeted mixture risk assessments have a role to play for well-characterised, defined scenarios (see Guide 6). However, for protecting human health and wildlife from multiple chemicals from all exposure sources this approach is not feasible. The data gaps of these unintentional mixtures will not be filled any time soon, and will always be an underestimate.

The MAF is a tool to address the concerns about mixture effects by compensating for the unknowns and the existing data gaps. Avoiding exposures altogether is not a realistic option. There is no alternative to applying a MAF to ensure better protection.

The proposal to use the MAF in REACH registration will affect all chemicals. Is it not better to develop a more targeted approach?

In fact, inserting the MAF in REACH registration would only apply to substances produced/imported in quantities above 10 tonnes per year in the EU. This is a major limitation. But at least for those above 10 tonnes the MAF will be easy to apply as part of chemical assessments by inserting an additional factor into established procedures. Crucially, additional risk-management measures will only be triggered when the risks are exceeded.

6.1 MAF as a tool in REACH

The EU's main chemicals law, REACH, is being revised, and discussions on how to increase protection against mixture effects have started. A 2020 workshop held by Sweden and the Netherlands proposed the introduction of a MAF in REACH [16] based on previous work [89,90]. CHEM Trust, together with several NGOs, supports this proposal as a first step while pointing to additional measures needed, including a horizontal approach across EU laws and a stronger emphasis on substitution of harmful chemicals [91,92]. A recent paper from the German Environment Agency discusses options for addressing chemical mixtures, including a MAF, in the different parts of the REACH framework [93].

MAF in REACH registration: When companies want to market an industrial chemical, they have to fill in a registration dossier, providing data on hazards and uses. For all chemicals produced/imported in quantities of more than 10 tonnes per year a chemical safety assessment is required and companies are obliged to demonstrate safe use of the chemical. Currently this process is limited to a single substance approach and companies are allowed to ignore risks from combined exposure with other chemicals.

This has to change. **Companies must consider the contributions of their chemicals to an overall mixture effect. This can be done by dividing the estimated 'safe' levels of exposure to a chemical by the MAF (value to be determined, see Guide 5) to create a higher safety margin (Figure 5).**

The alternative to using a MAF would be to require a detailed safety assessment of all mixture scenarios. This would mean an increased demand for high-quality data on hazards and exposures and specific knowledge of all possible mixture exposure scenarios. Even if current data gaps on single substances in REACH registration dossiers are addressed over time and dossier quality improves, it is unrealistic to expect assessments for all unintended mixture situations across the whole life-cycle of a single chemical.

MAF in REACH restrictions and authorisations: When risks are exceeded, authorities usually impose risk-management measures such as restrictions on the use and manufacture of a chemical substance. For Substances of Very High Concern a separate authorisation procedure decides whether the specific chemical is allowed to be used for a certain purpose, based on an application from industry. **So far, consideration of mixture toxicity in REACH restriction has been ad hoc and not systematic.** An example is the restriction of four phthalates based on human biomonitoring data [85] and the application of a MAF for the restriction of 4,000 chemical substances in tattoo inks [20]. **In CHEM Trust's view a more systematic approach is needed to apply a MAF in all assessments.** This is particularly important for single substances belonging to a chemical group for which there are known co-exposures to other similar substances such as bisphenols, phthalates, PFAS etc. Single-substance or chemical group assessments should no longer be performed without consideration of joint exposure to other chemicals from multiple sources.

The use of a MAF to assess mixture toxicity generically will still allow the use of targeted mixture risk assessment in specific situations or legal contexts when required (see Guide 6). However, such assessments are currently usually sector specific and do not include exposure to the same or similar substances from all other sources (see Chapter 5.3). Therefore, these approaches could be complemented with the MAF concept.

Guide 5 – Setting the value of the MAF

An obvious challenge of the MAF approach is choosing a value that will adequately protect for a wide range of chemical substances and combinations. The value might depend on the number of chemicals expected to be combined; their modes of action, and the ways in which they add or act together; and on the safety margin incorporated to protect human health or the environment. **In keeping with the precautionary approach laid out both by REACH and the Chemical Strategy for Sustainability, the largest reasonable MAF should be used.** This factor should be applied in all cases to cover real-life combined exposure to multiple chemicals from multiple sources.

A 2015 analysis by the Swedish Chemical Agency KEMI suggested that, for a mixture of *n* chemicals, a MAF of about '*n*' would be protective. This assumes that the concentration addition model is followed and that no single chemical exceeds its 'safe' level [90]. The large numbers of chemicals present in the aquatic environment has been shown in many studies; and information about the occurrence of hundreds of chemicals in European rivers or groundwater can be accessed via the NORMAN database[21]. Gustavsson et al. [56] detected up to 53 out of 141 pesticides in one water sample. Markert et al. found 98 out of 153 substances including pesticides, pharmaceuticals and industrial chemicals [96]. The EU research project SOLUTIONS[22] modelled pressure on ecosystems from mixtures of up to 1,785 chemicals [97]. One could therefore argue in theory for a support of a very large MAF, even implying a MAF above 1,000. However, this constitutes the worst-case scenario, assuming that all chemicals contribute equally to the mixture. This would be an overestimation of the contribution of each substance, so an adequate MAF will be smaller than the number of chemicals in the potential mixture.

A 2019 report for the Swedish government on combination effects summarised the regulatory context and scientific background, and made recommendations for improving the protection from chemical mixtures. It also included a review of current proposals for the value of a MAF which range from 4 to 100 [95].

[21] https://www.norman-network.com/nds/empodat/
[22] https://www.solutions-project.eu/

Guide 5 – continued

A more recent **KEMI report, from 2021** [98], analysed published mixture risk assessments and concluded that a MAF of 10 would be sufficiently protective for mixtures of up to 30 chemicals, while a MAF of 20 would protect against 95% of the analysed mixtures and **MAF of 50** would be sufficient for all of the mixtures investigated in that project. **However, this analysis is still an underestimation of real-world scenarios:** 1) it was based on available data and only a small number of chemical substances are monitored in the environment, leaving out unidentified pollutants which may significantly contribute to the mixture risk; 2) substances without regulatory thresholds were excluded from the MAF calculation – many substances do not have these thresholds set.

Research has shown that mixtures in the real world can be more complex, with many more unidentified chemicals from various, sometimes unknown, sources and with levels varying over time. Therefore, in CHEM Trust's view a MAF to protect the environment and human health needs to cover this uncertainty. It should therefore be set at 100 to **cover exposure to all chemicals, from all potential sources.**

Our proposal to establish a MAF of 100 includes:

1. **A factor of 10 addressing the different chemicals contributing to a mixture** (several hundred chemicals are usually present in real-life samples; however, it has been found that about 10% of chemicals present are responsible for 90% of the mixture toxicity [99];
2. **A factor of 10 addressing different exposure sources** (ranging from biocides, cosmetics, pesticides and detergents; to uses in food contact materials, toys and other consumer products as well as from ambient air, soil, and food and drinking water), and the other uncertainties.

This approach would address:

- the risk of mixture effects due to the combined exposure to other chemicals;
- the risk of combined exposures to the same chemical from different sources;
- the uncertainties coming from exposure to unknown chemicals with unknown toxicity.

The MAF introduction in REACH would be a very important step forward in more widely accounting for unintentional co-exposures in chemicals legislations. In order to protect vulnerable groups it is essential that chemical assessments cover the most sensitive toxicological impacts, including considerations of critical windows of exposure such as early-life development - as indeed should be the case for every single-substance safety assessment.

6.2 Bypassing the regulatory silos: consider combination effects in all chemical-related laws

In its Chemicals Strategy for Sustainability the European Commission highlighted the need to "take account of the **combination effects in other relevant legislation,** such as legislation on water, food additives, toys, food contact material, detergents and cosmetics" [5].

CHEM Trust strongly supports regulatory action on combination effects beyond REACH and recommends that an action plan with dedicated timelines should be developed. Researchers have also recommended an overarching systematic approach to set research and policy objectives on mixtures. Otherwise, policies to address mixtures will remain insufficient [87].

In sector/product-specific laws: Chemicals' 'safe' level of exposure should no longer be decided on the risk assessment of a single substance in its regulatory silo. Cumulative risk assessments in any sector/product-specific laws should also consider co-exposures to chemicals regulated under different laws (see Guide 6). A clear legal mandate for such an approach should be inserted in all laws. Even if product-specific legislation could ensure that all known exposures fit in the risk cup (Figure 5), we run the risk of overflowing when we add the many unknown, unanticipated or background environmental exposures to which we are all subject. Such complex assessments are taking a lot of time and resources, and include many uncertainties. Therefore, there is a need for a more pragmatic way forward – to add a generic MAF for mixture assessment.

The upcoming revisions of various EU laws are the perfect opportunity to implement these provisions (e.g. industrial chemicals (REACH), cosmetics, toys, food contact materials). The aim is to improve companies' safety assessments as well as strengthen the possibilities for authorities to act on known co-exposures to harmful chemicals and to consider the unknowns.

In media-oriented laws: Mixture assessment must go beyond sector/product-specific regulations. It should also be integrated into retrospective, media-oriented legislation that aims to protect the environment, such as the **Water Framework Directive (WFD) and in deriving environmental quality standards (EQS).**

For instance, to improve the protection of aquatic environments from exposure to multiple pollutants, the European Collaborative Project SOLUTIONS[23] recommended updating the WFD technical guidance with a "comprehensive mixture assessment framework" and improving "coordination across all pieces of European chemicals legislation" [100].

It will also be important to prioritise resources to expand our knowledge of pollutants that occur in the environment, as it is critical to perform comprehensive mixture assessments. **The EU platform IPCHEM[24] will play an increasing role in searching, accessing and retrieving chemical occurrence data collected and managed in Europe. But despite significant investment of effort in large-scale monitoring over recent years, these data are still only showing the tip of the iceberg.** Efforts such as those carried out under the SOLUTIONS project, to develop tools that predict the occurrence of chemical pollutants on a European scale, are useful in helping to fill these gaps [97].

[23] https://www.solutions-project.eu/
[24] https://ipchem.jrc.ec.europa.eu/

Guide 6 – Improving current approaches to targeted mixture risk assessments

When all the chemicals present in a given mixture are known, as well as their concentration and all hazard properties, it is possible to make a prediction of the toxicity of the mixture using the concentration addition model (see chapter 4.2). The WHO/IPCS, OECD and EFSA have described various approaches to perform targeted mixture assessments [74,78,101]. The EU research project EuroMix[25] has also provided a useful overview of the different scientific approaches [102] and a handbook for mixture risk assessment [103].

These approaches are mostly aimed at addressing a specific exposure scenario. They do not consider the overall real-life exposure to chemicals, including the unknowns. They can be applied to intentional mixtures of known compositions, such as a cosmetic product. They can also be useful in retrospective mixture risk assessments of specific sites for which monitoring data are available; for instance, in a contaminated area where specific mitigation measures need to be decided.

In most real-life scenarios the majority of key information necessary to perform comprehensive targeted mixture risk assessments is missing and it is therefore very limited. Applying a MAF would partly fill the gaps. Targeted assessments certainly have their role to play in addressing the risks from exposure to some mixtures – in particular, whenever sufficient data and the resources needed to perform such assessment are available.

The overall usefulness of mixture risk assessments can be improved by:

1 – Avoiding too narrow a focus by considering all substances with similar harmful effects from various sources, beyond their regulatory silos (e.g. pesticides, pharmaceuticals, industrial chemicals).

2 – Highlighting the uncertainties and limitations when communicating conclusions and safety recommendations derived from the assessment. When applying a certain methodology, all assumptions and decisions taken need to be transparent and well-documented.

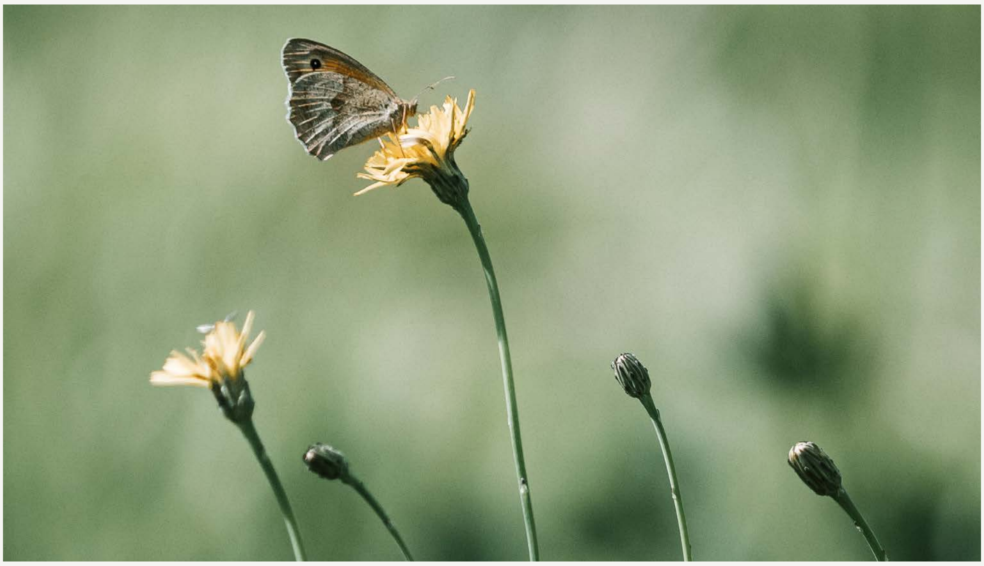
[25] https://www.euromixproject.eu/

6.3 Immediate action: lowering the overall burden of chemical exposure

A critical way to reduce the risk from exposure to mixtures of chemicals is to lower the overall burden of exposure to harmful chemicals from all sources.

To speed up the substitution of chemicals of concern with safer alternatives, CHEM Trust proposes two key actions:

1. establish an EU action plan to reduce exposure to the most common combination of chemicals detected in people and the environment;
2. assess and manage chemicals in groups of related substances rather than as single substances.



1. Developing policy priorities to reduce the most common exposures to harmful chemicals detected in ecosystems and people: Developing methodologies to identify ways of prioritising exposure scenarios will be a useful step forward. It is important to differentiate between a prospective risk evaluation for future use based on exposure modelling and a retrospective risk assessment based on monitoring data. The most relevant findings from human biomonitoring and environmental monitoring studies should be used to develop common exposure scenarios to prioritise the setting of regulatory controls. This is one way of speeding up the substitution of substances of concern and minimising the combined exposure of the general population and the wider environment to harmful chemicals.

As a caveat it should be noted that chemical analysis of environmental and human samples relies on the availability of analytical reference standards This means that many substances potentially present in the environment and our bodies are being missed. Reference standards should be provided by chemical producers to facilitate their identification and quantification in any sample.

2. Increasing the use of grouping of chemicals: CHEM Trust has argued for several years that chemicals from the same group or with the same function should be regulated together (e.g. bisphenols, phthalates, PFAS, brominated flame retardants). This is necessary to minimise chemical exposure and speed up the substitution of hazardous chemicals with safer alternatives, while avoiding regrettable substitution [104]. Work by ECHA on the assessment of more than 450 substances in 19 groups, in an effort to speed up regulatory action on chemicals of concern [105], is a welcome development in that direction.

In the absence of good data to show the contrary, chemicals in the same group, with a similar structure, should be assumed to have the toxicological properties as harmful as those of the most toxic known chemical in the group. The exception would be where industry comes forward with substantial data to prove that a chemical does not have these properties. Such an approach reverses the burden of proof, which is currently mostly on the regulators, and encourages industry to move away from problematic groups of chemicals. Currently, absence of data is one of the best ways to keep a chemical on the market - and this incentivises companies to challenge any attempt to get more data. Grouping of chemicals enhances producer responsibility. It needs to be used in REACH and other chemical regulations, such as the laws on chemicals in food contact materials.

7
CONCLUSIONS AND RECOMMENDATIONS

Currently, the general population is exposed to a large number of chemicals with highly concerning properties which can lead to irreversible and serious health impacts, including birth defects and cancer. When it comes to exposure to developmental neurotoxic chemicals and endocrine disrupting chemicals, brain development and reproduction of future generations are at stake. Therefore, **it is imperative to apply precautionary approaches for protection against exposures to mixtures of chemicals now, rather than postponing action until more data and resources for complex mixture assessments are available.** The same holds true for protecting nature from chemical pollution as part of urgent efforts to avert the biodiversity crisis.

Evidence from recent EU research projects has demonstrated that the current EU chemicals laws systematically underestimate the risk to human health and the environment from combined exposures to chemicals. The need to consider the risk of combination effects of mixtures was already highlighted by the 7th EU Environment Action Programme (7th EAP) in 2013 [106]. This commitment to action has been ignored by the European Commission for too long, but at last there is some momentum for change. The new EU Chemicals Strategy for Sustainability includes important policy commitments to address the risks from mixture exposures. This is a critical window of opportunity which should not be missed. **Science has delivered tools which can be integrated into legislation – now it is time for policy makers to act.**

CHEM Trust urges the European Commission and Member States to act now to improve the protection of human health and the environment from mixture effects.

CHEM Trust recommends the following measures for EU chemical policy on mixtures:

1. Incorporating mixture assessment into all EU chemical regulations

- **A Mixture Assessment Factor (MAF) should be incorporated in all chemical assessments.** We assess that a factor of 100 would be optimal to cover the contributions of different chemicals to mixture toxicity, the different sources of exposure, and additional uncertainties related to unknown chemicals.

- This MAF should be introduced to the main EU industrial chemical law, REACH, as soon as possible, as part of implementation of the Chemicals Strategy for Sustainability. This is an uncertainty factor that should be incorporated into the chemical uncertainty assessment of individual substances when they are registered or their registrations are updated. The MAF will be an important step forward but its ability to be a gamechanger depends on the provisions that detail how and when it will be applied.

- **A legal requirement for mixture assessments should be integrated into other EU chemicals laws during upcoming revisions, including those stipulated by the Chemicals Strategy for Sustainability.** It is essential to integrate approaches to address mixture toxicity in all relevant EU laws and in many cases the best option will be a MAF approach. Where targeted mixture assessments are used they must be improved, e.g. by widening the number and scope of substances covered and by introducing more transparency about inherent uncertainties and limitations.

2. Identify and control the use of the most hazardous chemicals, to reduce the quantity of hazardous chemicals we are exposed to

- **There should be more resources put into biomonitoring and environmental monitoring programmes in the EU, and harmful chemicals found in humans and the wider environment should be prioritised for regulatory action.** It is particularly important to reduce exposure to persistent chemicals and endocrine (hormone) disrupting chemicals.

- **Regulatory processes for controlling the use of chemicals must become faster and more protective. One tool in achieving this is through grouping of chemicals for regulatory measures.** Chemicals from a group (e.g. bisphenols, phthalates, PFAS, brominated flame retardants) should be regulated together under REACH, and in other chemical-related laws to speed up substitution with safer alternatives.

While further research activities will be useful to fine-tune chemicals assessments and tools, **it is crucial to avoid making the problem too big to solve.** The ultimate goal is to protect human health, wildlife and the wider environment from the harmful impacts of combined exposures to multiple chemicals. **This is the gap that needs to be closed now, acting on the clear scientific warnings to deliver the aspirations and promises of the European Green Deal.**

GLOSSARY AND ABBREVIATIONS

ECHA	European Chemicals Agency
EDC MixRisk	Integrating Epidemiology and Experimental Biology to Improve Risk Assessment of Exposure to Mixtures of Endocrine Disruptive Compounds
EFSA	European Food Safety Authority
EQS	Environmental Quality Standards
EuroMix	European Test and Risk Assessment Strategies for Mixtures
EU-ToxRisk	An Integrated EUropean 'Flagship' Programme Driving Mechanism-based TOXicity Testing and RISK Assessment for the 21st century
HBM4EU	European Human Biomonitoring Initiative
IPCHEM	Information Platform for Chemical Monitoring
JRC	Joint Research Centre
KEMI	Swedish Chemicals Agency
MAF	Mixture Assessment Factor or Mixture Allocation Factor
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NORMAN	Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances
OECD	Organisation for Economic Co-operation and Development
PAHs	Polycyclic aromatic hydrocarbons
PANORAMIX	Providing risk assessments of complex real-life mixtures for the protection of European citizens and the environment
PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PFAS	Per- and polyfluoroalkyl substances
POPs	Persistent organic pollutants
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	Dutch National Institute for Public Health and the Environment
SOLUTIONS	Solutions for present and future emerging pollutants in land and water resources management
SVHC	Substances of Very High Concern
WFD	Water Framework Directive

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This report was produced by CHEM Trust – a collaboration between CHEM Trust, a UK registered charity, and CHEM Trust Europe eV, a charity based in Germany – working at UK, EU and international levels to protect humans and wildlife from harmful chemicals.

CHEM Trust's overarching aim is to prevent human-made chemicals from causing long-term damage to wildlife or humans. Our particular concerns are endocrine disrupting chemicals, persistent chemicals, the cocktail effect of chemicals and the role of chemical exposures in the early life of wildlife and humans.

CHEM Trust engages with the scientific, environmental, medical and policy communities to improve the dialogue concerning the role of adverse effects of chemicals in wildlife and humans and to harness a wide coalition to drive improved chemicals policy and regulation.

About the authors

A first draft of the report was written by Rye Howard, an environmental public health scientist with a broad background in epidemiology, toxicology, and research translation. They hold Doctoral and Master of Public Health degrees in environmental health from the Boston University School of Public Health, where their research examined the combination effects of chemical mixtures.

Further drafts of the report including the policy recommendations were written by Dr Ninja Reineke, Dr Julie Schneider and Pia Juul Nielsen of CHEM Trust, informed by the state of the science, the views of the scientists and CHEM Trust's experience of following chemicals policy development for more than two decades.

Scientific review

The scientific content of this report has been peer reviewed by Dr Olwenn V Martin, a a Lecturer in Global Challenges at Brunel University, London.

Building on an academic interdisciplinary background in natural sciences and social sciences, she has expertise in the translation and application of both fundamental and observational research into policy.

Her research is focused on emerging issues for the risk assessment of contaminants, such as mixtures and endocrine disruptors. She has a continuing interest in methods for evidence integration such as systematic review, meta-analysis, weight-of-evidence as well as socio-economic evaluation.

Acknowledgements

CHEM Trust thanks Dr Martin for her scientific review and useful comments on the draft report.

We would also like to thank Natacha Cingotti, Angeliki Lyssimachou, Helene Loonen and Anna Lennquist for discussions and feedback on drafts of the report.

All final editorial decisions were made by CHEM Trust.

CHEM Trust gratefully acknowledges the support of thewaterloofoundation.
The expressed views and interpretations herein do not necessarily reflect the official opinion of any of the institutions providing financial support. Responsibility for the content lies entirely with CHEM Trust.

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Editing and proofreading by
Adam Bradbury

CHEM Trust UK Charity Register Number: 1118182; EU Transparency Register Number: 27053044762-72.

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