Toxicity Eliminating Threats to Planetary and Human Health





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Our eight-month investigation, funded by The Grantham Foundation involved an extensive analysis of peer-reviewed scientific papers as well as interviews with researchers, non-profit leaders, entrepreneurs and investors. The investigation uncovered links between toxic chemicals and several human and environmental health concerns, some of the promising innovations to remedy these and the gaps and opportunities to fill them. Here we present some important highlights from the research.

Some key findings

- 1 Contamination of humans is endemic: Over 3,600 synthetic chemicals from food contact materials alone are found in human bodies, 80 of which have hazard properties of high concern.
 - PFAS are found in almost all humans tested with 14 % of European teenagers having blood levels high enough to risk adverse health effects.
- 2 Contamination of the environment is endemic: Rainwater in many locations contains so much PFAS that it is unsafe to drink.
- 3 Evidence is building that toxic chemicals are likely to be undermining the capacity for humans to reproduce.

- Our understanding of toxicity is outdated, relying on the 500-year-old concept that "the dose makes the poison." Regulators and corporations still mainly rely on an outdated toxicology framework which disregards non-monotonic dose responses, the combined effects of multiple chemicals and sex differences and which uses high doses to estimate safe thresholds and therefore often misses the toxic effects of low exposures, particularly to endocrine disrupting chemicals.
- The industrial economy has created over 100 million chemicals not found in nature, with somewhere between 40,000 and 350,000 currently in commercial use and production having increased fifty-fold since the 1950s.
- More than 90% of the global population is currently exposed to air pollution exceeding WHO guidelines.

This report outlines links between toxic chemicals and a range of health conditions. These include cancer, obesity, Alzheimer's, pregnancy issues, ADHD, fertility problems, heart conditions, and respiratory ailments. Beyond human health, our research also outlines damage to the wider environment and critical ecological systems.





Supported by the Grantham Foundation for the Protection of the Environment, this timely report defines toxicity as "the threat to human and planetary thriving posed by chemicals that damage human and ecosystem health." It charts the pathways of these harmful chemicals through the critical interfaces of air, water, and food, exposing their widespread contact with both humanity and the planet.



Should we be concerned about toxicity?



Before exploring toxicity, it is important to first answer the question: should we be concerned about toxicity?

On the surface it may appear that there is no emergency, since societies around the world and the global economy are so far able to function despite increasing production of toxic chemicals. Given this apparent indifference or resilience to chemical pollution, would it be a wise allocation of resources to focus on this problem when there are so many other pressing demands on societies such as military defence, pandemic preparedness, ageing populations, climate change mitigation and adaptation, and the threats and opportunities from artificial intelligence and quantum computing?

The answer is a resounding "yes". Societies began slowly changing their behaviour and allocation of resources in response to climate change from the 1990s onwards, despite the fact that very few of the predicted effects had yet materialised. What could have been mistaken as an Earth system which was surprisingly impervious to greenhouse gas emissions, was of course an Earth system with finite resilience and a time lag between pollution and its effects, which we see all too clearly today. While it is difficult to objectively compare two all encompassing and complex phenomena, toxicity appears to be a threat to the thriving of humans and nature of a similar order as climate change. However, with toxicity we are still in the 1990s in terms of public awareness and action, but we're in 2025 in terms of consequences.

Nonetheless, the public is gradually becoming aware that the population is experiencing chronic health conditions at a higher frequency and at earlier ages than in previous generations, despite increasing life expectancy.

Of particular concern are the increases in the age adjusted rates of several cancers as shown in the table below. Of course some cancers are decreasing, but most concerning is a 79% increase over two decades in the incidence of all cancers below the age of 50.

DISEASE	CHANGE	TIME	REGION
Early onset cancer	+ 79 %	1990 - 2019	Global
<u>Testicular cancer</u>	+27 %	1993 - 2019	UK
Breast cancer	+24 %	1993 - 2019	UK
<u>Prostate cancer</u>	+53 %	1993 - 2019	UK
<u>Liver cancer</u>	+177 %	1993 - 2019	UK
<u>Melanoma</u>	+147 %	1993 - 2019	UK
<u>Thyroid cancer</u>	+186 %	1993 - 2019	UK
<u>Kidney cancer</u>	+92 %	1993 - 2019	UK

But cancer is not the only concerning health trend. Between 1990 and 2022, the global rate of childhood obesity more than quadrupled, while in the UK the incidence of youngonset type 2 diabetes increased by 40 % in only five years. In the UK, obesity costs the National Health Service £6.5 billion per year, which is 3.6% of its entire budget. Rates of immune system related diseases asthma, type 1 diabetes, celiac disease, and inflammatory bowel disease also sharply increased in recent decades, as have the neurological conditions Alzheimer's, Parkinsons, depression, ADHD, and Autism. Of course, in some cases some increased incidence may be explained by improved diagnoses and detection, however this would appear to be unlikely to account for all of the increases.

Perhaps even more consequential than increasing obesity and cancer rates is declining reproductive capacity. One in six people globally experience infertility at some point in their lives. As is now quite well known, sperm counts appear to have decreased globally by 52% between 1973 and 2011, with the rate of decline per year having increased from 1.2% per year between 1972 to 2000 to 2.6% per year from 2000 to 2018. It is important to note that some studies have not found decreases, but overall it appears more likely than not that a decrease is taking place

and given the potential severity of a fertility collapse this prospect should be taken seriously.

Although not as easily defined by a single number, there has also been a decline in female fertility, which may be even greater than the decline for males: between 1990 and 2017, the global age-standardised prevalence of infertility increased by 0.37% per year for females and by 0.29 % for males. Declining fertility is accompanied by a general worsening of reproductive health with declining testosterone and increasing rates of genital birth defects in males, and increases in polycystic ovary syndrome, endometriosis, and uterine fibroids in females.

Decreasing reproductive capacity may be compounding the effect of people waiting until they are older before trying to conceive, leading to a fertility gap. For example, in the UK only two babies are born for every three babies wanted. Declining birth rates are a serious social and economic problem for many countries faced with rapidly ageing populations in which working age citizens struggle to support a large elderly cohort. Today, two-thirds of the world's population live in countries where the number of births per woman is less than the replacement rate of 2.1, which leads over time to shrinking populations. Already today, some of the world's largest economies: China, Japan, Italy, and Poland, have shrinking populations, while on the extreme end

of the scale South Korea has the lowest fertility rate in the world of 0.72, which will result in its population halving in just fifty years. The combination of people living longer, experiencing chronic health conditions from an earlier age, but with fewer babies being born constitutes a perfect economic storm.

These human health trends are concerning enough on their own, but they are unfortunately accompanied by equally concerning ecological trends. The total population of wild animals has decreased by 69% since 1970, with the population of migratory fish declining by a stunning 81% over the same period. Concerningly for food security, 40% of insect species are now threatened by extinction and 16% of global soil has a lifespan of less than 100 years.

These threats to human and ecological thriving of course have many causes. For example, obesity, cancer, and infertility are affected by diet and other lifestyle factors, while the expansion of farmland and cities in conjunction with climate change has affected wildlife populations.

However, as is explained in the coming pages, researchers have amassed correlational and causal links between exposure to toxic chemicals, and many health and ecological problems. While toxicity is rarely the only cause, it is very often a major contributor.

To illustrate this point, a few examples will be given on the next page.



PESTICIDES AND INFERTILITY

Correlational Evidence

A meta-analysis across 20 studies found that higher pesticide exposure was correlated with lower sperm concentration.

A study of 325 women undergoing fertility treatment found that higher consumption of pesticide residues on fruit and vegetables was correlated with a decreased probability of pregnancy and live birth.

Iranian women who worked on pistachio farms during their pregnancies, exposing them to pesticides, had a 9.2 fold increase in the likelihood of miscarriage compared to those who did not.

2015-2018 NHANES USA study (659 women): top tertile of organophosphate pesticide exposure (DMP) have X2.5 increased likelihood of infertility (failed conception).

Casual Evidence

Pyrethroid pesticide exposure in mice at ecological concentrations was found to cause a dosedependent reduction in successful pregnancies.

Exposure of mice to ecological organophosphate pesticide concentrations caused abnormalities in sperm morphology.

PFAS AND NUMEROUS HEALTH PROBLEMS

Correlational Evidence

High plasma concentrations of PFOA were associated with longer times to pregnancy in Danish mothers.

Men with high blood levels of PFOA and PFOS were found to have less than half the number of normal sperm than those with low blood levels.

Children with high blood concentrations of various PFAS were found to have a higher probability of having ADHD.

High blood concentrations of PFOA and PFOS were found to be associated with higher incidence of thyroid disease.

High blood concentrations of PFOA and PFOS were found to be associated with higher incidence of thyroid disease.

In utero exposure to PFOA was found to be linked to obesity in young women at age 20.

Casual Evidence

Numerous animal studies have shown PFOA and PFOS exposure to cause cancer, physical development delays, endocrine disruption, and neonatal mortality.

We have assessed correlational and causal data linking chronic and acute exposure with thriving threats (a threat to human or planetary health, such as cancer or trophic chain collapse) for a limited number of chemicals. A sample of this analysis is provided in the table on the next page.

	Heavy metals	Pesticides	PFAS	Microplastics (MPs)
Cancer	• •	• •	• •	•
CVD	• •	• •	• •	• •
IBD	• •	• •	?	• •
Fertility	• •	• •	• •	•
Immune	• •	• •	• •	?
Neuro.	• •	• •	• •	?
Mood dis.	• •	• •	?	•

KEY



Correlational data

Large cohort association studies linking toxic chemical exposure with thriving threats.



Causal data

Animal or in vitro models of toxic chemical exposure causing thriving threat in controlled conditions.

?

Insufficient data

Assessment of the causality of chronic toxic chemical exposure for 4 key pollutants and 7 key thriving threats, based on top 50 'best-matched' papers on Pubmed for each comparison 'square'.

CVD = cardiovascular disease IBD = irritable bowel disease Neuro. = neurodegeneration Mood dis. = mood disorder





There are correlational or causal data linking toxic chemical classes with direct thriving threats, including to: reproductive, immune, neurological, cardiovascular, respiratory, liver, kidney, and metabolic systems, and with indirect thriving threats, including: trophic chain collapse, soil fertility, and the socioeconomic burden of disease.

Our conclusion is therefore that there is sufficient evidence for the harms caused by toxicity that this issue should be taken very seriously.

It is famously challenging to make accurate estimates of the economic costs associated with public health problems, and even harder when attributing cause to chemical exposures. Nonetheless, it is thought provoking to consider the following studies, the results of which would be startling even if they were overestimates. The economic costs to the USA of disability and disease from phthalates alone are estimated to be \$67 billion per year, while PBDE exposure is estimated to cost the USA a total of 162 million IQ points across its population. Globally, it has been estimated that reductions in exposure to BPA, PBDEs, and phthalates would have constituted \$1.5 trillion in economic benefits. It is estimated that lead exposure from leaded gasoline reduced the average IQ of children in the USA by between 2-5 points, increasing the number of intellectually disabled people by over 50 % and that the subsequent banning of leaded gasoline resulted in a cumulative economic benefit of over 8 trillion dollars since 1980. While regulation can bring enormous benefits, the cost of cleanups when they fall short can be eye watering. The cost of environmental PFAS remediation if production continues unabated may even exceed global GDP, while the annual indirect health costs from PFAS exposure are estimated to be between 52 and 84 billion euros in Europe and 37 to 59 billion dollars in the USA, which omits out the health costs in Asia which now houses the majority of production.

It is well established that the timing of chemical exposures in particular developmental windows is one of the most important factors for eventual health outcomes which can be understood through the lens of the developmental origins of health and disease (DOHaD). It was previously believed that genes and environment were the main determinants of lifelong health, but a new understanding is emerging that conditions in utero and in early infancy, including exposures to endocrine disrupting chemicals, can have an outsized effect on lifelong health. As the world's population ages and life expectancy increases, reducing exposure to toxic chemicals in critical developmental windows and thereby improving the health of future generations could have considerable long term economic benefits. Aside from the economic costs of poor health, since governments are already offering generous financial assistance to increase birth rates amid warnings that shrinking working-age populations could reduce GDP per capita in Western Europe by \$10,000 per year, reducing toxic exposure to improve reproductive health would likely be economically advantageous.

But more fundamentally, eliminating toxicity is a worthwhile goal for its own sake. It would improve our population's health and the state of our natural environment.





Toxicity Ranking

The causal and correlational data linking toxicity and human and ecological thriving is striking.

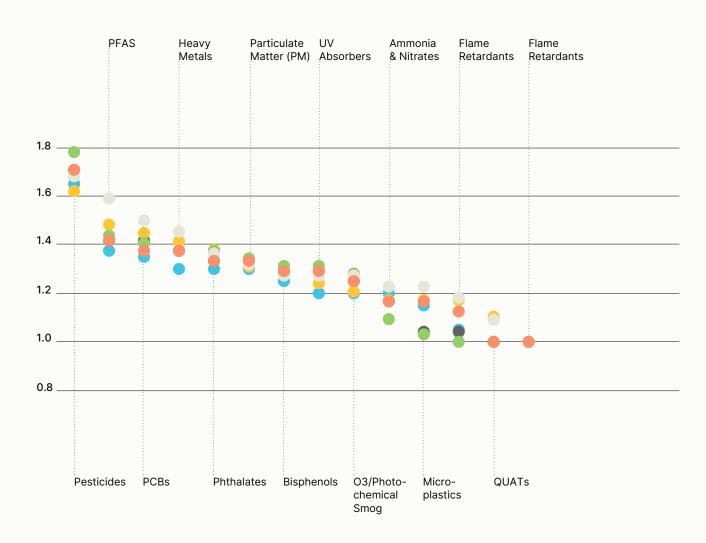
When moving towards identifying suitable intervention points to drive change it is however important to be able to compare different toxic chemical classes to help triage and prioritise efforts.

To achieve an indicative ranking we developed a framework around 9 indicators. Those include quality of evidence focused on the robustness of data supporting toxicity, including human association studies, controlled animal models, and in vitro studies. Others, like ecosystem coverage and thriving threat coverage, assessed the breadth of ecological and physiological damage caused by these toxic chemicals. Specific metrics such as persistence (e.g., how long toxic chemicals remain in the environment or biological systems) and production trends (present and future) were also considered. More details about the methodology can be found on this Figure and in the Appendix.

Key Findings

We have applied the framework to compare 14 major toxic chemical classes (Bisphenols, Heavy metals, PFAS, UV absorbers, O3/photochemical smog, Flame retardants, Ammonia/ nitrates, PCBs, QUATs, Parabens, Microplastics, Pesticides, Phthalates, Particulate Matter). The detailed ranking information and collected evidence can be found in the Appendix and an overview of the normalised ranking results are shown in the figure below, taking different differential weightings to specific indicators into account.

Normalised toxicity ranking, comparing different differential weighting to specific indicators





Pesticides consistently emerged as the most concerning toxic chemical class across all indicators and weighting scenarios due to their extensive ecosystem coverage, human exposure, and contribution to thriving threats like biodiversity loss.

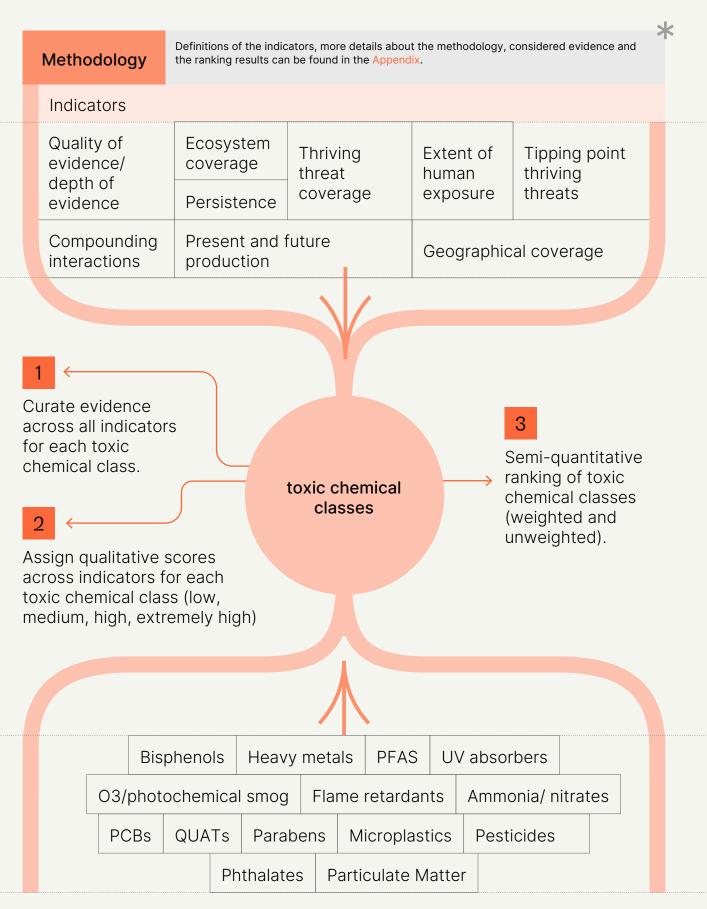
However, our results also highlighted the context-dependent nature of toxicity, which shifts based on how different factors are weighted. For example, PFAS ranked higher when persistence or human exposure was given greater emphasis, whereas microplastics ranked lower due to limited data on thriving threats despite significant environmental persistence. Certain toxic chemical classes, such as flame retardants, microplastics, QUATs, and parabens, consistently ranked lower. This may reflect insufficient data rather than an absence of toxicity, warranting further investigation.

In the following of this chapter we will dive deeper into some of these toxic chemicals, their exposure interfaces and the specific thriving threats they cause.

Limitations and future directions of the toxicity ranking framework

The toxicity ranking was constrained by several factors, including a limited scope of 14 toxic chemical classes, reliance on qualitative rankings with low resolution (four categories), and the arbitrary weighting of indicators, which was applied primarily to demonstrate the methodology. Furthermore, a lack of comparative studies across toxic chemical classes and gaps in available data hindered precise evaluations. Notably, missing data should not be interpreted as evidence of low toxicity. Importantly, we selected the 14 toxic chemical classes based on the scoping of the area we had completed at the time, but this leaves out many compounds, some of which are likely to be even more concerning than those in the 14 classes listed.

Future work should expand the number of toxic chemical classes included and integrate quantitative data, such as percentage decreases in pollinator fitness or specific metrics to ascertain oxidative stress effects. Incorporating comparator studies to standardise relationships between exposure levels and harmful effects will further improve robustness. Developing empirical methods to weight toxicity indicators, i.e. coming to an evidence-based consensus on the importance of different toxicity factors, would also be extremely valuable.







Defining Toxicity



Toxicity encompasses the production, environmental transport and transformation, interfaces of exposure, and physiological mechanisms through which chemicals and materials threaten human and planetary thriving.

To build our understanding of this complicated topic, Deep Science Ventures (DSV) created a knowledge map that describes toxicity as a 'flow' between its sources and each of the "thriving threats" it causes. A detailed description of the methodology can be found in the Appendix.

The full knowledge map served primarily as an internal tool for unpicking and structuring this this space and access may be granted on a case by case basis on request as it contains some sensitive information. However, the full map is not necessary to understand this report as we have pulled out and structured the findings herein.

The scoping of the toxicity space was performed systematically - accounting for the full 'flow' of toxicity from source, through the environment, to human and ecosystem exposure. During this work, DSV consulted relevant experts.

In this chapter we are first sharing our definition of toxicity and key findings from the knowledge mapping exercise. Thereafter we deep dive into specific pollutants, key exposure interfaces and specific human and ecological thriving threats.

Defining Toxicity



DSV has formulated the following definition of toxicity, which will be used in the remainder of this report.



Toxicity is the threat to human and planetary thriving posed by chemicals and materials that damage human and ecosystem health.

Toxic chemicals are ubiquitous features of modern economic activity that overwhelmingly originate in the industrial and manufacturing sectors. Their effects depend on the environmental and biochemical mechanism(s) through which humans and ecosystems become exposed.

Some key learnings from the knowledge map

- A large number of concerning pollutants are used in pesticides and plastics.
- There is a surprisingly large overlap between the chemicals used in plastics and personal care products.
- Diet is a major exposure interface for a large number of pollutants.
- The toxicity of many compounds can be increased in the environment via secondary production mechanisms, such as the chlorination of organic pollutants in wastewater treatment plants and microbial bioconversion of mercury to the more toxic methylmercury.

- A very common mechanism of toxicity which is often the first domino to fall on the path to an adverse health outcome is the generation of reactive oxygen species.
- Another common mechanism is endocrine disruption, and this has the greatest potential to cause poor health and disease when the exposure occurs in utero.
- Perhaps surprisingly, a significant quantity of toxic chemicals are produced as unintentional byproducts or are added to products unintentionally, for example because they are impurities, because formulations and mixtures lack transparency or because they migrate from processing equipment.

CONTENTS **↗**

Key nodes in the knowledge map for toxicity

In the following chapter we are deep diving into specific nodes in the knowledge map and insights gained through the toxicity ranking describing specific pollutants, key exposure interfaces and thriving threats.

The first section focuses on key **Pollutant** nodes within the first section of the knowledge map which address the question: **How and why are toxic chemicals produced?** This section focuses on explaining why particular toxic chemicals are produced rather than others by investigating the relationship between their structure and their properties, which reveals how they fulfil their functions, and the relationship between their structure and their industrial synthesis which explains the economic push for these compounds to be selected over others with similar properties.

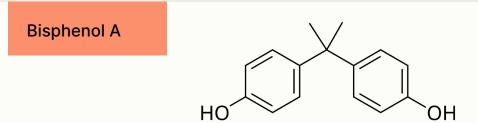
The second section explicates key **Exposure interface** nodes within the second section of the knowledge map which address the question: **How do toxic chemicals move from their sources to the interfaces of exposure?** This section highlights the most concerning pollutants at each exposure interface, identifying their sources as well as the ways in which they expose the human population. Steps being taken to reduce exposure are highlighted and suggestions for further improvements suggested.

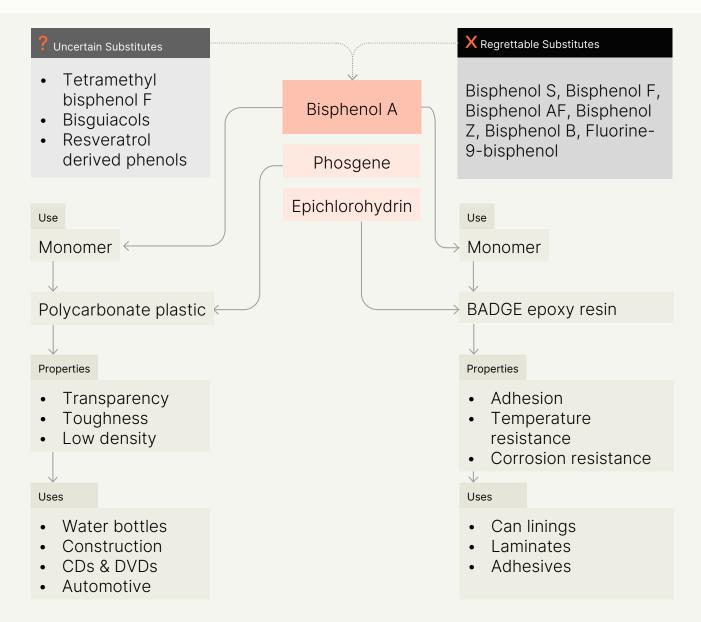
The third section describes key **Thriving threat** nodes within the final section of the knowledge map which addresses the question: **How does exposure to toxicity harm human and planetary thriving?** The key pollutants for human and environmental health outcomes, the physiological mechanisms by which they affect organisms, and the causal and correlational evidence for these effects are explained.

The **Key Nodes** section of the report therefore aims to show, via particular examples, the ways in which toxic chemicals affect the world from their production and use, to their environmental transportation all the way to their effects within the cells of organisms.

How and Why Are Toxic Chemicals Produced?

For this section of the knowledge map, we highlight some of the most concerning pollutants, how they are produced, and what they are used for.





Production

BPA was first produced for use as a synthetic estrogen and is now manufactured by a very large number of companies at a global annual production rate of 10 million tonnes per year. It is synthesised by condensing acetone with phenol.

Because BPA is synthesised from simple chemical building blocks and is produced on such a large scale, it is very low in cost at only 1,367 USD/t. This is one factor which makes the introduction of safer substitutes challenging, with the other being that downstream processes using the chemical are designed to use BPA, which means the majority of substitutes have been drop in replacements in which the phenol functional groups remain unchanged but the linking functional group is different.

97 % of phenol is made via the cumene process in which benzene and propylene and oxygen are reacted to produce phenol and acetone. Similarly, over 80 % of acetone is made via the cumene process. The cumene process is however only economical if there is

sufficient demand for the acetone byproduct. The largest use of phenol at, 46 %, is the production of BPA, and the second largest use of acetone, at 28 %, is BPA production. There is therefore somewhat of an economic lock-in effect in which the synthesis of BPA creates a very significant proportion of the both supply and demand for phenol and acetone. If we take a step further back, around 20 % of benzene is used for the cumene process, and large proportions of the total benzene and propylene production come from the naphtha fraction of crude oil, which further illustrates the economic convenience of BPA in petrochemical production. BPA's drive of benzene production is a significant factor in its hazard, especially for people living close to benzene production facilities.

Uses

The main use for BPA is in the production of polycarbonate plastics, accounting for 70 %, with the remainder being used to make epoxy and vinyl ester resins.

Polycarbonate Plastic

The global production capacity for polycarbonate plastic is over 7 million tonnes per year with China producing 60 %. Aside from its low cost at around 2,300 USD/t, polycarbonate has the useful properties transparency, toughness, and low density which make it suitable for use in construction for sheeting, roofing, and glazing, in food contact materials such as drinks bottles, in CDs and DVDs, and use in car headlights and bumpers. Concerns over the endocrine disrupting effects of BPA leaching from polycarbonate bottles have motivated the marketing of "BPA free" bottles, however some of these have simply replaced BPA with other endocrine disrupting bisphenols.

2 Epoxy Resins

Aluminium cans are lined with coatings composed of organic molecules to prevent reaction between the contents and the metal. The most established coatings are bisphenol A-diglycidyl ether (BADGE) epoxy resins which are produced by reacting bisphenol A (BPA) with epichlorohydrin

$$\rightarrow$$

BADGE epoxy resins have become widely used for can linings because they have the useful properties of adhering well to metal surfaces, capable of withstanding the high temperatures at which food and drink may be added to cans or pasteurised, and resistant to corrosion in a variety of food media across wide pH ranges.

Alternatives

BPA and bisphenol A-diglycidyl ether (BADGE) leach from cans into food and beverages.

The growing base of evidence on the toxicity of BPA motivated the approval of a ban on BPA in food contact materials by an EU expert committee in 2024, meanwhile the prevalence of BPA can linings in the USA has fallen dramatically, coinciding with a reduction in exposure. Unfortunately, the transition from BPA has been mired by early false starts due to naïve regrettable substitutions to structurally similar bisphenol substitutes such as BPS, which have been found to have similar toxic effects to BPA. Regrettable substitutions have also been made to other unsafe chemistries such as vinyl coatings made using vinyl chloride, which is associated with liver cancer. Furthermore, unknown compounds in can linings, which may include reaction by-products, cross-linkers and lubricants, also contribute to the toxic contamination of food and beverages.

No perfect solution has yet been found, however Valpure V70, an epoxy coating produced from tetramethyl bisphenol F (TMBF) rather than BPA has been shown not to have the estrogenic effects of BPA, but did show some anti-estrogenic and anti-androgenic effects. Nonetheless, a significant advantage of Valpure V70 is that there is significantly less free monomer in the lining compared with BPA based linings, which means much less is available to leach into beverages. Polyester can linings are also available and are likely to be safer than BPA based linings, but may not be suitable for as wide a range of beverages.

More generally, non-bisphenol alternatives show promise in replacing BPA across its many applications. Bisquiacols show an apparently scalable synthesis route as well as reduced toxicity compared to BPA, as do polycarbonate plastics made from biologically derived resveratrols, however it is likely that more extensive toxicity testing is required before these compounds can be designated as good substitutes. A lower volume use of BPA, but nonetheless one important for human exposure is thermal paper coatings (i.e. receipts) in which BPA can be safely replaced with Vitamin C.

Polybrominated diphenyl ethers (PBDEs)

$$Br_m$$
 Br_n

✓ Safer Substitutes

- Ammonium polyphosphate
- Aluminium hydroxide
- Aluminium diethyl phosphate
- Melamine polyphosphate

X Regrettable Substitutes

- Decabromodiphenyl ethane
- Organophosphate esters

PBDEs

Properties

Forms radicals upon heating Forms char upon heating

Uses

- Flame retardant
- Electronics
- Polymer insulation
- Furniture
- Textiles
- Automotive

Production

PBDEs are a class of 209 congeners which differ from each other by their degree of bromination and the positions of the bromines. They are produced by reacting the toxic gas bromine with diphenyl ether with the ratio of bromine added determining the number of bromine atoms in the PBDE. Diphenyl ether itself is synthesised by reacting phenol with bromobenzene. PBDE production is thought to have peaked in the early 2000s at around 0.09 million tonnes per year, but production has significantly ramped down in recent years due to concerns around their negative health effects and environmental persistence.

PBDEs and some other brominated flame retardants are among the chemicals covered by the Stockholm convention, which requires signatories to reduce pollution from them and eventually phase out their use. Very limited production of DecaBDE for specialised applications continues. Unfortunately, an almost structurally identical compound decabromodiphenyl ethane continues to be produced today, mainly in China. PBDEs themselves remain a health and environmental hazard due to their presence in already manufactured products and the environment.

Uses

PBDEs, along with other brominated flame retardants, work by decomposing to release bromine radicals which then forms hydrogen bromide which quenches radicals generated in a flame. They also have a secondary mechanism of flame retardancy in which they promote the formation of char. The full mechanism is illustrated in the figure below.

The bromine breaks down to form a bromine radical which then reacts with the hydrocarbon to form HBr.

The HBr removes the high energy H and OH radicals by reaction. The high energy radicals are replaced with low energy bromine radicals.

$$HBr + OH \bullet \longrightarrow H_2O + Br \bullet$$

 $HBr + H \bullet \longrightarrow H_2 + Br \bullet$

The HBr consumed is regenerated by reaction with the hydrocarbon.

Bromine is the most effective halogen to use for radical quenching because its bonding to carbon is neither too weak nor too strong and so it is liberated from the hydrocarbon within a temperature range which is well suited for disrupting combustion.

However, it is likely that in many applications brominated flame retardants do more harm than good. Once a large fire starts, they are not powerful enough to extinguish it themselves and a dedicated extinguisher such as a sprinkler system is required. While PBDEs can slow or prevent the spread of flame, this is not the most important metric because the majority of fire deaths are caused by the inhalation of carbon monoxide, hydrogen cyanide, other respiratory irritant gasses and soot, which can be increased by the presence of fire retardants.

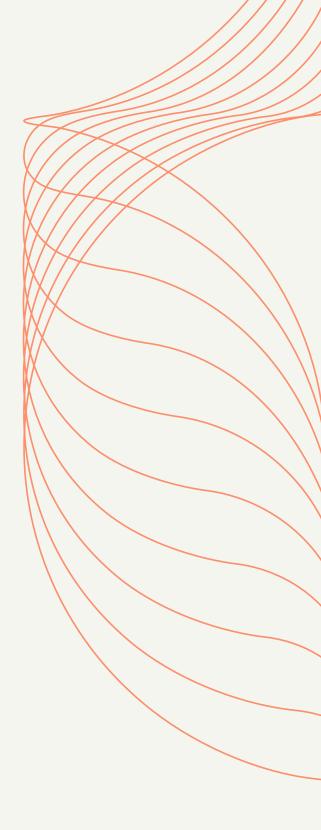


Flame retardants are commonly used because households have become filled with plastic goods and synthetic soft furnishings often made from polyurethane foams which release many toxic gasses, including hydrogen cyanide, when burning.

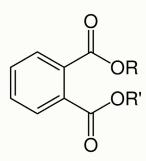
PBDEs were blended into plastics melts, or even bonded to polymer chains for hard plastics used to make electronic goods such as televisions, and coated onto soft plastics such as polyurethane foams.

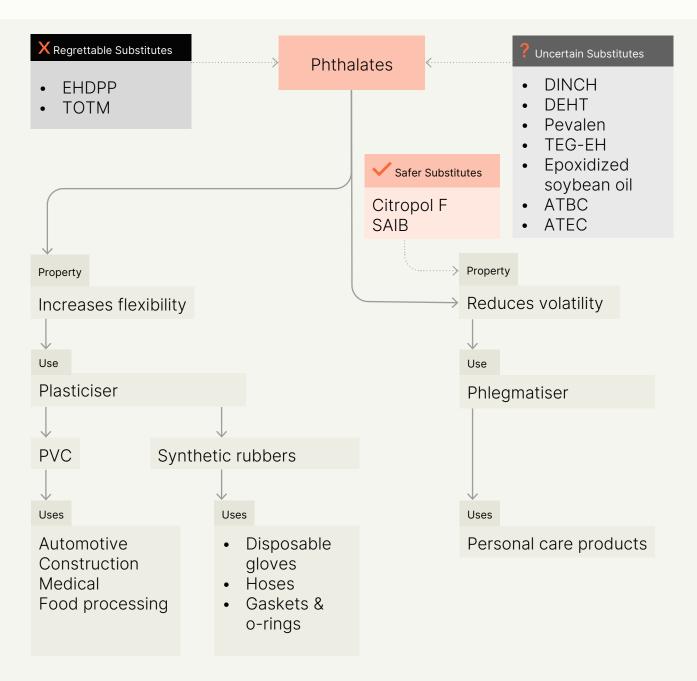
PBDEs are endocrine disruptors, interfering with the reproductive and thyroid systems. This has motivated the use of other safer alternatives with different mechanisms for retarding fire such as aluminium hydroxide, which releases water upon heating in an endothermic decomposition and can even act as a smoke suppressant.

Some companies such as CottonSafe have designed mattresses made only from cotton and wool which are fire retardant by design and produce less toxic smoke than synthetic mattresses treated with fire retardants.



Phthalates





Production

Phthalates are esters of phthalic acid which are produced by reacting phthalic anhydride with alcohols. There are around 30 common phthalates, which vary based on the alcohol used. For example, the reaction to produce diethyl phthalate using ethanol is shown below.

O-xylene itself, like the benzene which ultimately forms BPA and PBDE, is mainly produced by catalytically cracking the naphtha fraction of crude oil. The global annual production volume of phthalates is around 8 million tonnes, with phthalate production increasing despite the proliferation of alternatives, due to the rapidly growing market for PVC.

Use

Plastics

By far the largest use for phthalates is as plasticisers in plastics. Plasticisers are molecules added to polymers to modify their mechanical properties, usually increasing flexibility and softness. Around 90 % of phthalates



are used as plasticisers in PVC, which is very hard and brittle without plasticisers. The mechanical properties of PVC can be easily tailored depending on the percentage composition of the plastic which is made up of phthalates, which can be as high as 86 % by weight in extremely flexible PVC, but is commonly as high as 33 % in flexible PVC. Since phthalates are not chemically bonded to the polymer, they migrate and are released from the plastic over time, resulting in environmental and human exposure. PVC itself is used across a wide variety of applications. Some of the most familiar are for electrical cable sheaths, shower curtains, car parts, water pipes, and construction components such as window frames.

PVC is one of the highest volume produced plastics, with over 51 million tonnes produced per year and making up 11 % of the total global production of plastics.

The exact mechanisms by which plasticizers increase the flexibility and softness of polymer chains are not entirely understood, however it is generally thought that they reduce strength of intermolecular interactions between polymer chains by physically "getting in between" adjacent polymers. For plasticisers to effectively shield adjacent polymer chains from intermolecular interactions without simply generating new and powerful intermolecular attraction between the polymer chains and the plasticizer, they usually medium sized molecules of molecular weights of between 300 to 600 g/mol. This size range allows plasticisers to effectively fit into the spaces between polymer chains. Another requirement for plasticisers is that they are relatively non-volatile so that they do not rapidly degas from the plastic, which means that most plasticizers are high boiling point liquids in their pure states. A common structural property of plasticisers is that they tend to have flexible alkyl chains for example between two and twelve carbon atoms in length.

Phthalates and other plasticizers are added to plastics for a wide variety of reasons. As discussed it is often to tune the flexibility and hardness of the final plastic product to levels

desired for its end use application, however phthalates are also added to make plastic processing easier by reducing the melting point or glass transition temperature as well as viscosity. Phthalates are also added as compatibilizers: molecules which stabilise blends of one or more immiscible polymers. Phthalates are widely found in food, but their presence is sometimes surprising since they have been found to leach from non-PVC polymers like PET, possibly as contaminants. They surprisingly may be present in low concentrations in polyolefins due to their use in catalyst formulations. Phthalates are also used in plastic coated aluminium foils such as those used for disposable dishes and foil packaged foods such as butter. A significant source of phthalates in food is food contact materials in food processing such as plastic tubing, conveyor belts and milking equipment.



A particularly concerning use of phthalate plasticisers is in medicine for blood bags and intravenous tubing, which is particularly concerning as this likely results in high exposure for people who are medically vulnerable, including newly born children.

Alternative Plasticisers

The structural requirements for a molecule to be a good plasticiser appear to be quite broad, and in fact it appears there is nothing particularly special about the structure of phthalates which makes them suitable. Therefore there already exist a large number of commercially available non-phthalate plasticisers replacing phthalates across many applications. But surprisingly, it appears that while some substitutes are safer than the phthalates they are replacing, the commercialised phthalate replacements either have little publicly available toxicity data or exhibit at least some concerning toxicity. A large number of alternative plasticisers are used, with at least four gaining significant market penetration, however as yet there are no commercial alternatives which are rated as "Prefer - Safer Chemical" by GreenScreen for Safer Chemicals.



For phthalate replacements the highest rating so far achieved is merely "Use - but there is still opportunity for improvement" which includes ATBC, DEHT, and epoxidized soybean oil. However, some substitutes which have quite significant market penetration are scored even lower as "Use - but search for safer substitutes." This includes DINCH, which makes up around 10 % of the alternative plasticizers market, and TOTM, which makes up 8 %. An important recommendation is therefore to expand the publicly available toxicity data for alternative plasticisers and continue to develop safer alternatives across the many applications of phthalates.

Personal care products

Perhaps surprisingly, phthalates are also present in many personal care products and cosmetics where they perform functions as fragrance fixatives or "phlegmatizers"; reducing the volatility of fragrance molecules, emollients; moisturising the skin, and solvents; increasing the solubility of components. Since these products are often directly applied to the skin, there is the potential for high exposure. For example, greater use of certain personal care products such as lotions is correlated with higher phthalate metabolite concentration in urine in children. These ingredients also find their way into water systems via municipal sewers, meaning they also have the potential impact aquatic ecosystems. Furthermore, it

is currently difficult for consumers to easily find out which chemicals they are exposing themselves to because mixtures are often concealed beneath an umbrella word such as "fragrance" or "parfum" because these can be protected as trade secrets.

The presence even of phthalates does not need to be disclosed. The Europea

not need to be disclosed. The European Union banned 12 phthalates from being used in personal care products in 2009, however there is no nationwide ban in place in the USA.

Alternatives for personal care products

Many of the alternatives for use in plastics are also used in personal care products, however some phthalate alternatives have been specifically developed for use in personal care products. For example, P2 Science has developed polycitronellols to replace phthalates and silicones as phlegmatizers and emollients. Sucrose acetate isobutyrate (SAIB) is also a non-toxic alternative which is also used as a food additive.



Perhaps overlooked is the fact that phthalates are used in enteric film coatings for drug capsules and tablets. This means they are directly ingested. Enteric film coatings allow capsules to remain intact in the highly acidic stomach but dissolve to release their contents in the less acidic small intestine. Exposure to phthalates from drugs was found to negatively affect sperm motility.



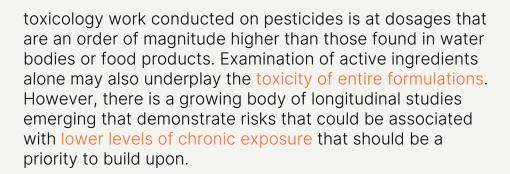
Globally, 3.45 million tonnes of pesticides are used each year, approximately 50% of which are herbicides and the remainder split between insecticides (c. 25%) and fungicides / bactericides (c. 25%).

Historically, pesticide development has been characterised by the demand for broad spectrum active agents that enable comprehensive pest control via simple delivery mechanisms such as powders or sprays. As a result, insecticide use is dominated by classes that target the insect nervous system, including neonicotinoids, organophosphates, pyrethroids and carbamates. Similarly, leading herbicides such as glyphosate 2,4-D and atrazine all disrupt fundamental plant growth processes, while popular fungicides such as azoles and ethylene bis dithiocarbamates (EBDCs) target the disruption of key biochemical processes such as ergosterol biosynthesis and lipid metabolism.



However, the characteristics that have made these classes of pesticide so popular also underlie their negative impacts on humans and the environment. Factors including over-application, water-solubility and residue retention in foods mean that pesticide exposure beyond the field is widespread. This environmental escape and acute toxicity of many pesticides to insects, fish, birds and plants can have catastrophic impacts. In 2020, one or more pesticides were detected above thresholds of concern at 22% of monitoring sites in rivers and lakes across Europe - despite being one of the most tightly regulated regions globally.

The threat this poses is exemplified by one German study that documented a 76% decline in flying insects - which form a cornerstone in many ecosystems - in protected areas over 27 years and identified pesticides as a primary driver. Similarly, there is evidence for the human health risks associated with pesticide exposure via both environmental and dietary routes, including endocrine disruption, genotoxicity, mental health and beyond. Care is needed when extrapolating these risk assessments, as much of the

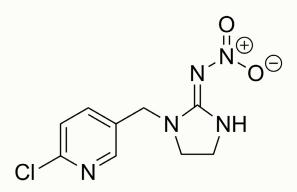


Despite the concerns, efforts to supersede broad spectrum pesticides remain challenging due to a variety of 'lock-in' effects. Even when precise and effective solutions to key pests and diseases have been developed, the use of broad-spectrum inputs is often still observed to mitigate the yield impacts of diverse secondary pests. Reflecting this, global synthetic pesticide use grew approximately 70% over the past 20 years, driven by forces spanning from an explosion in demand in regions such as South America to the development of crops that are tolerant to higher herbicide use.

Different classes of pesticides present specific issues. For example, organophosphates exhibit particularly high acute toxicity and human health risks, while neonicotinoids are more mobile and persistent in the environment. Contrastingly, glyphosate has lower acute toxicity but it remains concerning in part due to the sheer volume used (up to 2kg applied per hectare).

Continued work across pesticide classes will be essential to properly understand the respective risks and opportunities for alternatives, but within the scope of this report we will focus primarily on neonicotinoids as a case study due to their position as one of the most widely used insecticides globally and the extent of evidence for both human and ecological toxicity threats.

Neonicotinoids



Safer Substitutes

- **RNAi-Based Pesticides**
- Peptide-Based Pesticides
- Pheromone-Based Solutions
- GM Bt crops
- Insecticide glues & oils

Neonicotinoids

Water soluble

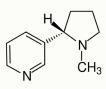
Properties

Acetylcholine receptor binder

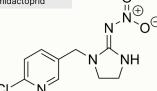
Use

Insecticide





Imidactoprid



Clothianidin

$$\begin{array}{c} O \\ N \\ N \\ O \\ O \\ CI \\ N \\ H \\ H \end{array}$$

Flupyradifurone

Thiactoprid

Sulfoxator

Dinotefuran

Nitenpyram

Neonicotinoids

Neonicotinoids, as their name suggests, are a class of insecticides defined by their relationship to nicotine. The neuroactive effects of nicotine are mirrored by neonicotinoids: nicotine activates nicotinic acetylcholine receptors which are found in the central and peripheral nervous systems of animals, but only in the central nervous systems of insects. Nicotine itself was previously used as a pesticide - killing insects by overstimulating nerve cells.

A key advantage of neonicotinoids is that they are selectively more acutely toxic to insects than mammals because they bind more strongly to insect neuron receptors than those of mammals. Unfortunately, this does not make them non-toxic to mammals. As is detailed in the thriving threats

section, low dose exposure causes disease via endocrine disruption and oxidative stress among others. A common, but not universal, structural feature of neonicotinoids is a pyridine ring, which is present also in nicotine, functionalised with a substituent such as chlorine in the ortho position relative to nitrogen.

Production

Unlike phthalates, neonicotinoids are interrelated as a class by their biological action rather than by chemical structure. Nonetheless, some neonicotinoids share common synthetic feedstocks. For example, one of the largest production volume neonicotinoids - imidacloprid - is synthesised using 2-chloro-5-(chloromethyl)pyridine (CCMP), as on the next page.



CCMP is also used in the synthesis of flupyradifurone, nitenpyram, thiacloprid, and acetamiprid. CCMP itself is synthesised from pyridine or pyridine derivatives. Pyridine, in turn, is most commonly synthesized by reacting acetaldehyde and formaldehyde with ammonia. Acetaldehyde is predominantly produced from ethylene, which is produced from cracking the naphtha fraction of crude oil or from steam reforming ethane, while formaldehyde is produced via the oxidation of methanol, which is predominantly produced from syngas derived from natural gas.

Uses

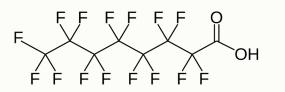
Neonicotinoids are the most widely used insecticides and in 2014 made up 25 % of the global pesticides market. Their high water solubility means they can be easily absorbed by plants and move from roots up into leaves and other plant tissues which makes them more effective at deterring pests. Their high water solubility means they can also be added to water used for irrigation. Neonicotinoids dominate the market for insecticide seed treatments: In the USA in 2011, 80 % of corn, 50 % of cotton, and 40 % of soybean acres were planted with seeds treated with neonicotinoid insecticides. Neonicotinoids are particularly popular also because they are toxic to a broad range of insects and have a perceived low acute toxicity to non-target organisms compared to alternatives such as organophosphates.

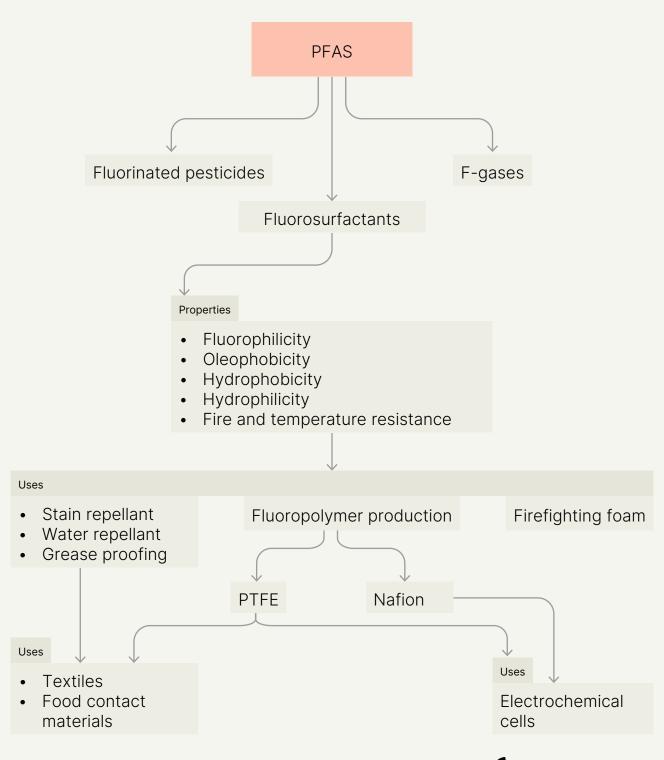
Chief among the hazards of neonicotinoids is off-target toxicity for insects other than pests, including essential pollinators, as well as chronic toxicity to humans exposed via food and water. The high water solubility and relatively long half lives of neonicotinoids, means they are easily transported and can contaminate drinking water sources and have been detected in 30 % of treated water sources in the USA. As discussed in later sections, neonicotinoids cause oxidative stress and are toxic to the reproductive system at low dose levels.

Alternatives

Concern over the toxicity of neonicotinoids has prompted strict regulation, particularly in Europe, and efforts to find safer alternatives. These are discussed in detail in SOTA Between, Exposure Interface and Thriving threat sections.

PFAS - Perfluoroalkyl acids





There are two possible definitions of PFAS: perfluoroalkyl substances and polyfluoroalkyl substances. Perfluoroalkyl substances are those in which all carbon atoms which would be typically bonded to hydrogen are instead bonded to fluorine. Polyfluoroalkyl substances, also known as organofluorines are those in which only some hydrogens are replaced with fluorine. There are over 14,000 unique substances which are categorised as PFAS. PFAS as a whole are such a large class, that this section will focus on one of the most concerning sub-groups of PFAS for toxicity: perfluoroalkyl acids PFAAs, which includes fluorosurfactants. However, to set them in context a brief overview of some of the other categories in PFAS will first be given, all of which pose serious toxicity concerns of their own.

It should be noted that this is still not a comprehensive overview of the categories and uses of PFAS which have found applications in pants and coatings, cosmetics, semiconductor and electronics manufacturing, plastics, and many others.

Fluorinated pesticides

The previous section on neonicotinoids included insecticides which are classed as PFAS because they contain carbon-bonded fluorine atoms. As is discussed in more depth in the section Outcome: Attribution of Toxicity to Companies/ Organisations, many other pesticides such as fungicides are PFAS and are of particular concern not only for their direct toxicity, but the toxicity and environmental persistence of their degradation products.

Fluorinated pharmaceuticals

Perhaps surprisingly, some drugs are fluorinated similarly to pesticides and some can also degrade to release similar persistent fluorinated byproducts.

Examples of fluorinated drugs include anaesthetics, bicalutamide for prostate cancer, fluoxetine (prozac) for depression, sitagliptin for diabetes.

Fluorinated pesticides

The previous section on neonicotinoids included insecticides which are classed as PFAS because they contain carbon-bonded fluorine atoms. As is discussed in more depth in the section Outcome: Attribution of Toxicity to Companies/ Organisations, many other pesticides such as fungicides are PFAS and are of particular concern not only for their direct toxicity, but the toxicity and environmental persistence of their degradation products.



F-gases

F-gases are, as the name suggests, fluorinated gases. These tend to be relatively low molecular weight molecules which are fully or partially fluorinated - i.e. hydrofluorocarbons (HFCs). One of the largest uses of F-gases is as refrigerants in air conditioning systems and heat pumps as replacements for ozone-depleting CFCs. They are also used as blowing agents for the production of polymer foams such as those used in polyurethane mattresses. However, F-gases tend to have very high global warming potentials and, as with PFAS pesticides, degrade to form the persistent toxic chemical trifluoroacetic acid (TFA). Lower global warming potential hydrofluoroolefins (HFOs) unfortunately also degrade to TFA.

Fluorosurfactants

Fluorosurfactants are similar to hydrocarbon surfactants in that they are generally comprised of a hydrophobic body and a hydrophilic head functional group such as sulfonate or carboxyl. The bodies of hydrocarbon surfactants are oleophilic, however the bodies of fluorosurfactants are oleophobic as well as hydrophobic. This is a very special property of PFAS: fluoroalkyl chains experience intermolecular attractions between themselves, but not with water or hydrocarbons.



Production

Since there are many potential structures for fluorosurfactants, there are many possible synthesis routes, however the predominant industrial production methods are electrochemical fluorination and telomerisation.

For example, perfluorinated carboxylic acids like PFOA are formed in the by electrochemical fluorination in the following way: Organic acid chlorides react with hydrofluoric acid to form perfluorinated acid fluorides, which are then hydrolysed to give the perfluorinated acids. Electrochemical fluorination only produces around 10 to 15 % of the desired product, and produces many by-products - principally cyclic perfluoroethers from which the desired is separated by distillation.

Contrariwise, perfluorinated carboxylic acids are produced by telomerization in the following way: Tetrafluoroethylene reacts with a perfluorinated organoiodine compound to five oligomers of varying carbon chain lengths terminated with iodine, which are then oxidised to give the acids. Once again, distillation is required to isolate the acid of the desired chain length from the by-products.

Uses

Fluoropolymer Manufacturing

One of the most important uses of fluorosurfactants is the manufacturing of fluoropolymers. Fluorosurfactants are required in the manufacturing of fluoropolymers such as PTFE. The polymerisation of tetrafluoroethylene to make PTFE is carried out in two ways: dispersion polymerisation and suspension polymerisation. Both techniques rely on the use of surfactants for stabilising small particles of monomer, but these surfactants must be hydrophilic and fluorophilic to stabilise the monomer droplets in water, hence the requirement for fluorosurfactants.

Historically, the fluorosurfactant most commonly used for fluoropolymer production was perfluorooctanoic acid (PFOA), which has largely been phased out of use in Europe and the USA but is still used and manufactured in China Historically and even today, the release industrial wastewater from fluoropolymer production containing fluorosurfactants has resulted in

widespread environmental contamination and consequent human health problems. Fluorosurfactants can also directly expose humans because they remain as residues in PTFE products such as non-stick cookware and are emitted during cooking. Recently there have been process innovations to reduce the concentration of fluorosurfactants remaining in fluoropolymers, however it appears that when heated during cooking, small chain length perfluoroalkyl carboxylic acids resembling fluorosurfactants are emitted due to thermal decomposition of PTFE anyway.

Because the original long chain fluorosurfactants such as PFOA and PFOS were found to be so persistent and harmful to health, companies in Europe and the USA moved to using shorter chain fluorosurfactants for polymerisation. Given their own environmental persistence, these are almost certainly regrettable substitutions.



Textiles

Since the body of fluorosurfactants is both oleophobic and hydrophobic, fluorosurfactants are used as surface coatings capable of a two-in-one waterproofing and stain proofing since oleophobicity means oily foods repelled as well as water. They are often applied to waterproof and greaseproof clothing. Similarly, one of the most famous textile coatings was ScotchGard, which used perfluorooctane sulfonic acid (PFOS) and which was applied to furniture and carpets and was also applied, post-production, by consumers. PFOS was later replaced with a shorter chain alternative: perfluorobutane sulfonic acid (PFBS) because it has a half life of one month in the body compared to 5.4 years. A recent study as well as the experience of textile manufacturers have shown that PFAS textile stain proofing is not particularly effective and their use is therefore likely to be largely unnecessary.



Food Contact Materials

One of the most concerning uses of all of fluorosurfactants is in food contact material coatings, from which they can directly migrate into food. Fluorosurfactants have been used to water and greaseproof food packaging such as microwave popcorn bags and pizza boxes, although they are now being phased out of use in food contact.



Firefighting Foam

Hydrocarbon fires, are best extinguished with aqueous film forming foam (AFFF) fire extinguishers. Fluorosurfactants can lower the surface tension of water more effectively than hydrocarbon surfactants and so have been included as ingredients in AFFF fire extinguishers because they can spread more quickly over the surface of the fuel and thereby deprive the fire of oxygen. Furthermore, they are more chemically stable and less combustible than hydrocarbons, which allows them to continue to work as surfactants for a longer period of time in a fire.

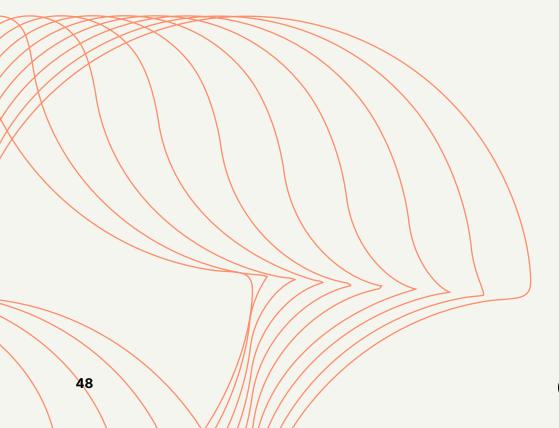
AFFF fire extinguishers are routinely used for drills at airports and military bases, leading to contamination of drinking water supplies. They are also used to extinguish fires in many industrial settings such as oil refineries and oil storage facilities. For example, the largest fire in peacetime Europe at the Buncefield national oil storage facility was extinguished exclusively with AFFF, causing contamination of drinking water. AFFF was also used to extinguish oil fires in Kuwait during the first Gulf War.

Alternatives

Because the original long chain fluorosurfactants such as PFOA and PFOS were found to be so persistent and harmful to health, companies in Europe and the USA moved to using shorter chain fluorosurfactants such as hexafluoropropylene oxide dimer acid also known as GenX. The development of GenX has unfortunately, but unsurprisingly, turned out to be a regrettable substitution and has once again lead to serious water pollution and many detrimental health effects similar to those of the initial fluorosurfactants.

Overall, as with PFAS in general, it appears that the use of fluorosurfactants is not as essential to as many of their applications as was previously thought. For example, textile waterproofing can be achieved with hydrocarbon based formulations such as Nikwax, and there is now a reformulated ScotchGard without PFAS. Similarly, Fluorosurfactant free AFFF fire extinguishers are now being produced by a number of companies, claiming equivalent performance achieved via reformulation. Although often marketed as essential, fluorosurfactants appear to be sometimes unnecessary, and in many cases more of a "nice to have" performance enhancer.

PFAS free greaseproof papers have recently been developed by changing the paper manufacturing process to increase the density and decrease the porosity of the surface which stops grease and foodstuffs from sticking to the paper.





How do toxic chemicals move from their sources to the interfaces of exposure?

In this section we highlight the three exposure interfaces through which the majority of human end ecosystem exposure to toxic chemicals occurs.

Exposure Interface: Drinking Water

Description

Drinking water encompasses the formal (for example, accessed through municipal water systems) and informal (for example, collected from rivers) sources of freshwater ingested by human populations.



Chemical contamination of drinking water originates primarily from industrial and municipal discharges, agricultural runoff, and household waste. It introduces a wide range of harmful substances, including heavy metals, pesticides, pharmaceuticals, and nutrients, into freshwater systems. These substances pose significant risks to human and ecosystem health, the exact nature of which varies according to differences in industrial and agricultural activities, regulations, and capacity for water treatment between regions.

Key Conclusions

There remain large global disparities in the pollutant burden in drinking water between developed and developing countries. In developed countries, conventional water pollutants are relatively well addressed by municipal and industrial water-treatment systems. However, concerns remain in the capacity to monitor and remove emerging, persistent water pollutants to the standard mandated by recent regulations such as the EPA's National Drinking Water Standard. In developing countries, both emerging and conventional water pollutants are of high concern, and resourcing for water treatment remains inadequate in addressing either. Of particular concern are household wells, which often exempt from water quality standards and highly vulnerable to contamination.

Current and Future Progress

Innovations in water treatment, non-point source and remote monitoring of pollutant sources, and updated regulatory frameworks are all essential in preventing and remediating water pollution. Technologies such as advanced oxidation processes, bioremediation, and membrane filtration show promise in addressing emerging, persistent pollutants. However, these technologies will not be sufficient without concurrent commitments to sustainable practices across agriculture, industry, and waste management. Progress across both technologies and sustainable practises could be driven by regulations that more comprehensively address non-point sources of pollution and emerging pollutants such as PFAS and PPCPs.



Exposure Interface: Atmospheric and Indoor Air

Description

Atmospheric and Indoor Air refers to the air to which human populations are exposed to and breathe. It encompasses urban air, rural air, and indoor air, all of which have distinct pollution characteristics and challenges.



Air pollution originates primarily from industrial emissions, vehicular exhaust, agricultural activities, and residential sources like burning fuels for cooking or heating. It introduces a wide range of harmful pollutants, including particulate matter (PM), nitrogen oxides (NOx), sulfur dioxide (SO $_2$), ozone (O $_3$), volatile organic compounds (VOCs), and greenhouse gases. These substances pose significant risks to human health - particularly respiratory and cardiovascular systems - as well as to ecosystems. The severity and type of air pollution in a given region depends on the interactions between industrialization, urbanization, regulations, and air-quality monitoring capacity.

Key Conclusions

Air pollution is a pervasive concern in both developed and developing nations. In both cases, key threats to human health are particulate matter and photochemical smog (a type of air pollution formed when sunlight reacts with nitrogen oxides (NOx) and volatile organic compounds (VOCs) in the atmosphere, producing ground-level ozone and other harmful secondary pollutants). Air pollutants also have compounding influences on local and global climate. While the effects of air pollution on human health are relatively well constrained and regulated against, weak monitoring and enforcement in both developed and developing nations means that > 90% of the global population is currently exposed to air pollution exceeding WHO guidelines. Hazardous air pollutants (HAPs) such as ethylene oxide and benzene are a particular health concern for people living close to petrochemical plants. So called fenceline communities experience higher disease burdens and exposure.

Current and Future Progress

Advancements in emission-control technologies, compliance with stricter regulatory frameworks, and international cooperation to address transboundary threats are all essential in mitigating air pollution. Innovations such as catalytic converters, low-emission fuels, and air-filtration systems show promise in reducing harmful emissions. However, implementation of these technologies requires more concrete commitments to emissions control across transportation, energy production, and waste management. In developed nations, progress in addressing urban air pollution is limited because relatively stringent air-quality targets are not adhered to in the absence of high-resolution monitoring systems. In developing nations, air quality targets are more disparate and are often hindered not only by monitoring capabilities but by unregulated practises such as biomass and plastic waste burning.



Exposure Interface: Food (agricultural products/natural stocks)

Description

Food (agricultural products/natural stocks) encompasses the diverse foods that human populations ingest, including from agricultural sources, natural foraging, and artificial processing and production. These can introduce a variety of harmful chemicals, either intentionally or inadvertently, into the human diet.



Human populations are commonly exposed to toxicity in food through the additives and residues that are introduced at multiple points within the food supply chain. These include pesticides (commonly present in food as residual residues), food contact materials migrants (such as plasticisers and heavy metals), and intentional additives (such as preservatives, colourants, or flavour enhancers). Acute and chronic exposure to such chemicals is associated with health risks including endocrine disruption, carcinogenicity, and immune and neurological degeneration. Exposure levels and associated risks vary between (sub-)populations as a function of dietary consumption, agricultural practises, and regulatory frameworks.

Key Conclusions

There are widespread attempts to address the ingestion of harmful chemicals in food through regulation, but conventional frameworks - based on 'safe' exposure limits - are frequently inadequate in protecting against chronic, low-level exposure which an emerging scientific evidence suggests causes harm to human health. This problem is further exacerbated by systematic flaws within regulatory systems, such as those that allow food additives to bypass safety designation (e.g. GRAS regulation by the FDA), or those that influence agricultural practises through voluntary compliance (e.g. the Basel Convention). Food processing equipment is a major source of toxic chemical and is often overlooked relative to food packaging in this regard.

Current and Future Progress

Efforts to mitigate chemical exposure through food include stricter regulatory standards, improved testing methodologies, and the promotion of responsible agricultural practices. Innovations such as precision farming to reduce pesticide use are promising technological solutions, but have yet to achieve scale. The trend towards biodegradable food packaging could reduce the emission of persistent microplastics, but will likely not decrease the immediate toxic burden unless safer additives are used. Developed nations face challenges in updating regulations to address cumulative and low-level risks, while developing nations often struggle with insufficient infrastructure to enforce even the current standard of regulations. Long-term solutions rely on scaling of safer alternatives for food production and preservation, implementation of responsible agricultural practises, and revision of conventional regulatory frameworks to account for chronic exposure risks.



How does exposure to toxicity harm human and planetary thriving?

In this section we highlight key physiological mechanisms through which toxic chemicals threaten human and ecosystem health.

The thriving threats explored in the following pages are selected from our broader analysis to illustrate the approach applied throughout the toxicity knowledge graph. They emphasise critical physiological pathways and systemic risks, including oxidative stress-induced threats such as infertility, cancer, neurodegeneration, and cardiotoxicity. We also explore the acute ecological impacts of pesticide toxicity on non-target insect populations and the widespread effects of endocrine disruptors on reproductive and developmental health.

Each section outlines the pathways linking exposure to specific health or ecological outcomes, supported by data from large-scale studies and model systems. To define the relevant ontology:



Mechanism of toxicity

The biochemical and biological process(es) by which toxic chemicals cause harm.



Effector System

Physiological entity or process necessary for the proper functioning of an organism.



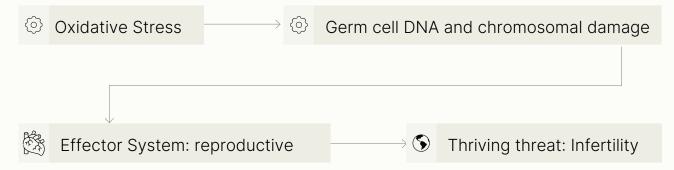
Thriving threat

The undesired effect of pollution on human and planetary thriving.

For each selected thriving threats, we include supporting evidence in two principal categories. Firstly, we reference exemplar studies which analyse correlations between a specific thriving threat and toxic chemical exposures in Humans. Secondly, we demonstrate apparent causality between toxic chemical classes and the thriving threat of interest by highlighting experimentally controlled exposure studies conducted in animals or on human cells *in vitro*.

1 Oxidative Stress (OS)

1a OS-induced DNA Damage and Infertility



Description

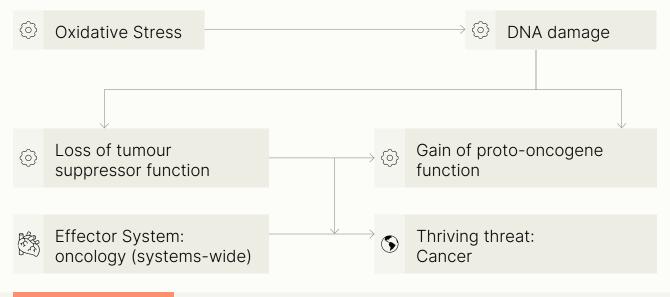
Oxidative stress is an imbalance between free radicals and antioxidants where free radicals overpower antioxidants and the excess free radicals cause harm to cells. Oxidative stress (OS)-induced DNA damage is a critical factor influencing both reproductive health and cancer development, with far-reaching implications for public health and environmental safety. Mechanistically, OS causes DNA strand breaks, structural distortions, and chromosomal aberrations, while also impairing DNA repair pathways, leading to the accumulation of mutations. In fertility, these effects manifest as reduced sperm count, motility, and viability, as well as chromosomal damage in oocytes (egg cells), resulting in lower fertilization rates, early embryonic loss, and increased risk of genetic defects in offspring.

Key evidence

Findings from NHANES data show elevated urinary arsenic and cadmium levels in women correlate with significantly higher infertility risk, demonstrating a dose-dependent relationship. Another study on PFAS exposure in a Singaporean cohort linked higher plasma levels of PFOS and PFOA to decreased odds of clinical pregnancy, and lower live birth rates. Animal model studies provide causal insights; for example, arsenic exposure in male mice induces ROS generation, mitochondrial dysfunction, and DNA strand breaks, impairing sperm quality and fertility. Prenatal and postnatal exposure to microplastics in mice disrupts meiotic

processes and reproductive (germ) cell development via oxidative stress, leading to reduced fertility. These observations extend to other toxic chemicals such as pesticides too. For example, human exposure to pesticides significantly correlates with decreased sperm count and animal model data proves the direct effect of pesticide exposure on germ cell viability. Together, this underscores oxidative stress as a critical mechanism linking toxic chemicals to infertility.

1b OS-induced DNA Damage and Cancer



Description

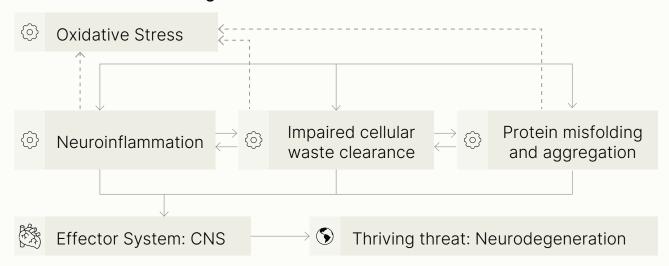
OS contributes to cancer by disrupting the balance between proto-oncogenes, genes that normally promote controlled cell growth, and tumor suppressors, genes which act as brakes on unchecked division. When proto-oncogenes become overactive or tumor suppressors are inactivated by mutation, cells grow uncontrollably, leading to cancer. Environmental agents, including heavy metals, PFAS, pesticides, and microplastics damage DNA via OS, increasing the risk of oncogenic mutations.

Key evidence

Environmental exposures are increasingly recognised as significant contributors to cancer risk. Correlational studies have linked pesticide use, microplastics, heavy metals, and perfluoroalkyl substances (PFAS) to heightened cancer risks across diverse populations. In the U.S., county-level analyses have revealed strong positive correlations between pesticide usage and risks of cancers such as non-Hodgkin's lymphoma, bladder, lung, and pancreatic cancer. Similarly, increased lung cancer risk has been documented in pesticide-exposed workers in Korea. Heavy metal exposure, particularly arsenic and zinc, is associated with prostate cancer, and integrated heavy metal exposure correlates with higher DNA damage burdens in human tumors. PFAS exposure is also a significant concern, with studies showing a 56% increase in thyroid cancer risk per doubling of serum levels and elevated hepatocellular carcinoma risk in a multiethnic cohort.

Causal evidence provides deeper insight into mechanisms driving these associations. PFAS exposure, for example, reprograms the epigenetic landscape of human breast cells into a pro-proliferative and oncogenic state. In animal models, cadmium exposure exacerbates breast cancer progression and induces malignant transformations in bronchial epithelial cells through ROS, ERK, and AKT signaling pathways. Microplastics have shown concerning results, with polystyrene nanoparticles accelerating ovarian cancer development in mice.

1c OS-induced Neurodegeneration



Description

Neurodegeneration is driven by oxidative stress, protein misfolding, impaired autophagy (clearance of cellular waste), and chronic inflammation. Protein misfolding disrupts cellular functions and impaired autophagy leads to accumulation of toxic waste. Chronic inflammation further damages neurons, compromising CNS integrity. These mechanisms underlie Alzheimer's Disease (AD) and Parkinson's Disease (PD). In AD, OS and impaired autophagy drive accumulation of amyloid-beta and tau aggregates, leading to disrupted neuronal communication and synaptic dysfunction. In PD, OS damages dopaminergic neurons, while alpha-synuclein aggregates form toxic Lewy bodies. Chronic inflammation exacerbates neuronal loss in both diseases, driving cognitive and motor impairments.

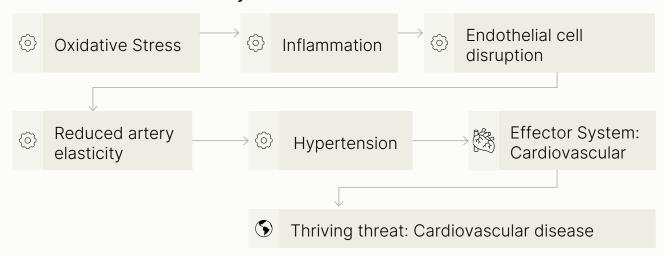
Key evidence

Emerging research highlights the critical role of environmental exposures in driving Parkinson's disease (PD) and Alzheimer's disease (AD). For PD, correlational studies identify over 50 pesticides which significantly increase disease risk, with 18 of the 25 most highly implicated pesticides still actively registered by the EPA. Experimental evidence establishes causality, showing pesticide exposure at environmental concentrations induces dopaminergic neuronal death, the hallmark of PD. Furthermore, individuals with genetic mutations in antioxidant-

related genes are at higher PD risk when exposed to pesticides, This suggests pesticide-induced oxidative stress is a key mechanism driving dopaminergic neurodegeneration. For AD, environmental toxic chemicals, including heavy metals, are increasingly implicated in disease progression. Biomarkers of AD have been shown to rise significantly in patients with higher concentrations of heavy metals, suggesting a direct link between environmental exposure and the development of the disease. Correlational studies also identify a strong positive relationship between pesticide exposure and AD risk.



1d OS-induced Cardiotoxicity



Description

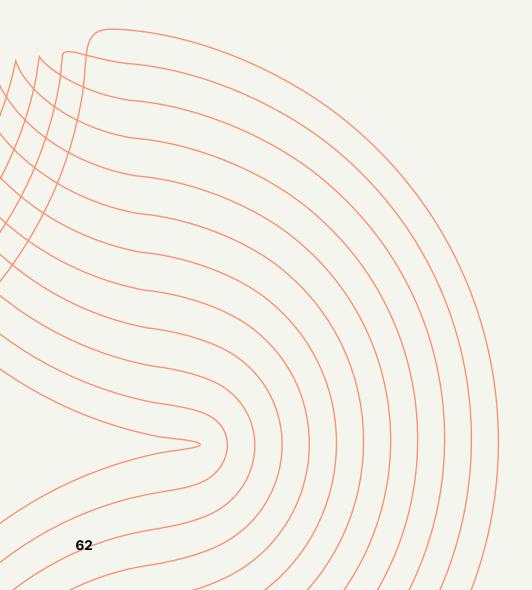
Cardiotoxicity entails dysfunction of endothelial cells which line artery walls, reduced arterial elasticity and subsequent hypertension (high blood pressure), atherosclerosis, and cardiovascular events e.g. heart attacks or strokes. Reactive oxygen species initiate this cascade, causing inflammation which damages endothelial cells. Endothelial dysfunction impairs the blood vessels' ability to regulate flow, marked by decreased production of nitric oxide (a vasodilator that relaxes vessels). This leads to stiffening of arterial walls and increased blood pressure, often culminating in heart attacks, strokes, and other severe outcomes. Contributing factors such as oxidised LDL cholesterol, a product of oxidative stress, can worsen inflammation and vascular injury.

Key evidence

Environmental exposures, including pesticides, heavy metals, and microplastics, are increasingly linked to cardiovascular disease (CVD) through both correlational and causal evidence. Longitudinal studies in occupationally exposed populations, such as Japanese-American workers, show a significant increase in CVD risk associated with pesticide exposure. Retrospective studies further link elevated serum levels of organochlorine pesticides with higher cardiovascular event rates.

Heavy metals, particularly cadmium, exhibit strong positive correlations with CVD risk, while emerging research highlights the potential role of microplastics in cardiovascular pathology. A multicenter study found that patients with micro and nanoplastics (MNPs) in carotid artery plaques had a significantly higher risk of myocardial infarction, stroke, or death compared to those without MNPs, underscoring the potential clinical impact of these emerging pollutants.

Causal evidence supports these correlations, revealing the mechanistic pathways through which these exposures contribute to cardiovascular disease. For instance, rotenone exposure induces oxidative stress and autophagic dysfunction in human cardiomyocytes, while organophosphate pesticides cause oxidative damage and cardiac hypertrophy in animal models. Microplastics have also been shown to induce cardiotoxicity in human and mouse organoids, further implicating their role in cardiovascular health risks.



2 Acute Pesticide Toxicity (off-target insect toxicity) Carbamate/ Organochlorine **Pyrethroid** Neonicotinoid Organophosphate Inhibition Overstimulation **ACh** Activation of of GABA- \Rightarrow 0 Voltage-gated \Rightarrow 0→ ⟨ˆ⟩ of nicotinic ACh esterase gated CI receptors inhibition Na channels Channels Neuronal Cholinergic crisis \rightarrow \bigcirc CNS effects hyperexcitability Acute toxicity to pollinators and **(\$) Chronic toxicity** loss of biodiversity (humans and animals) Primarily mediated by oxidative stress. See previous thriving threats.

Description

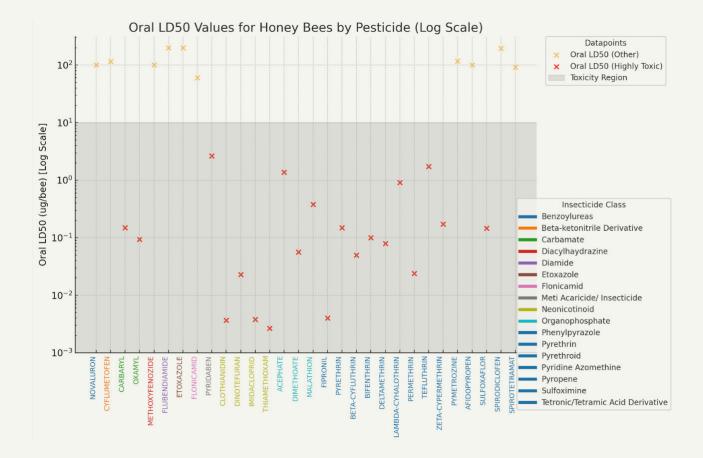
Neonicotinoids, designed to overstimulate nicotinic acetylcholine receptors (nAChRs) in target pests, indiscriminately affect non-target insects by causing excessive nerve signaling. This leads to a cholinergic crisis, a condition of prolonged and uncontrolled neuronal activity, resulting in disorientation, paralysis, and eventual death in beneficial species like bees and butterflies. Similarly, carbamates and organophosphates, which inhibit acetylcholinesterase (AChE) - the enzyme that degrades acetylcholine - prolong nerve signaling in pollinators, further inducing neuronal hyperexcitability and disrupting normal nervous system function. These mechanisms, though intended to protect crops, directly harm non-target insect populations that are essential for pollination and ecosystem balance.

Organochlorines and pyrethroids introduce additional risks to non-target species by targeting different aspects of the insect nervous system. Organochlorines and some pyrethroids cause overactivation of voltage-gated sodium channels, leading to persistent neuronal firing and hyperactivity. Meanwhile, pyrethroids also inhibit GABA-gated chloride channels, reducing inhibitory signals in the central nervous system (CNS) and further amplifying neuronal hyperexcitability. These toxic effects, compounded by their widespread and indiscriminate application, contribute to the decline of critical pollinator populations, with cascading effects on plant reproduction, food security, and ecological stability.



Evidence for off-target pesticide toxicity (acute)

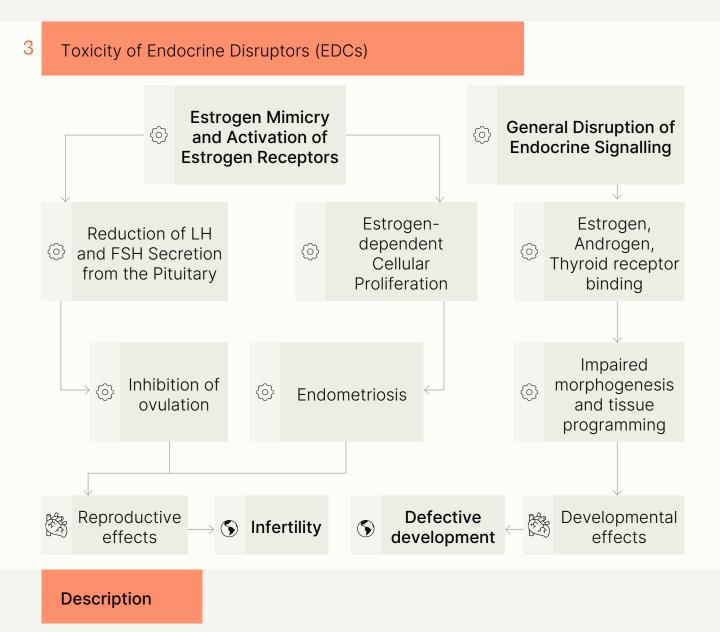
Pesticides, including neonicotinoids, carbamates, organophosphates, organochlorines, and pyrethroids, pose significant risks to non-target insects through mechanisms that lead to acute and often lethal toxicity. As an exemplar, focusing on Honey Bees, the below graph shows LD50 values (concentration required to kill 50% of a target population) for numerous pesticides. The majority of these pesticides have an LD50 value sufficiently low to be considered 'Highly toxic', according to the EPA.



Oral LD50 values for a range of pesticides with respect to Honey Bees (ug/bee, log scale). Values below 10ug (10^1 ug)/bee indicate significant toxicity. Values below 2ug (10^0.3)/bee indicate high toxicity. Data obtained from Minnesota Department of Agriculture.

The ecological impact of acute pesticide toxicity is profound. Indeed, pesticides are a significant driver of wild bee population declines, particularly in regions with intensive agricultural activity. For instance, research across the United States suggests high pesticide use contributes to a 43.3% decrease in site occupancy for certain bee families, such as Apidae (bumblebees), which are critical for pollination in both natural ecosystems and agriculture. It is also worth noting the sublethal toxic effects of pesticides on pollinator populations. For example, chronic exposures are associated with reduced colony weight, loss of foraging behaviour and suppressed egg laying in bees.





Endocrine disrupting chemicals (EDCs) are exogenous chemicals which interfere with any aspect of hormone action. The best studied pathways are estrogen, androgen and thyroid, however there is increasing research into several other endocrine pathways which can be disrupted by EDCs. Estrogen mimics can reduce LH and FSH hormone secretion, inhibiting ovulation and causing contraceptive effects. Additionally, EDCs promote estrogen-dependent cellular proliferation which can cause endometriosis. Developmental pathways are also disrupted by EDCs e.g. tissue differentiation and organ morphogenesis. This can result in congenital malformations, miscarriages and neurodevelopmental issues.

Key evidence

Human studies link EDCs such as bisphenol A (BPA), phthalates, and flame retardants to developmental defects and reproductive health issues. Epidemiological research shows prenatal exposure to polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) correlates with neurodevelopmental delay and altered thyroid function, which is critical for fetal development. Phthalates, for example, are associated with reduced thyroid hormone levels and decreased anogenital distance (AGD) in male infants, a marker for later reproductive disorders. Additionally, higher BPA levels in women correlates with lower ovarian reserves and infertility risks, whilst exposure to flame retardants and PFAS reduces IVF success rates, with fewer eggs retrieved and lower live birth outcomes.

Evidencing causality, exposure to BPA and phthalates disrupts fetal testicular development, reduces AGD, and causes urogenital abnormalities in rodents. BPA-treated animals exhibit impaired ovulation due to hormonal dysregulation. Experimental models also link BPA to estrogen receptor-driven endometriosis, where exposure promotes ectopic endometrial growth and inflammation.





Owing to the complexity in scoping the science, research, and technology across the entire toxicity landscape, we have broken down the state of the art research occuring in startups and companies of all sizes according to which nodes in the knowledge graph they are most relevant.

We begin by describing the state of the art (SOTA) around the Use: Personal care products, followed by the Exposure interfaces: Drinking water, Atmospheric and indoor air, and Food with a deepdive within food into pesticides. The final section explores the SOTA research which applies between exposure interfaces and thriving threats. A table summarising key companies working on toxicity, technologies, R&D organisations, etc. can be found in the Appendix.

Key features of the current competitive landscape

The number of synthetic chemicals in personal care products and cosmetics is vast, and accordingly there is innovation across the majority of these, particularly the classes of plastic packaging, silicones, fragrances, preservatives, surfactants, colourants, solvents, surfactants, antimicrobials, UV absorbers, and insect repellents.

In general, it appears that the majority of the innovation is being undertaken by startups and small to medium sized businesses. For example, medium sized businesses such as Green People, Dime, and Attitude offer full ranges of safer personal care products and cosmetics, and generally market their products to ethically aware consumers and therefore these products tend to be vegan, organic, and animal cruelty free.

The Environmental Working Group is a very important player in this area, since it operates the most useful consumer information resource: The EWG Skin Deep Database, which rates personal care products based on the transparency and safety of their

ingredients lists and offers EWG VERIFIED status to companies who apply, provide the necessary information on product ingredients and substantiation and meet the EWG's safety criteria.

There is a trend towards greater ingredient transparency in the sector with resources other than skin deep such as Smart Label, Cosmethics, and Clearya allowing consumers to better inform themselves.

A hotspot for important innovation is the creation of safe organic UV-absorbers, of which there is a currently a dearth of safe commercial options. The safe absorbers: titanium dioxide and zinc oxide, can leave residues behind and so are not always preferred by consumers. However, interesting new approaches are being taken such as producing melanin via fermentation. making mycosporine-like amino acids (which naturally protect microbes from UV damage) using cyanobacteria, and synthesising new peptide based UV-absorbers.

Opportunities for innovation

Low cost safe product lines

Today, the majority of safer products charge a premium, which may be part of the reason people on lower incomes have higher exposures to toxic chemicals. Part of this premium potentially comes from "nice to have" marketing properties such as ingredients being plant derived. However, it may be the case that cheaper synthetic chemicals can be used in personal care products which are just as low in hazard.



Non-toxic packaging

Most of the new packaging products in this area focus on degradability, and there is less effort directed towards creating packaging which does not contaminate the products themselves with toxic chemicals which could be absorbed by the consumer.

Critical gaps in current research



As is mentioned in the sub-section on phthalates in the Key Nodes: Pollutants section, there is a surprisingly large gap in data on safe fragrance fixatives (a.k.a phlegmatizers) and fragrance solvents, with few options available to replace phthalates for which there are full toxicology data. This is likely not helped by the general lack of transparency in the fragrance industry.



More research is also required to elucidate which compounds are being used in fragrances to provide the fragrance itself. It is unlikely that all fragrances currently provided by synthetic molecules can be replaced with safe, natural alternatives and so the development of safe synthetic fragrances molecules with full toxicological testing is essential.



Rapid antimicrobial efficacy screening

A major constraint holding back the introduction to market of safer antimicrobials is the fact that they perform differently in different products because they may be inactivated at particular pHs or by interactions with other ingredients in the formulation. This means new antimicrobials must be tested for each individual product before they can be used. One way to speed up the adoption of safer antimicrobials would be to speed up the process of testing, which is currently done by challenge testing in which products are inoculated with bacteria, mould and yeast in petri dishes and observed for property changes with assays of microorganism populations taken at time intervals. Manufacturers are beginning to automate this process for higher throughput, and it might be possible to significantly accelerate the process by combining robotic test protocols with real time sensors to measure proxies of microbial growth such as oxygen consumption, rather than traditional colony counting.



Increasing the potency of natural antimicrobials

Another reason for the lack of safe antimicrobials is that natural products tend to have a lower potency and so have to be used at higher concentrations which increases cost, can cause issues such as phase separation in formulations, and can result in changes to smell. Several simple chemical functionalization strategies can be used to decrease the required concentrations of several classes of natural antimicrobials.

Key features of the current competitive landscape

Diverse Technological Approaches

A diversity of technologies are currently being employed, from biological treatments (Aquacycl, BioFiltro) to advanced physical-chemical processes (Revive Environmental, Aclarity) and smart monitoring systems (KETOS, CertusBio). These technologies are often pollutant- or application-specific.

Focus on Energy Efficiency and Sustainability

Many companies are emphasizing the energy efficiency of their solutions (e.g., Swirltex, Aquacycl) or the use of renewable energy sources (e.g., Oneka Technologies). This trend aligns with growing concerns about the energy intensity of water treatment processes.

Emerging Contaminants

There is an increasing focus on addressing emerging contaminants, particularly PFAS (e.g., Aclarity, Enspired Solutions, Puraffinity).

Decentralized and On-Site Solutions

Many companies are now offering decentralized or on-site treatment solutions (e.g., Epic Cleantec, Indra Water).

Integration with Existing Infrastructure

Some technologies, like Enspired Solutions' PFAS treatment, are designed to integrate with existing water treatment systems.

Circular Economy and Resource Recovery

Several companies (e.g., WASE, Gross-Wen Technologies) are not just treating water but also recovering valuable resources from the process, such as energy or fertilizers.

Opportunities for innovation

Emerging Contaminants

Technologies - perhaps most importantly bioremediation - could be extended or redeveloped to effectively treat emerging contaminants that have a high degree of neglect relative to PFAS (for example, PPCPs). A priority is pollutants whose persistence means that regulating against usage would not lead to significant reductions in concentration in drinking water; perhaps most importantly PCBs.

Sustainable and Biodegradable Treatment Materials

Current technologies often use materials that can lead to secondary contamination or disposal issues. Opportunity may exist in the development of materials for water treatment that do not create secondary waste streams (e.g. sludge, which is being phased out of use as fertiliser due to toxicity concerns), or in the development of solutions that combine engineered systems with natural processes (e.g., constructed wetlands enhanced with advanced materials).

Integrated Multi-Contaminant Solutions

Most current solutions focus on specific contaminant types. Opportunities may exist in technologies that can simultaneously address multiple types of pollutants, including emerging contaminants like PFAS and other POPs.

Modular and Scalable Solutions

Many current technologies are too complex or expensive for widespread adoption, especially in resource-limited settings or at incumbent water-treatment facilities. Opportunity may exist in the development of scalable solutions that can be integrated or deployed with modularity.

Critical gaps in current research



Emerging Contaminants such as Microplastics, POPs, and Pharmaceuticals and Personal Care Products (PPCPs)

Human Health Effects

Research into the long-term effects of exposure to microplastics, persistent organic pollutants (POPs), and pharmaceuticals and personal care products (PPCPs) remains inconclusive. For example, microplastics have been shown to induce oxidative stress, inflammation, and DNA damage, potentially leading to chronic health issues, but most studies focus on short-term effects or high concentrations, leaving gaps about low-level, prolonged exposure impacts.

Ecosystem Impact

Synthetic hormones, like ethinylestradiol from contraceptives, have demonstrated severe effects on aquatic species, such as feminization in fish. However, the broader ecological consequences, including food web impacts and population dynamics, remain understudied.



Water Treatment and Reuse

Treatment Technologies

Existing methods struggle to remove microplastics, PPCPs, and POPs effectively from water. Advanced treatment methods, such as membrane bioreactors and advanced oxidation processes, show promise but require further optimization to balance cost and efficiency.

Aging Infrastructure

There is limited research on how water quality evolves during distribution in aging systems, especially regarding microbial growth and chemical interactions. This knowledge gap is critical for ensuring safe water delivery.



Complex Interactions in the Environment

Groundwater-Surface Water Coupling

The interaction between surface water and groundwater under pollution stress is poorly understood, particularly in how pollutants transfer between these systems over time

Pollutant Interactions

The synergistic or antagonistic effects of multiple contaminants in aquatic ecosystems, such as the combined toxicity of metals and PPCPs, remain underexplored.



Monitoring and Detection Methods

Real-Time Monitoring

Affordable, real-time monitoring tools for contaminants are scarce, especially in resource-limited settings. This produces a global disparity in the availability of comprehensive water quality data.

Source Tracking

Current techniques inadequately pinpoint pollutant sources in watersheds with mixed anthropogenic inputs, complicating mitigation strategies.

Advanced Technologies

While satellite imagery and GIS have potential for large-scale water quality assessment, their integration into routine monitoring programs is still limited.

Key features of the current competitive landscape

Emphasis on compliance

In emission-prevention, most technologies address the pollution-control standards required to comply with air-quality regulation in specific industrial applications. This has precipitated advancements in selective catalytic reduction (SCR) and ultra-low NOx burners for NOx emissions, and scrubbers for SO2 control.

Emerging advancements in monitoring through sensor networks

Cloud-based platforms and IoT frameworks are increasingly being used to link networks of sensors such as LiDAR, Open-Path Fourier Transform Infrared (OP-FTIR) sensors, and Miniature Continuous Emission Monitoring Systems (Mini-CEMSs). This is enabling a transition towards automated rather than manual pollution control, most often in industrial applications (e.g. Aeromon, Aclima, Aeroqal).

Indoor air remediation focussed on pathogens

Multiple companies are offering filtration or absorption/adsorption solutions to improve indoor air quality through small modular devices suitable for single consumer- to building-scale use. The focus of these technologies is predominantly on pathogen removal (e.g. Mila Cares, Molekule), with very few capable of addressing non-pathogenic pollutants like VOCs and PM.

Urban air pollution focussed on individual protection

Most technologies offering protection from urban air pollution are wearables suitable for an individual consumer (e.g. BeNosy, Shellios, Nirvana Being, Resprana). There are very few technologies attempting to remove pollution from urban air at scales relevant to whole populations.

Opportunities for innovation

Integrating disparate air-quality data sources

There are a proliferation of companies offering low-cost sensors (LCS) to monitor indoor and outdoor air quality, but the utility of LCS data is currently hindered by the challenges of integration with conventional (e.g. remotesensing) datasets. If LCS data can be validated and coordinated with conventional air-quality data, it may create the opportunity for powerful, actionable insights at greater resolution and scale than is currently available through either LCS or remote-sensing alone.



Air remediation

Very few companies are attempting to improve either indoor or urban air quality by directly removing non-pathogenic pollutants from air. Developing scalable urban air purifiers that could be deployed across extensive city areas, or that address non-pathogenic pollutants in indoor air, would offer the opportunity to significantly reduce human exposure to toxicity in these environments. Bioremediation and biofiltration may be particularly promising emerging technologies for this purpose.



Low cost fire-safe non-toxic textiles

Inhalation of household dust is a major source of exposure to fire retardants from furniture. As mentioned in the Key Nodes: Pollutants section, alternatives to polyurethane foams for furniture can be produced with no need for fire retardants from natural materials. However, these are currently expensive. Methods for achieving greater scale and lower cost could accelerate adoption.

Critical gaps in current research

Emission Inventories

Diffuse Source Uncertainties

Diffuse sources such as agriculture, wood burning, and non-methane organic gases (NMOGs) contribute to significant uncertainties in emission inventories. Improving methodologies for quantifying these emissions, particularly integrating local emissions into broader inventories, is critical. For example, studies highlight variability in ammonia emissions from agriculture, which account for over 80% of emissions from this sector in Europe, as a key area requiring better data accuracy.

Source Apportionment Models

The development of models capable of resolving high temporal resolution emission data, especially in urban settings, remains a challenge. Enhanced resolution in these models is crucial for understanding short-term pollution events and formulating local mitigation strategies.

High spatial- and temporal-scale monitoring/modeling/prediction of air quality

Low-Cost Sensors

The proliferation of low-cost air quality sensors (LCS) offers an opportunity to access high-resolution air-quality data, but the varying accuracy and reliability of LCS necessitates the development of protocols to validate these data and integrate them into official monitoring systems.

Climate-Pollution Interaction

Interactions between pollution, meteorology, and climate significantly affect urban air quality. Research addressing how changing climate patterns may exacerbate air pollution levels and influence public health outcomes - such as through integrated earth-system modelling - is crucial.



Indoor Air Quality

Indoor pollution sources, especially non-combustion emissions like volatile organic compounds (VOCs) from household products, remain under-studied. These contribute significantly to total exposure, necessitating comprehensive investigations of indoor air quality dynamics.



Health Impact Assessments

Longitudinal Studies

There is a pressing need for longitudinal studies that assess long-term exposure to multiple air pollutants and their combined effects on public health. For example, further research is needed to define clearer exposure-response relationships between particulate matter (PM) characteristics and health outcomes, particularly focusing on long-term and combined exposure impacts on vulnerable populations.

Vulnerable Populations

Research into how specific demographics (e.g., children, pregnant women, and the elderly) are differentially impacted by pollution is critical. This can guide policies targeting at-risk groups and addressing equity in public health interventions.

Key features of the competitive landscape



- Many of the companies innovating in eliminating toxicity from food are focusing on food packaging and pesticides, which is good because those are very likely to be the two largest sources. More detail is given on pesticides in particular in the following pages.
- Within food packaging, many companies, such as Notpla, are focused on producing biologically derived alternatives to petroleum-based plastics from feedstocks such as seaweed and algae. Marine biodegradable and compostable plastics and plastic alternatives is another highly occupied area.
- Aside from safer plastics and plastic alternatives for food packaging, fibre and paper based alternatives receive significant attention.

Opportunities for innovation



Non-toxic polymer additives

The current innovation in degradable and bio-derived plastics is promising, however there is still an enormous space for innovation in finding ways to reduce the toxicity from additives to plastics and non-plastics. Notpla are blazing the trail in this area with additive free materials, however for other materials which do require additives to achieve mechanical, optical, or chemical properties without exposing the consumer to toxicity will either require innovations in polymer processing, polymer synthesis, or additives. There is potentially a large opportunity for high throughput testing of already approved food additives to bestow colour, resistance to oxidation, and plasticity to food contact plastics. This is an urgent need, since degradable plastics laden with toxic additives could pose a significant risk to the food supply if they are intentionally composted.

Low cost synthesis of PFAS-free non-stick coatings

Currently, consumers and caterers still face a cost premium when choosing PFAS-free nonstick cookware. Most coatings are currently made via a sol-gel process, so there are opportunities to intensify this process for improved economics, or alternatively to find lower cost methods of creating non-stick coatings.

Vigilante food testing

Perhaps out of frustration with government oversight, Plasticlist tested a selection of common foods found in the San Francisco Bay Area for chemicals found in plastic, alerting consumers to the fact that plastic chemicals were ubiquitous in food. There is an opportunity for similar vigilante testing in other parts of the USA and in other countries, and if the trend spreads it could increase public awareness of exposure and increase scrutiny of regulators.

Microplastic-free farmed fish

It is estimated that there are now at least 24 trillion microplastic particles in the upper layers of the ocean and so contamination of seafood with microplastics is unsurprising. Farmed fish are unfortunately even more susceptible since fish feed itself can be contaminated with microplastics. However, farmed fish actually represent an opportunity to provide fish with a much smaller microplastic concentration since systems are already in place to control their water quality and diet.

Critical gaps in current research



Plasticisers in Food Packaging

Replacements

The safety and health implications of increasingly-used replacements like DEHT and DINCH remain poorly understood. More research is needed on the long-term effects of exposure to alternative plasticisers, particularly focussing on endocrine disruption and reproductive health.

Migration

The migration of plasticisers and other chemicals into food over time, especially under varying conditions, remains poorly understood. For example, the concentrations of non-phthalate plasticizers entering food are not well known. Studies highlight the need for better quantification and risk assessment models.



Micro and nano plastics in Food

· Prevalence in food

A recent study found 240,000 micro and nano plastic particles per litre of bottled water, while others have even found them in fruit and vegetables, fish, and sea salt.

Prevalence in humans

Micro and nano plastics (MNPs) have been found in several organs in the body including the liver, bone marrow, testes, lungs, arteries and even the placenta, as well as bodily fluids such as semen, blood, and breast milk. Unfortunately even the brain has been infiltrated with microplastics, with a recent study finding the brain to be 0.5 % plastic by weight.



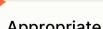
Critical Gaps in Current Research (cont.)

Contamination of food

Fruit and vegetables are most likely contaminated via direct contamination of the soil from the spreading of sewage sludge from wastewater treatment plants contaminated with microplastics directly onto farmland.

Understanding of health effects

Investigations into the health effects of MNPs have only recently begun and are largely not understood, however they have been found to induce oxidative stress across multiple organ systems and have been linked to increased risk of cancer, infertility, liver failure, neurodegeneration, and heart disease. More research is urgently required to understand the risks.



Appropriate toxicology data for food additives

In many jurisdictions, data required to assess the risks associated with
consumption of additives directly or inadvertently added to food are
inadequate. For example, in the FDA's own database, almost 80% of
chemical additives directly added to food lack the relevant information
needed to estimate the amount that consumers can safely eat, and 93%
lack reproductive or developmental toxicity data. Of the totality of FDAregulated additives - both directly and indirectly allowed in food - almost
two-thirds don't have publicly available feeding data.



Emerging Contaminants

Risk assessment

There are a lack of comprehensive studies on emerging contaminants (e.g. cleaning agents and additives) in food and packaging, including their identification and toxicity assessment. This hinders the ability to assess their cumulative health risks accurately.



Critical Gaps in Current Research (cont.)

Bioaccumulation

Persistent contaminants, including the POPs, often accumulate in trophic chains, but the extent and health consequences of such bioaccumulation are underexplored. For example, early studies indicate an acute risk of PFAS exposure through consumption of freshwater fish, and yet consumption advisories remain poorly developed or absent.

Pesticides

Chronic exposure through diet

The health effects of chronic exposure to permitted levels of pesticide residues on food are poorly understood. Comprehensive, longitudinal studies are critical in quantifying these chronic effects. More research is also needed on the effects of pesticide mixtures and overall dietary intake patterns, rather than focusing solely on single pesticide residues.

Effect of pesticide exposure on ecosystems

Research on the sublethal effects of various contaminants, particularly during different life stages of organisms (e.g., honey bees), is inadequate. There are also insufficient data on the combined effects of pesticide mixtures and how these interact with non-chemical stressors within ecosystems.

Analytical Methods for Diverse Food Matrices

Effective sample preparation procedures and analytical methods are needed for pesticide residue measurement in complex food matrices, particularly cereals and feedstuffs. This is critical in monitoring compliance with MRLs.

Toxicity of Pesticide Degradation Products

There is currently a limited understanding of the toxicity of pesticide degradation products, despite evidence suggesting they may be as, or more, harmful than the parent compound. This is exacerbated by the complexity of food matrices and their numerous degradation pathways.

The final word on safer alternatives

As discussed in the Key Nodes: Pollutants section, early efforts have now been made to produce safer chemistries for food contact materials. BPA replacements are a good example: Tetramethyl bisphenol F based epoxy resin coatings are likely to be much safer than BPA and other bisphenols, however it is not perfect and shows some endocrine disrupting effects. Tritan co-polyester as a replacement for bisphenolbased polycarbonate plastic is also likely safer alternative, however a researcher published a study showing it had estrogenic effects.

The ChemSec Marketplace, rates and recommends chemicals and materials based on their toxicity, however the advice such a body can give is limited in how definitive it can be by the paucity of data for safer alternatives. The adoption of safer alternatives could be bolstered by increasing the comprehensiveness of in vitro and in vivo testing of compounds marketed as non-toxic replacements.

General note on the challenges facing existing solutions

Speaking very broadly, there a set of challenges that make superseding conventional pesticides challenging. Cost is definitely one.

Taking the baseline of something like pyrethroids or neonicotinoids that can cost less than \$60 per hectare, then look to some innovations that are being marketed - for example the per hectare cost of sterile insect technique is >\$160 per hectare and can cost upwards of \$1000. Biocontrol (e.g. nematodes) is similarly expensive, costing hundreds of dollar per hectare (with unpredictable efficacy in some cases). However another layer of constraints is around specificity, which is both the goal and challenge. Developing pest control options like RNAi or peptide insecticides are attractive because of their specificity. However, that specificity also presents a barrier.

To take an analogy, wheat breeders focus on developing resistance to key diseases like yellow rust, but farmers still use fungicides on highly resistant crops because they want the yield bump from also wiping out all the potential secondary / minor fungal infections that could be an issue (not ones that would wipe out the crop, but hold back yield). Therefore the key question with any solution that focuses on specificity of mode of action is whether it is possible to effectively stack multiple targets together into a single product and still maintain a cost-effective solution. Otherwise, feasible solutions point to targeting specificity of location, rather than specificity of target.

Competitive Landscape and State of the Art

RNAi-based pesticides

Key Companies: Bayer (BioDirect™), RNAissance Ag, Syngenta.

Constraints Addressed

- High off-target toxicity of traditional pesticides.
- Environmental persistence and transfer through matrices
- Evolving pest resistance

Technology Examples

- Bayer's BioDirect™: Utilises dsRNA molecules designed to silence essential genes in specific pests. Bioinformatics tools ensure minimal offtarget effects, significantly reducing harm to pollinators and non-target organisms. Application methods include foliar sprays, seed treatments, or root drenches.
- RNAissance Ag: Specialises in RNAi-based agricultural pest control, leveraging dsRNA for precise gene silencing. Their platform targets pest-specific genes to disrupt their biological functions while preserving ecosystem balance.
- Syngenta: Focuses on integrating RNAi solutions with its existing pest management portfolio. The company's research includes enhancing the systemic movement of dsRNA within plants for improved efficacy.

Mechanism

- Application: dsRNA can be applied via sprays or seed treatments, where it is absorbed by plants and ingested by pests.
- Action: After ingestion, dsRNA is processed into small interfering RNAs (siRNAs) that guide the RNA-induced silencing complex (RISC) to degrade target pest mRNA, leading to mortality or reduced pest fitness.

Insecticide glues and oils

Competitive Landscape and State of the Art (cont.)

Key Companies

Bioworks (SuffOil-X), Certis USA (Trilogy Neem Oil).

Constraints Addressed

- Off-target insect and animal toxicity
- Off-target geographical spread of pesticide action
- Frequent application requirements.

Technology Examples

- Bioworks's SuffOil-X: Targets mites, insects, and fungi with enhanced spreading and adhesion properties to reduce reapplication needs.
- Certis USA's Trilogy Neem Oil: Combines neem oil with emulsifiers for better pest control coverage.

Peptide-Based Pesticides

Key Company

SOLASTA Bio.

Constraints Addressed

- Stability issues in field conditions.
- Cold chain requirements for conventional protein-based solutions.
- Non-target toxicity in traditional pesticides.

Technology Example

SOLASTA Bio's Peptide Bioinsecticides: Targets specific pest receptors
to disrupt behaviors like egg-laying. The peptides are stable under field
conditions and do not harm pollinators or humans, positioning them as
eco-friendly alternatives to synthetics.

Pheromone-Based Solutions

Competitive Landscape and State of the Art (cont.)

Key Companies

ISCA Inc., BASF, Pherosyn.

Constraints Addressed

- Evolutionary resistance to conventional pesticides
- Risks of unintended effects on non-target beneficial species.

Technology Examples

- ISCA Inc.: Genetically engineered Camelina sativa to produce pheromone precursors like (Z)-11-hexadecenoic acid. These plant-derived pheromones match synthetic efficacy at a fraction of the cost.
- BASF's Lepidopteran Pheromones: Create pheromone "clouds" to disrupt pest mating.
- Pherosyn: Develops synthetic pheromones optimised for cost and performance.

Genetically Modified Crops (Bt Crops)

Constraints Addressed

- Scalability- this strategy moves the pesticide factory to the plant, cutting out large portions of the manufacturing and supply chain.
- Off-target toxicity of conventional chemical pesticides (pest-specific action).

Technology Example

 Bt Cotton and Corn: Engineered to produce Bacillus thuringiensis toxic chemicals for pest control. While effective, resistance is becoming a major issue.

SOTA constraints and opportunities for innovation

Resistance Evolution in Bt Crops and RNAi Technologies

While Bt crops and RNAi-based pesticides are highly targeted, evolutionary escape remains a significant constraint:

Bt Crops

Pests such as Helicoverpa armigera are developing resistance to Bt toxic chemicals, threatening the sustainability of this solution. Over time, selective pressure drives pest populations to evolve resistance pathways, undermining the long-term efficacy of Bt technology.

RNAi Pesticides

Silent nucleotide substitutions can prevent RNAi from targeting essential pest genes, allowing resistance to evolve. This is particularly problematic because RNAi relies on sequence-specific gene silencing.

- Develop combinatorial RNAi strategies to simultaneously target multiple essential genes and "block" resistance escape pathways, reducing the likelihood of pests evolving resistance.
- Implement technologies which combine RNAi or GMO crops with pheromone or semiochemical-based solutions, adding layers of redundancy and increasing evolutionary durability.

SOTA constraints and opportunities for innovation

Manufacturing and Scalability of Pheromone-Based Solutions
Pheromones offer evolutionary "checkmate" potential, as resistance would impair pest reproduction or survival. However, major downstream constraints limit their application:

High Production Costs

The conventional chemical synthesis of pheromones remains expensive, particularly for low-value row crops. Large-scale production of multi-component pheromone blends is technically challenging and cost-prohibitive.

Field Application Sensitivity

Pheromone dispersion is affected by environmental factors such as wind, rain, humidity, and temperature, which reduce efficacy and require frequent reapplication.



- Develop genetically engineered "bio-pesticide factories" which continuously produce pheromone precursors in plants. ISCA Inc.'s transgenic Camelina demonstrated successful production of (Z)-11hexadecenoic acid, showing field efficacy comparable to synthetic pheromones.
- Optimise controlled release systems to address environmental volatility, ensuring consistent pheromone dispersion.

SOTA constraints and opportunities for innovation

Stability and Delivery Challenges of RNAi-Based Pesticides

RNAi pesticides represent a highly specific approach to pest control but face critical challenges in delivery and environmental stability:

- Environmental Degradation
 - Double-stranded RNA (dsRNA) molecules degrade rapidly under environmental stressors such as UV radiation, moisture, and temperature fluctuations. This reduces the bioavailability of RNAi agents before they can be ingested by target pests.
- Limited Systemic Movement
 Ensuring dsRNA reaches pests feeding on different plant tissues is a major constraint. Effective systemic delivery of dsRNA through plants remains a focus of ongoing research.

- Develop nanocarriers or encapsulation methods to protect dsRNA from environmental degradation and ensure delivery to pest tissues. Stable delivery systems could include lipid-based nanoparticles, biodegradable coatings, or other novel carriers.
- Enhance systemic movement of dsRNA within plants to offer multi-tissue protection, enabling application flexibility (foliar sprays, seed treatments, or root drenches).

Continuous Application and Coverage Limitations in Insecticide Glues and Oils

While insecticide glues and oils are non-toxic and effective for localised pest control, their downstream challenges remain substantial:

· Repeated Application

Oils like BASF's SuffOil-X and Certis USA's Trilogy neem oil require frequent application, driving up labor and operational costs.

Coverage Gaps

Adhesive solutions often fail to protect underground parts of plants or pests located in hard-to-reach areas, limiting their overall efficacy.



- Engineer plants to continuously secrete adhesive compounds using glandular trichomes or epidermal pathways. This would transform plants into self-sustaining pest control systems, eliminating reapplication needs.
- Develop adhesive compounds capable of degrading after a certain period, minimizing unintended ecological impacts and accumulation in the environment.

Visibilising toxicity

Competitive Landscape and State of the Art

Direct toxic chemical Detection

Direct detection strategies aim to identify and quantify toxic chemicals, such as pesticides, PFAS, heavy metals, and microplastics, in environmental or biological samples. Companies like Grapheal are developing graphene-based sensors capable of detecting PFAS at trace levels (100 ng/L) with high sensitivity and portability. These sensors are integrated into credit card-sized devices that can link with smartphones, offering scalable, real-time monitoring solutions.

Similarly, electrochemical sensors provide low-cost platforms for detecting heavy metals like lead and cadmium and can be integrated into portable devices for real-time human exposure tracking. Bio-colorimetric sensors, on the other hand, offer visible detection of pesticides and metals in water and soil, providing field-deployable, lower cost solutions. Critically, these innovations address limitations of traditional mass spectrometry methods, which, despite their sensitivity, are expensive, complex, and low-throughput, making them impractical for large-scale or real-time applications. Millionmarker provide urine tests for common EDCs.

Visibilising toxicity

SOTA constraints and opportunities for innovation

Biomarker Measurement

Additionally, wearable sensors represent a growing frontier, offering non-invasive, continuous monitoring of toxic chemicals through sweat, saliva, or urine. These solutions, particularly for PFAS and heavy metals, hold promise for personal health tracking and cumulative exposure analysis. However, challenges remain in improving specificity for chemically similar toxic chemicals, enhancing detection limits, and ensuring affordability through lower cost materials and scalable manufacturing technologies like printed electronics.

Instead of detecting toxic chemicals directly, biomarker strategies measure downstream effects like oxidative stress, a critical indicator of toxic chemical-induced damage and a driver of diseases such as neurodegeneration, cardiovascular disease, and cancer. Companies such as Teal Omics focus on biological markers in blood which reflect organ-specific oxidative stress and aging. This approach allows for targeted health monitoring and actionable insights based on organ-specific vulnerability, addressing the need for more precise diagnostics. Aptamer-based platforms, like those offered by Somalogic, provide high-throughput proteomic analysis to discover oxidative stress biomarkers across diverse disease areas. Similarly, MyDNAge uses epigenetic markers, specifically methylation profiles, to assess biological aging, a proxy for oxidative damage.

Visibilising toxicity

SOTA constraints and opportunities for innovation

State of the Art Constraints

While technologies such as graphene-based sensors, electrochemical platforms, and aptamer-based assays provide significant advancements over mass spectrometry, critical downstream constraints remain. Scalability and cost are major barriers, as these technologies rely on expensive nanomaterials and complex production processes, limiting affordability for large-scale use. Similarly, for state of the art biomarker detection, repeatability can be constrained by resource-intensive workflows that prevent frequent or real-time measurements, hindering dynamic tracking.

Sensitivity challenges also persist, particularly for ultratrace detection of toxic chemicals like PFAS, where portable alternatives fail to match the precision of mass spectrometry. This is further complicated by matrix interference from non-target compounds in environmental or biological samples, reducing sensor accuracy without time-consuming purification. At the level of human health, current technologies are not able to link toxic chemical exposure with biological impacts. Finally, while strategies like Teal Omics' blood biomarker detection offer organ-specific health insights, they remain costly and difficult to scale, limiting their broader applicability.



Opportunities for innovation

To overcome these challenges, innovation should focus on scalability, sensitivity, real-time monitoring, and actionable insights:

- Improving Scalability and Cost
 Use printed electronics and automated production methods to reduce the cost of sensors and assays, enabling large-scale deployment. Transitioning from complex proteomics workflows to antibody-based or biodetection kits may offer a scalable solution for routine toxic chemical and biomarker monitoring.
- Real-Time, Repeatable Monitoring
 Develop wearable, non-invasive biosensors for continuous tracking of toxic chemical exposure and oxidative stress through sweat or saliva. These tools would provide dynamic, real-time insights into cumulative health risks.
- Enhancing Sensitivity
 Integrate advanced nanomaterials like carbon nanotubes and hybrid electrochemical systems to achieve ultra-trace detection that meets regulatory thresholds for PFAS, heavy metals, and microplastics.
- Minimising Matrix Interference
 Implement smart sensor coatings to improve accuracy in complex samples by selectively binding toxic chemicals while rejecting interfering compounds.
- Delivering Actionable Insights

 Combine direct toxic chemical detection with downstream biological monitoring in the same device. To measure oxidative stress at organ-specific resolution, one could develop scalable antibody or peptide-based kits to detect oxidised versions of tissue-specific proteins. Although technically challenging, this type of technology could provide actionable health insights at scale.

Predicting toxicity

Competitive landscape and state of the art

Toxicity prediction has advanced through Quantitative Structure-Activity Relationship (QSAR) and Quantitative Structure-Property Relationship (QSPR) modelling, which use computational approaches to predict biological or chemical properties based on molecular structure. These methods, employed by companies like Schrödinger, Insilico Medicine, and BenevolentAl, reduce the need for extensive experimental testing by leveraging machine learning and statistical tools. QSAR models rely on chemical descriptors and datasets to predict toxicity, but their accuracy depends heavily on the quality and relevance of the training data. To address the gap between computational outputs and human biology, organoid-based systems are emerging as promising tools. These humanderived, 3D tissue models offer data on more nuanced biological responses. However, limitations persist, including heterogeneity, poor human-to-organ translatability, and a lack of inter-organ interaction or pharmacokinetics (PK) modelling.

Despite advances, significant downstream challenges limit the full potential of toxicity prediction models. Training data limitations remain a central issue, as QSAR/QSPR models often rely on narrow datasets from a few model organisms, which poorly reflect human biology or environmental complexity. Incorporating human-relevant organoid data into training sets offers an opportunity to enhance accuracy, particularly for human safety evaluations. Similarly, current models struggle to predict sublethal toxicity, as specific and/or chronic biological impacts are harder to assay. High-content screening using organoid systems could generate more nuanced sublethal toxicity data to improve prediction capabilities.

SOTA constraints and opportunities for innovation

While organoids bridge the gap between in vitro models and human biology, their poor scalability present major obstacles for high-throughput screening. Investment in automation, robotics, and advanced imaging technologies could increase scalability and reduce costs, enabling organoid data integration into QSAR workflows. Additionally, QSAR models fail to account for species variation and environmental transfer of chemicals, limiting their utility for ecological risk assessments. Expanding datasets to include diverse species and simulating chemical transformations in environments (e.g., bacterial metabolism or UV irradiation) would address these constraints.

Lastly, QSAR models lack human translatability due to their inability to simulate inter-organ effects or PK/PD dynamics. Combining multiple organoid systems to replicate inter-organ interactions and/or integrating organoid-based data into computational PK models could significantly improve prediction accuracy for human systems. Addressing these challenges through investment in scalable organoid technologies, better data integration, and advanced AI tools has the potential to unlock powerful toxicity predictions.



Anti-toxicity therapeutics

Competitive landscape and state of the art

Current approaches to mitigating toxicity include metal chelators, dietary interventions, and emerging nanotechnology-based solutions. Chelation therapies, such as EDTA and phytochelatins, bind metals like cadmium and mercury but their side effects prohibit long term use, while activated charcoal and ion exchange resins, though effective for PFAS removal, lack selectivity and are unsuitable for long-term use.

Emerging strategies, such as peptide binders, and nanoparticle therapies, show promise but face barriers. Modified metallothioneins (MTs) are currently limited to non-human species whilst nanoparticle systems face technological, safety, stability, and regulatory challenges. Efforts to address oxidative stress, such as antioxidant vaccines/gene therapies, remain hindered by high costs, complex manufacturing and safety concerns, making them impractical for broad use.



SOTA constraints and opportunities for innovation

The key challenges for anti-toxicity therapeutics lie in selectivity, scalability, chronic exposure efficacy, and regulatory acceptance. Chelators, activated charcoal, and current nanotechnologies remain non-specific, risking unintended effects, while emerging advanced therapies are expensive and face untenable safety and regulatory risks. This creates opportunities for innovation in cost-effective, scalable solutions that balance efficacy with safety.

Improving therapeutic solutions for toxicity requires addressing key challenges around selectivity, chronic exposure, cost, and regulatory barriers. Developing engineered enterosorbents such as hydrogels with high specificity and selectivity for toxic chemicals could reduce systemic risks by targeting toxic chemicals within the gut while avoiding nutrient interference. The requirement for long-term efficacy, currently neglected by existing treatments, presents opportunities for microbial-based systems which continuously sequester and/or neutralise toxic chemicals.

As aforementioned, whilst antioxidant vaccines/gene therapies offer potential for addressing toxic chemical-induced oxidative stress, their high cost and regulatory uncertainties limit viability. Instead, combining scalable biomarker detection with de-risked, existing antioxidant therapies may provide a more practical approach (see here). Finally, addressing regulatory barriers may require prioritising high-risk occupationally-exposed populations in order to accelerate approval and adoption.

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The following pages give relatively concise summaries of our findings and recommendations regarding regulations of toxic chemicals and funding for innovation to reduce exposure. Unlike the preceding sections of the report, these are kept brief so we can convey the high level conclusions we have distilled from the larger bodies of work with high confidence rather than an accurate, fine grained analysis which was harder to achieve on these topics.

Recommendations for future work would be discussions between epidemiologists, chemical manufacturers and policymakers to determine the best specific regulatory approaches for specific jurisdictions as well as jurisdiction-specific investment reviews. In the history of toxicity reduction, although litigation has often spurred improvements, regulation and invention have been the two pillars of progress. Possibly the earliest action to eliminate an industrial toxic chemical was the phase out of white phosphorus in matches. A combination of brave industrial action, the development of safer red phosphorus matches, and an international treaty achieved its elimination from British matchmaking in 1910.

In the best cases, regulation and invention can work synergistically, with a robust regulatory environment providing an incentive for the development of safer chemicals and a vibrant research and venture ecosystem providing the safer alternatives which make phaseouts of hazardous chemicals easier to achieve.

The most important change we recommend for improving toxicity regulation is to broaden the range of scientific studies used to inform the opinions of regulators.

The impact this can have is best exemplified by the reduction of the tolerable daily intake (TDI) of bisphenol A by a factor of 20,000, which lead to its banning in food contact materials in the European Union. This incredibly dramatic change occurred because the European Food Safety Authority (EFSA) included independent academic studies as well as the typically used "guideline studies" which follow the Good Laboratory Practices (GLP) framework. GLP was introduced in the 20th century to improve standardisation between labs, but certain features of guideline studies unfortunately mean they can underestimate toxic effects, especially of endocrine disrupting chemicals (EDCs).



The main problems with guideline studies are as follows:

Dose-response curves are assumed to be linear and monotonic.

In layman's terms this means that these studies assume that high doses of a chemical cause a high biological response and the response should decrease as dose decreases. Unfortunately, many chemicals, particularly EDCs have non-monotonic dose-response curves meaning for example that low doses can cause large effects, medium doses small effects, and large doses large effects once more.

Recommendation Include studies which show non-monotonic responses.

Guideline studies are generally designed for high dose effects.

Effects at high doses are often extrapolated to low doses to predict low dose effects and estimate safe levels of exposure without tests at low doses actually being conducted.

Recommendation
Include studies
which investigate
effects at
environmentally
relevant doses,
i.e. doses at which
humans are likely
to be exposed in
the real world.

Guideline studies assume there should be no sex difference in response.

Significant sex differences in response are common, especially for EDCs which often mimic sex hormones.

Recommendation Include studies which show sex differences in response.

In the case of BPA, once independent academic studies were included in the EFSA's decision making, it became clear that adverse health effects would likely occur at significantly lower doses than was previously appreciated. This example highlights an deeper problem with the dominant understanding of toxicity, which originates from the work of Paracelsus over 500 years ago and assumes that safe doses exist for every toxic chemical.



Further to the above recommendations which specifically address shortcoming in quideline studies, regulatory decisions could be better informed by implementing the following measures

- Include studies which measure the effects of chemical mixtures relevant for humans. Perhaps surprisingly, toxic effects can occur from mixtures in which the concentrations of several each individual chemical are below their individual no observed adverse effect levels (NOAEL). In real life, people are not exposed to one chemical at a time, so TDIs are best decided when studies of mixture effects are taken into consideration.
- Include studies which measure transgenerational effects. EDC exposure can result in effects over multiple generations, which means the effects of exposures today can potentially compound the effects of exposures decades ago.
- Include studies which investigate epigenetic changes. Related to the above point, EDCs can change gene expression, which is an underappreciated mechanism for toxic effects.



In conjunction with the above recommendations for the types of study which should inform regulatory decisions we also make the following general recommendations

Regulate chemicals as groups with similar structural features rather than individually. In 2012 the FDA banned the use of BPA based polycarbonate plastic for infant feeding bottles and in 2013 it banned the use of BPA in epoxy resins used in packaging for infant formula. This lead to the creation and marketing of many "BPA free" products, however many of these were regrettable substitutions of BPA with at least six other bisphenols such as BPS which so far appear to exhibit similar or worse endocrine disrupting effects, but which are not as well studied as BPA. A further benefit of regulating by class is that it is likely to be significantly more time and resource efficient than assessing large numbers of structurally similar molecules.

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- Increase transparency of the chemicals in mixtures and products. An example is fragrance mixtures which do not need to be disclosed and can be labelled "fragrance" or "parfum". The simultaneous protection of consumers and the intellectual property of manufacturers could be achieved by adopting solutions such as ChemFORWARD's SAFER™ trade name designation which allows third party assessors to determine the safety of confidential ingredient mixtures under NDA.
- Find and close loopholes. Perhaps obviously, all regulatory frameworks have loopholes, however it is still important to emphasise the importance of closing them. A good example is the generally recognised as safe (GRAS) loophole in the USA. Since the year 2000 99 % of food chemicals have been greenlighted by the food and chemical industries rather than by the FDA. At present, a minimum of 1,000 GRAS substances are estimated to be on the market without any independent safety review or the FDA having even been notified that they are added to food. Furthermore there are many GRAS substances which are known to pose health risks: for example the endocrine disruptor propyl paraben, which has been banned as a food additive in the EU since 2004 because in vivo studies revealed it to negatively affect sperm count. Similarly, azodicarbonamide is GRAS in the USA, but is banned in the EU because it is reasonably anticipated to be a human carcinogen.

Government funding of toxicity reduction by governments is challenging to quantify because funding programmes relevant for toxicity often cover several areas of sustainability action including climate change and biodiversity protection as well as the circular economy, which sometimes overlap with toxicity reduction and sometimes do not. Exceptions to this statement are for example the pollution prevention grants in the US and the Sustainable product initiative in Europe.

In philanthropic funding, toxicity action appears to be severely underfunded. In 2021, "toxics and pollution" received the lowest value of total grants in Europe out of 13 environmental categories, receiving a total of 7 M EUR compared to the "climate and atmosphere" category

which with 393 M EUR was the best funded. We believe that the toxicity represents a threat to humanity of at least a similar order to climate change and so this enormous discrepancy in philanthropic funding represents an opportunity if greater emphasis can be brought to toxicity.

Similarly to philanthropy, venture funding for toxicity action appears to be disproportionately small. To our knowledge Safermade is the only venture capital firm dedicated to the reduction of toxicity, whereas there are well over 50 dedicated to mitigating climate change. In general, we found that the majority of start-ups and private investors in toxicity reducing companies were located in the USA, with a small number of European corporate investors nonetheless making a significant impact.

The disproportionately low funding for efforts to reduce toxicity represents a neglected opportunity because there are several indications that there is strong consumer demand for safer products particularly in the categories of personal care products, food, food contact materials, and water.







Appendix

Reading the knowledge map

The knowledge map follows the following narrative:

- 1 How and why are toxic chemicals produced?
 Pollutant → Property → Use → Source
- 2 How do toxic chemicals move from their sources to the interfaces of exposure?:

Source \rightarrow Vector \rightarrow Secondary Vector, \rightarrow Release Mechanism, \uparrow Concentration Mechanism, \circlearrowleft Secondary Production Mechanism, and \downarrow Loss Mechanism \rightarrow Exposure Interface

How does exposure to toxicity harm human and planetary thriving?

Exposure Interface → Toxicokinetics → Mechanism of toxicity →

Effector System → Thriving threat

Our ontology for toxicity

Pollutant

 Atom, ion, molecule, or other chemical species responsible for toxic effect on humans or ecosystem. E.g. Hg, which could include metallic, methylmercury and aerosol forms of Hg

Property

• Chemical activity or functionality attributable to one or multiple pollutants. E.g. hydrophobicity, fire retardancy

Use

Intended application of pollutant or pollutant precursor. E.g. flame retardant

By-product route

• The process by which a chemical by-product is formed. E.g. Polychlorinated biphenyls (PCBs) produced accidentally in the production of pigments for paint.

Safer substitute

• A replacement chemical which provides the necessary properties with lower risk to human and planetary thriving.

Uncertain substitute

• A replacement chemical which provides the necessary properties with but for which it is unknown if the risk to human and planetary thriving is improved relative to the original.

Regrettable substitute

• A replacement chemical which provides the necessary properties but which still poses a significant risk to human and planetary thriving.

Source

- Locus from which pollutants or precursors to pollutants enter a primary vector (or interface of exposure).
- O E.g. the exhaust pipe of a car, a Teflon pan, or the wastewater stream from a chemical plant.

Vector

- System responsible for the transportation of toxicity between source and interface of exposure
- O E.g. surface water

Secondary Vector

 System responsible for the transportation of toxicity between a primary vector and another primary vector or an interface of exposure, e.g. surface runoff

Release Mechanism

• A mechanism by which toxicity is released in the environment from a source, e.g. leaching releasing heavy metals from sediments

Concentration Mechanism

• A mechanism by which toxicity is amplified/concentrated in the environment, e.g. bioaccumulation

Secondary Production Mechanism

 A mechanism by which distinct secondary toxic chemicals are produced in the environment, e.g. conversion to a more bio-available form (such as Hg^0 → methylmercury) or secondary O3 formation

Loss Mechanism

• A mechanism by which toxicity is eliminated in the environment, e.g. photochemical degradation to non-toxic compound

Exposure Interface

• The interface at which environmental toxicity is ingested, e.g. drinking water, indoor air

Toxicokinetics

 How toxic chemicals are absorbed, distributed within, processed and excreted from living organisms

Mechanism of toxicity

• The biochemical and biological process(es) by which toxic chemicals cause harm.

Effector System

Physiological entity or process necessary for the proper functioning of an organism

Thriving threat

The undesired effect of pollution on human and planetary thriving.
 O E.g. Increased probability of disease such as neurodegeneration, cardiovascular decline or cancer, impaired fitness such as lowered IQ, reduced food security due to pollinator population collapse, reduced economic security due to harvest failures.

Definition of indicators

- Quality of Evidence: robustness of data supporting toxicity, including human association studies, in vivo, and in vitro studies
- Ecosystem Coverage: breadth
 of ecological damage caused
 by these toxic chemicals. E.g.
 is it a toxic chemical that only
 occurs in industrial settings
 and thus represents risk at
 the specific workplace or are
 we looking at a toxic chemical
 like microplastics that are
 very widely distributed in the
 environment
- Thriving Threat Coverage: breadth of physiological and environmental damage caused by these toxic chemicals. E.g. cancer, Neurological disorders, infertility, biodiversity collapse
- Extent of Human Exposure:
 What proportion of the global population is exposed?
- Tipping Point Thriving
 Threats: Is the toxic chemical contributing to thriving threats which may have non-linear or cliff edge dynamics, i.e. most couples needing assisted reproduction, or most farms not having enough pollinators?

- Compound Interactions: Does
 the toxic chemical compound
 the effects of other toxic
 chemicals, or other causes of
 thriving threats. i.e. do mixture
 effects of one endocrine
 disruptor multiply the effects of
 others, or does off target insect
 toxicity compound the effects
 of global warming on insect
 populations?
- Persistence: how long toxic chemicals remain in the environment or biological systems?
- Present and Future Production: How many tonnes do we produce per year now, and is this projected to increase or decrease?
- Geog. Coverage: In which regions is the toxic chemical causing problems?

Methodology



Based on the evidence of the respective indicators, toxic chemical classes were assigned a qualitative rank for each indicator, ranging from low to extremely high (e.g., PFAS persistence ranked extremely high, while ecosystem coverage for pesticides also ranked extremely high). For a breakdown of key evidence across indicators and toxic chemical classes, see here.

To refine the analysis, we implemented a semi-quantitative scoring system, assigning numeric values to qualitative ranks (low=1, medium=2, high=3, extremely high=4). Aggregate scores were calculated across all indicators for each toxic chemical class, providing an initial ranking. Subsequently, we applied differential weighting to specific indicators (multiplying specific scores by 3) to simulate various scenarios prioritising different toxicity factors. This raw data can be found here.

Limitations and future directions



This analysis was constrained by several factors, including a limited scope of 14 toxic chemical classes, reliance on qualitative rankings with low resolution (four levels), and the arbitrary weighting of indicators, which was applied primarily to demonstrate the methodology. Furthermore, a lack of comparative studies across toxic chemical classes and gaps in available data hindered precise evaluations. Notably, missing data should not be interpreted as evidence of low toxicity.

Future work should expand the number of toxic chemical classes included and integrate quantitative data, such as percentage decreases in pollinator fitness or specific metrics to ascertain oxidative stress effects. Incorporating comparator studies to standardise relationships between exposure levels and harmful effects will further improve robustness. Developing empirical methods to weight toxicity indicators, i.e. coming to an evidence-based consensus on the importance of different toxicity factors ,would also be extremely valuable

Unweighted rankings

Osimple scoring: low-1, medium-2, high-3, extremely high-4.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Pesticides	Extremely High (4)	Extremely High (4)	Extremely High (4)	High (3)	Extremely High (4)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	33
PFAS	Medium (2)	High (3)	Medium (2)	Extremely High (4)	High (3)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (4)	27.5
PCBs	High (3)	High (3)	High (3)	High (3)	High (3)	High (3)	High (3)	Medium (2)	Extremely High (4)	27
Heavy Metals	Extremely High (4)	Medium (2)	High (3)	Medium (2)	High (3)	High (3)	High (3)	High (3)	High (3)	26
Phthalates	High (3)	Medium (2)	High (3)	Extremely High (4)	High (3)	High (3)	Low (1)	Extremely High (4)	High (3)	26
Particulate Matter (PM)	Extremely High (4)	Medium (2)	High (3)	Extremely High (4)	Medium (2)	High (3)	Medium (2)	Medium (2)	Extremely High (4)	26
Bisphenols	High (3)	Medium (2)	High (3)	High (3)	High (3)	High (3)	Low (1)	Extremely High (4)	High (3)	25
UV Absorbers	High (3)	High (3)	High (3)	High (3)	High (3)	High (3)	Medium (2)	Medium (2)	Medium (2)	24
O3/ Photochemi cal Smog	Extremely High (4)	High (3)	High (3)	High (3)	Medium (2)	Extremely High (4)	Low (1)	Medium (2)	Medium (2)	24
Ammonia and Nitrates	Medium (2)	High (3)	Low (1)	X High (3)	Low (1)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	24
Microplastics	Low (1)	High (3)	Medium (2)	High (3)	Medium (2)	Medium (2)	High (3)	Extremely High (4)	High (3)	23
Flame Retardants	Medium (2)	Medium (2)	High (3)	Medium (2)	Medium (2)	Medium (2)	High (3)	High (3)	Medium (2)	21
QUATs	Medium (2)	Medium (2)	Medium (2)	High (3)	Medium (2)	Medium (2)	Medium (2)	Medium (2)	High (3)	20
Parabens	Medium (2)	Medium (2)	Medium (2)	Extremely High (4)	Medium (2)	Medium (2)	Low (1)	Medium (2)	High (3)	20

CONTENTS ↗

Weighted rankings (Evidence-driven)

- Osimple scoring: low-1, medium-2, high-3, extremely high-4.
- Weighted scoring: Score X3.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Pesticides	Extremely High (12)	Extremely High (4)	Extremely High (4)	High (3)	Extremely High (4)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	41
Heavy Metals	Extremely High (12)	Medium (2)	High (3)	Medium (2)	High (3)	High (3)	High (3)	High (3)	High (3)	34
Particulate Matter (PM)	Extremely High (12)	Medium (2)	High (3)	Extremely High (4)	Medium (2)	High (3)	Medium (2)	Medium (2)	Extremely High (4)	34
PCBs	High (9)	High (3)	High (3)	Medium (2)	High (3)	High (3)	High (3)	Medium (2)	Extremely High (4)	33
Phthalates	High (9)	Medium (2)	High (3)	Extremely High (4)	High (3)	High (3)	Low (1)	Extremely High (4)	High (3)	32
O3/ Photochemic al Smog	Extremely High (12)	High (3)	High (3)	High (3)	Medium (2)	Extremely High (4)	Low (1)	Medium (2)	Medium (2)	32
PFAS	Medium (6)	High (3)	Medium (2)	Extremely High (4)	High (3)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (4)	31
Bisphenols	High (9)	Medium (2)	High (3)	High (3)	High (3)	High (3)	Low (1)	Extremely High (4)	High (3)	31
UV Absorbers	High (9)	High (3)	High (3)	High (3)	High (3)	High (3)	Medium (2)	Medium (2)	Medium (2)	30
Ammonia and Nitrates	Medium (6)	High (3)	Low (1)	High (3)	Low (1)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	28
Microplastics	Low (3)	High (3)	Medium (2)	High (3)	Medium (2)	Medium (2)	High (3)	Extremely High (4)	High (3)	25
Flame Retardants	Medium (6)	Medium (2)	High (3)	Medium (2)	Medium (2)	Medium (2)	High (3)	High (3)	Medium (2)	25
QUATs	Medium (6)	Medium (2)	Medium (2)	High (3)	Medium (2)	Medium (2)	Medium (2)	Medium (2)	High (3)	24
Parabens	Medium (6)	Medium (2)	Medium (2)	Extremely High (4)	Medium (2)	Medium (2)	Low (1)	Medium (2)	High (3)	24

Weighted rankings (Exposure-driven)

- Osimple scoring: low-1, medium-2, high-3, extremely high-4.
- Weighted scoring: Score X3.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Pesticides	Extremely High (4)	Extremely High (4)	Extremely High (4)	High (9)	Extremely High (4)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (12)	47
PFAS	Medium (2)	High (3)	Medium (2)	Extremely High (12)	High (3)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (12)	43
Particulate Matter (PM)	Extremely High (4)	Medium (2)	High (3)	Extremely High (12)	Medium (2)	High (3)	Medium (2)	Medium (2)	Extremely High (12)	42
PCBs	High (3)	High (3)	High (3)	High (9)	High (3)	High (3)	High (3)	Medium (2)	Extremely High (12)	41
Phthalates	High (3)	Medium (2)	High (3)	Extremely High (12)	High (3)	High (3)	Low (1)	Extremely High (4)	High (9)	40
Ammonia and Nitrates	Medium (2)	High (3)	Low (1)	High (9)	Low (1)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (12)	38
Bisphenols	High (3)	Medium (2)	High (3)	High (9)	High (3)	High (3)	Low (1)	Extremely High (4)	High (9)	37
Heavy Metals	Extremely High (4)	Medium (2)	High (3)	Medium (6)	High (3)	High (3)	High (3)	High (3)	High (9)	36
Microplastics	Low (1)	High (3)	Medium (2)	High (9)	Medium (2)	Medium (2)	High (3)	Extremely High (4)	High (9)	35
UV Absorbers	High (3)	High (3)	High (3)	High (9)	High (3)	High (3)	Medium (2)	Medium (2)	Medium (6)	34
03*	Extremely High (4)	High (3)	High (3)	High (9)	Medium (2)	Extremely High (4)	Low (1)	Medium (2)	Medium (6)	34
Parabens	Medium (2)	Medium (2)	Medium (2)	Extremely High (12)	Medium (2)	Medium (2)	Low (1)	Medium (2)	High (9)	34
QUATs	Medium (2)	Medium (2)	Medium (2)	High (9)	Medium (2)	Medium (2)	Medium (2)	Medium (2)	High (9)	32
Flame Retardants	Medium (2)	Medium (2)	High (3)	Medium (6)	Medium (2)	Medium (2)	High (3)	High (3)	Medium (6)	29
Heavy Metals Microplastics UV Absorbers O3* Parabens QUATs Flame	Extremely High (4) Low (1) High (3) Extremely High (4) Medium (2) Medium (2)	Medium (2) High (3) High (3) High (3) Medium (2) Medium (2) Medium	High (3) Medium (2) High (3) High (3) Medium (2) Medium (2)	Medium (6) High (9) High (9) Extremely High (12) High (9)	High (3) Medium (2) High (3) Medium (2) Medium (2) Medium (2) Medium (2)	High (3) Medium (2) High (3) Extremely High (4) Medium (2) Medium (2)	High (3) High (3) Medium (2) Low (1) Low (1) Medium (2)	High (4) High (3) Extremely High (4) Medium (2) Medium (2) Medium (2)	High (9) High (9) Medium (6) Medium (6) High (9) High (9)	36 35 34 34 34 32

Weighted rankings (Threat-driven)

- Simple scoring: low-1, medium-2, high-3, extremely high-4.
- Weighted scoring: Score X3.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Pesticides	Extremely High (12)	Extremely High (4)	Extremely High (12)	High (3)	Extremely High (12)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	57
Heavy Metals	Extremely High (12)	Medium (2)	High (9)	Medium (2)	High (9)	High (3)	High (3)	High (3)	High (3)	46
PCBs	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	High (3)	Medium (2)	Extremely High (4)	45
Phthalates	High (9)	Medium (2)	High (9)	Extremely High (4)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	44
Particulate Matter (PM)	Extremely High (12)	Medium (2)	High (9)	Extremely High (4)	Medium (6)	High (3)	Medium (2)	Medium (2)	Extremely High (4)	44
Bisphenols	High (9)	Medium (2)	High (9)	High (3)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	43
UV Absorbers	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	Medium (2)	Medium (2)	Medium (2)	42
03*	Extremely High (12)	High (3)	High (9)	High (3)	Medium (6)	Extremely High (4)	Low (1)	Medium (2)	Medium (2)	42
PFAS	Medium (6)	High (3)	Medium (6)	Extremely High (4)	High (9)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (4)	41
Flame Retardants	Medium (6)	Medium (2)	High (9)	Medium (2)	Medium (6)	Medium (2)	High (3)	High (3)	Medium (2)	35
Microplastics	Low (3)	High (3)	Medium (6)	High (3)	Medium (6)	Medium (2)	High (3)	Extremely High (4)	High (3)	33
Ammonia and Nitrates	Medium (6)	High (3)	Low (3)	High (3)	Low (3)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	32
QUATs	Medium (6)	Medium (2)	Medium (6)	High (3)	Medium (6)	Medium (2)	Medium (2)	Medium (2)	High (3)	32
Parabens	Medium (6)	Medium (2)	Medium (6)	Extremely High (4)	Medium (6)	Medium (2)	Low (1)	Medium (2)	High (3)	32

Weighted rankings (Persistence-driven)

- Simple scoring: low-1, medium-2, high-3, extremely high-4.
- Weighted scoring: Score X3.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Pesticides	Extremely High (12)	Extremely High (4)	Extremely High (12)	High (3)	Extremely High (12)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	57
Heavy Metals	Extremely High (12)	Medium (2)	High (9)	Medium (2)	High (9)	High (3)	High (3)	High (3)	High (3)	46
PCBs	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	High (3)	Medium (2)	Extremely High (4)	45
Phthalates	High (9)	Medium (2)	High (9)	Extremely High (4)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	44
Particulate Matter (PM)	Extremely High (12)	Medium (2)	High (9)	Extremely High (4)	Medium (6)	High (3)	Medium (2)	Medium (2)	Extremely High (4)	44
Bisphenols	High (9)	Medium (2)	High (9)	High (3)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	43
UV Absorbers	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	Medium (2)	Medium (2)	Medium (2)	42
03*	Extremely High (12)	High (3)	High (9)	High (3)	Medium (6)	Extremely High (4)	Low (1)	Medium (2)	Medium (2)	42
PFAS	Medium (6)	High (3)	Medium (6)	Extremely High (4)	High (9)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (4)	41
Flame Retardants	Medium (6)	Medium (2)	High (9)	Medium (2)	Medium (6)	Medium (2)	High (3)	High (3)	Medium (2)	35
Microplastics	Low (3)	High (3)	Medium (6)	High (3)	Medium (6)	Medium (2)	High (3)	Extremely High (4)	High (3)	33
Ammonia and Nitrates	Medium (6)	High (3)	Low (3)	High (3)	Low (3)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	32
QUATs	Medium (6)	Medium (2)	Medium (6)	High (3)	Medium (6)	Medium (2)	Medium (2)	Medium (2)	High (3)	32
Parabens	Medium (6)	Medium (2)	Medium (6)	Extremely High (4)	Medium (6)	Medium (2)	Low (1)	Medium (2)	High (3)	32

Weighted rankings (Production-driven)

- Osimple scoring: low-1, medium-2, high-3, extremely high-4.
- Weighted scoring: Score X3.

Toxic chemical Class	Quality of Evidence	Eco. Coverage	Thriving Threat Coverage	Human Exposure	Tipping Point Thriving Threats	Compound Interactions	Persistence	Present and Future Production	Geog. Coverage	Agg. Score
Heavy Metals	Extremely High (12)	Medium (2)	High (9)	Medium (2)	High (9)	High (3)	High (3)	High (3)	High (3)	46
PCBs	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	High (3)	Medium (2)	Extremely High (4)	45
Phthalates	High (9)	Medium (2)	High (9)	Extremely High (4)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	44
Particulate Matter (PM)	Extremely High (12)	Medium (2)	High (9)	Extremely High (4)	Medium (6)	High (3)	Medium (2)	Medium (2)	Extremely High (4)	44
Bisphenols	High (9)	Medium (2)	High (9)	High (3)	High (9)	High (3)	Low (1)	Extremely High (4)	High (3)	43
UV Absorbers	High (9)	High (3)	High (9)	High (3)	High (9)	High (3)	Medium (2)	Medium (2)	Medium (2)	42
03*	Extremely High (12)	High (3)	High (9)	High (3)	Medium (6)	Extremely High (4)	Low (1)	Medium (2)	Medium (2)	42
PFAS	Medium (6)	High (3)	Medium (6)	Extremely High (4)	High (9)	Medium (2)	Extremely High (4)	Medium/ High (3)	Extremely High (4)	41
Flame Retardants	Medium (6)	Medium (2)	High (9)	Medium (2)	Medium (6)	Medium (2)	High (3)	High (3)	Medium (2)	35
Microplastics	Low (3)	High (3)	Medium (6)	High (3)	Medium (6)	Medium (2)	High (3)	Extremely High (4)	High (3)	33
Ammonia and Nitrates	Medium (6)	High (3)	Low (3)	High (3)	Low (3)	Extremely High (4)	Medium (2)	Extremely High (4)	Extremely High (4)	32
QUATs	Medium (6)	Medium (2)	Medium (6)	High (3)	Medium (6)	Medium (2)	Medium (2)	Medium (2)	High (3)	32
Parabens	Medium (6)	Medium (2)	Medium (6)	Extremely High (4)	Medium (6)	Medium (2)	Low (1)	Medium (2)	High (3)	32
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Quaternary ammonium compounds (QUATs)

Indicator	Key evidence
Quality of evidence/depth of evidence - Medium	Female nurses exposed to QUATs from disinfecting equipment had longer times to pregnancy than those who did not. Exposed mice had reduced fertility.
Ecosystem coverage - Medium	Mainly <u>released to water systems</u> via household wastewater, but bind strongly to sludge and so are largely removed in wastewater treatment plants. However, a portion of waste ends up on fields due to biosolids spreading. Generally toxic to <u>aquatic organisms</u> .
Thriving threat coverage - Medium	Infertility, birth defects, skin irritation, asthma, antimicrobial resistance, aquatic ecosystem degradation
Extent of human exposure - High	Commonly used in consumer products and personal care products such as disinfectants, fabric softeners, and in shampoos and conditioners. High concentrations have been found in human blood and breast milk.
Tipping point thriving threats - Medium	Infertility, toxicity to aquatic ecosystems
Compounding interactions - Medium	Likely compound the effects of other compounds causing infertility and irritation
Persistence - Medium	Some QUATs are persistent
Present and future production - Medium	20 kt per year in the USA alone.
Geographical coverage - High	China is the largest <u>exporter</u> , followed by the Netherlands and the USA. Used in common consumer products globally.

Organic UV absorbers

Indicator	Key evidence
Quality of evidence/depth of evidence - High	Broad in vivo and in vitro <u>evidence</u> exists that several commonly used UV absorbers are endocrine disruptors. Evidence of endocrine disrupting effects for some particular compounds is still being established.
Ecosystem coverage - High	Found in rivers, especially downstream of wastewater treatment plants, also found in aquatic invertebrates and fish. Also found in soils and plants. Some UV absorbers biomagnify in aquatic ecosystems.
Thriving threat coverage - High	Endocrine disruption, mutagenesis, hepatoxicity, infertility
Extent of human exposure - High	Used widely in cosmetics and plastics
Tipping point thriving threats - High	Infertility: male exposure increases time to pregnancy
Compounding interactions - High	Compounds the effects of other endocrine disruptors and mutagens
Persistence - Medium	Some, but not all are persistent
Present and future production - medium	20 kt of OMC alone, 1.8 kt of benzophenone in the USA per year Production is expected to grow as the plastics market grows and more UV absorbers are added to personal care products
Geographical coverage - High	North America <u>produces</u> the most, followed by Europe. Human and ecosystem exposure is global due to their ubiquity in plastics and personal care products.

Bisphenols

Indicator	Key evidence
Quality of evidence/depth of evidence - High	A <u>very large body of evidence</u> links BPA to several adverse health outcomes
Ecosystem coverage - Medium	Found mainly in <u>surface waters</u> and landfill leachate with negative effects on aquatic life
Thriving threat coverage - High	Fertility, obesity, cancer, ADHD, autism, cardiovascular disease, diabetes, reproductive disorders
Extent of human exposure - High	More than 90 % of people are <u>exposed</u>
Tipping point thriving threats - High	Fertility: strong evidence for detrimental effects to female and male fertility
Compounding interactions - High	Likely compounds the effects of other endocrine disruptors and carcinogens
Persistence - Low	Not persistent
Present and future production - Extremely High	10 million tonnes per year for BPA alone
Geographical coverage- High	Bisphenols are used widely with the majority of production in Asia

Phthalates

Indicator	Key evidence
Quality of evidence/depth of evidence - High	Good <u>evidence</u> linking human phthalate exposure in the womb to disrupted sexual development. Evidence for ecological effects is weaker.
Ecosystem coverage - Medium	Found mainly in <u>surface waters</u> and sediments.
Thriving threat coverage - High	Decreased fertility, low birthweight, endometriosis, decreased testosterone, ADHD, Type 2 diabetes and breast/uterine cancer., reproductive disorders.
Extent of human exposure - (Extremely) High	Nearly all humans are <u>exposed</u> .
Tipping point thriving threats - High	Infertility: Likely contributing to the decrease in semen quality and can likely cause epigenetic changes down generations.
Compounding interactions - High	Likely compounds the effects of other endocrine disruptors and carcinogens.
Persistence - Low	Not persistent and break down quickly in the body.
Present and future production - extremely High	5.5 million tonnes per year today. Will likely double with plastic production on current course.
Geographical coverage	Used in consumer products, construction and transport materials globally. China is the largest user, accounting for 45 % of all use.

PFAS

Indicator	Key evidence
Quality of evidence/depth of evidence - Medium	The field of PFAS toxicity is less explored relative to other toxic chemicals. For example, whilst there are 50,000 peer-reviewed publications on heavy metal toxicity since 2000, there are less than 1000 papers in the same timeframe published on PFAS toxicity. However, there is compelling causal and human association data across thriving threats.
Ecosystem coverage - High	PFAS can be detected throughout a wide range of environmental matrices inlcuding soil, air, water and biological ecosystems. Bioaccumulation of PFAS in living systems allows it to spread prolifically through trophic chains on land and in water.
Thriving threat coverage - Medium	Whilst less populated than other research fields in the toxicity space, there is compelling human association evidence and causal animal model data to support PFAS-mediated toxicity across many thriving threats, from cardiotoxicity to cancer, infertility and impaired neurodevelopment. Limited studies like this one suggest PFAS exposure can increase pollinator mortality and failure to thrive but the literature depth is poor, with more studies needed in this field.
Extent of human exposure - Extremely High	Humans are consistently exposed to PFAS chemicals globally, with the highest PFAS concentrations detected in human serum from the USA, Canada, Greenland, Iceland, Norway, Sweden, the UK, Spain, Poland, and Australia. Exposure interfaces include drinking water, food, contaminated air and house dust.
Tipping point thriving threats - High	PFAS chemicals are shown to decrease fertility across several human association studies, supported by animal model data proving a causal relationship. As mentioned above, studies like this one suggest PFAS exposure can increase pollinator mortality and failure to thrive but the literature depth is poor, with more studies needed in this field.
Compounding interactions - Medium	PFAS production itself generates greenhouse gases e.g. HCFC-22, a chemical thousands of times more potent than CO2. This poses a threat to planetary thriving via climate change. For example, in 2019 The plant of the PFAS manufacturer Daikin in Decatur, Alabama, released about 240,000 pounds of HCFC-22 in 2019, the equivalent of over one billion pounds of carbon dioxide.

PFAS

Indicator	Key evidence
Persistence - Extremely High	PFAS chemicals <u>are incredibly persistent in the environment</u> , owing to their multiple C-F bonds which exhibit extreme enthalpic stability. <u>There is a dearth of known biological enzymes capable of breaking this bond</u> , compounding its persistence in the environment.
Present and future production - High	Efforts to phase out PFAS chemicals are underway globally. For example, In Europe, a ban on over 10,000 PFAS compounds has been proposed by five EU countries, with a final decision expected in 2025, alongside strict limits of 0.5 µg/l for PFAS in drinking water under the recast Drinking Water Directive. The UK has implemented similar measures, including cumulative limits on PFAS in drinking water and restrictions on PFHxA. However, PFAS production has continued to rise in Asia and legislation to reduce PFAS emissions often excludes novel variant chemical forms. This, combined with their exceptional persistence, renders PFAS chemicals a continued threat to planetary thriving.
Geographical coverage- Extremely High	Humans are consistently exposed to PFAS chemicals globally. PFAS is detectable in human serum across all continents- Asia, Africa, North America, South America, Antarctica, Europe, and Australia. China is now the world's largest producer.

Pesticides

Indicator	Key evidence
Quality of evidence/depth of evidence - (extremely) Extremely High	> 25,000 peer-reviewed publications since 2000 on pesticide toxicity. Strong causal and human association data across thriving threats.
Ecosystem coverage - (extremely) High	Exposure and accumulation across many ecosystemssoil, aquatic ecosystems, bioaccumulation in fish, birds and insect populations.
Thriving threat coverage - (extremely) High	Strong causal and human/animal association data across thriving threats from infertility to cardiovascular, cancer, neurodegeneration and many other inflammatory disorders.

Pesticides

Indicator	Key evidence
Thriving threat coverage - (extremely) High	Strong causal and human/animal association data across thriving threats from infertility to cardiovascular, cancer, neurodegeneration and many other inflammatory disorders.
Extent of human exposure - High	Some studies report up to 82% detection rate in general population (urine analyses). Exposure routes include food residue, aquatic bioaccumulation and food consumption, water, dust.
Tipping point thriving threats - Extremely high	Pesticides are partly responsible for precipitous decline in pollinators, iincluding bees, butterflies, and other species vital to the reproduction of up to 75% of global food crops. These chemicals, through both lethal and sub-lethal exposures, impair navigation, foraging, immunity, and reproduction in pollinators, jeopardizing food security and biodiversity. Beyond pollinators, pesticides cause acute and chronic toxicity in non-target species, including fish, birds, and mammals.
Compounding interactions - Extremely high	Pollinator toxicity interacts with the threat of wider food chain collapse, as does pesticide-driven fertility decline. The widespread, well-validated effects of pesticides on human health, particularly age-related conditions (such as cardiovascular disease, neurodegeneration and cancer) may be compounded by pesticide-induced infertility. For example, an elderly population in need of social care and medical treatment may struggle to have their needs met if a) there is less family support and b) if the economy is not supported by a younger, working population.
Persistence - Medium	Depends on the pesticide class. Some pesticides are short-lived but toxicity only requires transient exposure. Other pesticides, including organochlorines can have half-lives of up to a year in animal species.
Present and future production- Extremely high	Pesticide use is a staple of modern farming globally, reducing economic injury. Global pesticide use continues to increase. 3.7 million tonnes are used annually.
Geographical coverage- Extremely high	Pesticide use is extremely high globally.

Microplastics

Indicator	Key evidence
Quality of evidence/depth of evidence - Low	MP research is still in its infancy relative to other toxic chemicals. For example, whilst there are >50,000 peer-reviewed publications on heavy metal toxicity since 2000, there are less than 1000 papers in the same timeframe published on MP toxicity. There is sparse causal and human association data across thriving threats.
Ecosystem coverage - High	Mostly studies in the context of aquatic ecosystems but MPs (microplastics) are increasingly abundant in soils and other biospheres.
Thriving threat coverage - Medium	Linked to quality of evidence- some human association and causal animal model data supports the role of microplastics in cardiotoxicity, infertility and cancer but these studies are sparse. For other thriving threats, e.g. neurodegeneration, human association studies are lacking almost entirely. For non-human/indirect thriving threats such as pollinator decline, studies are limited and critical knowledge gaps remain.
Extent of human exposure - High	Massive indirect human exposure through multiple foodchains and direct exposure via food packaging etc. Global drinking water frequently contaminated with MPs too.
Tipping point thriving threats - Medium	Some evidence that MPs/NPs reduce thriving of bees/pollinators, but not a deep literature on this at all. Some evidence MP exposure drives human and animal infertility but the field acknowledges more data is needed, particularly human association studies.
Compounding interactions - Medium	Microplastics sequester and leach toxic additives, including heavy metals and endocrine-disrupting chemicals, into the environment which can compound their toxicity.
Persistence - High	MPs are not naturally biodegradable. Across multiple environments, MPs persists for many years.

Microplastics

Indicator	Key evidence
Present and future production - Extremely high	Global plastics production has doubled in the last two decades and continues to trend upwards.
Geographical coverage- High	Both in terms of <u>emissions</u> and <u>exposure</u> plastic and microplastic pollution is a global problem with wide geographical coverage.

Heavy Metals

Indicator	Key evidence
Quality of evidence/depth of evidence- (extremely) Extremely High	>50,000 peer-reviewed publications since 2000 on pesticide toxicity. Strong causal and human association data across thriving threats.
Ecosystem coverage - Medium	Heavy metals contamination is <u>often concentrated in specific</u> hotspots, particularly industrial zones, mining areas, and regions with heavy agricultural chemical use. However, metals <u>can spread</u> efficiently and accumulate in aquatic vectors such as rivers.
Thriving threat coverage - High	Strong causal and human/animal association data across thriving threats from infertility to cardiovascular, cancer, neurodegeneration and many other inflammatory disorders.

Heavy Metals

Indicator	Key evidence
Extent of human exposure - Medium	Whilst high exposures are most frequently documented in areas close to anthropogenic or natural sources, the general population is subject to heavy metal exposure too.
Tipping point thriving threats - High	Human association studies and animal models prove the causal relationship between heavy metal exposure and infertility.
Compounding interactions - High	The widespread, well-validated effects of heavy metals on human health, particularly age-related conditions (such as cardiovascular disease, neurodegeneration and cancer) may be compounded by heavy metal-induced infertility. For example, an elderly population in need of social care and medical treatment may struggle to have their needs met if a) there is less family support and b) if the economy is not supported by a younger, working population.
Persistence - High	Heavy metals are resistant to biodegradation and persist in soil and water.
Present and future production - High	Heavy metals emissions are <u>declining in Europe</u> and these trends are repeated in US and developing countries, <u>partly aided by UN mandates</u> . However, heavy metals are currently still integral to the function of batteries, other electronics and the construction industry.
Geographical coverage- High	Heavy metal pollution is a global-scale problem. For example, the global average values of Cr, Mn, Co, Ni, As and Cd exceeded WHO and USEPA guidelines.

Particulate Matter (PM)

Indicator	Key evidence
Quality of evidence/depth of evidence - Extremely High	Significant body of evidence linking PM exposure to multiple adverse health, ecological, and societal outcomes
Ecosystem coverage - Medium	PM is a pervasive threat in most urban and household environments. PM exposure is also a problem in rural environments with high levels of natural or anthropogenic biomass burning.
Thriving threat coverage - High	Dose-response data linking PM to <u>cardiovascular</u> , <u>cerebrovascular</u> , <u>and neurological diseases</u> , <u>cancers</u> , <u>pre-term births</u> , <u>and decreases in fertility</u> . In 2019, the WHO estimated that <u>6.7 million premature</u> <u>deaths</u> could be attributed to ambient and household air pollution by PM2.5.
Extent of human exposure - Extremely High	PM2.5 and PM10 levels exceed the threshold defined by the WHO as 'safe' in 83% of high-income cities and 99% of low-income cities that are monitoring air quality (note: many cities lack the capacity to adequately monitor air quality). 90% of the world's population breathes air that exceeds WHO targets for PM.
Tipping point thriving threats - Medium	Fertility: <u>causal studies</u> and <u>strong association</u> data in human populations demonstrate the dose-dependent effect of PM exposure on <u>declining fertility in both males and females</u>
Compounding interactions - High	Compounding interactions between PM exposure and other forms of air pollution lead to amplification of health and climatic effects.
Persistence - Medium	PM2.5 is removed from the air via vegetation. The efficiency of this process is suppressed in many urban environments with high PM2.5 because of a lack of <u>vegetation</u> .
Present and future production - Medium	The sign and magnitude of future PM2.5 changes are uncertain. Anthropogenic PM2.5 sources are expected to decline, but sources from wildfires and natural systems are expected to increase in response to climate change. The likely net effect of these factors is to increase overall PM2.5 levels.

Particulate Matter (PM)

Indicator	Key evidence
Geographical coverage - Extremely High	PM is a global problem, with 90% of the world's population exposed to unsafe levels in both high-income cities (83% exceeding WHO guidelines) and low-income cities (99% exceeding WHO guidelines).

03/Photochemical Smog

Indicator	Key evidence
Quality of evidence/depth of evidence - Extremely High	Decades of epidemiological and toxicological research links photochemical smog to health problems. Association and in-vivo studies consistently associate smog exposure with respiratory, cardiovascular, and systemic inflammation effects.
Ecosystem coverage - High	Photochemical smog is a threat in urban and suburban areas, particularly those with high vehicular emissions, industrial activities, and sunny climates. Its effects are most acute in densely populated cities like Los Angeles or Beijing, but it can also extend to rural areas due to atmospheric transport.
Thriving threat coverage - High	Smog contributes to respiratory issues (asthma, bronchitis), cardiovascular diseases (heart attacks, strokes), neurodevelopmental and cognitive decline, and systemic inflammation. Long-term exposure is also associated with chronic conditions like COPD and lung cancer.
Extent of human exposure - High	Globally, billions are exposed to smog, with urban populations facing the highest risks. 99% of the global population breathes air that exceeds WHO air quality limits. While it is challenging to partition the effects of photochemical smog and O3 from PM, independent measurements of ground-level NO2 suggest that 77% of cities have NO2 concentrations in excess of the WHO's guidelines.

03/Photochemical Smog

Indicator	Key evidence
Tipping point thriving threats - Medium	Associative and in-vivo data link smog and O3 with declines in fertility and reproductive health. Ecosystems are also adversely affected, as smog alters plant growth, soil chemistry, and water quality.
Compounding interactions - Extremely High	Smog <u>exacerbates the effects of other pollutants</u> like fine particulates (PM2.5) and allergens, intensifying health risks. For example, it can enhance the toxicity of heavy metals or amplify oxidative stress when combined with other environmental stressors.
Persistence - Low	Photochemical smog is a transient phenomenon, typically dissipating when atmospheric conditions (e.g., wind, precipitation) change. However, the pollutants that form it, such as ozone and particulates, may persist for longer in the environment.
Present and future production - Medium	Smog formation is driven by fossil fuel combustion and industrialization. Without stricter emission controls, global smog production is expected to increase, particularly in rapidly urbanizing regions like Southeast Asia and Sub-Saharan Africa. Climate change is also projected to increase the frequency of smog events.
Geographical coverage - Medium	Smog affects nearly every continent, with hotspots in the urban centers of Asia, North America, and Europe. Its effects are amplified by transboundary pollution, allowing smog to impact regions far from its origin.

Flame Retardants

Indicator	Key evidence
Quality of evidence/depth of evidence - Medium	Research has linked flame retardants to various health effects including endocrine disruption, neurotoxicity, and cancer through laboratory, epidemiological, and environmental data. However, the evidence is stronger for certain compounds like polybrominated diphenyl ethers (PBDEs) and organophosphate flame retardants (OPFRs), and gaps remain in understanding the impacts of emerging compounds.
Ecosystem coverage - Medium	Flame retardants are present in homes, workplaces, vehicles, and public spaces, as they are commonly used in furniture, electronics, textiles, and building materials. High exposure levels are observed in areas where these materials degrade or burn, such as recycling facilities.
Thriving threat coverage - High	Exposure to flame retardants is associated with endocrine disruption, cancer, reproductive toxicity, neurodevelopmental issues, immune system damage, and adverse outcomes during fetal and child development.
Extent of human exposure - Medium	Humans are exposed to flame retardants primarily through ingestion of dust, inhalation, and skin contact. Studies have detected these chemicals in human tissues, breast milk, and blood, indicating widespread exposure in the general population.
Tipping point thriving threats - Medium	Flame retardants are linked to <u>declines in human fertility</u> , with evidence showing impacts on sperm quality, hormonal balance, and reproductive development. In ecosystems, they may <u>bioaccumulate</u> and can disrupt aquatic food webs and wildlife reproduction, particularly in species exposed to contaminated sediments.
Compounding interactions - Medium	Flame retardants may <u>alter the body's metabolism of other toxicants</u> , potentially amplifying endocrine-disrupting and neurotoxic effects.
Persistence - High	Many flame retardants are <u>persistent in the environment</u> due to their resistance to degradation. They accumulate in sediments, wildlife, and humans, with long-lasting impacts on ecosystems and potential for global transport through air and water.



Flame Retardants

Indicator	Key evidence
Present and future production - High	Global production of flame retardants is substantial, exceeding 2.7 million tons in 2022, with organophosphates becoming more common as alternatives to PBDEs. Production is expected to rise due to demand in fire safety regulations, though some regions are phasing out harmful compounds.
Geographical coverage - Medium	Exposure is global, with higher concentrations detected in industrialized areas and regions using significant amounts of treated materials. Developing countries may face elevated risks due to informal recycling practices and lack of regulations.

Amonia and Nitrates

Indicator	Key evidence
Quality of evidence/depth of evidence - Medium	There is robust evidence from both epidemiological studies and animal data for effects of ammonia on respiratory irritation. The effects of nitrates are also well-studied; in particular their role in methemoglobinemia ("blue baby syndrome") and their potential carcinogenicity when converted to nitrosamines. However, research on reproductive effects and the effect of chronic exposure are both limited.
Ecosystem coverage - High	Ammonia exposure is prevalent in industrial and agricultural settings, while nitrates significantly impact drinking water supplies due to agricultural runoff and improper waste disposal. Nitrate from agriculture is now the most common chemical contaminant in the world's groundwater aquifers. The maximum contaminant level for nitrates in drinking water is defined by the WHO as 10 mg/L, but in developing countries more than 20-50% of wells have nitrate levels exceeding 50 mg/L.



Amonia and Nitrates

Thriving threat coverage - Low	Chronic exposure to ammonia can cause long-term respiratory issues. Nitrate exposure is linked to methemoglobinemia, gastrointestinal cancers due to nitrosamine formation, and endocrine disruption. Both chemicals can exacerbate pre-existing respiratory or cardiovascular conditions.
Extent of human exposure - High	Exposure to nitrate concentrations above recommended levels is pervasive in both developed and developing regions. In the US more than 100 million people are at risk of nitrate exposure through drinking water, while in developing countries more than 20-50% of wells have nitrate levels exceeding 50 mg/l. Direct respiratory exposure to ammonia tends to be more closely linked to occupational factors.
Tipping point thriving threats - Low	Excess nutrients from agricultural runoff can lead to algal blooms, which deplete oxygen in water bodies, creating 'dead zones' devoid of aquatic life. These affect over 245,000 square kilometers globally. A minimum of 1.3 billion people are now at risk of chronic health effects from nitrate exposure.
Compounding interactions - Extremely High	Eutrophication <u>exacerbates the effect</u> of warming water on oxygen-depleted 'dead zones' in freshwater and coastal ecosystems. Ammonia pollution is a <u>key contributor to the formation of particulate matter.</u>
Persistence - Medium	Ammonia typically persists in the atmosphere for hours to days, but nitrates are highly persistent, with groundwater contamination lasting decades due to slow natural attenuation processes.
Present and future production - Extremely high	Ammonia production reached 235 million metric tons in 2022, with demand expected to grow at 3-5% annually due to increasing agricultural needs. The FAO predicts that worldwide use of synthetic N fertilisers will increase by 50% between 2012 and 2050.
Geographical coverage - Extremely High	Ammonia exposure tends to be associated with agricultural and industrial activities, but nitrate is the most common chemical contaminant in aquifers and affects drinking water supplies globally. A minimum of 1.3 billion people are now at risk of chronic health effects from nitrate exposure.



Polychlorinated Biphenyls (PCBs)

Indicator	Key evidence
Quality of evidence/depth of evidence - High	There is substantial evidence of the harms caused by PCBs, which resulted in their intentional production and use being banned in most countries.
Ecosystem coverage - High	Accumulation in soil, sediment and aquatic environments. They are soluble in fat tissue and so biomagnify in food chains.
Thriving threat coverage - High	Fertility, endocrine disruption, reduced IQ, cardiovascular disease, liver disease, cancer, acute toxicity in exposed workers, immune system suppression.
Extent of human exposure - High	As with PFAS, <u>everyone</u> in the world has PCBs in their body. 90 % of German sheep livers have levels above the food safety limit.
Tipping point thriving threats - High	Impacts fertility and ecosystems and so could contribute to human and wildlife population collapses
Compounding interactions - High	Believed to <u>compound</u> the effects of other carcinogens and endocrine disruptors across several endocrine systems
Persistence - High	Persistence is high and depends on the degree of chlorination. Half lives vary from 10 days to 1.5 years.



Polychlorinated Biphenyls (PCBs)

Indicators	Key evidence
Present and future production - Medium	Intentional production has been phased out, however it is <u>estimated</u> that their production as a by-product in pigments and dyes may now exceed peak intentional production.
Geographical coverage - Extremely High	North Korea still intentionally produces PCBs but they are unintentionally produced as by-products in all countries producing pigments and dyes. Alarmingly, they contaminate cooking oils still used in Africa, and they are used in welding oils in Sri Lanka. They are transported far from their sources of production and so are present in people and environments globally.

Parabens

Indicator	Key evidence
Quality of evidence/depth of evidence - Medium	Evidence for harm is conflicting, partly due to understudy and initial testing focusing on lethality. Rodent studies however show significant effects on female reproductive health.
Ecosystem coverage - Medium	Present in surface waters including <u>drinking water</u> . Biomagnification occurs in <u>aquatic ecosystems</u> and feminisation of fish has been reported. Chlorination in wastewater treatment plants can create <u>chlorinated paraben products</u> .
Thriving threat coverage - Medium	Infertility, <u>cancer</u> , endocrine disruption, <u>obesity</u>



Parabens

Indicator	Key evidence
Extent of human exposure - Extremely High	Parabens are approved for use as food preservatives in the USA and China, and are also approved for use in personal care products in the EU. Human exposure is likely <u>universal</u> in industrialised nations.
Tipping point thriving threats - Medium	Infertility: female exposure reduces the chance of pregnancy, and appears to decrease ovarian reserve.
Compounding interactions - Medium	Likely compounds the effects of other endocrine disruptors, obesogens, and carcinogens
Persistence - Low	Parabens generally <u>degrade</u> in soils within days however their chlorinated products from wastewater treatment plants are more persistent.
Present and future production - Medium	110 kt per year for propyl paraben alone.
Geographical coverage - High	Exposure is higher in the USA and Europe than other regions.

