iMERMAID

D5.1: White paper on upstream solutions

Task 5.1: Assessment and recommendation of chemical and non-chemical alternatives

WP5: Multistakeholder roadmaps for uptake and scalability of the innovative solutions

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Date: 31 May 2024

Funded by the European Union

GRANT AGREEMENT NUMBER	101112824
ACRONYM/ FULL TITLE	iMERMAID/ Innovative solutions for Mediterranean Ecosystem Remediation via Monitoring and decontamination from Chemical Pollution
START DATE	01 June 2023
END DATE	31 May 2026
PROJECT URL	www.imermaid.eu
DELIVERABLE TITLE	White paper on upstream solutions
WORK PACKAGE	WP5
CONTRACTUAL DATE OF DELIVERY	31/05/2024
ACTUAL DATE OF DELIVERY	M12 (May 2024)
NATURE	Report
DISSEMINATION LEVEL	Public
LEAD BENEFICIARY	VTT
RESPONSIBLE AUTHOR	Mona Arnold, VTT. David Lucio, ITCL.
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ABSTRACT	Future upstream solutions for chemicals of emerging concern. A white paper

Document Revision Log

Version	Description of changes	Author	Role in the project
0.1	Draft	Mona Arnold (VTT)	Beneficiary
0.2	Agrochemicals contributions	David Lucio (ITCL)	Project Coordination Team
0.3	Pharmaceuticals and Plastic Additives contributions	Mona Arnold (VTT)	Beneficiary
0.4	Final first draft	Mona Arnold (VTT)	Beneficiary
0.5	First review	Yolanda Ballesteros, Esther Gómez (SOCAMEX)	Beneficiary
0.6	Second review	Christina Zeri (HCMR)	Beneficiary
0.7	Third review	Marcela Permann-Doubková (AIG)	Beneficiary
0.8	Quality check integrated	Mona Arnold (VTT)	Beneficiary
1.0	Final review and formatting	Rodrigo Sedano (ITCL)	Project Coordinator

Executive Summary

The European Commission defines the emerging pollutants as substances that have the potential to enter the environment and cause adverse ecological and human health effects but are still largely unregulated and whose fate and potential effects are poorly understood". The occurrence of emerging micropollutants (pharmaceuticals, pesticides, personal care products, industrial compounds, etc.) in the environment is considered a major threat to human health and aquatic eco-systems.

Source-directed approaches offer benefits by reducing the necessity and cost of end-of-pipe wastewater treatment upgrades and solid waste disposal, while also enhancing drinking water safety.

This white paper aims to give insight into the state of the art of selected chemicals of concern in three focal sectors; production of pesticides, pharmaceuticals and industry chemicals. The chosen sectors have been identified as major sources of micropollutants found in the aquatic environment. It gives an overview of their occurrence in the European environment and their impact on health and the environment when discharged into the environment. Moreover, it looks into social and regulatory drivers affecting their production and mode of use.

Regulation is a main driver for change and has seen to boost the development of substituting with less hazardous compounds. The study also shows that substitution of chemicals can be slow, and does not come without costs, depending on the availability of market- ready substitutes and necessary compliance processes. At the same time, it is an opportunity for chemical companies to develop new businesses. Though the development of safe alternatives to current chemicals of concern is the only fully sustainable solution, a combination of eco-design of products and end of pipe solutions, i.e., waste water treatment technologies is still essential to achieve a safer and healthier livelihood near future.

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Acronyms

AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient
ATBC	Acetyl Tributyl Citrate
BBP	Benzyl Butyl Phthalate
BPA	Bisphenol A
BPAF	Bisphenol AF
BPF	Bisphenol F
BPS	Bisphenol S
BPSIP	4-Hydro xyphenyl 4-Isopro oxyphenyl sulfone
CAGR	Compound Annual Growth Rate
CAP	Common Agricultural Policy
CSS	Chemicals Strategy for Sustainability
CoEC	Chemical of Emerging Concern
CLP	Classification, Labelling, and Packaging
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl Phthalate
DEHA	Di- (2-ethylhexyl) adipate
DEHP	Di (2-ethylhexyl) phthalate
DIBP	Diisobutyl Phthalate
DINCH	Di(isononyl)cyclohexane-1,2-dicarboxylate
DINP	Di isononyl pthalate
DOTP	Dioctyl terephthalate
DPHP	di (2-propylheptyl) phthalate
EAP	Environmental Action Programme
ECHA	European Chemicals Agency
EFSA	European Food Safety Agency
EPA	Environment Protecting Agency
EPR	Extended Producer Responsibility

ERA	Environmental Risk Assessment
ESBO	Epoxidized Soybean Oil Plasticisers
EU	European Union
FDA	Food and Drug Administration
GC	Green Chemistry
GIS	Geographic Information System
GM	Genetically Modified
GPS	Global Positioning System
HMW	High Molecular Weight
IoT	Internet of Things
IPM	Integrated Pest Management
IT	Information Technologies
LMW	Low Molecular Weight
ML	Machine Learning
MRL	Maximum Residue Levels
NMC	N-methyl carbamate
NSAID	Nonsteroidal anti-inflammatory drug
OECD	Organization for Economic Co-operation and Development
PDI	Photodynamic Inactivation
PETG	Polyethylene Terephthalate Glycol
PFAS	Per- and Polyfluorinated Substances
POP	Persistent Organic Pollutant
PVC	Polyvinyl Chloride
R&D	Research and Development
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
SSbD	Safe and Sustainability by Design
SUR	Sustainable Use of Pesticides Regulation
SVHC	Substances of very high concern
TOTM	Trioctyl trimellitate
TXIB	2,2,4-trimethyl 1,3-pentanediol diisobutyrate

USA	The United States of America
US EPA	United States Environmental Protection Agency
UWWTD	Urban Wastewater Treatment Directive
WHO	World Health Organisation
WWTP	Wastewater treatment plant

1. Introduction

The European Commission defines the emerging pollutants as "*substances that have the potential to enter the environment and cause adverse ecological and human health effects but are still largely unregulated and whose fate and potential effects are poorly understood*"[1] . Substances such as pharmaceuticals, newly registered pesticides, industrial plastic additives, personal care products and new flame retardants can be cited as belonging to the group of pollutants. The occurrence of emerging micropollutants (pharmaceuticals, pesticides, personal care products, industrial compounds, etc.) in the environment is considered an unknown threat to human health and aquatic ecosystems. Indeed, organic pollutants, such as pharmaceuticals, herbicides, pesticides and Plasticisers at concentration levels of $\mu g\ L^{-1}$ or even $ng\ L^{-1}$ are hardly removed during conventional wastewater treatment methods. In view of this, the opportunity to address the problem preventively with upstream solutions is an interesting and surely efficient strategy, however until now applied in only isolated cases.

Source-directed approaches are in line with the circular economy principles as they reduce the production of wastes, and the necessity and cost of end-of-pipe wastewater treatment upgrades and solid waste disposal, while also enhancing drinking water safety.

This white paper gives an analysis of selected chemicals of concern belonging to three major compound groups: pesticides, pharmaceuticals and industry chemicals. The three sectors have been selected based on: (i) the necessity to resolve the high concentrations of emerging pollutants derived from agriculture, which is of big relevance in the countries belonging to the consortium; (ii) the ubiquitous presence of pharmaceuticals and industry chemicals, detected based on qualitative advanced analyses; (iii) the relevant regulations (in force or upcoming, e.g. the WFD or the proposal for a new urban wastewater directive. It gives an overview of their occurrence in the European environment and their impact on health and the environment when discharged into the environment. Moreover, it looks into social and regulatory drivers affecting their production and mode of use. The outcome of the paper is a recommendation for upstream solutions, i.e., how and if these compounds can be substituted with less hazardous compounds.

Problem statement

Chemicals are pervasive in our everyday lives, with over 350,000 chemicals and mixtures registered for use globally. As a result of their widespread use, chemical contaminants including pesticides, pharmaceuticals, and industrial chemicals, are commonly detected in water, sediment, soil and biota.[2] Many of these chemicals are considered as contaminants of emerging concern (CoEC), which is broadly defined as 'a chemical for which there are increasing concerns regarding its potential risks to humans and ecological systems'.[3]

There is an increased concern of consumers about chemicals used in products which may have unintended consequences on human health and the environment. Recently, a growing number of chemicals have also received regulatory attention and they are addressed both in the US. and European environmental

[1] Tornero Alvarez, M. and Hanke, G. (2017) Potential chemical contaminants in the marine environment: An overview of main contaminant lists , EUR 28925 EN, Publications Office of the European Union, Luxembourg

[2] Neale P. et al (2023) ECHIDNA (Emerging Chemicals Database for National Awareness): a framework to prioritise contaminants of emerging concern in water. J. Water & Health 21 (9), 1357.

[3] Diamond, J., Latimer, H., Munkittrick, K., Thornton, K., Bartell, S. & Kidd, K. (2011) Prioritizing contaminants of emerging concern for ecological screening assessments. Environmental Toxicology and Chemistry 30 (11), 2385–2394.

legislation. Limits for discharge and drinking water concentrations have been given e.g., some PFAS and phthalates, which are in extensive use in the chemical and polymer industry. Also Europe's Candidate List of substances of very high concern (SVHC) contains several ortho-phthalates[4].

As a consequence, many companies are considering the use of contradictory compounds and looking for alternatives. Substitutes for CoECs are alternatives that can perform the same or similar functions as the original chemicals, but with fewer or no adverse effects. Substitutes can be other chemicals, non-chemical materials, or different processes or product designs. However, finding and evaluating substitutes for CoECs can be challenging, as there may be trade-offs between performance, cost, availability, and safety.

[4] https://echa.europa.eu/candidate-list-table

2.0 Agrochemicals

2.1 What, where and why?

Crop productivity is affected by a number of factors, including disease outbreaks. Approximately $220 billion is lost annually through the outbreak of diseases caused by several pathogens such as bacteria, fungi and viruses.[5] The global need to increase crop production has triggered the use of agrochemicals by farmers.[6] The current market size of the **agrochemical industry is about $230 billion and expected to grow annually 3% until 2027**.[7] Nonetheless, excessive chemical use creates serious environmental concerns, when part of not easily degradable pesticides applied to the fields leaches into the environment and finds it ways into natural waters.

The application of pesticides on crops can contaminate the environment at a local and global level. In particular, poor use and management of pesticides and other agricultural practices have caused global degradation of soil health and quality.[8] Many applied pesticides can be persistent in the environment, remaining in the soil for long periods, accumulating in non-human organisms and impacting humans through the food chain. Residues from **pesticide applications can contaminate terrestrial and aquatic ecosystems**, affecting human food, water quality and soil. Chemicals applied to crops can also remain in the soil and reach aquatic ecosystems outside the application area through surface runoff, exerting toxic effects on non-target species and causing damage to biodiversity and ecosystems. In 2014, chemical pollution (including pesticides) has been recognised as a major factor in the global decline in insect populations.[9]

The evidence of environmental contamination and adverse effects on biodiversity has led to efforts to develop new environmentally friendly chemicals that are less bioaccumulative and improve pesticide formulations to reduce contamination. Furthermore, the European Union regulation on Persistent Organic Pollutants (POPs) aims to comprehensively monitor the levels of harmful pollutants in the environment and facilitate the evaluation of control measures. Nevertheless, even with the cessation of their application, persistent chemicals used in the past are still present in soils, contributing to elevated levels of pesticides in the environment. No single technique has been found to remove all relevant agrochemical pollutants from wastewater. Thus, a broad-spectrum and large-scale **regulation is necessary to reduce the contamination associated with the use of agrochemicals**, leading to more sustainable models of their use so that they do not have a negative impact on human health and the environment.

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[5] Savary S., Willocquet L., Pethybridge S.J., Esker P., McRoberts N., Nelson A (2024). The global burden of pathogens and pests on major food crops. Nat. Ecol. Evol. 2019;3:430–439.

[6] Maluin, F. N., and Hussein, M. Z. (2020). Chitosan-based Agronanochemicals as a Sustainable Alternative in Crop Protection. Mol 25, 1611.

[7] Ivanov, V. M., Shevchenko, O., Marynin, A., Stabnikov, V., Stabnikova, E., Gubenia, O., & Salyuk, A. (2021). Trends and expected benefits of the breaking edge food technologies in 2021–2030.

[8] Mandal, A., Sarkar, B., Mandal, S., Vithanage, M., Patra, A. K., & Manna, M. C. (2020). Impact of agrochemicals on soil health. In Agrochemicals detection, treatment and remediation (pp. 161-187). Butterworth-Heinemann.

[9] Gill, H. K., & Garg, H. (2014). Pesticide: environmental impacts and management strategies. Pesticides-toxic aspects, 8(187), 10-5772.

The challenges to achieving sustainable pesticide use in the EU have led to the inception of the **Sustainable Use of Pesticides Regulation (SUR)**,[10, 11] dating back to the 6th Environmental Action Programme adopted in 2002. The SUR introduced relevant innovations within the pesticide framework, such as the concept of Integrated Pest Management and its principles. The Directive has been transposed into national legislation in all Member States.

The **European Green Deal**, launched in 2019, aims to make the EU economy sustainable by 2030 and establish Europe as the first carbon-neutral continent by 2050.[12] A set of strategies, action plans, and missions have been devised as part of the Green Deal, including the Farm to Fork Strategy,[13] Biodiversity Strategy,[14] Chemicals Strategy,[15] Zero Pollution Action Plan,[16] and the Horizon Europe Mission on Soil Health and Food.[17] Although, pesticide sales in all European countries had been on a downward trend up until 2020 (EUROSTAT data), between 2020 and 2021- there has been an increase of 2.7% in the volume of pesticides sold in the EU. Three Mediterranean countries (Spain, France and Italy) have reported the highest selling volumes among all EU countries. This increase in pesticide use could be linked to global increase of plant pathogens, associated with climate change.[18]

These initiatives have prompted a review of the EU pesticide policy framework to align it with the ambitious environmental goals of the Green Deal. To address the challenge of sustainable food systems, the **Farm to Fork Strategy** introduces two pesticide-related objectives, which are also included in the **Biodiversity Strategy**, aiming to reverse ecosystem degradation and protect nature by 2030:

1. to reduce overall chemical pesticide use and risk by 50%.
2. to reduce the use of the most hazardous pesticides by 50%.

Under the **Water Framework Directive**, the **Watch List strategy** has been developed with particular focus on the monitoring of a series of emerging contaminants that could be a risk for human health and the environment.[19] Although currently there is not enough data to determine the associated risks, the List is reviewed every 3 years to incorporate new contaminants or withdraw some of the existing. Within the

[10] European Parliament (2017). 'Directive 2009/128/EC on the sustainable use of pesticides European Implementation Assessment'. European Parliamentary Research Service.

[11] European Commission (2021). 'Sustainable use of pesticides'. European Commission, Food Safety.

[12] The European Green Deal (2019). Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions.

[13] European Commission (2020). 'Farm to Fork Strategy: For a Fair, Healthy and Environmentally-Friendly Food System'.

[14] European Commission (2020). Communication from the commission to the European parliament, the council, the European economic and social committee and the committee of the regions: EU Biodiversity Strategy for 2030. Bringing nature back into our lives.

[15] European Commission (2019). 'Chemicals Strategy'. European Commission, Environment.

[16] European Commission (2021). 'Zero pollution action plan: towards zero pollution for air, water and soil'. European Commission, Environment.

[17] European Commission (2020). 'Horizon Europe's Mission on Soil Health and Food'.

[18] Singh, B. K., Delgado-Baquerizo, M., Egidi, E., Guirado, E., Leach, J. E., Liu, H., & Trivedi, P. (2023). Climate change impacts on plant pathogens, food security and paths forward. Nature Reviews Microbiology, 21(10), 640-656.

[19] European Commission (2020). 'EU Mission: A Soil Deal for Europe: What this EU mission is, how EU Missions will be implemented, mission boards, meetings, news, events. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance document on Eutrophication assessment in the context of European water policies. WFD CIS Guidance Document No. 23.

framework of the iMERMAID project, a series of contaminants of emerging concern have been addressed, including the following agrochemical compounds (Table *1*):

Table 1: iMERMAID's project agrochemicals of emerging concern.

Class	Compound
Phenylurea pesticide	Diuron
	Isoproturon
	Fenuron
N-methyl carbamate	Carbofuran
	3,4,5-Trimethacarb
Triazine pesticide	Atrazine
	Cybutryne
	Simazine
	Terbutryn

2.2 Possible Solution

2.2.1 Description

Mitigating Contamination caused by the use of agrochemicals requires a **holistic assessment that considers the integration of different solutions**. With increasing population growth and changing demands, especially from emerging economies, it is necessary to consider how farmers can further adapt to meet consumer demand while maintaining their competitiveness in the global market.

Pesticides have enabled a substantial increase in agricultural yields by preventing and eradicating harmful plant organisms. This increase in food production has supported population growth throughout the 20th century. **Without physical, biological or chemical intervention, agricultural production losses could soar to an 70 %** on a global scale.[20] Therefore, assuming that the use of agrochemicals is essential to maintain the necessary crop levels required to supply the world population, it becomes essential to find balanced solutions to reduce environmental pollution while upholding essential agricultural productivity levels.

Technological advances, including bio- and nanotechnology, robotics, drone vehicles, artificial intelligence (AI), machine learning (ML) have provided a means to improve pest management and reduce dependence on pesticide use. Furthermore, R&D strategies are increasingly focused on alternative options to chemical pesticides, such as genetically modified (GM) crops, biological/plant, bio-stimulants and precision/smart agriculture. In the search for alternatives to pesticide use upstream, two types of solutions emerge: those

[20] Gupta, G. (2019). Land degradation and challenges of food security. Rev. Eur. Stud., 11, 63.

involving the use of substitute chemical compounds for the identified CoECs and non-chemical alternatives supported by the latest technological advances.

Non-chemical alternatives

Cultural control is one of the first alternatives designed to reduce the use of pesticides. It is the deliberate alteration of the production system by targeting the pest itself through agronomic practices to avoid or reduce pest injuries to crops. Crop rotation, intercropping, sanitation, trap crops and pest resistant crop plants are few examples of cultural control. These individual tactics of cultural control tend to be pest and crop specific.[21]

Physical and mechanical controls either kill insects and small rodents, or make the environment unsuitable for them by attacking, or setting up barriers. These methods are used for crop growing and household pest management.[22] Within these control techniques, methods include control through barriers, traps, fire, temperature, radiation and ultrasonic vibration.

Biological alternatives can be used as a replacement of chemical pesticides to leave the ecosystem undisturbed: Biological control involves the suppression of reproductive organisms through the actions of parasites, predators or pathogens to restrict pest population at a lower average density.[23] Biopesticides are based on pathogenic microorganisms or natural products that generally kill pests. Additionally, botanicals, *semiochemicals*[24] and transgenic plants can sometimes be described as biopesticides. Organisms that have altered genomes are known as transgenic organisms. Among them, genetic modification with recombinant DNA techniques is the most used way of generating pest-resistant plants. Resistance against plant pathogens has been achieved by transferring genes from viruses into plants, bacteria, fungi, and other plants and insects.[25]

Precision agriculture was established in the late 1980's on the basis of agricultural mechanization through the integration of global positioning system (GPS), geographic information system (GIS) and remote-sensing technologies.[26] Precision agriculture has recently been gaining more ground meaning that new pesticides could be designed to be applied more selectively and specifically, thereby reducing the amount of chemicals needed and minimizing unwanted exposure. The rapid evolution of robotics, drones equipped with remote sensors, deep learning, artificial intelligence, artificial vision and IoT technologies bode well for optimal land mapping and utilization of precision agriculture in the coming decades.

Integrated Pest Management (IPM) is a tool used for pest management involving minimal pesticide use. Its goal is to limit pesticide use to economically viable and ecologically justified levels, minimizing risks to human health and the environment,[27] as established in the Sustainable Use of Pesticides Directive. IPM

[21] Ferr, D. (2003). Cultural Control. Radcliffe's IPM World Textbook. Available from: http://ipmworld.umn.edu/ferro.
[22] Hossain, L., Rahman, R., & Khan, M. S. (2017). Alternatives of pesticides. Pesticide residue in foods: sources, management, and control, 147-165.
[23] DeBach, P., & Schlinger, E. I. (1964). Biological control of insect pests and weeds: 844-101.Deblonde, T., Cossu-Leguille C. and Hartemann, P. (2011), "Emerging pollutants in wastewater: A review of the literature", International Journal of Hygiene and Environmental Health, Vol. 214(6), pp. 442-448, DOI: org/10.1016/j.ijheh.2011.08.002.
[24] Greek word "semeon" means "signal"
[25] Kuiper, H. A., Kleter, G. A., & Noordam, M. Y. (2000). Risks of the release of transgenic herbicide-resistant plants with respect to humans, animals, and the environment. Crop protection, 19(8-10), 773-778.
[26] Huang, Y., & Brown, M. (2019). Advancing to the next generation of precision agriculture. Agriculture & food systems to, 2050, 285a.
[27] Dhawan, A. K., & Peshin, R. (2009). Integrated pest management: concept, opportunities and challenges. Integrated Pest Management: Innovation-Development Process: Volume 1, 51-81.

considers chemical control as the last option for pest management and encourages a combination of alternative control techniques, such as crop rotation and mechanical weeding. Conservation agriculture is a set of practices that promote permanent soil cover, minimal soil disturbance and plant species diversification. These practices aim to improve the productivity of existing agricultural lands and regenerate lands left in poor condition due to intensive crop production.

Chemical alternatives

Complementary to the efforts for adopting non-chemical alternatives, the development of new chemical pesticides with greater safety for humans and the environment, resistance management and integration with biological control will continue to be necessary for stable agricultural production.[28] As pests and diseases evolve and develop resistance to existing pesticides, new products will emerge to address these challenges. This includes development of pesticides with different modes of action or the use of techniques such as gene editing to create more resistant crops.

The growing demand for **new pesticides that are less toxic to non-target organisms** and degrade more rapidly in the environment has led to the development of new phytosanitary products, whose lower environmental toxicity needs to be confirmed over the coming years. Some examples of new pesticides with novel modes of action are the following: fungicide ipfufenoquin was developed by Nippon Soda to control many diseases of fruit trees and tea;[29] mefentrifuconazole, developed by BASF, inhibits biosynthesis of sterols in cell membranes with high efficacy to control key fungal diseases of pome and stone fruit, grapevine, potato, soybean and other crops;[30] tetrazolinone fungicide metyltetraprole, developed by Sumitomo Chemical, has been developed for the control of major diseases such as scab and bitter rot of apple and leaf blight of sugar beet.[31]

Recently, the use of **photodynamic inactivation** (PDI), traditionally used in cancer treatments, has been explored in agriculture as an alternative to traditional chemistries, mainly as a promising new approach for the eradication of pesticide-resistant strains. Several photosensitizers such as curcumin, porphyrin, methylene blue, coumarins or chlorophyllin-chitosan complex as been used against different fungi and bacteria species.[32]

Finally, the recent inclusion of **nanotechnology** for the development of new pesticides allows to create more effective and selective pesticides. Nanoparticles are commonly designed to gradually release agri-inputs in the current cropping system to achieve higher efficiency and reduce the need for frequent applications. As examples, zinc oxide nanoparticles have been used against *Botrytis cinerea* (Sclerotiniaceae

[28] Lamberth, C., Jeanmart, S., Luksch, T., & Plant, A. (2013). Current challenges and trends in the discovery of agrochemicals. Science, 341(6147), 742-746.
[29] National Center for Biotechnology Information (2024). PubChem Patent Summary for WO-2022243810-A1, Novel agrochemical composition comprising piperidine thiazole compounds.
[30] Gao, Y., Liu, Y., He, L., Zhu, J., Wu, B., Liu, F., & Mu, W. (2021). Activity of the novel fungicide mefentriflu-conazole against Colletotrichum scovillei. Plant Disease, 105(05), 1522-1530.
[31] Matsuzaki, Y., Watanabe, S., Harada, T., & Iwahashi, F. (2020). Pyridachlometyl has a novel anti-tubulin mode of action which could be useful in anti-resistance management. Pest management science, 76(4), 1393-1401.
[32] Islam, M. T., Sain, M., Stark, C., Fefer, M., Liu, J., Hoare, T., ... & Rosa, C. (2023). Overview of methods and considerations for the photodynamic inactivation of microorganisms for agricultural applications. Photo-chemical & Photobiological Sciences, 22(11), 2675-2686.

Ascomycote Fungi)[33] or silver nanoparticles against both *Staphylococcus aureus* (Staphylococcaceae Bacili Bacteria) and *Escherichia coli* (Enterobacteriaceae Pseudomonadota Bacteria).[34]

2.2.2 Benefits and bottlenecks

Reducing the use of pesticides has undoubted positive effects on the sustainability of both terrestrial and aquatic ecosystems and on people's health. However, there are a series of elements influencing the transition to greener agriculture, among which are political and legal, economic, technological and sociocultural factors.

The multiplicity of interests of stakeholders (such as the agrochemical industry, policymakers, farmers and citizens) makes it challenging to achieve the EU's objectives to reduce pesticide usage and its risks to the environment and human health. The current assessment and the potential planned revision of the aforementioned SUR are crucial for achieving these objectives. However, it is not the only piece of **EU legislation** that must be considered. The reform of the Common Agricultural Policy (CAP) could also play a significant role in achieving more sustainable pesticide use[35]. The **European Commission** aims to make the new CAP compatible with the European Green Deal, ensuring that the reform succeeds in making the agricultural sector greener. Financial incentives for climate and environmentally friendly practices, including eco-schemes and measures under the Rural Development Program, are of paramount importance. Stronger mechanisms to monitor Member States' progress in implementing their Green Deal objectives and National Strategic Plans are essential if success is to be achieved.

The economic factor is one of the most significant in the implementation of solutions leading to a reduction in pesticide usage, and consequently, the discharge of CoECs into the environment. It is important to highlight the **high volatility that both production costs and the sale price** of agricultural products in the market have experienced in recent years. The implementation of new technologies for the replacement of CoECs can have a direct impact on the profitability of an economic activity with narrow margins, and therefore, its competitiveness in the short-term market. This implies that the acceptance of such solutions by farmers depends on their specific economic situation. It is noteworthy that the volatility and the immediate cost of the implementation of new technologies have greater impact for small farmers than for large production companies.

From a **technological standpoint**, it is crucial to achieve an appropriate level of maturity in emerging technologies. One important factor to consider for the scale up of new solutions is that the agricultural sector is generally very traditional. Therefore, it will be essential to undertake efforts to approach, raise awareness and demonstrate the benefits of adopting new and more sustainable practices for their activity.

Current **sociocultural trends** and increased level of ecological awareness favour the arrival of more sustainable products in the market, which promote healthier consumption and cause less harm to the environment by reducing the production of CoECs. However, during times of economic recession, the price of the product could be the deciding factor among potential competitors, thus favouring the use of lower-cost pesticides. Regarding producers, another potential bottleneck will be the acceptance of technologies

[33] Kairyte, K., Kadys, A., & Luksiene, Z. (2013). Antibacterial and antifungal activity of photoactivated ZnO nanoparticles in suspension. Journal of Photochemistry and Photobiology B: Biology, 128, 78-84.
[34] Pudake, R. N., Mohanta, D. T. K., & Mahato, N. Opportunities and Challenges for Nanotechnology in Sus-tainable Agri-Food Production. Frontiers in Nanotechnology, 6, 1420192.
[35] European Commission. (2021). 'The new common agricultural policy: 2023-27'.

such as irradiation or genetic modification. As mentioned earlier, the agricultural sector is not particularly prone to adopting new technologies, so significant efforts will be required in information dissemination, education on new technologies and access to R&D project results.

2.3 Case study: Carbofuran

One of the most widely used pesticides is carbofuran [2,3-dihydro-2,2-dimethyl-7-benzofuranyl-N-methyl-carbamate], an anticholinesterase carbamate known for its effectiveness as an insecticide, nematicide and acaricide in gardening, forestry and agriculture[36]. **Carbofuran is a broad-spectrum pesticide** and is effective by killing nematodes, mites and insects following ingestion or contact[37]. It was frequently employed to eliminate pests located in the soil or on the leaves of fruit or vegetable crops[38]. The application rate of carbofuran is typically calculated in gram of active ingredient per hectare. Carbofuran has been widely employed since its development in the 1960s and has become one of the most prevalent pesticides globally. The demand for carbofuran was driven by its effectiveness in pest control and its relative affordability for farmers.

While carbofuran is generally considered effective as a pesticide, compared to other crop protection products such as organophosphates, **it has shown persistence in the environment and resistance to degrade in wastewater treatment processes**. Its presence in the environment is primarily attributed to runoff from agricultural fields and direct application to agricultural soils[39]. Despite its efficacy in pest control, the continued use of carbofuran has raised concerns about its impact on human health and the environment, leading to stricter regulations on its application and sales in some countries. Thereby, it was banned in the European Union since 2007 due to its serious risks to human health and the environment (Directive 91/414/EEC[40], later replaced by Regulation (EC) No 1107/2009[41] and Regulation (EU) 2015/399[42]). These regulations strictly govern the authorization, marketing and use of pesticides in the EU, as well as the

[36] Kempuraj, D., Zhang, E., Gupta, S., Gupta, R. C., Sinha, N. R., & Mohan, R. R. (2023). Carbofuran pesticide toxicity to the eye. Experimental eye research, 227, 109355.
[37] Grawe, G. F., de Oliveira, T. R., de Andrade Narciso, E., Moccelini, S. K., Terezo, A. J., Soares, M. A., & Cas-tilho, M. (2015). Electrochemical biosensor for carbofuran pesticide based on esterases from Eupenicilli-um shearii FREI-39 endophytic fungus. Biosensors and Bioelectronics, 63, 407-413.
[38] Brkić, D. V., Vitorović, S. L., Gašić, S. M., & Nešković, N. K. (2008). Carbofuran in water: subchronic toxicity to rats. Environmental toxicology and pharmacology, 25(3), 334-341.
[39] Otieno, P. O., Lalah, J. O., Virani, M., Jondiko, I. O., & Schramm, K. W. (2010). Soil and water contamination with carbofuran residues in agricultural farmlands in Kenya following the application of the technical formulation Furadan. Journal of Environmental Science and Health Part B, 45(2), 137-144.
[40] Comission Decision (2007). Concerning the non-inclusion of carbofuran in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance. Official Journal of the European Union. (2007/416/EC).
[41] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. Document 32009R1107. http://data.europa.eu/eli/reg/2009/1107/oj.
[42] Commission Regulation (EU) 2015/399 of 25 February 2015 amending Annexes II, III and V to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for 1,4-dimethylnaphthalene, benfuracarb, carbofuran, carbosulfan, ethephon, fenamidone, fenvalerate, fenhexamid, furathiocarb, imazapyr, malathion, picoxystrobin, spirotetramat, tepraloxydim and trifloxystrobin in or on certain products Text with EEA relevance. Document 32015R0399. http://data.europa.eu/eli/reg/2015/399/oj.

Maximum Residue Levels (MRL) of carbofuran originating from other compounds such as carbosulfan, benfuracarb or furathiocarb[43]. Despite its prohibition, in 2017 carbofuran levels exceeding the MRLs were published in water from various matrices, such as drinking water, phreatic aquifers and rainwater[44].

It is recorded that there are multiple side effects of this pesticide to humans through unintended human exposure[45]. There are multiple reports as recorded by US EPA indicating how individuals who have experienced carbofuran poisoning became exposed to the chemical including contact with eyes, face or hands following spraying application. It has also been reported respiratory toxicity and cardiac depression after oral ingestion[46]. Carbofuran presents significant risks to animals, aquatic environments and wildlife, with documented instances of both unintentional and intentional poisoning. Fish exposed to carbofuran have shown reproductive toxicity and cardiotoxicity[47]. Carbofuran's high solubility and low absorption on solids make it prone to surface water runoff, leading to its entry into natural water bodies. This runoff from localized spraying has led to fish kills attributed to carbofuran toxicity. Additionally, carbofuran is illegally used to intentionally kill wildlife, with reported cases in both countries where its agricultural use is permitted (Uganda) and countries where it is banned[48].

While alternatives for carbofuran as a nemacide are researched, a gap remains in identifying broader alternatives for carbofuran as a pesticide. Research on alternatives to pesticides encompasses various generic methods that could be adopted. These include cultural, physical and biological methods as alternatives to pesticides such as site selection, trap crops, adjusting planting time, elimination of food water or shelter, crop rotation, barriers, cold storage and heat treatment and the use of biopesticides.

The most promising specific alternatives to the use of carbofuran as a pesticide found in the literature are as follows:

Neem Leaf Extract (*Azadirachta indica*): Aqueous neem leaf extracts exhibit nematicidal properties and effectively target root-knot nematodes. Overall, their effectiveness was considered superior to carbofuran.[49]

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[43] Pesticide residue(s) and maximum residue levels (mg/kg). EU Pesticides Database (v3.2). Directorate-General for Health and Food Safety. European Comission. https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/mrls/details?lg-code=EN&pest_res_id_list=39&product_id_list=.

[44] Howard, P. (2017). Handbook of environmental fate and exposure data: for organic chemicals, volume III pesticides. Routledge.

[45] Sharma, R. K., Jaiswal, S. K., Siddiqi, N. J., & Sharma, B. (2012). Effect of carbofuran on some biochemical indices of human erythrocytes in vitro. Cellular and molecular biology, 58(1), 103-109.

[46] Yen, C. C., Hsieh, M. C., Tsai, M. J., & Chen, H. C. (2015). Human carbofuran intoxication with myocardial injury mimicking acute myocardial infarction. The Kaohsiung journal of medical sciences, 31(2), 112-113.

[47] Trotter, D. M., Kent, R. A., & Wong, M. P. (1991). Aquatic fate and effect of carbofuran. Critical Reviews in Environmental Science and Technology, 21(2), 137-176.

[48] Baharudin, N. S., Ahmad, H., & Hossain, M. S. (2024). Understanding the Degradation of Carbofuran in Agricultural Area: A Review of Fate, Metabolites, and Toxicity. Pertanika Journal of Science & Technology, 32(1).

[49] Nwankwo, E. N., Onuseleogu, D. C., Ogbonna, C. U., & Okorocha, A. O. E. (2016). Effect of neem leaf ex-tracts (Azadirachta indica) and synthetic pesticide (Carbofuran) on the root-knot nematode (Meloido-gynes pp.) of cowpea (Vigna unguiculata L. Walp). Int. J. Ento. Res, 3(1), 01-06.

Cow Dung (Organic Alternative): Application of cow dung to soil targets nematodes. While carbofuran demonstrated higher effectiveness over a shorter exposure time of three months, cow dung was deemed environmentally friendly and comparable results could be achieved with extended application periods.[50]

Mimosoid Tree Leaf Extract (*Leucaena leucocephala*): Aqueous application of crude extracts from mimosoid tree leaves is as effective as carbofuran against nematodes. Fractioned extracts have shown improved fruit yield in tomato crops while reducing nematode populations.[51]

Biological Control Fungi (*Trichoderma*): Trichoderma, a fungus colonizing near plant roots, provides a physical barrier against nematodes. It effectively reduces nematode populations and promotes plant growth.[52]

2.4 Future outlook

The **future scenario would include an estimated population increase** for 2050 (9.4-10 billion people) that will exert greater pressure on farmland, requiring increased productivity that can be achieved through various means, such as innovation strategies, digitization and automation of agricultural processes and alternative pest management strategies.

In Europe, due to limitations in land availability, agricultural yields are expected to primarily come from improved agricultural practices and continuous R&D. As such, **agricultural technology will be the main driver to increase yield productivity**, improve working conditions and meet environmental standards. At the global level, the agricultural technology market is expected to grow steadily, increasing from $17,442.7 million in 2019 to $41,172.5 million by 2027.[53] This growth will be driven by increased use of agricultural technology, greater horizontal and vertical integration of food chains and more investments in agricultural technology. It's likely that new European enterprises will continue to play a significant role in delivering major innovations in agricultural technology, including natural alternatives to chemical pesticides, urban farming, self-sufficiency and shorter supply chains.

With the aim of shaping future legislation, the European Union has considered 4 possible medium-term scenarios:[54]

- In one scenario, amid geopolitical instability and worsening climate change, the EU adopts inward-focused economic policies to bolster agricultural sector resilience. However, reductions in chemical pesticide use vary, requiring financial and policy support for innovation.

[50] Zafar, M. I., Khalid, A., Kali, S., Khan, F., Tahir, M., Ali, M., & Siddiqa, A. (2022). Organic amendments as an eco-friendly substitute of carbofuran for the suppression of nematodes associated with Malus pumila. South African Journal of Botany, 144, 187-193.

[51] Fabiyi, O. A., Claudius-Cole, A. O., Olatunji, G. A., Abubakar, D. O., & Adejumo, O. A. (2021). Response of Meloidogyne javanica to silver nanoparticle liquid from agricultural wastes. AGRIVITA, Journal of Agricul-tural Science, 43(3), 507-517.

[52] Shamalie, B. V. T., Fonseka, R. M., & Rajapaksha, R. G. A. S. (2011). Effect of Trichoderma viride and Car-bofuran (Curator) on management of root knot nematodes and growth parameters of gotukola (Centella asiatica L.).

[53] Preiss, M., Vogt, J. H. M., Dreher, C., & Schreiner, M. (2022). Trends Shaping Western European Agrifood Systems of the Future. Sustainability, 14(21), 13976.

[54] Joint Research Centre (2023). Imagining a sustainable Europe: four scenarios for 2050 and strategic areas for change. News Announcement.

- Another scenario depicts moderate economic growth and stable agricultural prices. Despite gradual consumer shifts towards eco-friendly diets, stronger regulatory incentives are lacking, leading to sustainability and innovation primarily driven by large corporations. Overall, chemical pesticide consumption declines.
- A third scenario prioritizes sustainable economic growth and environmental concerns, promoting alternative agricultural technologies and practices. Consumers' greener attitudes facilitate a rapid transition towards environmentally sustainable practices and reduced pesticide use.
- In a less favourable scenario, global recession shifts focus away from innovation and sustainability, resulting in limited resources for farmers to adopt new approaches. This leads to continued reliance on chemical pesticides, dominance of large corporations, and insufficient alternatives for pest management, despite stable agricultural production amidst climate change.

Additionally, there are various categories of **pesticides with different levels of risk**, some of which have been proposed as less harmful options for pest management (for example, biopesticides derived from living organisms), but which must adhere to environmental criteria to ensure crop sustainability. The replacement of old chemical compounds with phytosanitary activity with new compounds with less environmental impact would imply the appearance of new contaminants. The appearance of biotechnology or nanotechnology and its application in fertilizers and pesticides could lead to the emergence of new compounds that have not yet been identified and that would require a continuous surveillance effort by researchers, agronomists, technology providers and legislative authorities. Generally, these new contaminants will cause less harm to the environment and human health. Despite this, the development of new sensors for its detection, new studies on its bioaccumulation and new technologies for its elimination will continue to be necessary. The identification of these new contaminants is being addressed recently from a safe and sustainability by design (SSbD) approach, with the aim of identifying the environmental and human health hazards of new materials and processes before their implementation.

2.5 Conclusion

Addressing the utilization of pesticides containing CoECs and transitioning to safer, more sustainable alternatives is critical. These contaminants present significant threats to both human health and the environment, emphasizing the urgent need for innovative and responsible methods in agricultural pest management.

Effective management of pesticide usage is imperative for long-term sustainability. A variety of potential alternatives exist to mitigate pesticide reliance across different crops. These alternatives span from biological o Integrated Pest Management, organic farming, agroecological practices and technology-driven solutions like precision agriculture.

Policy strategies must establish a robust framework that enables farmers to adopt new practices with confidence, particularly during periods of economic downturn when investment in research and development may be limited. It's essential to consider the time required for implementing changes and provide support accordingly.

The adoption of solutions to prevent environmental contamination caused by the use of pesticides containing CoECs must begin with a **holistic approach**, which considers both reducing their use and replacing them with other compounds less harmful to the environment. To that end, policies should include the aforementioned strategies for reducing pesticides, as well as new innovative approaches and technological trends, which provide a range of opportunities not feasible in the past.

The establishment of **shared data spaces** within the European Union framework will serve as a significant trigger to accelerate the implementation of new data analytics-based technologies. To ensure that these solutions become effective as soon as possible, community policies must place significant emphasis on **disseminating the advantages of R&D projects**, especially to the numerous small farmers within the European Union (in comparison to other territories like the USA), in order to remove barriers to the adoption of new technologies and foster greater proactivity in their implementation following a participatory approach.

It is also crucial to continue focusing on CoECs that could arise in the future. Active surveillance should be conducted to monitor the emergence of new pesticide compounds, enabling the timely detection of potential environmental harms and immediate corrective measures. In this regard, the new European space data could expedite the detection and identification of these future CoECs.

Thereby, **governments, the agricultural industry and society** need to collaborate in driving this transition towards a more sustainable and environmentally respectful pest management.

3.0 Pharmaceuticals

3.1 What, where and why?

Approximately 2,000 active pharmaceutical ingredients (APIs) are globally dispensed in both prescription and non-prescription medications, as well as in veterinary drugs. As the global population and livestock numbers requiring healthcare continue to rise, the residues of these substances pose an increasing environmental concern.

Active pharmaceutical ingredients are found widely in the environment, in water, soil and taken up by plants. While the contribution of each emission source can vary by region and type, the primary sources of pharmaceutical contamination in the environment are untreated household wastewater and effluents from municipal wastewater treatment plants. Additionally, emissions from pharmaceutical manufacturing, as well as intensive agriculture and aquaculture, can create significant local pollution hotspots. Because pharmaceuticals are intentionally designed to interact with living organisms at low doses, even trace concentrations of pharmaceuticals in the environment can result in adverse effects on aquatic ecosystems.

The extent to which pharmaceuticals are removed in wastewater treatment plants (WWTPs) can vary significantly based on the specific types of pharmaceuticals present and the effectiveness of the wastewater treatment technologies employed. No single technique has been found to remove all relevant pollutants from wastewater. The removal rates of pharmaceuticals in WWTPs can vary widely, ranging from 0% to 97%, depending on the specific type of ingredient. Notably, anti-inflammatories, NSAIDs, are among the most resistant to the treatment processes currently in use (averagely 30-40 % removal rate)[55].

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a large group of drugs with analgesic, anti-inflammatory and antipyretic effects used in oral form as well as external application (e.g., ointments, gels) by humans and in the veterinary field. Consumption of these drugs worldwide is quite high with country-specific variations. NSAIDs include drugs such as ibuprofen, ketoprofen, naproxen, diclofenac and indomethacin. The fact that they are readily available, often without a prescription, relatively inexpensive and use considered safe, is contributing to the high consumption of these drugs.

Medications taken by humans or animals are retained in the body only to a small extent. A significant portion of them is removed from the body in their primary form or as metabolites with urine or faeces. Thus, high intake of NSAIDs results in significant amounts of them entering the environment through wastewater treatment plants, where they are disposed of in rivers, surface runoff or from farm discharges. Like most CoECs, NSAIDs are most often detected in the environment at rather low concentrations (~1-1000 ng/L) (Table *2*). However, these drugs can have a significant impact on the aquatic and terrestrial ecosystem. Scientific studies indicate that the presence of NSAIDs, in aquatic environments may disrupt microbial diversity, biomass composition, and enzymatic activity, thereby compromising crucial ecological processes and impacting indigenous species, leading to potential environmental risks[56].

[55] Deblonde, T., Cossu-Leguille, C., & Hartemann, P. (2011). Emerging pollutants in wastewater: a review of the literature. International journal of hygiene and environmental health, 214(6), 442-448.
[56] Wu, J. et al. (2023) Occurrence, removal and risk evaluation of ibuprofen and acetaminophen in municipal wastewater treatment plants: A critical review. Science of The Total Environment, 891:164600.

Table 2: Occurrence in aquatic environment.[57]

Analgesics and anti-inflammatories	Concentration, ng/L (Europe)	
	WWTP effluent	Inland Surface water
Naproxen	450-1,840	<0.3-146
Ibuprofen	134-7,100	14-44
Ketoprofen	225-954	<0.5-14
Diclofenac	460-3,300	21-41

3.2 Possible solutions

Green pharmacy initiatives involve developing manufacturing processes towards lower environmental impact or developing active pharmaceutical ingredients with lower environmental impact. For very toxic ingredients, even substance bans have been implemented. For example, diclofenac has been prohibited for veterinary use in India, Nepal and Pakistan due to the decline in vulture populations across the Indian subcontinent. Again, the German Environment Agency has recommended banning veterinary pharmaceuticals containing bioaccumulative and toxic substances. However, when considering a substance ban it is essential to weigh the potential loss of valuable human and animal health benefits against the cost of continued environmental damage. This decision also necessitates an alternatives assessment to ensure that a substitute pharmaceutical with lower environmental risk is available, rather than simply shifting pollution from one substance to another.

Manufacturing of active pharmaceutical ingredients (API) is known to produce significantly larger environmental impacts than manufacturing of commodity chemicals. This prompted the pharmaceutical industry to adopt sustainable manufacturing practices for API synthesis[58]. Despite the fact that the pharmaceutical industry has been at the forefront of adopting green chemistry (GC), the market penetration of green pharmaceuticals remains limited. Also, there is limited information available regarding the adoption of GC by generic drug companies and active pharmaceutical ingredient (API) manufacturers, which currently produce the majority of drugs on the market.

In 2018 it was revealed that the primary barriers to greater adoption of green chemistry are time pressures to develop new drugs and regulatory risks[59]. On the other hand, cost savings and environmental regulations are the key drivers promoting green chemistry adoption. While many companies have some activities in the area, the study also highlighted that the major part (81%) of these companies have not publicly committed to adopting green chemistry principles. Additionally, 43% did not employ any GC metrics, 24%

[57] OECD (2020). Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, IWA Publishing. 137 pp.
[58] Wang D., Cheow, W., Amalina, N., Faiezin, M., Hadinoto, K. (2021) Selecting optimal pharmaceutical excipient formulation from life cycle assessment perspectives: A case study on ibuprofen tablet formulations, Journal of Cleaner production, Vol.292,126074.
[59] Veleva, V., Cue, BW ; Todorova, S. (2018) Benchmarking Green Chemistry Adoption by the Global Pharmaceutical Supply Chain ACS Sust. Chem. & Eng. Vol 6(1) pp 2-14.

did not invest in green technologies, and 58% were not engaged in any external collaborations to further GC initiatives.

The use of biodegradable pharmaceuticals with low intrinsic toxicity can be an ecologically sound choice. However, the potency and stability of pharmaceuticals are often crucial for their effectiveness in human and animal health. A long-term strategy for reducing the environmental risks of pharmaceuticals at the source is the design and manufacturing of new green pharmaceuticals. These refer to the creation of drug molecules that are both biodegradable and pharmacologically active without accumulating in or harming the environment.

While the biodegradable alternatives to NSAID active ingredients are very limited, production has evolved towards processes generating less side products and less waste[60]. Few significant development steps have been taken also in the NSAID domain (e.g., ibuprofen) but these are still limited. However, success stories exist among other types of medicine. For instance, research on enzymes has led to innovative pharmaceuticals and cancer treatments with reduced waste[61]. New biodegradable antibiotics combined with targeted delivery mechanisms could minimize accumulation in freshwater ecosystems and reduce the development of antibiotic resistance.

One main reason is the lack of incentive to invest in pollution prevention and green chemistry. Most environmental, health, and safety regulations prioritize risk control through exposure reduction using end-of-pipe technologies, reflecting a regulatory focus on risk control rather than risk prevention.

In the design of commercial-scale processes for pharmaceuticals and pharmaceutical ingredients, it is crucial for process development to adhere to regulatory guidelines to secure regulatory approval upon product launch.[62] While several regulatory guidelines align well with the principles of green chemistry, certain expectations related to drug substance quality and process controls can pose challenges to the implementation of green chemistry principles and process modifications.

Overall, green chemistry is often complex and multidisciplinary, accompanied by significant uncertainties. The emerging field necessitates innovative approaches and connections between environmental science, green chemistry, and pharmacology. Many processes lack known greener alternatives. New formulations and degradation products must undergo rigorous toxicity testing, considering both the toxicity of the parent compound and its degradation products. The absence of clear definitions and metrics for researchers and decision-makers further complicates matters.

In 2023, the Commission put forward a "pharmaceutical package" to revise the EU's pharmaceutical legislation. It includes proposals for a new directive and a new regulation, which aim to make medicines more available, accessible and affordable, while supporting the competitiveness and attractiveness of the EU pharmaceutical industry, with higher environmental standards. The reform aims at promoting environmentally sustainable production of medicines. The new regulations are also designed to reinforce the

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[60] Grimaldi, F., Tran, N., Sarafraz, M., Lettieri, P., Morales-Gonzalez, O. and Hessel V. (2021) Life Cycle Assessment of an Enzymatic Ibuprofen Production Process with Automatic Recycling and Purification. ACS Sustainable Chem. Eng. Vol 9, 13135−13150

[61] UN Environment (2019), Global Chemicals Outlook II: From legacies to innovative solutions, United Nations Environment Programme.

[62] Becker, J., Manske, C., & Randl, S. (2022). Green chemistry and sustainability metrics in the pharmaceutical manufacturing sector. Current Opinion in Green and Sustainable Chemistry, 33, 100562.

mandatory environmental risk assessment (ERA) for all pharmaceutical companies introducing medical products into the EU market.

3.2.1 Description

Given the potential risks associated with NSAIDs, and that the demand for such substances is most likely to only increase in the future, exploring alternative treatments is essential. Herbal supplements with anti-inflammatory properties may offer natural alternatives. Other strategies encompass diverse physical approaches, including physical therapy, relaxation techniques, and complementary therapies such as acupuncture or massage.

Herbal supplements with anti-inflammatory properties may offer natural alternatives to synthetic persistent NSAIDs. Among others the following traditionally used herbs have been reviewed for their effects: St John's Wort,[63,64] ; Ginger[65]; various Chinese traditional medicinal ingredients e.g., *Corydalis yanhusuo, Ligusticum chuanxiong*, and *Aconitum carmichaeli,*[66,67] ; Curcumin (Turmeric)[51]; Capsaicin (red chili extract)[68,69] and Spirulina[70].

One main question about using herbal remedies to alleviate acute or chronic pain is related to their ability to respond quickly. The time to reach effect is usually longer compared to synthetic NSAIDs[71]. Also, some reviews indicate that herbal ingredients are most efficient in topical treatment. Only very few natural active ingredients have been officially approved as pain relief ingredient in the EU. One exception is the topical application of capsaicin, which has been approved in the European Union and by FDA in USA for the treatment of non-diabetic neuropathic pain[72].

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[63] Jahromi, B., Pirvulescu, I., Candido, K., Knezevic, N. (2021) Herbal Medicine for Pain Management: Efficacy and Drug Interactions. Pharmaceutics. 2021 Feb 11;13(2):251.

[64] Galeotti N., Vivoli E., Bilia, A., Vincieri, F., Ghelardini, C. (2010) St. John's Wort reduces neuropathic pain through a hypericin-mediated inhibition of the protein kinase Cgamma and epsilon activity. Biochem Pharmacol. 79(9):1327-36.

[65] Kopustinskiene, D. M., Bernatonyte, U., Maslii, Y., Herbina, N., & Bernatoniene, J. (2022). Natural herbal non-opioid topical pain relievers—comparison with traditional therapy. Pharmaceutics, 14(12), 2648.

[66] Luo, Y, Wang, C., Sawadogo, R., Tan, T. and Yuan, C. (2020) Effects of Herbal Medicines on Pain Management. Am J Chin Med.;48(1):1-16.

[67] Dasgupta, A. (2019) 'Chapter 4 - Antiinflammatory Herbal Supplements', in J.K. Actor and K.C. Smith (eds) Translational Inflammation. Academic Press (Perspectives in Translational Cell Biology), pp. 69–91.

[68] Mankowski, C.; Poole, C., Ernault, E., Thomas, R.; Berni, E., Currie, C., Treadwell, C., Calvo, J., Plastira, C., Zafeiropoulou, E.; et al. (2017) Effectiveness of the Capsaicin 8% Patch in the Management of Peripheral Neuropathic Pain in European Clinical Practice: The Ascend Study. BMC Neurol. 17, 80.

[69] Jahromi, B., Pirvulescu, I., Candido, K. D., & Knezevic, N. N. (2021). Herbal medicine for pain management: efficacy and drug interactions. Pharmaceutics, 13(2), 251.

[70] Abu-Taweel, G. et al. (2019) 'Spirulina consumption effectively reduces anti-inflammatory and pain related infectious diseases', Journal of Infection and Public Health, 12(6), pp. 777–782.

[71] Kopustinskiene, D. M., Bernatonyte, U., Maslii, Y., Herbina, N., & Bernatoniene, J. (2022). Natural herbal non-opioid topical pain relievers—comparison with traditional therapy. Pharmaceutics, 14(12), 2648.

[72] Arora, V., Campbell, N., Chung, M-K. (2021). Fight fire with fire: Neurobiology of capsaicin-induced analgesia for chronic pain, Pharmacology & Therapeutics, Vol 220, 107743.

In addition to traditional herbal supplements, phsyco-physical Interventions such as massage,[73,74,75] , studies on mindfulness, breathing and relaxation sessions [76,77] also indicate some pain-relieving effect and can be applied as supplement to chemical/natural ingredients, lowering the consumption and thereby the load on the environment of NSAIDs.

3.2.2 Benefits and bottlenecks

NSAIDs are widely used for their effectiveness in pain relief and anti-inflammatory properties. The widespread use of NSAIDs can be attributed to their affordability, making them accessible to a broad segment of the population. Additionally, NSAIDs are considered relatively safe with minimal side effects when used as directed. Their safety profile is supported by extensive research, and they are widely available over-the-counter in many countries, further contributing to their popularity and widespread use. Current producers base generally their operations on high volume production minor interest in developing competing agents.

While natural herbal medicines are available as alternatives, they are generally not perceived as being as efficient as NSAIDs. Complementary and alternative medicines such as herbal medicines are not currently part of the conventional medical system. As the popularity of and global market for herbal medicine grows among all age groups, with supporting scientific data and clinical trials, specific alternative treatments such as herbal medicine can be reclassified as a practice of conventional medicine. One of the most common conditions for which adults use herbal medicine is pain. However, herbal medicines carry safety concerns and may impact the efficacy of conventional therapies. Unfortunately, mechanisms of action are poorly understood, and their use is unregulated and often underreported to medical professionals.

3.3 Case: Ibuprofen

One of the most commonly applied anti-inflammatory drugs is Ibuprofen, renowned for its pain-relieving, anti-inflammatory, and antipyretic properties. Its widespread utilization highlights its pain reliving effectiveness and general availability. This over the counter, non-prescriptive drug is used for various symptoms, spanning from mild headaches to menstruation pains and chronic arthritic discomfort. Ibuprofen was developed rapidly since the end of the 1970s and is used widely throughout the world, becoming one of the most popular nonprescription drugs. In recent years, the sales of ibuprofen in Europe and the United States have increased with an average rate of 2%-4% per year in addition to a growth rate of approximately 10%

[73] Kutner, J. et al. (2008) Massage Therapy versus Simple Touch to Improve Pain and Mood in Patients with Advanced Cancer, Annals of Internal Medicine, 149(6), pp. 369–379.
[74] Mitchinson, A. et al. (2014) 'Integrating Massage Therapy Within the Palliative Care of Veterans With Advanced Illnesses: An Outcome Study', American Journal of Hospice and Palliative Medicine®, 31(1), pp. 6–12.
[75] Pedersen, K. and Björkhem-Bergman, L. (2018) 'Tactile massage reduces rescue doses for pain and anxiety: an observational study', BMJ Supportive & Palliative Care, 8(1), pp. 30–33.
[76] De Paolis, G. et al. (2019) The effectiveness of progressive muscle relaxation and interactive guided imagery as a pain-reducing intervention in advanced cancer patients: A multicentre randomised controlled non-pharmacological trial. Complementary Therapies in Clinical Practice, 34, pp. 280–287.
[77] Beng, T. et al. (2019) 'The Effect of 20-Minute Mindful Breathing on the Perception of Suffering and Changes in Bispectral Index Score in Palliative Care Patients: A Randomized Controlled Study', American Journal of Hospice and Palliative Medicine®, 36(6), pp. 478–484.

in the South Asian subcontinent[78]. Market forecasts indicate a steady increase (2.5% CAGR) during the next decades. Geriatric patients form a widespread consumer base for ibuprofen APIs. As a non-steroidal anti-inflammatory drug, it aids in relieving pain, reducing fever, and decreasing inflammation. Moreover, demand for ibuprofen APIs is rising as the incidence of chronic diseases such as rheumatoid arthritis and migraine increases especially in developing nations[79].

While ibuprofen is generally considered a safe medical alternative with little side effects, compared to some other NSAIDS, e.g., acetylsalicylic acid, it has shown high resistance to removal in commonly applied wastewater treatment processes[80]. Its occurrence in the environment (Table *3*) is primarily attributed to direct discharges from wastewater treatment plants (WWTPs) and hospital wastewater into aquatic environments[81].

Table 3: Measured concentration ranges of ibuprofen in different sources, 2018-2019.

Sources	Concentration ranges, $ng \cdot L^{-1}$
Surface water	4–6300
WWTPs influent	46 –81000
Hospital wastewater	88 – 141000
Groundwater	49-750
Drinking water	0-97

Scientific studies indicate that the presence of NSAIDs, including ibuprofen, in aquatic environments may disrupt microbial diversity, biomass composition, and enzymatic activity, thereby compromising crucial ecological processes and impacting indigenous species, leading to potential environmental risks[82]. Furthermore, during its degradation process (chemical or biological), the transformation products produced are more toxic than the original compound, exacerbating the environmental contamination problem[83].

[78] Zhang, S., Qing, Q., Bai, Y., Mao, H., Zhu, W., Chen, Q., & Chen, Y. (2013). Rebamipide helps defend against non-steroidal anti-inflammatory drugs induced gastroenteropathy: a systematic review and meta-analysis. Digestive diseases and sciences, 58, 1991-2000.
[79] fmi (2024) demand for ibuprofen APIs is rising as the incidence of chronic diseases such as rheumatoid arthritis and migraine increases especially in developing nations. Ibuprofen API Market. Future Market Insights.
[80] Pope, C. 2023. What's the difference between aspirin and ibuprofen? https://www.drugs.com/medical-answers/
[81] Hernández-Tenorio, R.; González-Juárez, E.; Guzmán-Mar, J. , Hinojosa-Reyes, L. and Hernández-Ramírez, A. (2022) Review of occurrence of pharmaceuticals worldwide for estimating concentration ranges in aquatic environments at the end of the last decade. J. Haz. Mat. Adv. Vol 8.
[82] Wu, D., Sui, Q., Mei, X., Yu, X., Gu, Y., & Zhao, W. (2022). Non-antibiotics matter: Evidence from a one-year investigation of livestock wastewater from six farms in East China. Science of The Total Environment, 846, 157418.
[83] Jan-Roblero, J. and Cruz-Maya, J. 2023 Ibuprofen: Toxicology and Biodegradation of an Emerging Contaminant. Molecules. 28(5):2097.

While there is a lack of explicit mention of alternative drugs with lower environmental impacts compared to ibuprofen, some studies suggest that ibuprofen and diclofenac present a high ecotoxicological risk, while naproxen and ketoprofen pose a moderate risk to non-target organisms[84, 85].

The previous chapters discussing NSAIDs, revealed that finding effective, environmentally friendly substitutes with better degradability is challenging. Although we do not expect more eco-friendly alternatives to ibuprofen to emerge soon, the manufacturing process itself has evolved towards greener synthesis with reduced waste production. BHC Company, for instance, has developed an environmentally friendly industrial synthesis of ibuprofen that involves only three steps, resulting in minimal unwanted byproducts. This method boasts high material efficiency, with acetic acid being the sole by-product, which can be repurposed for other applications[86]. Furthermore, research into biochemical routes has shown promise in reducing the chemical load in manufacturing discharges[87].

3.4 Future Outlook

Compared to some other environmentally high-risk chemical applications, such as PFASs, the use of pharmaceuticals is not foreseen to decrease in the future. Market research foresee a steady increase in volumes during the next decade. Moreover, as the world's population ages, there is a high risk that the environmental challenges related to contamination by pharmaceutical will only become larger. Proper disposal of unwanted medicines, improved sewage treatment, and the development of more environmentally friendly drugs are crucial steps to address this issue. While the European legislation has recently taken steps towards imposing quaternary treatment in larger wastewater treatment plants and thereby focussing on end of pipe solutions, there is less policy emphasis on promoting the development of alternative, environmentally friendly substances.

Factors favouring the increased use of current NSAIDs include their safe and easy use compared to many other analgesics like opioids, their affordability, and the lack of a need for a prescription, making these products highly accessible to the general public. Conversely, it is also foreseeable that the currently limited environmental risk assessment data on pharmaceuticals will become more robust and widely shared in the future. This can support green procurement initiatives and guide consumers towards alternative choices with a lower environmental impact.

Looking broadly at solution to be applied throughout the life cycle of pharmaceuticals one can note that efficient measures are likely to take place already in the design phase. Incentives for innovation in green pharmacy, biological therapies and personalised or precision medicines are here of highest importance. Associated with marketing authorisation of a drug is enforcement of legislation and standardised

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[84] Praveenkumarreddy, Y., Vimalkumar K., Ramaswamy B., et al. (2021) Assessment of non-steroidal anti-inflammatory drugs from selected wastewater treatment plants of Southwestern India. Emerging Contaminants, 7, pp. 43–51.
[85] Wojcieszyńska, D., Guzik, H. and Guzik, U. (2022) 'Non-steroidal anti-inflammatory drugs in the era of the Covid-19 pandemic in the context of the human and the environment', Science of The Total Environment, 834:155317.
[86] Muresan, A. (2018) Ibuprofen: Original versus green synthesis. The annals of "DUNAREA DE JOS" University of Galati Fascicle IX. Metallurgy and materials Science No. 3.
[87] Grimaldi, F., Tran, N., Sarafraz, M., Lettieri, P., Morales-Gonzalez, O. and Hessel V. (2021) Life Cycle Assessment of an Enzymatic Ibuprofen Production Process with Automatic Recycling and Purification. ACS Sustainable Chem. Eng. Vol 9, 13135−13150.

methodology for environmental risk assessment. More stringent conditions for putting a pharmaceutical on the market that is of high risk for the environment (e.g., eco-labelling, prescription only).

There are several mitigation options for water quality improvement in the pharmaceutical life cycle, including improvements in the design (e.g., green pharmacy), registration and authorisation, production, use and waste phases, and finally technological interventions of WWTPs. A focus on preventive options early in a pharmaceutical's life cycle, may deliver the most long–- term and large-scale benefits. However, in combination with source-directed and use-orientated approaches, extra treatment at the level of WWTPs may play a role in reducing human pharmaceuticals reaching the environment, particularly in light of growing demand for pharmaceuticals by society.

3.5 Conclusion

No single policy instrument is capable of managing all sources of pharmaceutical pollution in the aquatic environment. Likewise, there is no single culprit responsible for pharmaceutical pollutants reaching water bodies.

A focus on preventive options early in the pharmaceutical life cycle, may deliver the most long-term and cost-effective benefits. Important actions to consider are the promotion of green pharmacy and good manufacturing practices and the inclusion of environmental risks in the risk-benefit analysis of marketing authorisation for new pharmaceuticals; and post-authorisation of those already approved on the market. Data sharing to practitioners and consumers is necessary to reduce the knowledge gaps and guide the use of environmentally high-risk substances.

Recommended actions include the development of clear and shared environmental criteria (and performance indicators) for sustainable 'green' procurement of pharmaceuticals and ensuring Environmental Risk Assessment (ERA) robustness, consistency, and transparency. For future mitigation of chemicalisation, it is important to place more stringent conditions for putting a pharmaceutical on the market that is of high-risk to the environment. These conditions could entail for example prescription only and developing an eco-labelling system, which could empower consumers to make environmentally conscious choices. The pharmaceutical industry should also be incentivized to advance green and sustainable pharmacy, so that current persistent pharmaceuticals can in the future be substituted with safer alternatives. In all, no drugs have been marketed or proved to have lower environmental impacts, emphasizing the need for further research on alternative drugs with reduced environmental impact.

Meanwhile the main strategy is mitigation of overuse and ensure safe disposal of persistent pharmaceuticals. Educate and engage with health professionals, veterinarians, farmers, and consumers to raise awareness about the environmental affects and improper disposal of medicines.

4.0 Plastics additives

4.1 *What, where and why*

Plasticisers, chemical additives used to enhance the flexibility and durability of plastics, have become an environmental concern due to their potential for leaching into ecosystems and causing adverse health effects in wildlife and humans. Bisphenol A (BPA) and phthalates are important chemical building blocks in the plastics industry. They have been frequently identified as contaminants in the human body, wildlife, and the environment[88, 89]. Despite longstanding questions over their safety, BPA and phthalates are still used in consumer products in many parts of the world because it has been difficult to develop economical and safe replacements[90].

A unique characteristic of BPA and phthalates compared with persistent organic pollutants (POPs) is their quick metabolism and lack of persistence and bioaccumulation. However, due to their wide distribution, exposure can be constant and also the metabolites can be toxic agents[91].

4.1.1 *Phtalates*

Phtalates are a group of Plasticisers[92] with a production volume of millions of tons per year. They are widely used in the manufacture of plastics, to make them soft and flexible, and in personal care products. They can be found in common products such as soaps, suntan lotion, soft plastic toys, plastic bottles, raincoats, shoes and food packaging. Phthalates are the most widely used type of Plasticiser and are often used in polyvinyl chloride (PVC) products such as flooring, cables, and toys.

Due to the increased demand for plastics, also the global Plasticisers market is anticipated to keep growing, with a compound annual growth rate (CAGR) of 4-5 % from 2021 to 2030[93]. This growth is much attributed to the increasing demand for flexible PVC across various applications, the use of lightweight materials in vehicles, the adoption of non-phthalate and high molecular weight phthalate Plasticisers, and the expansion of the packaging industries. Notably, Asia dominates the market in terms of both volume and growth. This dominance is driven by significant demand and production in China, as well as the rapid development of the market in India and other Asian countries.

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[88] CDC, Centers for Disease Control and Prevention (2018) Fourth Report on Human Exposure to Environ-mental Chemicals, Updated Tables. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/.

[89] Teuten, E. L., Saquing, J. M., Knappe, D., Barlaz, M., Jonsso,n S., Björn, A., Rowland, S., Thompson R., Galloway T., Yamashita R., et al. (2009). Transport and release of chemicals from plastics to the environment and to wildlife. Philos. Trans. R. Soc. Biol. Sci. 364, 2027–2045.

[90] Lowell Center for Sustainable Production (2011) Phthalates and their Alternatives: Health and Environmental Concerns. 24 p. https://www.sustainableproduction.org/downloads/PhthalateAlternatives-January2011.pdf

[91] Warner, G. and Flaws, J. 2018. Bisphenol A and Phthalates: How Environmental Chemicals Are Reshaping Toxicology. Toxicol Sci. Vol 166(2):246-249.

[92] Plasticisers are substances, which when added to a material, usually a plastic but also paint or an adhesive, makes it flexible, resilient and easier to handle. Modern plasticisers are manmade organic chemicals; the majority of which are esters, such as adipates and phthalates. (EEA).

[93] Plasticisers Market (2023). Factiva.

However, the growth in the phthalate market is relatively slower, particularly in Europe, due to strict regulatory bans on certain phthalates and concerns regarding the toxicity of PVC in industries such as automotive and IT. Phthalates currently represent about two-thirds of the global Plasticiser market, but their market share is declining under pressure from anti-phthalate activists.

The Candidate List of substances[94] (REACH regulation, EC 1907/2006) of very high concern (SVHC) includes several ortho-phthalates known for their harmful effects on reproduction. Five low-molecule ortho-phthalates are identified as substances of very high concern due to their endocrine disrupting properties: DIBP, DBP, BBP, DEHP (Di (2-ethylhexyl) phthalate) and dicyclohexyl phthalate (DCHP) for human health, with DEHP and DCHP also posing environmental risks, as reported by the European Chemicals Agency (ECHA) (Annex 1)[95]. There are numerous regulations limiting the employment of phthalates in manufacturing PVC, for instance REACH restriction on diisobutyl phthalate (DIBP) in 2018 (Annex XVII entry 51) and on DEHP, dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP) came into force 2020. Also in North America, where regulatory environmental restrictions are less common compared to Europe, Plasticiser producers prepare for the possible impact on the North American market and have launched on the market non-phthalate alternatives for medical applications[96]. Only in Washington state ortho-phthalates are to be restricted from use in vinyl flooring and personal care product fragrances sold in beginning of 2025.

Another trend affecting diminished use in of plasticiser in certain consumer goods are also the industries' efforts to diminish the use of PVC on somewhat voluntary basis. Many car manufacturers have phased out PVC from their car interiors, largely replacing it with polyolefins. Additionally, several major corporations, including Microsoft, IBM and Walmart, have announced initiatives to eliminate PVC from their products, components and packaging over fifteen years ago.

4.1.2 Bisphenols

Bisphenols are used to produce polymers and resins, which are then used to make plastic materials. They form a big family with many substances that have similar chemical structures and uses. Some of the most well-known ones are Bisphenol A (BPA) and Bisphenol S (BPS). Due to their hazardous properties, the use of some bisphenols has been limited or is being limited in the EU to protect people's health and the environment.

Bisphenols have been used in polycarbonate plastic and epoxy resin for decades. Polycarbonate plastic is a strong and tough material that can be moulded at high temperatures. Products made of polycarbonate plastic include common consumer goods, such as re-usable plastic tableware and bottles for drinks, sports equipment, CDs and DVDs. Epoxy resins are used to coat the insides of water pipes as well as food and drink cans to increase their shelf-life and avoid getting a metallic taste. They are also used in flooring, car body coatings and in adhesives. Bisphenols are also used in thermal paper, inks, textiles, paper or in board.

[94] https://echa.europa.eu/information-on-chemicals/registered-substances
[95] https://echa.europa.eu/hot-topics/phthalates.
[96] BCC Research (2022). Phthalates and Bisphenol A Market (Type: Phthalates [Benzyl Butyl Phthalate, Diisobutyl Phthalate, Dibutyl Phthalate, Diisodecyl Phthalate, Dipropylheptyl Phthalate, Diisononyl Phthalate, Di [2-ethylhexyl] Phthalate, and Others, and Bisphenol A) - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast, 2022-2031.

Many bisphenols may damage fertility and disrupt the hormonal systems of. They may also cause skin allergies and affect detrimentally the immune system.[97]

4.2 Possible solution: Alternative Plasticisers

4.2.1 Description

A number of substances have been identified as alternative Plasticisers. These alternatives include citrates, sebacates, adipates, and phosphates. They are being substituted in products that traditionally use phthalates, such as toys, childcare articles, and medical devices[98].

Alternatives to phthalates include several different chemicals, e.g., epoxidized oils, citrates, polyesters, terephthalates, aromatic sulfonates, cyclohexanoate diesters, polyol esters, benzoates, trimellitates and dibasic acid esters. Biobased epoxidized soybean oil Plasticisers (ESBOs) are more expensive on a cost-per-kg basis than petrochemical Plasticisers. They offer benefits, including low toxicity and heat and light stability for applications in food packaging and medical. ESBOs are most often used as a secondary Plasticiser due to mixing difficulties and the brittleness of plastic formulations that occur at higher concentrations.

One specific alternative that has gained attention is a compound called DINCH (di (isononyl)cyclohexane-1,2-dicarboxylate) or Hexamoll®. DINCH is specially intended for use in applications that involve human contact, and it has been approved for use in commercial products such as toys, medical devices, and food packaging. While less is known about the effects of this chemical compound on humans, initial studies have not shown evidence of endocrine disrupting properties[99].

Another solution for manufacturers is to choose a type of plastic that does not require a Plasticiser, including both petroleum-based and biobased plastics. This trend can be seen especially for PVC as was discussed above.

It is important to note that while these alternatives may not require major production process changes, they may also pose health and environmental concerns. Therefore, ongoing research is crucial to ensure the safety and sustainability of these alternatives.

4.2.2 Benefits and bottlenecks

As concerns about the health impacts of BPA emerged, alternative chemicals bisphenol S (BPS) and bisphenol F (BPF) have been used as substitutes. However, in 2022, BPS was included in the REACH Candidate List as a substance of very high concern.

The challenge in substituting phthalates lies in finding alternatives that can offer the same unique qualities to the plastic into which they are incorporated. Common alternatives include Hexamoll DINCH (DINCH),

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[97] EFSA Panel (2023) Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA Journal 21(4):6857.

[98] Lowell Center for Sustainable Production (2011) Phthalates and their Alternatives: Health and Environmental Concerns. 24 p. https://www.sustainableproduction.org/downloads/PhthalateAlternatives-January2011.pdf

[99] Wenzel, A., Reiner, J., Kohno, S. et al. (2021) Biomonitoring of emerging DINCH metabolites in pregnant women in Charleston, SC: 2011–2014. Chemosphere.

acetyl tributyl citrate (ATBC), dioctyl terephthalate (DOTP), 2,2,4-trimethyl 1,3-pentanediol diisobutyrate (TXIB), trioctyl trimellitate (TOTM), and di- (2-ethylhexyl) adipate (DEHA)[100].

In conclusion, the bottlenecks for substituting phthalates include finding alternatives that offer the same benefits as phthalates, ensuring these alternatives do not have adverse health or environmental impacts, and managing the potential for these alternatives to leach, resulting in possible human exposure.

The **cost** of substituting phthalates can vary greatly depending on the specific application and the alternative Plasticiser chosen. The possibilities of substituting previously used Plasticisers by new ones must be determined case by case for each product. It is feasible but manufacturers should not underestimate the length and cost incurred. There may be significant costs associated with researching and developing suitable alternatives, as well as testing them for safety and efficacy. Once a suitable alternative has been identified, there may be costs associated with changing production processes and implementing the new material. However, transitioning to alternatives can also reduce regulation-related costs, such as costs for compliance and authorization.

It is important to note that while there are costs associated with substituting phthalates, there may also be long-term benefits. These can include improved safety and health outcomes, increased market share due to consumer preference for phthalate-free products, and potential regulatory benefits. However, these benefits can be difficult to quantify and may not be realized immediately.

4.3 Case: BPA

Bisphenol A (BPA) is a widespread industrial contaminant primarily derived by polycarbonate plastics, which are used in numerous consumer products such as re-usable plastic tableware and bottles for drinks, sports equipment and electronic devices. In industrial manufacturing BPAs are used in epoxy resins, such as coatings for metal and concrete surfaces, in the production of adhesives, and as a lining for food and beverage cans to prevent corrosion. Moreover, BPA functions as colour developer in thermal paper, commonly used in cash register receipts, ATM receipts, and other similar applications. BPA is soluble, thus when it comes into contact with liquids or when it is heated, the bond it has formed with the plastic can be broken, and it can seep into the contents of the food or beverage.

Many studies are raising the awareness for its endocrine-disrupting effects in humans. The heightened BPA exposure is associated with several health issues, including infertility, diabetes, and brain development disorders. When drinking water undergoes chlorination treatment, BPA-containing products in the water can interact with chlorine, leading to the formation of chlorinated derivatives of BPA (Cl_xBPA). Cl_xBPA derivatives also possess endocrine-disrupting properties. BPA pollutants have been detected in human urine, serum, breast milk, among others[101].

[100] Wu, Y., Song, Z., Little, J. C., Zhong, M., Li, H., & Xu, Y. (2021). An integrated exposure and pharmacokinetic modeling framework for assessing population-scale risks of phthalates and their substitutes. Environment International, 156, 106748.

[101] Plattard, N., Dupuis, A., Migeot, V., Haddad, S., & Venisse, N. (2021). An overview of the literature on emerging pollutants: chlorinated derivatives of Bisphenol A (ClxBPA). Environment International, 153, 106547.

Though BPA is considered a degradable compound[102], it has been identified in coastal waters e.g., outside China and Malaysia in concentration ranges between 5-100 ng/L[103]. Bisphenols have also been detected in sludge from the United States (USA) wastewater treatment plants at concentration ranges 1-4700 ng/g dry weight). Concentrations of BPA in sewage sludge were an order of magnitude higher than those reported in China but like those in Germany. The author noted that as the usage of BPA is expected to decline further, the environmental emissions of substituting compounds, such as BPS and BPF, and BPAF (Bisphenol AF) are likely to increase in the future[104].

In the EU, BPA was banned in plastic infant feeding bottles already in 2011, whereas restriction for use in thermal printing paper came into force under REACH in 2020. The proposed directive COM/2022/540 on pollutants in EU waters proposed to include bisphenol A in priority substances[105]. Indeed, experts from EFSA concluded in 2023 that the health of people in all age groups is at risk from BPA in their diet[106].

Due to its adverse effects on both the environment and health, BPA has been progressively substituted with other chemicals known as BPA analogues. These substitutes include bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), and others. Research investigating the effects of these analogues on aquatic and terrestrial environments, as well as on human and animal health and reproductive performance, has revealed similar or even exacerbated impacts in some instances[107].

Bisphenol S (BPS) is one of the most widely used alternatives to BPA, e.g., in production of thermal paper. While BPS has similar chemical properties to BPA, it was generally considered to be less harmful to health. BPS is less biodegradable with risk for bioaccumulation. Again, Bisphenol F (BPF), like BPS, has chemical properties similar to BPA but is believed to be less estrogenic and thus potentially safer.

With increasing regulations on and a subsequent decline in, the use of BPA, its alternatives (foremost bisphenol S (BPS) and bisphenol F (BPF)) have increased in environmental monitoring. Findings from human biomonitoring data published in 2022 show that median levels of BPS and BPF in urine are increasing in all European regions[108]. These alternative bisphenols have a similar structure to BPA and unfortunately,

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[102] OECD (2012) SIDS Initial Assessment Profiles agreed in the course of the OECD HPV Chemicals Programme from 1993 to 2011. Series on Testing & Assessment No. 166. 298 p.

[103] Lu, S., Lin, C., Ming Xin, K-M., Wang, B., Ouyang, W., Liu, X. and He, M. (2021) Endocrine-disrupting chemicals in a typical urbanized bay of Yellow Sea, China: Distribution, risk assessment, and identification of priority pollutants, Environmental Pollution, 287: 117588,

[104] Yu, XH; Xue, JC; Kannan, K., et al. (2015) Occurrence and estrogenic potency of eight bisphenol analogs in sewage sludge from the US EPA targeted national sewage sludge survey. J. Haz. Mat. Vol. 299, p. 733-739.

[105] European Commission (2022). Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Directive 2000/60/EC establishing a framework for Community action in the field of water policy, Directive 2006/118/EC on the protection of groundwater against pollution and deterioration and Directive 2008/105/EC on environmental quality standards in the field of water policy. COM/2022/540 final. 2022/0344 (COD).

[106] EFSA Panel (2023) Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA Journal 21(4):6857.

[107] Bahelka, I., Citek, J. and Stupka, R. (2019) Bisphenol A and its analogues - occurrence and impact on wild animals and animal models. 11th Workshop on Biodiversity. Jevany.

[108] Govarts, E., Gilles, L., Martin, L. R., Santonen, T., Apel, P., Alvito, P., & Schoeters, G. (2023). Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021). International Journal of Hygiene and Environmental Health, 249, 114119.

evidence has shown they also have similar endocrine disrupting properties. In 2023, also BPS was added to ECHA's list of substances of very high concern (SVHC).

It is important to note that while many alternatives are generally considered to be safer than BPA, they may still have their own set of concerns. Therefore, it is essential to carefully evaluate and monitor the safety and performance of these substitutes in the specific applications where they are used. Keminer and co-workers identified through literature and a patent search a total of 43 possible substituents of which 33 were commercially available[109].

Facing the difficulties in finding fully safe alternatives to BPA, one option is to develop BPA free materials and products. Several commercially solutions are available, like for example BPA free plastics, the applications of which depends on intended use. Polyethylene Terephthalate Glycol (PETG) is resistant and naturally transparent and has become a popular choice in the food and beverage industry. Furthermore, some manufacturers are developing polycarbonate blends that are free from BPA but still offer the durability and clarity associated with traditional polycarbonate. In some applications, silicone is used as an alternative to BPA-containing materials due to its flexibility, durability, and heat resistance and various epoxy resin formulations that are BPA-free have been developed for use in coatings, adhesives, and other applications.

The ban of BPA also affected the thermal paper sector in Europe and USA. Still in 2019, BPA was clearly still the most used colour developer, and when substituted, BPA was generally replaced by BPS: Interestingly, this took place also in USA where BPA was officially banned only in two member states and in Japan. This demonstrates that retailers may also voluntarily abandoned use of potentially hazardous products without legal enforcement.

BPS is now recognised as "toxic to reproduction" and a hormone disruptor and has been added to the EU's candidate list for Substance of Very High Concern (SVHCs), a common first step on the road to restriction[110]. Alternative commercially available colour developers are the so-called Pergafast® 201 (PF201), a urea-based compound and D-8 (also known as Wincon-8, or BPSIP)[111]. Most of the other substances that can be used as an alternative to BPA in thermal paper have been less studied so far and suffer from significant data gaps[112].

The process of substituting BPA after a ban with non-restricted chemicals whereby one harmful chemical is replaced by another chemical, with a similar structure, that is later found out to also be harmful. In order to prevent such regrettable substitution, ECHA stated in 2022 that a robust and comprehensive restriction on all bisphenols in consumer products is required. Assessing chemicals in groups can be a worthier approach as it makes it faster to identify which chemicals need regulatory action or more data, or those chemicals for which no further action is currently needed. Chemical companies can use this information to avoid surplus changes in processes, also avoiding extra costs.

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[109] Keminer, O., Teigeler, M., Kohler M., Wenze, l., Arning, J., Kassner, F., Windshugel, B., Eilebrecht, E. (2020) A tiered high-throughputscreening approach for evaluation of estrogen and androgen receptor modulation by environmentally relevant bisphenol A substitutes. Science of the Total Environment 717.

[110] ECHA adds nine hazardous chemicals to Candidate List. ECHA. [Online] 2023. https://echa.europa.eu/-/echa-adds-nine-hazardous-chemicals-to-candidate-list.

[111] 4-Hydroxyphenyl-4′-isopropoxyphenyl-sulfone (the compound has shown some indication of ecotoxicity).

[112] Demierre, A., Reinhard, H., Zeltner, S. and Frey, S. (2024) Evaluating the efficiency of the 2020 ban of BPA and BPS in thermal papers in Switzerland, Regulatory Toxicology and Pharmacology, Vol. 146,105526.

4.4 Future Outlook

The future trend of using phthalates is shifting due to environmental and health concerns. The Plasticiser market has changed in response to the restriction of low molecular weight phthalate Plasticisers such as Di (2-ethylhexyl) phthalate (DEHP) due to their hazardous properties. As a consequence of the restrictions, there has been a significant decrease of restricted phthalates in both indoor and aquatic environment. This is accompanied by their substitution with high molecular weight (HMW) phthalates and non-phthalates[113].

Environmental samples indicate that di isononyl phthalate (DINP) has replaced DEHP as the dominant Plasticiser. Also, the occurrence of di (2-propylheptyl) phthalate (DPHP) is increasing. Similarly, the proportion of non-phthalates in the total Plasticiser concentration show an upward trend, especially in indoor samples.

Despite these changes, phthalate Plasticisers are foreseen to still be the dominant type and production volume globally in the future, but those of long-chain (C_9–C_{10}) alcohol-based esters and non-phthalate Plasticisers will increase largely.

However, it is important to note that the substitution of low molecular weight (LMW) phthalates is characterised by a significant shift towards other Plasticisers which also can possess potentially hazardous properties. Therefore, there is a need for integrated chemicals management to safeguard the transition to a non-toxic environment. In this context, a promising alternative are biodegradable Plasticisers which may be derived from renewable sources such as vegetable oils. This makes them more eco-friendly than traditional Plasticisers. Hence, inclination toward bio-based Plasticisers can create lucrative opportunities for phthalate and non-phthalate Plasticiser manufacturers, provided that their compounding properties are satisfactory and their price somewhat compatible for industrial purposes. Rising adoption of less harmful products along with the implementation of strict environmental regulations are set to propel demand for non-phthalate Plasticisers through 2033.

Continuous innovation in Plasticisers resulting in generation of its biodegradable types and R&D activities for producing new applications by different market players are projected to provide numerous opportunities for development of the Plasticiser market.

4.5 Conclusion

The substitution of dangerous chemicals is included in both the current strategies to reduce risks of chemicals on human health and the environment, and the industry's approach for sustainable development. However, finding suitable alternatives to chemicals of concern is not a small challenge. Alternatives should be safer with a lower hazard and risk potential, but still have similar performance than their counterpart, and be economically viable and sustainable.

Studies on the occurrence of BPA and BPS indicate that despite restrictions, banned substances can still occur in products and thus end up in the environment[114]. Also, this shows that the European market is not uniform, and that the state of play differs from one member state to another.

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[113] Nagorka, R., Birmili, W., Schulze, J. and Koschorrek, J. (2022) Diverging trends of Plasticisers (phthalates and non-phthalates) in indoor and freshwater environments—why? Environ Sci Eur 34, 46.

[114] Demierre, A., Reinhard, H., Zeltner, S. and Frey, S. (2024) Evaluating the efficiency of the 2020 ban of BPA and BPS in thermal papers in Switzerland, Regulatory Toxicology and Pharmacology, Vol. 146,105526.

Substituting chemicals also goes beyond finding a drop-in chemical alternative and can include systems, materials, or process changes. However, there are challenges and barriers to the substitution of dangerous chemicals. These include resistance to change, reluctance to experiment with the unknown, fears for regrettable substitution, company policies, lack of guidance and clarity on how to conduct a successful assessment of potential alternatives, and the need for specific training and education in this area.[115] Despite these challenges, the concept of substitution is increasing and included in policy and regulatory measures for the management of chemicals of concern.

It's important to note that while there are costs associated with substituting phthalates, there may also be long-term benefits. These can include improved safety and health outcomes, increased market shares due to consumer preference for phthalate-free products, and potential regulatory benefits. However, these benefits can be difficult to quantify and may not be realised immediately.

[115] OECD (2016) Synthesis Report from the OECD Workshop on Alternatives Assessment and Substitution of Harmful Chemicals. https://www.oecd.org/chemicalsafety/risk-management/substitution-of-hazardous-chemicals/

5.0 Recommendation

5.1 Policy instruments and eco-design

Environmental regulations and chemical safety concerns have shown to be among main factors that induce companies to carry out technological innovation and increase R&D intensity for green innovations. Therefore, the EU and national policies should devise regulations which are highly targeted and practical. One example is the proposed new UWWTD (Urban Wastewater Treatment Directive) which includes the extended producer responsibility for the removal of CoECs[116]. The regulation is suggested to apply to Europe's pharmaceuticals and cosmetics sectors. At the same time, governments need to increase scientific research support, stimulate technological innovation behaviour, and provide funding for R&D activities. Enterprises again, should also set up a long-run vision, increase R&D intensity and investment in environmental protection. Enterprises need to improve the technical level by increasing the investment on eco-design and thereby lower the burden on the environment.

In this context, the evaluation of the impact of different policy becomes important. One need to recognise the differences in resource endowment and the environmental regulation varies across regions, neither is the degree of social and economic development the same. Second, there are many types of environmental regulations, and the impact of each on enterprises will also be different. In this context, the EPR-system has originally been planned to incentivise firms to carry out technological innovation for eco-design[117]. Though many studies have shown a positive relationship between environmental regulations and green innovation, it is not fully clear how and under what conditions this relationship is established, considering the different environmental policy mechanisms and different approaches to green innovation in companies.

Western countries have taken different approaches in pharmaceutical regulation. For example, the United States tends to lean towards a more market-driven model, characterised by numerous partnerships between the public and private sectors. In contrast, Europe operates within a regulatory framework, relying notably on regulatory approaches, key policies and instruments being CSS (Chemicals Strategy for Sustainability), REACH, Classification, Labelling and Packaging (CLP) of Chemical Substances[118]. Insights into policy and regulatory instruments could be valuable, detailing their implementation, impact, and effectiveness within their respective contexts. These could include:

- Providing fiscal incentives or financial support to enterprises, facilitating elements of the substitution process such as funding for research, taxes, or subsidies.
- Establishing or supporting networks and partnerships to disseminate information to stakeholders, including consumers, and fostering public-private collaborations for data and knowledge exchange.

[116] European Comission (2014). Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment. Document 31991L0271.
[117] Guillaume Ragonnaud, Members' Research Service (2023). Ecodesign for sustainable products. EPRS | European Parliamentary Research Service. PE 751.382 – July 2023.
[118] Frost & Sullivan (2023) The Impact of Regulations on the Chemical Industry. May 2023. 133 p. https://store.frost.com/wip/PE52-01-00-00-00

- Stimulating demand to encourage new product development in the nascent market, perhaps through public procurement policies or purchase subsidies.

Overall, product development to include less hazardous compounds requires a multidisciplinary approach, involving collaboration between scientists, engineers, regulatory experts, suppliers, and other stakeholders.

Substitution of chemicals can be slow, and does not come without costs, depending on the availability of market ready substitutes (without adverse effects of its own) and necessary compliance processes. At the same time, it is an opportunity for chemical companies to gain new businesses. From the environmental point of view, a ban on a chemical is mirrored in lower environmental concentrations only with a time lag. A combination of eco-designed products or processes with end of pipe, i.e., wastewater treatment technologies are still essential for a safer and healthier near future.

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7.0 Annex: Overview on phthalate Plasticisers

	Compound	Abbreviation	CAS	MW
Low molecular weight phthalates				
	Dimethyl phthalate	DMP	131-11-3	194.2
	Diethyl phthalate	DEP	84-66-2	222.3
	Di-n-butyl phthalate	DnBP	84-74-2	278.3
	Di isobutyl phthalate	DIBP	84-69-5	278.3
	Benzylbutyl phthalate	BBP	85-68-7	312.4
	Dicyclohexyl phthalate	DcHP	84-61-7	330.4
	Di isoheptyl phthalate	DIHP	71888-89-6	362.5
	Di (2-ethylhexyl)phthalate	DEHP	117-81-7	390.6
High molecular weight phthalates				
	Diisononyl phthalate	DINP	28553-12-0, 68515-48-0	418.6
	Diisodecyl phthalate	DIDP	26761-40-0, 68515-49-1	446.7
	Di(2-propylheptyl)phthalate	DPHP	53306-54-0	446.7
	Diisoundecyl phthalate	DIUP	85507-79-5	474.7

The Mediterranean Sea and its surrounding regions support a diverse variety of essential socioeconomic activities. It is one of the highly exploited water ways and the influence of anthropogenic activities on its marine habitats and ecosystems has grown significantly since the industrial revolution. Because of this, the Mediterranean Sea basin is very vulnerable to chemical contamination and build-up. To safeguard the Mediterranean Sea basin from contaminants for emerging concerns (CoEC), iMERMAID will integrate, coordinate, and synergize innovative preventive, monitoring, and remediation solutions. iMERMAID will build an evidence-based multidimensional framework that will guide policy-making and transform societal perceptions to reduce CoEC usage, emissions, and pollution. Furthermore, next generation sensor and remediation solutions will be developed within iMERMAID to monitor and remove prioritized chemicals from its source while reducing upstream pollution. iMERMAID builds an ideal interdisciplinary team by bringing together prominent SMEs, researchers, regulators, and innovation professionals who have been essential in improving the knowledge and awareness of CoEC. Beyond state-of-the-art techniques, iMERMAID will strive to strengthen regulations against CoEC, expand economic possibilities and competitiveness, improve the standard of living for EU residents, while preventing the accumulation of chemical pollution in the Mediterranean Sea basin. iMERMAID will empower the efforts to create a zero pollution, contaminant free waters by enabling the Chemical Strategy's goals to become a practical reality.

iMERMAID

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the European Union