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IntechOpen Series
Environmental Sciences, Volume 40

Persistent Organic Pollutants

Monitoring, Treatment Technologies,
and Health Effects

Edited by Mohamed Nageeb Rashed



Persistent Organic Pollutants - Monitoring, Treatment Technologies, and Health Effects

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Published in London, United Kingdom

Persistent Organic Pollutants – Monitoring, Treatment Technologies, and Health Effects
<http://dx.doi.org/10.5772/intechopen.1008079>
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First published in London, United Kingdom, 2025 by IntechOpen

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British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Persistent Organic Pollutants – Monitoring, Treatment Technologies, and Health Effects
Edited by Mohamed Nageeb Rashed
p. cm.

This title is part of the Environmental Sciences Book Series, Volume 40

Topic: Pollution

Series Editor: J. Kevin Summers

Topic Editors: Ismail Md. Mofizur Rahman and Zinnat Ara Begum

Print ISBN 978-1-83634-020-1

Online ISBN 978-1-83634-019-5

eBook (PDF) ISBN 978-1-83634-021-8

ISSN 2754-6713

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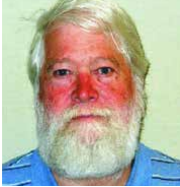
Volume 40

Aims and Scope of the Series

Scientists have long researched to understand the environment and man's place in it. The search for this knowledge grows in importance as rapid increases in population and economic development intensify humans' stresses on ecosystems. Fortunately, rapid increases in multiple scientific areas are advancing our understanding of environmental sciences. Breakthroughs in computing, molecular biology, ecology, and sustainability science are enhancing our ability to utilize environmental sciences to address real-world problems.

The four topics of this book series - Pollution; Environmental Resilience and Management; Ecosystems and Biodiversity; and Water Science - will address important areas of advancement in the environmental sciences. They will represent an excellent initial grouping of published works on these critical topics.

Meet the Series Editor



J. Kevin Summers is a Senior Research Ecologist at the Environmental Protection Agency's (EPA) Gulf Ecosystem Measurement and Modeling Division. He is currently working with colleagues in the Sustainable and Healthy Communities Program to develop an index of community resilience to natural hazards, an index of human well-being that can be linked to changes in the ecosystem, social and economic services, and a community sustainability tool for communities with populations under 40,000. He leads research efforts for indicator and indices development. Dr. Summers is a systems ecologist and began his career at the EPA in 1989 and has worked in various programs and capacities. This includes leading the National Coastal Assessment in collaboration with the Office of Water which culminated in the award-winning National Coastal Condition Report series (four volumes between 2001 and 2012), and which integrates water quality, sediment quality, habitat, and biological data to assess the ecosystem condition of the United States estuaries. He was acting National Program Director for Ecology for the EPA between 2004 and 2006. He has authored approximately 150 peer-reviewed journal articles, book chapters, and reports and has received many awards for technical accomplishments from the EPA and from outside of the agency. Dr. Summers holds a BA in Zoology and Psychology, an MA in Ecology, and Ph.D. in Systems Ecology/Biology.

Meet the Volume Editor



Prof. Mohamed Nageeb Rashed is a Professor of Analytical and Environmental Chemistry at the Faculty of Science and the Head of the Unit of Environmental Studies at Aswan University, Egypt. His research interests have been analytical and environmental chemistry. He has published 95 scientific papers in peer-reviewed international journals. He has participated as an invited speaker at 35 international conferences worldwide. He was selected as an examiner for several Ph.D. theses in analytical chemistry from India, Azerbaijan, Malaysia, KSA, and Botswana. Prof. Rashed serves as the editor-in-chief of the Aswan University Journal of Environmental Studies and as an editorial board member for several international journals. He received the Egyptian State Award for Environmental Research in 2001. He was recognized by Stanford University's list of the world's top 2% of scientists in 2020, 2021, 2022, and 2023.

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Preface

Toxic organic compounds known as persistent organic pollutants (POPs) are resistant to breakdown by biological, chemical, and photolytic processes in the environment. Currently, a significant number of POPs are utilized as industrial chemicals, solvents, medications, and insecticides. POPs bioaccumulate and have an impact on the environment and human health globally due to their persistence. It can spread from one nation to another through wind and water, meaning it can have a significant impact on people and wildlife far beyond the areas where it is used and discharged. According to the UN Environment Programme (n.d.), exposure to POPs has the potential to lead to the following health issues: cancer, allergies, nervous system effects, and Immune system effects.

This book will compile recent research by leading experts in the fields of monitoring, treatment technologies, and the health effects of persistent organic pollutants. It will appeal to a wide readership from universities and industry. Additionally, readers will gain access to updated information on monitoring, treatment technologies, and the health effects of persistent organic pollutants.

This book, “Persistent Organic Pollutants – Monitoring, Treatment Technologies, and Health Effects”, focuses on several aspects of POPs monitoring, treatment technologies, and health effects. The book is divided into three sections, with six chapters. The first section, “Introduction”, includes one chapter, the “Introductory Chapter”. The second section, “Monitoring and Health Effects”, includes two chapters. The third section comprises three chapters that explain the various technologies for treating POPs.

In this book, readers will obtain updated information on all aspects of persistent organic pollutants (POPs). Scientists from various scientific fields reported their findings in this book.

The book “Persistent Organic Pollutants – Monitoring, Treatment Technologies, and Health Effects” offers an important information source for researchers and professionals working in the POPs field.

Additionally, I would like to express my gratitude to Ms. Mia Vulovic, the IntechOpen Publishing Process Manager. I am also grateful to the book authors for their hard work and worthy contributions.

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Section 1

Introduction

Introductory Chapter: Persistent Organic Pollutants – Health Effect and Treatment Techniques

Mohamed Nageeb Rashed

1. What are persistent organic pollutants (POPs)?

Persistent organic pollutants (POPs) are organic substances that resist degradation through chemical, biological, and photolytic methods. They are classified as a bioaccumulative chemicals group that has the ability for long transportation and prolonged retention in environmental media without breaking down into less harmful forms. Particularly concerning are the detrimental health effect and endocrine-disrupting capabilities of several of these substances [1]. The majority of POPs are pesticides or insecticides, with others being pharmaceuticals, solvents, and industrial chemicals [2]. While some POPs occur naturally, the majority are produced by humans. POPs can bioaccumulate and biomagnify, as well as bypass existing treatment methods [3]. The inherent semi-volatility and lipophilicity of these pollutants enhance their extensive environmental distribution and bioaccumulation. The lipophilic nature of POPs facilitates their movement through the lipid bilayer of cell membranes and results in their accumulation in fatty tissue, where they can reach harmful concentrations [4].

2. Sources of persistent organic pollutants (POPs) to water body

The origins of POPs can be traced back to human activities, agricultural practices, and industrial processes. The primary contributor to POPs is wastewater released into the environment from a variety of sources [5]. Wastewater is composed of a mix of discharges from industrial, domestic, agricultural, institutional, and commercial activities [6]. Some known types of POPs include pharmaceuticals, personal care items, hormones, industrial chemicals, organic dyes, and pesticides. These pollutants are organic substances, either naturally occurring or man-made, that remain stable for extended periods and are resistant to photolytic, chemical, and biological degradation [7].

3. Stockholm convention on persistent organic pollutants

POPs are listed and recognized by the United Nations Environment Programme (UNEP); Intergovernmental Negotiating Committee, Montreal, Canada; International POPs Elimination Network (IPEN); and the Stockholm Convention [8].

There were 12 POPs listed in the Stockholm convention, which are industrial chemicals, pesticides, and by-products, while 16 new POPs were included as of 2017 by 181 parties [9].

The United Nations Environment Programme decided that POP regulation needed to be addressed globally for the future. The purpose statement of this agreement is to protect the environment and human health from POPs [10].

3.1 Compounds on the Stockholm convention list

There are 12 chemicals recognized at Stockholm Convention for their responsibility for causing adverse effects on ecosystem and human [10]. These include Chlordane, Aldrin, Dieldrin, Heptachlor, Endrin, Hexachlorobenzene, Toxaphene, Mirex, Polychlorinated biphenyls, Dichlorodiphenyltrichloroethane, Polychlorinated dibenzofurans, and Dioxins.

3.2 New POPs on the Stockholm convention list

Since 2001, the Stockholm Convention list has been expanded to include some polycyclic aromatic hydrocarbons (PAHs), brominated flame retardants, and other compounds. Additions to the initial 2001 Stockholm Convention list are the following POPs [10]. These new POPs are α -Hexa chloro cyclohexane, β -Hexachlorocyclohexane, Chlordecone, Decabromodiphenylether, Dechloraneplus, Dicofol, Hexabromodiphenyl, Hexabromocyclo dodecane, Hexabromodiphenyl ether, heptabromodiphenyl ether, debromination and the production of bromodiphenyl ethers, Hexachlorobutadiene, Lindane, Methoxychlor, Pentachlorobenzene, Perfluorooctanesulfonic acid, Endosulfans, Tetrabromodiphenyl ether, and pentabromodiphenyl ether.

4. Health effect of POPs

Exposure to anthropogenic POPs has acute and chronic effects on the human health, such as obesity, diabetes, neurological disorder, reproductive impairment, cancer, and damage to the kidney, liver, lung, and nervous system. Long-term environmental persistence allows POPs to accumulate and move up the food chain from one species to another, eventually ending up in the body fat of living things. According to the UN Environment Programme (n.d.), exposure to POPs has the potential to lead to the following health issues: cancer, allergies, nervous system effects, and immune system effects. People and animals primarily encounter POPs through what they eat, during occupational activities, or while developing in the womb. For individuals who are not exposed to POPs through accidents or work-related situations, more than 90% of their exposure is derived from consuming animal-derived foods, as these substances accumulate in fat tissues and move up through the food chain [11].

5. Different techniques for POPs treatment

Typically, there are three main methods applied to degrade organic pollutants: the chemical method, the physical method, and the biological method.

5.1 Chemical approach

Advanced oxidation technologies (AOTs) represent a crucial aspect of chemical methods, encompassing electrochemical procedures, sonolysis, photocatalysis, ozonation, photo-Fenton, and Fenton's reaction. AOTs are innovative, straightforward, economical, and environmentally friendly techniques that do not produce secondary pollutants and efficiently break down resistant organic contaminants like aromatic amines and polycyclic aromatic hydrocarbons (PAHs).

5.2 Physical approach

Physical methods are currently being developed and include techniques like nano-filtration, membrane filtration, coagulation, ultrafiltration, and adsorption (including powdered activated carbon and granular activated carbon), alongside irradiation, ion exchange, reverse osmosis, and osmosis. Traditional methods include incineration, adsorption, landfill stabilization/curing, composting, solvent extraction, coagulation-flocculation-sedimentation, ozonation, membrane filtration, biological techniques, phytoremediation, and catalytic membrane reactors. Textile dyeing sludge is typically disposed of in landfills, but this poses significant environmental risks due to the presence of toxic aromatic amines that can leach into the soil [12].

5.3 Biological approach

The biological approach utilizes specific microorganisms for the degradation of undesirable substances found in the environment, including textile dyes, pesticides, organic pollutants, and hydrocarbons. Common techniques that fall under the biological approach include bioventing, composting, biosparging, land farming, biostimulation, slurry reactors, mycoremediation and bioaugmentation [13]. Biological processes typically involve living organisms such as fungi, bacteria, plants, and algae for the removal of pollutants. Bioremediation is an effective method characterized by high efficiency, affordability, and environmentally friendly attributes. It employs microorganisms for the removal of organic pollutants in both anaerobic and aerobic environments [14].

Phytoremediation involves various processes, such as phytodegradation, rhizoremediation, phytovolatilization, phytoaccumulation, and phytoextraction. Biological approaches are often ineffective for the degradation of complex organic pollutants. Furthermore, physical and chemical techniques also struggle with degradation due to the untreated chemicals and the challenges associated with sludge treatment [15].

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Section 2

Monitoring and Health Effects

Persistent Organic Pollutants: Dual Threats to Environmental Integrity and Human Health

Sally M. Salaah

Abstract

Anthropogenic activities affect all aspects of life on Earth; persistent organic pollutants (POPs) have existed in the environment for decades, continually growing since the Industrial Revolution. They are resistant to degradation and can accumulate across the environmental components (air, water, and soil), triggering long-term ecological challenges. Their unique properties enable them to aggregate in living organisms and biomagnify through the food web. Humans are exposed to POPs risks through many routes, including ingestion, inhalation, skin contact, and maternal. The exposure to POPs has been associated with numerous health issues, including diabetes, tumors, cancer, endocrine and immunity alterations, birth defects, and heart disease. This chapter addresses the environmental and human health risks associated with POPs pollution, highlighting the required effort to mitigate this multidimensional threat in the future.

Keywords: POPs, ecotoxicology, exposure routes, endocrine disruption, carcinogenic effects, metabolic disorders, immunotoxicity

1. Introduction

The earth's ecological system is constantly degraded by numerous contaminants, varying by type and source. Some pollutants can resist the environmental degradation process (such as biological, chemical, and photolytic), making them ecologically persistent substances [1, 2]. Persistent organic pollutants (POPs) are pollutants that remain in the ecosystem for an extended period of time. POPs are significant pollutants that include pesticides, industrial chemicals, and industrial byproducts, which can persist in the environment for a long period of time and reach remote areas. POPs have been documented in regions that have no anthropogenic activities, such as the two poles. These contaminants can build up in the food web, causing numerous health hazards and substantial ecological impacts. Governments and non-governmental organizations, as well as scientists, are so bothered about these contaminants. Monitoring and modeling are applied to analyze the POPs-related environmental hazards [2].

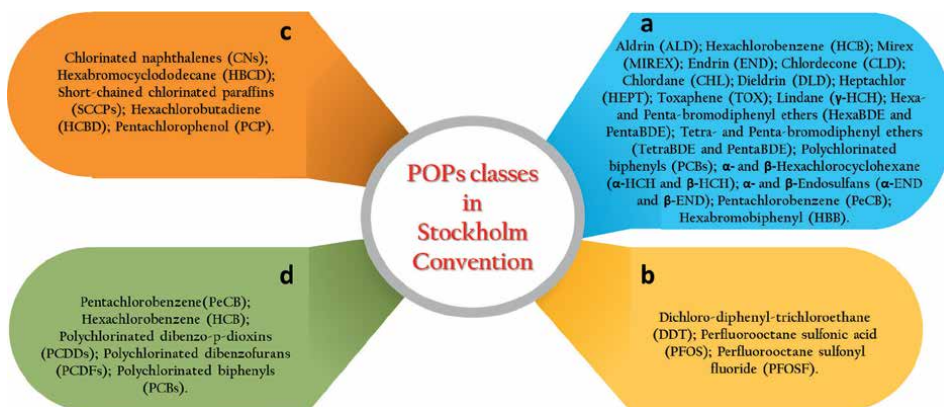


Figure 1.
Listing the POPs classes according to Stockholm convention.

Some studies have been conducted on key toxic pollutants, addressing the dangers and risks of POPs [3–7]. Many international organizations and agreements have identified different types of POPs, including the Stockholm Convention, the United Nations Environment Programme (UNEP), the International POPs Elimination Network (IPEN), and the Inter-governmental Negotiating Committee. Based on the Stockholm Convention, POPs are divided into four classes: (a) targeted for elimination, (b) allowed under limited or specific conditions, (c) produced unintentionally during industrial processes, and (d) under scientific assessment (**Figure 1**). Many international communities are working to reduce the production, usage, and discharge of these chemicals. This chapter tackles both the ecological and health risks associated with POPs pollution, emphasizing the mutual effort required to address this growing challenge [8].

2. POPs pathways

POPs are typically semi-volatile and lipid-soluble, with very low volatility (at 25°C vapor pressure fluctuating from 10^{-4} to 10^{-11} atmosphere), while some POPs are water-soluble. In organisms, POPs tend to accumulate for extended periods of time. POPs can bind to aerosols and translocate from one area to another [9, 10]. Typically, POPs' fate is directly related to their chemical and physical features. POPs can be found in pesticides, industrial wastes, and by-products of industrial operations [11].

In addition to natural origins of POPs, such as volcanic events and wildfires, many anthropogenic activities are attributed to the release of POPs into the environment, including municipal, industrial, medical, agricultural, horticultural, and forestry activities [12]. The aquatic environment is the main sink of POPs that are known as noxious, bioaccumulative, and resilient to ecological degradation; both hydrophilic and hydrophobic POPs could be retained in sediment and water. Although 1 week is enough for POPs to blend with atmospheric air, it may take many years for them to transport from one area to another. Semi-volatile POPs can disseminate across large spatial scales through air and aerosols [13]. The transportation routes of POPs are influenced by climatic circumstances, physicochemical characteristics, and photochemical detoxification reactions [14]. POPs are transferred from the earth's surface to the air in two phases: changing from liquid/solid to vapor and diffusing through

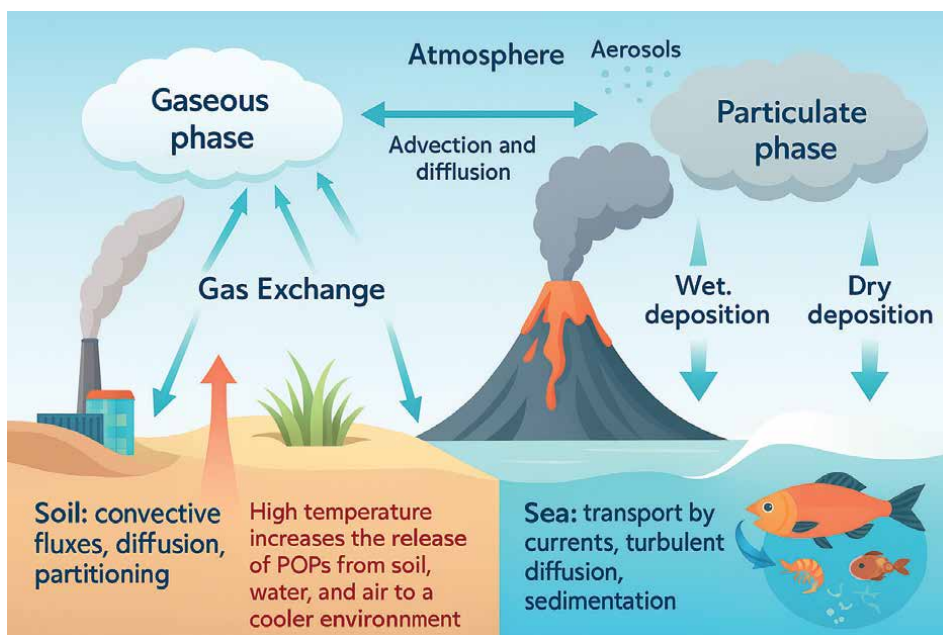


Figure 2.
 Showing environmental fate of persistent organic pollutants (POPs): sources, pathways, and bioaccumulation: image was generated using microsoft copilot.

blending [15]. Thus, POPs could be found globally, even in distant locations like the Arctic and deep sea. In high temperatures, POPs may be released from soils, vegetation, and water to the air, traveling long distances from their origins [16].

POPs travel from warmer to cooler climates, ultimately stabilizing in cryogenic environments; this phenomenon inserts POPs levels and emission patterns into the global warming ramification [17]. The bioaccumulation manner of POPs is a crucial feature that intensifies their ecotoxicity. The hydrophobic nature of POPs increases their rates of bioaccumulation and persistence [18]. POPs often undergo biomagnification as they are transferred from one organism to another through the food web, aggregating in large quantities, as demonstrated in **Figure 2**.

3. Environmental risks

The ecological components, such as air, water, and living organisms, are closely interconnected; any variation can affect the ecosystem either directly or indirectly. Accordingly, POPs pollution disrupts the ecological equilibrium and poses a hazard to the health of both the environment and humans. POPs accumulate in aquatic animals, causing their demise and altering the marine ecosystem equilibrium [1].

Globally, the POPs levels have been continuously increasing since the Industrial Revolution. Many POPs can easily evaporate, contaminating our surroundings and piling up at high levels, as they can propagate across the environmental components and enter our bodies through many routes [19, 20].

POPs have a very high resistance to natural degradation forces; hence, they are known as persistent pollutants. Due to their lipophilic nature, POPs pollutants can accumulate in lipids within the cells and organisms and travel long distances *via* the atmosphere [18].

These characteristics of POPs promote their biomagnification and bioaccumulation in animals, inducing risks to human and ecosystem health. These pollutants disturb the trophic network, therefore endangering the endurance of all creatures on Earth for a long period. Both humans and animals are at risk from extended contact with POPs, which can accumulate in the fatty tissues of living organisms, amplifying their levels as they move through the food web [21, 22].

Systematic evidence addresses the damaging effect of POPs on human health; contacting these chemicals can lead to numerous health problems, including tumors, diabetes, hormonal disturbance, heart diseases, and congenital anomalies, as well as immunity and reproductive impairments [22]. Basically, organisms and microorganisms are exposed to POPs toxicity in either a direct or indirect way. The environmental effects of POPs on wildlife are stated in many literatures, such as sex ratio alterations, cancer, infertility, and further physical irregularities, as mentioned below.

4. Routes of exposure to POPs

Generally, our bodies are exposed to POPs through daily activities (see **Figure 3**). POPs accumulate in the body typically through ingestion. Due to the lipophilic nature of POPs, they tend to accumulate in fat-containing food materials. Inhalation is another route of POPs exposure. Since some POPs could be transferred through the atmosphere, such as aerosols and filming tiny particles, people inhabiting polluted areas casually inhale POPs [12].

Dermal contact is the third exposure route of POPs. Whether during bathing using POPs-contaminated water, contact with contaminated soil, or contact with contaminated items, POPs can penetrate our skin and enter the circulation. Although

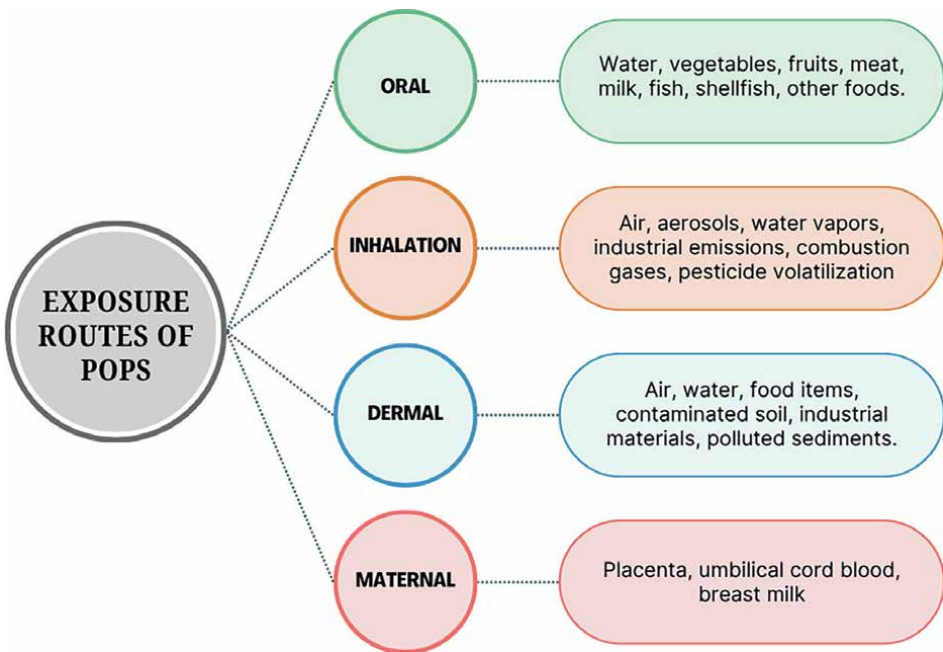


Figure 3.
Demonstrating the common routes of POPs-exposure in humans.

dermal exposure is generally less hazardous than ingestion and inhalation, it remains a common route of POPs exposure for humans. These pathways demonstrate the pervasive occurrence of POPs in our environment and underscore the critical role of recognizing them in conserving human health [22].

5. POPs in food

Generally, the main aspect that determines the occurrence of ecological contaminants in food, regardless of whether they are naturally or conventionally formed, is the immediacy of human-caused pollution sources [23–26]. Due to their lipophilic nature and capacity to bioaccumulate in the trophic network, POPs have a high potential to build up in the fatty tissues, leading to the damaging effects on human well-being. Subsequently, POPs can reach humans through consuming polluted fish and other food. Aquatic organisms can exhibit the advanced levels of POPs linked to their neighboring water setting; aquatic animals serve as excellent bioindicators of water pollution [27].

Typically, for individuals not intentionally exposed to POPs, the major contamination route is ingestion of contaminated food or water. To follow up on the accumulation of POPs in humans, biological monitoring involves studying body fluids like breast milk, blood, saliva, and urine, as well as hair and fingernails, using both invasive and non-invasive methods. These specimens deliver perspectives into POPs accumulation in the tissues attributable to contact and allocation of POPs from the placenta and breast milk from mother to child, as well as the excretion of POPs and their metabolites through various bodily fluids [28]. Research revealed that the primary pathway of POPs accumulation in human fluids is through consuming contaminated food. A secondary route of POPs exposure includes inhalation of pollutants from e-waste sites and contaminated farms [29].

6. Health risks

POPs are very harmful pollutants due to their bioaccumulation and environmental durability. In heavily contaminated environments, most individuals have POPs in their own bodies. Exposure to POPs has been associated with many health consequences, such as cognitive impairment, hepatotoxicity, and other health problems linked to POPs pollution (**Figure 4**). These consequences underscore the importance of healthcare, further research, and awareness regarding the health risks associated with POP pollution [12].

POPs have been detected in both embryos and newborns, and they collect more POPs from our polluted environment. Unfortunately, POPs are detected in individuals of every lifespan, particularly in older individuals [2, 30]. As demonstrated in **Table 1**, contact with POPs can lead to major health issues such as endocrine malfunction, heart disease, cancer, overweight, fertility and neurological disorders, dyslexia, and diabetes. Furthermore, POPs can trigger embryos' deformities [7].

Many international bodies interested in pollution management had issued varying reports. For instance, the Environmental Protection Agency (EPA) in 1994 has identified dioxins as a major cause of cancer [87], while the WHO and the International Agency for Research on Cancer (IARC) in 1997 identified 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) as the most hazardous and carcinogenic POP [88]. On the

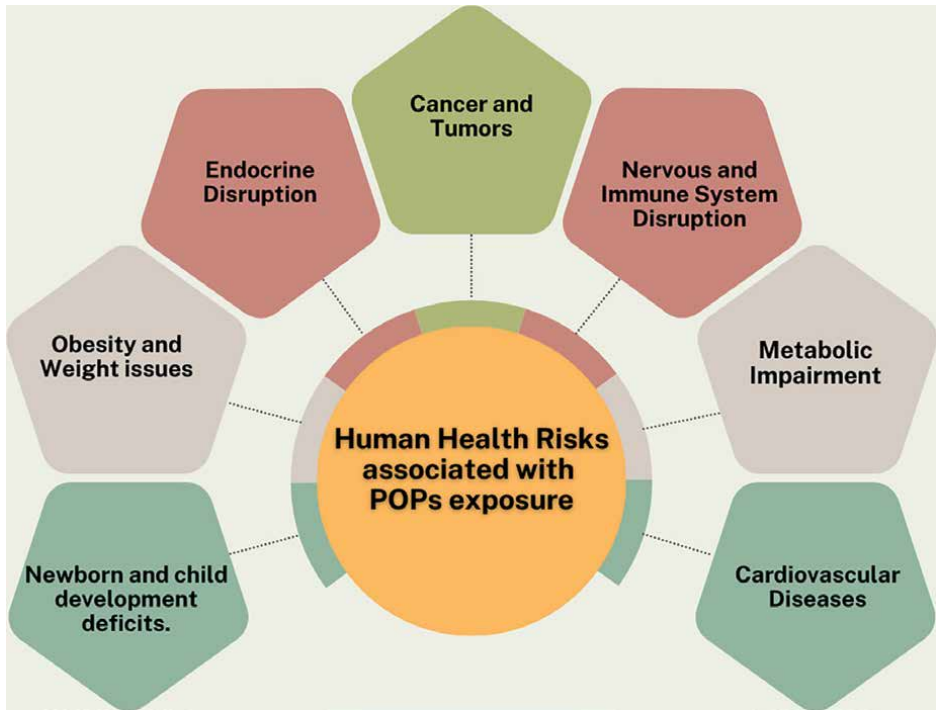


Figure 4.
Showing the health risks associated with POPs pollution.

Health outcome	Implicated POPs	References
Cardiovascular complications	PBDEs, PCBs, OCPs, and dioxins/furans are among the contributing pollutants	[31–33]
Endocrine system interference	Linked to HBCD, PCBs, dioxins/furans, OCPs, and both alpha and beta-isomers of hexachlorocyclohexane	[34–37]
Reproductive dysfunction	Associated with hexabromocyclododecane (HBCD), PBDEs, PAHs, OCPs, chlordecone, DDT, hexachlorobenzene (HCB), and PCBs	[36, 38–42]
Obesity	Exposure to PBDEs, PCBs, and OCPs has shown associations	[43–47]
Malignancy development	Includes compounds such as polychlorinated diphenyl ethers (PCDE), polychlorinated naphthalenes (PCN), polybrominated diphenyl ethers (PBDE), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides (OCPs), dichlorodiphenyltrichloroethane (DDT), endrin, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), and dioxins/furans	[48–51]
Immune dysfunction	Immunotoxicity has been observed with polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated biphenyls (PCBs), and dichlorodiphenyltrichloroethane (p, p'-DDT), and PCBz	[52–56]
Metabolic disorders (diabetes, insulin resistance)	POPs such as PBDEs, PCBs, OCPs, and dioxins/furans have been implicated	[57–61]

Health outcome	Implicated POPs	References
Digestive system disturbances	Aldrin and chlordane are associated with gastrointestinal issues	[62, 63]
Hypertension	Dioxins/furans and OCPs have been linked to elevated blood pressure	[64–66]
Renal impairment	Toxaphene, mirex, Aldrin, hexachlorocyclohexane isomers, and dieldrin are linked to kidney damage	[40, 49, 67, 68]
Neurological effects	POPs such as PCBs, OCPs, DDT, aldrin, and chlordane are associated with neurotoxicity.	[62, 69–71]
Liver toxicity	Involves PCBs, Aldrin, chlordecone, PFOS, HCB, pentachlorobenzene (PCBz), toxaphene, hexachlorocyclohexane isomers, and chlordane	[72–75]
Behavioral and cognitive impairments in children	Dioxins/furans, and HBCD have been linked to developmental delays, behavioral changes, and language deficits	[76–79]
Respiratory and genetic damage	POPs are known to contribute to respiratory ailments, oxidative stress, DNA damage, and mutagenic/carcinogenic outcomes	[80–86]

Table 1.
Health effects associated with persistent organic pollutants (POPs).

other hand, many studies reported that the most hazardous PCB relatives are the most toxic polychlorinated biphenyl (PCB) types: PCB-77 (3,3',4,4'), PCB-126 (3,3',4,4',5), and PCB-169 (3,3',4,4',5,5') [89]. Mrema et al. [90] explored the pathogenic mechanism of organochlorine pesticides (OCPs), including DDT and its metabolites, HCB, β -HCH, and endosulfan POPs, addressing two major pathways (genetic and non-genetic) in charge of several health concerns and disorders.

While individual POPs pose a health risk, organisms are exposed to multiple POPs simultaneously in the environment. Therefore, addressing the cumulative and synergistic effects of POPs on organisms is extremely challenging. Studying the additive approach of exposing organisms to multiple POPs simultaneously and monitoring their toxicity helps understand the interaction of POPs, as mixtures of POPs are more toxic than single exposure [91].

7. Physiological effects

7.1 Endocrine malfunction

The endocrine system consists of glands secreting various hormones, which promotes the crucial functions in the body, like growth, maturation, and metabolism. Consequently, alterations in the endocrine system can result in many changes in reproduction, immunity, locomotion, and the nervous system. Regrettably, many POPs are reported as endocrine disruptors, varying many hormones and fundamental functions, affecting individuals from the fetal development through lifespan [34, 36].

Organochlorine insecticides (such as endosulfan, DDT, toxaphene, dieldrin, and chlordane) are the most profound endocrine disruptors among POPs. These estrogen-like chemicals can disturb the genital organs [35, 37]. In addition, neurological dysfunctions were reported in children with a higher tendency to panic, decreased neuromotor responses, and reaction capacity. These were manifested by diminished

reflexes, disturbed vision, and temporary memory retention at about 7 months. The discrepancies, such as obesity, attenuated response, and reduced visuoperceptual ability, were manifest at the age of four. Moreover, both dioxin and PCBs have induced alterations in neurobehavioral activities in children [92, 93].

A previous study declared that POPs pollution from large-scale industrial activities across three decades spanning (1955–1984) in East Slovakia is still detectable in the environmental matrices, where some inhabitants exhibited the altered levels of thyroid hormones and urinary iodine, in addition to high concentrations of up to 15 PCBs in their blood with strong symptoms of endocrine interruptions [94]. Moreover, another study stated the individuals exposed to PCBs and other pesticides have reported impairment in hearing, metabolic activity, and neuromotor dysfunctions. They also studied the effect of POPs-contaminated food on embryos during pregnancy for more than two hundred women and their infants. The researchers confirmed the toxic effects of POPs on the hormonal system, triggering morpho-functional alterations of the gonadal systems [95].

7.2 Reproductive impairments

Reproductive issues and illnesses are abnormalities in the male and female reproductive systems. These include congenital deformities, premature birth, developmental irregularities, low neonatal mass, incapability, sterility, and ovarian cycle disorders. The toxic effect of POPs on the reproductive systems is well-documented by many scientists.

Gao and Wu [96] discussed the response of different testicular cells, such as spermatogenic cells, interstitial endocrine cells, and somatic support cells, against PCBs, revealing the adverse effects of PCBs on reproductive cells.

Another study highlighted the negative effects of POPs exposure on sperm performance and amount; in addition, these toxins impaired the male-to-female ratio, precocious puberty, and endometriosis in females [97].

Vizcaino et al. [98] confirmed that 35 different POPs (14 OCPs, 7 PCBs, and 14 PBDEs) were actively transferred from the pregnant females to their embryos and reported that the levels of POPs in maternal serum were significantly higher than in both the placenta and umbilical cord. Also, Vafeiadi et al. [99] stated that the infants' weight, head, and chest perimeter were lesser in mothers exposed to POPs during the prenatal period.

7.3 Heart and blood vessels

Globally, vascular dysfunction is the predominant cause of death, which includes high blood pressure, myocardial ischemic pain, and abnormal heart rhythm [31, 32]. Cardiovascular diseases account for around one-third of global mortality, contributing to an estimated 19.8 million deaths (32% of all deaths) in 2022 [100]; high blood pressure is the top cardiovascular risk factor. WHO evaluated that more than 1.2 billion individuals have hypertension worldwide. In 2023, about 54% of hypertensive grown person were identified, 42% treated, and only ~21% controlled [101]. POPs are lipophilic and aggregate in high-density lipoproteins, triggering the cardiovascular issues [31]. POPs such as organochlorine insecticides, polychlorinated biphenyls, and polybrominated biphenyl are associated with cardiovascular issues. Lee et al. [102] investigated 90 individuals subjected to POP, reporting several cardiovascular disorders among these people. Exposure to high levels of POPs was also interrelated

to hypertension [103]. Likewise, Uemura et al. [104] stated that high doses of dioxins and PCBs were linked to metabolic disorder, hyper-pressure, higher glucose, and triglyceride sensitivity.

7.4 Carcinogenic risk

Cancer is triggered by the uncontrolled development and propagation of aberrant cells. Cancer is the second leading cause of mortality globally. Cancer remains irredeemable in its advanced and terminal phases. Over 50% of cancer cases were found in the developing countries [105].

The levels of POPs in low-density lipoproteins are associated with different malignancies [106]. This underscores the possible health consequences of bioaccumulated pollutants in food chain. A previous study established a link between POPs-polluted seafood and associated carcinogenic risk [107].

Yu et al. [108] investigated the association between marine food intake and cancer risk. The authors detected PCBs, OCPs, PBDEs, PCDDs, dioxin, and non-dioxin-like PCBs in sea foodstuffs from different countries, while European customers exhibited the greater risk of POPs exposure than both Asians and Americans.

Many researchers studied the effects of POPs on different cell lines, reporting the carcinogenic effects of POP on breast cell lines. Moreover, a high breast carcinogenic risk in women contacting PFOS and PFOA was documented [109–111].

7.5 Obesity body mass

Obesity is the gathering of extra fat in the body tissues, which can cause many health concerns. Obesity has been linked to several ailments, including infertility, osteoarthritis, cardiovascular disease, cancer, and sleep-disordered breathing [112]. Scientists anticipated that obesity will be the major public health issue in the twenty-first century. The highest obesity was reported in the United States, followed by New Zealand, Australia, the United Kingdom, and Canada [113]. Although obesity has been attributed to POPs pollution and bioaccumulation, there is limited knowledge of the exact mechanism of POPs in obesity [47].

A previous study tackled the potential obesity-causing effects of PCBs and organochlorine insecticides (OCIs), investigating the body mass index of one hundred overweight individuals and fifty thin ones. The researchers recorded an adverse relation between PCB relatives and overweightness and also stated that exposure to POPs at low doses had a more complicated diabetogenic impact as compared to a simple obesogenic effect [114].

Moreover, individuals with high serum POPs levels revealed increased susceptibility to obesity and dyslipidemia [60, 61]. Another study conducted on a broad sample population (>12,000 workers) who experienced PCB-contaminated food recorded the high rates of obesity and 621 cases of obesity consequences, while another interesting study established the multidimensional effect of POPs through disrupting the endocrine system and triggering obesity through assessing the levels of obesity marker genes [115].

7.6 Diabetes mellitus

Diabetes mellitus (DM) refers to a group of metabolic disorders characterized by the elevated glucose levels in the blood. Serious consequences include nonketotic

hyperosmolar coma and diabetic acidosis. Long-term risks of DM include foot abscesses, stroke, heart disease, renal malfunction, and blindness [116].

Some POPs, such as chlorinated pesticides and polychlorinated biphenyls, have been related to insulin resistance syndrome and enhanced the POPs bioaccumulation in humans. People exposed involuntarily to dioxin-like POPs (PCDDs, PCDFs, and PCBs) showed a significant incidence of metabolic syndrome, specifically insulin resistance [117].

A study carried out by Tanaka et al. [118] investigated the association between PCBs levels and diabetes in Japanese participants and revealed a direct relationship between 2,2',3,4,5',6-hexachlorobiphenyl and 2,2',3,4,4',5,5'-heptachlorobiphenyl, while 2,3,3',4',5,6-hexachlorobiphenyl, 2,3,3',4',5',6-hexachlorobiphenyl, and 2,2',3,3',4,4'-hexachlorobiphenyl were inversely correlated. Moreover, Langer et al. [119] reported the diabetic problems in children due to involuntary exposure to pesticides and PCBs. Rignell-Hydbom et al. [120] also documented a strong link between PCBs and insulin-resistant diabetes mellitus (type 2 diabetes). Likewise, a previous study revealed that individuals who were exposed to POPs involuntarily at high doses reported higher type 2 diabetes by twofold, especially in obese individuals [121].

8. Future directions

Undoubtedly, population, industrial, and crop production are always growing and continuously release POPs into the ecosystem, although the establishment of many POP-control legislations limited studies, documents, and textbooks, particularly in developing nations. However, a number of developing nations do not follow those requirements owing to limited economic resources, schooling, and consciousness. As a result, the consequences of POPs control measures are not predicted to be implemented in the very near future.

Furthermore, the environmental prevalence of POPs is a profound concern. Humans are continually exposed to them. So, it seems like we cannot avoid their negative impacts anytime soon. Yet, we anticipate a POP-free atmosphere in the next century, when the majority of nations will be evolved. Multiple approaches have been used to estimate the potential effects of POPs. Those simulations are based on mechanical, chemical, and biological foundations. Arnot et al. [122] proposed a risk assessment endpoint pecking order verified for the Stockholm Convention, using hexabromocyclododecane (HBCD) as a case study. Johnson et al. [123] explored POPs' future difficulties, biological consequences, and the assessment of ecological hazards in humans and aquatic organisms.

Han et al. [124] represented an inclusive evaluation of fugacity-based models applied to simulate the ecological destiny of POPs across local, national, and international scales. These advanced systems integrated to evaluate the structural properties, strengths, and confines, with a special attention to biotic models to improve the study of POPs behavior.

Kong et al. [125] used the Baltic-multimedia POPs material pathway model to investigate the future changes in wind speed, temperature, precipitation, and organic carbon concentrations in the Baltic Sea. Weber et al. [126] examined the prospective issues of POPs, discussing the role of climate change in enhancing the leaching of POPs *via* landfills and natural degradation processes.

Abass et al. [127] conducted toxicokinetic simulation for the health risk associated with PCB153. The research team emphasizes the urgent need for additional

investigation to promote human health. Although there have been articles on modeling to predict subsequent views, there is no conventional model for projecting POPs hazards.

Hence, academics and researchers ought to assess various approaches to understand POPs. In summary, we have to deal with future problems related to POP dangers and tackle these persistent challenges together, with the synchronized and research-driven policies.

9. Conclusion

Currently, our globe is facing a serious challenge due to POPs contamination. Many POPs pose a significant threat to the health of both the environment and humans. The lipophilic nature of these pollutants, along with their resilience, promotes their bioaccumulation in living organisms and transforms them into lethal toxicants. Many adverse health conditions are related to POPs, such as obesity, insulin resistance, diabetes, hormonal disorders, cancer, circulatory and fertility issues, neonatal deficits, and others. In addition, POPs are challenging our environment's integrity and equilibrium, while climate change is predicted to exacerbate the effects of POPs and intensify their related risks. In conclusion, POPs pose a hidden threat to both the environment and human health, requiring collaborative efforts to mitigate their impact, raising awareness on the toxic effects of POPs, especially among farmers, fishermen, and unrepresented communities. The regimes should firmly monitor the production and practice of POPs worldwide. In addition, faster and more active POPs remediation and elimination approaches should be adopted to provide a worldwide strategy to address this issue.

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Persistent Organic Pollutants from Plastics: Sources, Environmental Monitoring, Toxicity, and Remediation Strategies

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Abstract

Persistent organic pollutants (POPs) are toxic chemicals that persist in the environment, accumulate in organisms, and pose significant risks to human health and ecosystems. The widespread use of plastics has exacerbated the environmental challenges posed by these pollutants, as plastics both act as sources and carriers of POPs. POPs can be embedded in plastics as additives such as flame retardants, plasticizers, bisphenols, and per- and polyfluoroalkyl substances (PFAS), or adsorbed onto plastics from surrounding environments. Environmental factors such as temperature, UV radiation, and mechanical stress influence the release of these chemicals, with degradation, weathering, and leaching contributing to their mobility and persistence. These pollutants bioaccumulate and biomagnify through food webs, affecting wildlife and human health. This chapter reviews the sources and formation pathways of POPs from plastics, examines environmental monitoring techniques, and evaluates current and emerging remediation strategies. It also discusses the health and ecotoxicological impacts of POPs, highlighting the need for stronger regulations, improved monitoring, and the development of safer, biodegradable plastics to address the growing concerns associated with plastic-derived POPs.

Keywords: persistent organic pollutants, plastics, sources, toxicity, environmental monitoring, remediation strategies, regulations

1. Introduction

Plastics have become essential in modern society, revolutionizing sectors from packaging to healthcare due to their lightweight, durability, and low cost, with global production exceeding 400 million metric tons annually [1, 2]. However, their widespread use raises significant environmental concerns, particularly due to their association with POPs, toxic synthetic compounds characterized by chemical stability,

lipophilicity, persistence, bioaccumulation, and toxicity [3]. POPs can resist degradation, accumulate in organisms, and magnify across food chains, threatening biodiversity and human health worldwide. Plastic-associated POPs include additives such as polybrominated diphenyl ethers (PBDEs) used as flame retardants [4], phthalates as plasticizers in polyvinyl chloride (PVC) [5], and bisphenols like bisphenol A (BPA) employed in polycarbonate plastics and epoxy resins [6]. Other hazardous POPs linked to plastics include halogenated flame retardants, polychlorinated biphenyls (PCBs), and perfluoroalkyl and polyfluoroalkyl substances (PFAS) used for water and oil repellency [7], as well as styrene oligomers found in polystyrene plastics [8].

Plastics influence POP dynamics through two main pathways: as carriers adsorbing POPs from contaminated environments (notably micro- and nano-plastics with high surface-area-to-volume ratios) and as sources *via* inherent toxic additives (**Figure 1**). Adsorbed POPs, including PCBs, dioxins, and organochlorine pesticides (OCPs), accumulate on plastics and enter food webs through ingestion, promoting bioaccumulation and biomagnification [9]. This dual role makes plastics vectors for global POP dispersal, contaminating remote ecosystems such as deep oceans and polar regions. Human exposure to plastic-associated POPs occurs *via* ingestion of contaminated food and water, inhalation of airborne particles, and dermal contact [10]. Such exposure is linked to endocrine disruption, reproductive toxicity, neurodevelopmental deficits, and cancer [9, 11, 12]. Given their persistence and toxicity, POPs pose serious risks to biodiversity, food security, and public health [9, 11–14]. Advanced environmental monitoring using techniques such as gas chromatography–mass spectrometry (GC-MS) and high-resolution mass spectrometry (HRMS) is vital to detecting and quantifying POPs in various matrices, informing risk assessments [15–18]. In parallel, remediation strategies such as physical adsorption, advanced oxidation processes (AOPs), and bioremediation show promise but face challenges in scalability and environmental compatibility, necessitating integrated approaches [19]. Policy frameworks like the Stockholm Convention have advanced POP regulation, yet enforcement gaps and emerging contaminants demand stronger, coordinated global actions [3]. Tackling plastic-derived POP pollution requires a multifaceted approach



Figure 1.
Key POPs associated with plastics: Embedded as additives or adsorbed from environmental contaminants.

combining scientific innovation, effective regulation, and sustainable material development to safeguard ecosystems and human health from these persistent threats.

2. Sources and formation of POPs from plastics

POPs associated with plastics originate from multiple sources (**Table 1**), stemming both from the intentional addition of chemicals during plastic manufacture (primary source) and from environmental processes leading to their formation or adsorption onto plastic debris (secondary source). Understanding these sources and formation

Category	Description	Common POPs/Examples	References
Primary sources (additives in plastics)	Chemicals intentionally added during plastic manufacturing to enhance properties.	• Plasticizers: DEHP, DBP, BBP, DINP, DIDP, adipates, citrates • Flame retardants: PBDEs (BDE-47, BDE-99, BDE-209), (HBCDD, TBBPA, OPFRs) • UV stabilizers: Benzotriazoles (UV-327, UV-328), HALS, benzophenones (BP-3) • Bisphenols: BPA, BPF, BPS • Antimicrobials: Triclosan, triclocarban, silver nanoparticles • Antioxidants: Butylated hydroxytoluene (BHT), phosphite antioxidants • PFAS: PFOA, PFOS, fluorotelomers, emerging PFAS compounds	[20–24]
Secondary sources (adsorbed environmental POPs)	POPs adsorbed onto plastics from contaminated environments (water, soil, sediment).	• PCBs: PCB-28, PCB-52, PCB-118, PCB-153, PCB-180 • PAHs: Naphthalene, phenanthrene, pyrene, benzo[a]pyrene • Dioxins (PCDDs): 2,3,7,8-TCDD and related congeners • Furans (PCDFs): Polychlorinated dibenzofurans congeners • Organochlorine pesticides: DDT, DDE, DDD, lindane (γ-HCH), chlordane, endosulfan, heptachlor	[6, 25–28]
Formation processes	Environmental or anthropogenic processes generating or releasing POPs from plastics.	• Plastic degradation and weathering: Photodegradation, oxidative degradation • Thermal degradation and incineration: Generation of dioxins, furans, and PAHs during the burning of plastics	[6, 20–28]

Category	Description	Common POPs/Examples	References
Transport vectors	Physical carriers facilitating POP mobility and bioavailability.	• Macroplastics • Microplastics • Nanoplastics	[6, 20–28]

Table 1.
Key sources, formation pathways, and transport vectors of POPs linked to plastics, including additives, environmental adsorption, and plastic degradation processes.

pathways is critical to grasping the environmental persistence and risks of POP contamination linked to plastics.

2.1 Primary sources

During the production of plastic materials, a wide range of chemical additives are introduced to enhance physical and chemical properties such as flexibility, durability, flame retardancy, and UV resistance [6]. Several of these additives fall under the category of POPs due to their toxicity, persistence, and bioaccumulative nature. These additives include flame retardants, plasticizers, UV stabilizers, antimicrobials, antioxidants, PFAS, and bisphenols.

2.1.1 Flame retardants

Flame retardants are critical additives used in plastics, textiles, and electronic materials to reduce flammability and enhance fire safety. Among them, PBDEs remain widely detected in consumer products such as electronics and furniture foams despite phasedown efforts, due to their persistence and bioaccumulative nature [29, 30]. Other brominated flame retardants such as hexabromocyclododecane (HBCDD) and tetrabromobisphenol A (TBBPA) continue to be employed in insulation foams and printed circuit boards, respectively, and are increasingly detected in environmental samples worldwide [31]. These compounds are introduced into the environment throughout the plastic lifecycle during manufacturing, product use, abrasion, recycling, and disposal *via* leaching, atmospheric emissions, and waste [32]. Due to their strong hydrophobicity and affinity for plastic surfaces, these flame retardants readily adsorb onto macroplastics and microplastics in aquatic and terrestrial environments, facilitating long-range transport and enhancing bioavailability to organisms [31, 32]. This adsorption effect elevates the role of plastics as vectors for flame-retardant POPs, contributing to contamination of remote ecosystems and bioaccumulation through food webs. The persistent and widespread presence of flame-retardant POPs in plastic waste presents ongoing challenges for environmental management and necessitates improved regulation and remediation strategies to mitigate their impact [33].

2.1.2 Plasticizers

Plasticizers, particularly phthalates, are widely incorporated into plastics such as PVC to enhance flexibility and durability [6, 25]. These chemicals are not covalently bound to polymer chains, making them prone to leaching into the environment during manufacturing, product use, and disposal. Phthalates such as di(2-ethylhexyl) phthalate

(DEHP) and dibutyl phthalate (DBP) persist in soils and waters and bioaccumulate in organisms, classifying them as POPs [34, 35]. Their environmental presence is further exacerbated by adsorption onto microplastics and nanoplastics, which serve as vectors transporting plasticizer-associated POPs through aquatic and terrestrial ecosystems [36]. Emerging non-phthalate plasticizers, though designed as alternatives, may similarly persist and exhibit POP-like behaviors due to structural similarity [37]. The continuous release and environmental transformation of plasticizers during the entire plastic life cycle, from production to degradation, make them significant sources of POP contamination, complicating efforts to manage plastic pollution and its toxic legacy.

2.1.3 UV stabilizer

UV stabilizers are chemical additives incorporated into plastics to protect them from degradation caused by UV radiation exposure. These compounds prolong plastic durability and prevent discoloration, brittleness, and loss of mechanical integrity. Common classes of UV stabilizers include benzotriazoles, hindered amine light stabilizers (HALS), and benzophenones, many of which exhibit persistence, bioaccumulation, and toxicity, thereby qualifying as persistent organic pollutants (POPs) or POP-like substances [38, 39]. During the plastic lifecycle, UV stabilizers can leach into the environment through weathering, abrasion, and fragmentation processes. Additionally, microplastics with adsorbed or incorporated UV stabilizers act as vectors for long-range transport of these pollutants [40]. Environmental degradation or photolysis may transform UV stabilizers into secondary POPs or toxic metabolites, increasing their ecological risks [41]. The continuous release of UV stabilizers from plastic products and their persistence in various ecosystems contribute significantly to the global burden of plastic-associated POP contamination.

2.1.4 PFAS

PFAS are a large group of synthetic fluorinated chemicals widely used in plastic production and surface coatings to impart water-, stain-, and grease-resistant properties. These substances are often applied as additives or incorporated as polymer processing aids in plastics used for food packaging, textiles, nonstick cookware, and industrial applications. Due to their strong carbon-fluorine bonds, PFAS are exceptionally persistent, resistant to environmental degradation, and highly mobile in water and soil systems [42]. During the manufacturing, use, weathering, and disposal of PFAS-containing plastics, these substances can leach or be released into the environment, contaminating water bodies, soils, and air [20–22]. Microplastics serve as vectors for PFAS transport and facilitate their bioavailability to aquatic and terrestrial organisms [7]. Furthermore, environmental degradation can produce a variety of PFAS transformation products, many of which maintain persistence and toxicity, contributing to the growing concern over their ecological and human health impacts [43]. The widespread use and release of PFAS in plastics thus make them significant contributors to the global burden of POP contamination, necessitating enhanced monitoring and remediation efforts.

2.1.5 Antimicrobials and antioxidants

Antimicrobials and antioxidants are commonly incorporated into plastics to inhibit microbial growth and prevent oxidative degradation, thereby enhancing product lifespan and safety. *Antimicrobials* such as triclosan and silver-based compounds are added to

consumer plastics, medical devices, and packaging materials to reduce bacterial colonization. Many antimicrobials are persistent and bioaccumulative, exhibiting POP-like characteristics that enable them to persist in environments and biota [23]. Similarly, *antioxidants*, including hindered phenols and phosphites, are added to plastics to prevent oxidative chain reactions during processing and use. Certain antioxidants degrade into POPs with toxic potential, contributing to environmental POP contamination [44]. Both classes of additives can leach from plastics into soil, water, and air through weathering, abrasion, or disposal and adsorb onto microplastics, facilitating their environmental dispersal [44]. The transformation and persistence of these compounds complicate their environmental fate, making antimicrobials and antioxidants significant, yet often overlooked, contributors to the plastic-associated POP burden.

2.1.6 Bisphenol A

Bisphenol A (BPA) is a widely used chemical additive in the production of polycarbonate plastics and epoxy resins, commonly found in food containers, water bottles, medical devices, and coatings for metal products. BPA's role as a plasticizer and polymer precursor makes it a pervasive component of many plastic products. Due to its *incomplete polymerization* and weak bonding to polymer matrices, BPA can leach into surrounding environments during the manufacturing process, product use, and disposal stages [24]. Environmental degradation of BPA-containing plastics through UV exposure, heat, or mechanical stress can further facilitate its release. BPA exhibits persistence in the environment and potential for bioaccumulation, contributing to its classification as an endocrine-disrupting chemical with toxic effects on both wildlife and humans [45]. Microplastics may also adsorb BPA from contaminated environments, acting as vectors for its transport and trophic transfer [24]. The continuous release and environmental presence of BPA highlight its significance as a major source of plastic-associated POPs, with implications for ecological and human health that necessitate improved monitoring and regulatory control.

2.2 Secondary sources

Microplastics act as passive samplers, accumulating POPs from the surrounding environment. Some POPs, such as PCBs, polycyclic aromatic hydrocarbons (PAHs), and dioxins from industrial discharges, wastewater, and urban runoff, adsorb onto microplastics in rivers and oceans. Pesticides such as Dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexanes (HCHs), and chlordanes from agricultural runoff bind to microplastics in soil and water [46]. Airborne POPs (e.g., PCBs, PBDEs) settle on microplastics *via* dry or wet deposition. Legacy POPs (banned but persistent) and emerging POPs (e.g., perfluorinated compounds) accumulate on floating microplastics. In addition to inherent additives, plastics act as environmental sinks and vectors for POPs present in the surrounding media. Especially in aquatic and terrestrial ecosystems, plastic debris, including macroplastics, microplastics (<5 mm), and nanoplastics (<100 nm), adsorbs hydrophobic organic pollutants from water, sediments, and soil due to their hydrophobic surfaces and large surface-area-to-volume ratios [6, 25, 26].

2.2.1 PCBs

PCBs are a class of synthetic chlorinated organic chemicals historically used in electrical transformers, capacitors, hydraulic fluids, and various industrial

applications due to their chemical stability and insulating properties. Although their production was banned or severely restricted globally starting in the late 1970s due to their toxicity and persistence, PCBs remain ubiquitous environmental contaminants owing to their *high persistence, low degradability, and lipophilicity* [11, 46]. PCBs have a strong affinity for organic matter and hydrophobic surfaces, which facilitates their adsorption onto plastics present in aquatic and terrestrial environments. Microplastics and nanoplastics, with their high surface-area-to-volume ratios and hydrophobic surfaces, serve as effective sorbents of PCBs from contaminated water, sediments, and soils [10, 30, 47]. This adsorption enhances the environmental mobility of PCBs, allowing them to be transported across ecosystems and increasing their bioavailability to aquatic organisms and terrestrial wildlife through ingestion of contaminated plastics [9]. Environmental weathering of plastics can also release adsorbed PCBs back into the surrounding media, perpetuating contamination cycles. The interaction between PCBs and plastics thereby significantly contributes to the global dispersal and persistence of these harmful POPs, complicating remediation efforts and increasing ecological and human exposure risks.

2.2.2 PAHs

PAHs are a class of organic compounds composed of fused aromatic rings, primarily formed during the incomplete combustion of organic materials such as fossil fuels, wood, and waste. PAHs are widespread environmental contaminants due to their *persistence, hydrophobicity, and toxicity*, including mutagenic and carcinogenic properties [48]. These compounds readily adsorb onto plastic debris, particularly microplastics and nanoplastics, in aquatic and terrestrial environments owing to the hydrophobic surfaces of plastics [25]. Plastics serve as vectors facilitating the transport of PAHs across ecosystems and promoting bioavailability to organisms through ingestion of contaminated plastics [48]. Additionally, the weathering and degradation of plastics can enhance the sorption capacity for PAHs while releasing adsorbed contaminants back into the environment under certain conditions [49]. The adsorption and desorption dynamics of PAHs on plastics complicate their environmental fate, contributing to their persistence and widespread distribution in food webs, thereby posing significant ecological and human health risks.

2.2.3 Dioxins

Dioxins, a group of chemically related polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs), are highly toxic persistent organic pollutants formed primarily as unintentional byproducts of combustion processes, including waste incineration, industrial activities, and forest fires. Due to their *extreme persistence, lipophilicity, and toxicity*, dioxins readily accumulate in environmental matrices and biota [27]. In aquatic and terrestrial ecosystems, dioxins can adsorb onto plastics and microplastics, which act as vectors facilitating their transport and bioavailability [28]. The hydrophobic nature of plastics enhances the sorption capacity for dioxins, enabling these pollutants to travel long distances and enter food webs through ingestion by marine and terrestrial organisms [27, 28]. Environmental weathering of plastics may influence the desorption and remobilization of dioxins, contributing to their persistence and complicating remediation efforts. Consequently, plastics serve as important carriers in the global cycling and distribution of dioxins, exacerbating their ecological and human health risks.

2.2.4 Organochlorine pesticides

Organochlorine pesticides (OCPs), such as *DDT*, *lindane* (γ -HCH), and *chlordane*, are synthetic chemicals extensively used in agriculture and vector control during the mid-twentieth century. Despite bans and restrictions in many countries due to their toxicity, persistence, and bioaccumulative properties, OCPs remain widespread environmental contaminants [46]. Their high hydrophobicity enables strong adsorption onto plastics and microplastics present in soils, sediments, and aquatic systems. These plastics act as vectors, facilitating long-range transport and increasing bioavailability of OCPs to organisms upon ingestion of contaminated debris [50]. Environmental weathering of plastics can lead to the release or transformation of adsorbed OCPs, further perpetuating contamination cycles. The interaction between plastics and OCPs exacerbates ecological and human health risks, complicating remediation efforts and necessitating continued monitoring (**Table 1**).

2.3 Environmental factors influencing POPs release

The release of POPs from plastics into the environment is a dynamic process influenced by a variety of environmental factors that affect the stability, degradation, and mobility of both the plastics and the associated chemicals. Understanding these factors is essential to accurately predict the environmental fate, bioavailability, and ecological risks of plastic-associated POPs.

2.3.1 Temperature

Temperature plays a crucial role in accelerating the physical and chemical degradation of plastics, thereby facilitating the release of embedded or adsorbed POPs. Higher temperatures increase the diffusion rates of additives and pollutants out of the polymer matrix and enhance photochemical reactions that break down plastic polymers [51]. For instance, thermal stress during summer months or in tropical environments can increase the leaching of flame retardants and plasticizers [52]. Conversely, colder conditions may slow degradation but promote the accumulation of POPs in ice and sediment matrices.

2.3.2 UV radiation

Exposure to sunlight, particularly UV radiation, initiates photodegradation of plastic polymers, altering their chemical structure and surface morphology. This process not only weakens the plastic but also leads to the breakdown or transformation of incorporated additives into secondary POPs or facilitates the desorption of adsorbed pollutants [53]. UV-induced weathering enhances surface roughness, increasing the surface area available for environmental adsorption and microbial colonization, further influencing POP dynamics.

2.3.3 Mechanical stress and abrasion

Mechanical forces such as wave action, wind, and physical abrasion cause fragmentation of plastics into micro- and nanoplastics. These smaller particles with higher surface-area-to-volume ratios promote increased sorption capacity and potentially greater release rates of POPs [54]. Abrasion can also expose previously

embedded additives or adsorbed pollutants to the environment, enhancing bioavailability and transport potential.

2.3.4 Chemical environment

The surrounding chemical environment significantly affects POP release kinetics. Variations in pH can alter the solubility and speciation of certain POPs, influencing their partitioning between plastics and water or sediments [54]. Salinity gradients, particularly in estuarine and marine environments, can impact the sorption/desorption equilibrium of hydrophobic POPs on plastic surfaces. Additionally, the presence of organic matter, surfactants, or competing contaminants can modify POP interactions with plastics, either facilitating release or enhancing retention [55].

2.3.5 Microbial activity

Microorganisms colonizing plastic surfaces (the “plastisphere”) can contribute to the biodegradation of plastics and associated POPs. Microbial enzymatic activity may degrade polymer backbones, releasing embedded additives, or transform adsorbed POPs into more or less toxic metabolites [56]. The composition and activity of microbial communities are influenced by environmental factors such as nutrient availability, temperature, and pollution levels, thereby affecting POP release rates.

2.3.6 Environmental medium

The matrix in which plastics are found, whether freshwater, marine water, soil, or sediment, influences POP release due to differences in temperature, microbial communities, hydrodynamics, and chemical composition. For example, sediment environments often promote longer plastic retention times and may facilitate slow release of POPs, while turbulent marine waters may enhance desorption and dispersal [54].

The release of POPs from plastics is a complex interplay of environmental factors, including temperature, UV exposure, mechanical forces, chemical conditions, microbial processes, and the specific environmental medium. These factors determine the rate, extent, and pathways through which POPs enter ecosystems, impacting their persistence, bioavailability, and toxicological effects. Comprehensive environmental risk assessments and effective remediation strategies must account for these variables to mitigate the impacts of plastic-associated POP pollution.

3. Environmental monitoring of POPs from plastics

Monitoring the presence and distribution of POPs originating from plastics is an essential step in understanding their environmental and human health impacts. Their detection and quantification demand sensitive, selective, and standardized analytical techniques tailored to the complex matrices of air, water, sediments, and biota. Although there are not yet international standardized techniques for research on microplastics, the literature reports some rigorous and common strategies, from sampling to laboratory analysis of POPs from MPs.

3.1 Sampling strategies for POPs in microplastics

Monitoring microplastics and their associated POPs requires diverse sampling strategies across environmental matrices. Techniques vary depending on the target

medium—water, sediment, air, soil, or biota—and are selected based on their suitability for capturing both microplastics and POPs. Methods such as trawling, coring, and passive air or deposition sampling offer insights into the distribution, transport, and fate of contaminants. Each approach has distinct advantages and limitations in terms of spatial coverage, detection sensitivity, and logistical requirements, as summarized in the following **Table 2**.

3.2 Laboratory separation and extraction

Given the low concentrations of POPs in microplastics and the complexity of the matrices, advanced preconcentration and cleanup techniques are crucial before characterizing and quantifying these pollutants. Cleanup methods such as gel permeation chromatography (GPC), silica or Florisil column chromatography, and activated carbon columns are commonly used to remove matrix interferences and

Matrix	Technique	Description	Advantage	Limitation
Water column and surface sampling	Neuston nets and manta trawls [57]	Used to collect floating microplastics from marine and freshwater systems.	Efficient for sampling large areas and buoyant plastics.	Underestimates mid-water and sediment plastics. Requires boat access and calm weather.
	Sediment coring [18, 58]	Retrieves microplastics from riverbeds, lakes, and ocean floors where POPs accumulate.	Captures buried microplastics and POPs; allows historical analysis through sediment layers.	Equipment-intensive; may not capture very small or loosely bound plastics.
	Grab sampling [59]	Manual collection of shoreline plastics for localized POP analysis.	Simple, low-cost, and effective for hotspot assessment.	Limited spatial and temporal coverage; can be biased by visual sorting.
Airborne microplastic sampling	High-volume air samplers [60]	Capture atmospheric microplastics and adsorbed POPs.	Enables quantification of airborne microplastics over time.	Equipment is expensive; requires a power source and long sampling durations.
	Deposition traps [16]	Measure the fallout of microplastic-bound POPs in urban and remote areas.	Passive, low-cost, and suitable for long-term monitoring.	Limited to particle fallout; does not capture resuspended or airborne fibers.
Soils	Soil core sampling [61]	Collects vertical profiles of soils to detect microplastics and bound POPs.	Allows depth profiling and tracking of contamination over time.	Labor-intensive and may miss small-scale heterogeneity or very small particles.
Biotic sampling	Bioindicator species analysis [62]	Mussels, fish, and seabirds are analyzed for microplastic ingestion and POP bioaccumulation.	Indicates ecological exposure and trophic transfer potential.	Invasive, may require sacrificing organisms; results may vary by species and feeding habits.

Table 2.
Summary of sampling techniques for detecting microplastics and associated POPs in various environmental matrices.

ensure the purity of the sample [63]. For separating microplastics from organic matter, density separation using sodium chloride (NaCl) or sodium iodide (NaI) solutions is applied [64]. Additionally, oxidative digestion methods, utilizing hydrogen peroxide (H₂O₂) or Fenton's reagent, are used to remove organic debris without degrading the plastics [65].

When it comes to extracting POPs from the plastic matrix, several techniques are employed, including Soxhlet extraction, solid-phase extraction (SPE), accelerated solvent extraction (ASE), ultrasonic-assisted extraction (UAE), and QuEChERS.

Soxhlet extraction is a traditional, classical method that involves continuous solvent cycling through a solid sample using heat and condensation, ensuring exhaustive extraction. However, it is time-consuming and uses large volumes of solvent [66]. SPE involves passing a liquid extract through a cartridge containing a sorbent that selectively retains the analytes or impurities. It is a widely used method for the cleanup and concentration of POPs due to its efficiency and simplicity [67]. ASE improves upon traditional extraction methods by applying elevated temperatures and pressures to enhance solvent penetration and analyte solubilization, reducing both extraction time and solvent use [48].

Ultrasonic-assisted extraction (UAE) utilizes ultrasonic waves to disrupt sample matrices, thus improving solvent access to embedded compounds. It is valued for its speed, reduced solvent consumption, and ease of use [68]. QuEChERS (*quick, easy, cheap, effective, rugged, and safe*), originally developed for pesticide analysis, involves an extraction step with acetonitrile followed by a salt-induced partitioning and cleanup. It has been adapted for POPs and offers a quick, cost-effective method for extracting pollutants from complex biological or food samples [48].

3.3 Analytical techniques for POP detection

Detecting POPs in environmental matrices such as water, soil, sediment, biota, and plastic is critical for understanding their distribution, environmental impact, and bioavailability. Various analytical techniques have been developed and refined to quantify POPs at trace levels. These methods provide essential data for risk assessment, regulatory compliance, and remediation monitoring. After separation and extraction of POPs, spectrochemical methods and chromatography are applied to qualify and quantify them (Table 3).

3.4 Challenges

Monitoring persistent organic pollutants associated with microplastics presents several critical challenges. The inherent heterogeneity of microplastic samples, arising from differences in polymer composition, particle size, and degrees of environmental weathering, can significantly influence the adsorption behavior of POPs. Additionally, the risk of background contamination during sampling and laboratory analysis requires strict control measures to prevent interference from solvents, equipment, or airborne particles. The typically low concentrations of POPs on microplastics further complicate detection, often necessitating advanced preconcentration techniques such as solid-phase extraction. Compounding these issues is the absence of standardized analytical protocols, which hinders data comparability across studies and underscores the urgent need for harmonized global methodologies.

Category	Technique	Description / Target POPs
Chromatographic methods	High-Resolution Gas Chromatography-High-Resolution Mass Spectrometry (HRGC-HRMS)	High precision for identifying and quantifying trace-level volatile and semi-volatile POPs.
	Gas Chromatography-Electron Capture Detector (GC-ECD)	Highly sensitive to chlorinated POPs like PCBs and HCHs.
	Gas Chromatography-Mass Spectrometry (GC-MS)	Common for organochlorine pesticides, PCBs, and PBDEs.
	Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)	Preferred for polar and heat-sensitive compounds such as PFAS and certain PAHs.
	Pyrolysis-GC-MS	Breaks down polymers thermally to analyze embedded POPs like flame retardants.
	Liquid Scintillation Counting (LSC)	Used for radiolabeled POPs in sorption/desorption studies.
Spectrochemical methods	Fluorescence Spectroscopy	Used for detecting compounds like benzo(a)pyrene in complex samples.
	Fourier Transform Infrared Spectroscopy (FTIR)	Identifies microplastic polymer types and surface-adsorbed POPs.
	Scanning Electron Microscopy-Energy Dispersive X-ray Spectroscopy (SEM-EDS)	Provides surface structure and elemental analysis of pollutants associated with plastics.

Table 3.
Overview of analytical techniques for detecting POPs in plastics.

4. Remediation strategies for POPs from plastics

The strategies to remove plastic-associated POPs represent a complex yet urgent priority, as conventional waste management practices like landfilling and incineration often exacerbate pollution through incomplete degradation or the release of toxic byproducts. Current strategies include physical, chemical, biological, or integrated approaches. Each technique offers specific advantages and may face distinct limitations, necessitating their integration for effective POP management [69].

4.1 Physical removal techniques for POPs mitigation

Physical methods for the remediation of POPs associated with plastics focus on removing, isolating, or concentrating these contaminants from environmental matrices such as water, soil, and sediment. These techniques rely on physical separation processes that do not chemically alter the pollutants but reduce their bioavailability and mobility, thus limiting exposure risks. A prominent physical approach is adsorption, which exploits the affinity between hydrophobic POP molecules and sorbent materials. In this process, POPs concentrate onto the adsorbent's surface, effectively removing them from water or soil pore water [69].

Porous sorbent materials such as activated carbon and biochar are widely used in water treatment due to their ability to immobilize contaminants. Research has shown that these materials are particularly effective at capturing POPs from aquatic

environments, making them suitable for application in plastic-laden ecosystems. Biochar has shown excellent performance due to its microporous structure, expansive surface area, and aromatic carbon framework enriched with polar functional groups [70]. These characteristics enhance its affinity for organic compounds, such as PAHs, and have been demonstrated in studies on reducing PAH uptake in root vegetables [71]. Additionally, the interaction between biochar and microplastics can amplify POPs removal by exploiting complementary surface characteristics.

POPs can also be removed from plastics using partitioning techniques, where POPs diffuse into the porous matrix of adsorbents. This process relies on hydrophobic interactions and surface adsorption within materials such as MPs, where the contaminants migrate into the pores [72]. Studies of biochar and aquatic contaminants underscore the significance of material structure in pollutant capture. FTIR spectroscopy has shown that adsorbents undergo structural changes, such as dehydration and biopolymer breakdown, during the adsorption process, which generates volatile byproducts [73].

Filtration and membrane separation are also promising techniques for removing POPs from microplastics. These methods utilize selective barriers or membranes that separate contaminants based on size exclusion, charge, or affinity. Technologies such as nanofiltration and reverse osmosis can efficiently retain dissolved POPs and microplastics while allowing clean water to pass. Filtration technologies, leveraging separation and adsorption principles, are central to removing POPs. Methods like media-based filtration (sand, activated carbon, or biochar in slow/rapid systems), ultrafiltration, and reverse osmosis have shown high efficiency in isolating microplastics and adsorbed POPs. Reverse osmosis, for example, can reduce microplastics by up to 99% by trapping particles larger than the membrane pores [74].

Physical collection is another effective method, which directly removes plastic debris that serves as a POP reservoir from environmental compartments. This approach prevents further pollutant leaching and distribution. However, physical techniques such as adsorption and partitioning face challenges in terms of energy consumption, byproduct management, and scalability for large-scale operations.

To address these limitations, innovations in material design and hybrid approaches are essential to improve the efficiency of these methods while maintaining environmental safety. Additionally, a key strategy in mitigating POPs linked to microplastics in water systems is intercepting and recycling plastic debris. Preventing the interaction between POPs and plastics involves measures such as phasing out single-use plastics and hazardous additives and advancing the development of biodegradable substitutes. Transitioning to a circular economy model, focusing on reuse and closed-loop systems, presents a more sustainable pathway to curb plastic pollution.

4.2 Chemical degradation

4.2.1 Advanced oxidation processes (AOPs)

Advanced oxidation processes (AOPs) generate highly reactive radicals, particularly hydroxyl radicals ($\cdot\text{OH}$), which are capable of breaking down complex POP molecules into simpler, often less toxic compounds [75]. Photocatalysis, for instance, utilizes semiconductors such as TiO_2 activated by UV light to produce hydroxyl radicals, efficiently degrading POPs like PBDEs and phthalates in aqueous solutions. Similarly, ozonation and Fenton's reagent have demonstrated strong oxidative potential in degrading a wide range of POPs [76]. Despite high removal efficiency, AOPs

require careful process control to avoid incomplete degradation that may lead to the formation of harmful byproducts. Moreover, AOPs often demand substantial energy input, which can limit their sustainability for large-scale applications. Notably, AOP techniques can also help in the removal of microplastics by targeting POPs adsorbed onto the particles, showing promise in addressing both complex POP contamination and microplastic pollution simultaneously.

4.3 Thermal treatment

Thermal desorption is effective in volatilizing POPs from heated plastics but faces practical limitations, including high energy demands and the potential release of secondary pollutants. Incineration at high temperatures (greater than 850°C) can completely decompose POPs adsorbed onto plastics, converting them into harmless byproducts such as CO₂, water, and inorganic salts. However, uncontrolled combustion can lead to the formation of highly toxic compounds like dioxins and furans, necessitating sophisticated emission control systems to prevent environmental contamination. Alternatively, pyrolysis and gasification processes, conducted in oxygen-limited conditions, can convert plastic waste and associated POPs into useful products such as syngas, oils, and char with significantly reduced emissions [77]. These methods offer promising solutions, but their commercial viability and environmental safety still require further optimization. For example, a hydrothermally coupled Fenton system developed for polyethylene decomposition has achieved 95.9% mineralization, demonstrating the potential for efficient plastic waste treatment. During the degradation process, POPs associated with MPs may also degrade through the volatile system, offering an additional pathway for pollutant removal [78].

4.4 Bioremediation approaches for POPs in microplastics

Bioremediation utilizes biological agents such as microorganisms and enzymes to decompose or stabilize POPs associated with microplastics. Microorganisms naturally colonize the surfaces of MPs, where they enzymatically degrade POPs into less toxic byproducts. Certain bacterial strains, such as *Sphingomonas*, *Pseudomonas*, and *Phanerochaete chrysosporium*, have shown remarkable capabilities in metabolizing POPs and plastic-derived compounds as energy sources in aquatic environments. Studies have highlighted the efficacy of *Bacillus* sp. and *Enterobacter asburiae* in degrading MPs, while bacteria like *Stenotrophomonas*, *Comamonas*, and *Delftia* thrive in polyethylene-rich environments, utilizing MPs as their sole carbon source over extended periods [54]. These bacteria form biofilms on MPs, which accelerates the enzymatic breakdown of POPs. Fungal species also play a vital role in enhancing bioremediation by secreting ligninolytic enzymes (e.g., manganese peroxidase) that can dismantle complex POP structures. Their colonization of microplastics creates synergistic biofilms that further amplify pollutant breakdown. While bioremediation offers eco-friendly solutions for POP removal, it is hindered by limitations such as slow processing times and reduced efficacy against highly halogenated POPs, which may be less susceptible to biological degradation [79].

4.5 Integrated strategies and novel solutions for plastic-associated POPs

To sustainably address POPs in plastics, long-term strategies should focus on containment and neutralization to prevent ecosystem release. Key innovations include:

Redesigning polymers with pollutant-capturing properties: Modifying the crystallinity of polymers (e.g., HDPE or PP) enhances their pollutant-capturing abilities. These dense matrices minimize free spaces, physically entrapping POPs and hindering their migration. Such polymers are designed to be more resistant to UV radiation and thermal degradation, ensuring long-term POP retention.

Integration of adsorbent materials: Incorporating biochar or activated carbon into plastics exploits their hydrophobic properties and π - π interactions to irreversibly bind POPs. These materials' stability ensures they remain effective for centuries, transforming plastics into permanent pollutant sinks [79].

Impermeable layer applications: Coating plastics with impermeable materials such as graphene oxide or silica creates diffusion-resistant shields that block POP leaching. These coatings enhance the plastics' ability to trap pollutants and prevent their release into the environment.

Nano-bioremediation: Nanoparticles combined with biological agents (e.g., microbes or enzymes) offer enhanced contaminant removal capabilities. For instance, Fe_3O_4 nanoparticles synthesized from eco-friendly precursors show promise in adsorbing and degrading POPs. Fe_3O_4 -microplastic composites could amplify the adsorption process, but further research is needed to optimize efficiency and scalability.

The remediation of POPs from plastics requires a comprehensive, integrated approach involving physical, chemical, and biological methods. Physical methods like adsorption and filtration offer immediate pollutant removal, while chemical degradation and bioremediation strategies provide longer-term solutions. Emerging innovations, such as engineered polymers, adsorbent integration, and nano-bioremediation, hold promise for enhancing remediation efficiency. However, challenges related to scalability, byproduct management, and environmental compatibility remain. Addressing these challenges through multidisciplinary approaches and regulatory support will be critical to mitigating the environmental and health risks posed by POPs from plastics (**Figure 2**).

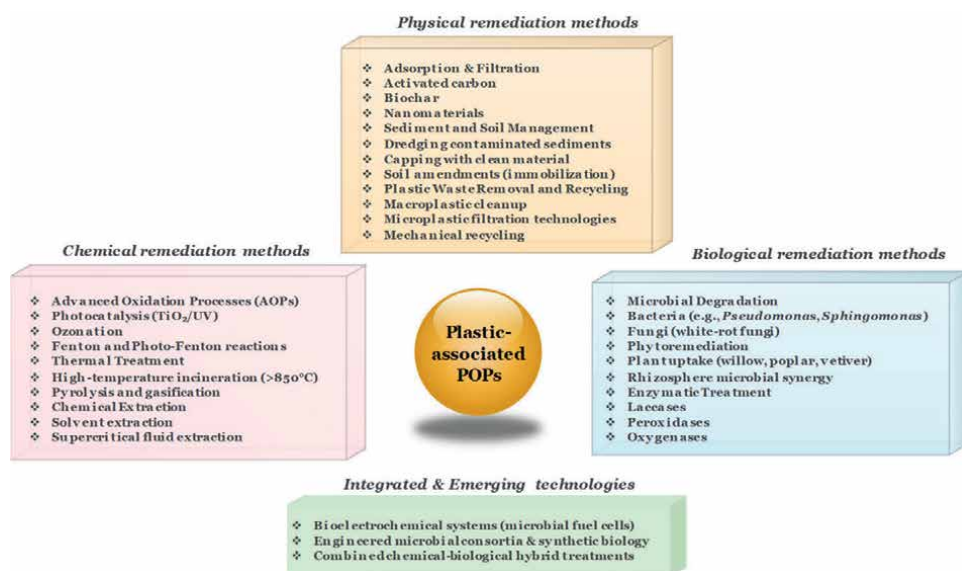


Figure 2.
Overview of remediation strategies used for POPs from plastics.

5. Health and ecotoxicological impacts of POPs from plastics

POPs associated with plastics exhibit toxicity through various mechanisms, leading to detrimental effects on organisms. Research has shown that exposure to these pollutants results in a wide range of issues, including reproductive, developmental, immunological, carcinogenic, and neurotoxic effects. The severity of these effects is influenced by the size of the microplastics, with smaller microplastics typically exacerbating toxicity, while larger ones may mitigate it. The toxic chemicals associated with micro- and nanoplastics can impair growth, increase mortality rates, and disrupt essential biological processes [9, 13].

5.1 Bioaccumulation and biomagnification

The persistence of POPs is driven by their lipophilicity and hydrophobicity, which enable accumulation in biological tissues and movement through food webs. These properties contribute to bioaccumulation, the buildup of pollutants within an organism over time, and biomagnification, the increasing concentration as pollutants move up the food chain [9].

To quantify these processes, key metrics are used:

- Bioconcentration Factor (BCF) and Bioaccumulation Factor (BAF) capture pollutant uptake from the environment into organisms but do not account for trophic transfer.
- Biomagnification Factor (BMF) measures pollutant concentration in predators relative to prey, while Trophic Magnification Factor (TMF) assesses pollutant amplification across food webs.

BMF and TMF are essential for evaluating ecological risks, with BMF being the most widely used. However, most BMF data come from aquatic food webs, and terrestrial ecosystems are less studied. For example, PBDEs show different bioaccumulation patterns in aquatic (BDE-47, BDE-99, BDE-100) and terrestrial species (BDE-153, BDE-209), indicating species- and habitat-specific pathways. Trophic dynamics differ between aquatic and terrestrial systems. Hydrophobic compounds like nona-BDEs, BDE-209, and DBDPE are common in terrestrial organisms, but the mechanisms driving trophic transfer remain unclear, especially for terrestrial invertebrates, which are underrepresented in current BMF data. Biomagnification potential is influenced by the logKow of pollutants, with higher values (>5) important for aquatic species and values between 5 and 8 for air-breathing organisms. Biological factors, including diet, metabolism, digestion, and elimination, further complicate predictions, particularly for terrestrial invertebrates with complex feeding behaviors. Traditional BMF studies often oversimplify predator-prey dynamics, leading to over- or underestimation of biomagnification. Quantitative fatty acid signature analysis (QFASA) provides more accurate dietary reconstruction, improving BMF assessment by matching fatty acid profiles of predators to their prey [10, 80, 81].

Case studies highlight the importance of QFASA in refining biomagnification models. For instance, QFASA revealed that albatrosses primarily consume fish offal, leading to higher exposure to POPs. Similarly, in Alaska, QFASA identified the unexpected consumption of corn-based plants by eiders, linking them to less hydrophobic POPs like PCBs. A study in South China found that over 60% of the diet of waterbirds

consisted of aquatic insects, offering valuable insights into POP exposure. BMFs calculated by QFASA (ranging from 0.02 to 858) differed significantly from traditional methods (0.1–2080), underlining the importance of accurate dietary models. These examples emphasize the need for refined models in biomagnification studies, with QFASA playing a critical role in understanding the impacts of POPs, especially in complex or opportunistic feeders like waterbirds.

5.2 Human, animal, and plant exposure pathways to POPs from plastics

Figure 3 illustrates different exposure pathways to plastic-associated POPs. Humans are exposed to POPs from plastics through various pathways, primarily ingestion, inhalation, and dermal absorption. POPs can enter the human body through contaminated food and water, particularly *via* microplastics that carry these pollutants up the food chain. Plastics in food packaging, such as polycarbonate plastics and PVC, can leach chemicals like bisphenols (e.g., BPA) and phthalates directly into food. Airborne microplastic particles, released from degrading plastics, are also inhaled, leading to respiratory exposure. Furthermore, dermal absorption occurs when individuals come into contact with plastic-based products, such as medical devices, personal care products, or plastic packaging that leaches toxic chemicals [82].

For animals, exposure to POPs from plastics primarily occurs through ingestion of contaminated food or water. Aquatic organisms, such as fish and invertebrates, ingest microplastics, which accumulate POPs that biomagnify as they move up the food chain. Terrestrial animals are similarly exposed through direct contact with contaminated water, soil, or sediment. In some cases, animals can inhale airborne microplastics, leading to respiratory exposure to these toxic substances. As POPs accumulate through ingestion and environmental contact, wildlife, especially those higher in the food chain, are at risk for significant health impacts, including reproductive and developmental issues [11, 12, 56].

Plants are exposed to POPs through contaminated soil and water. As plastics degrade in the environment, POPs leach into the soil, where plants absorb them through their roots, potentially impacting their growth, reproduction, and overall health. Aquatic plants are exposed to contaminated water, where microplastics release POPs into their tissues. Additionally, plants can absorb POPs from the rhizosphere, where plant roots interact with soil and microbes, further contributing to

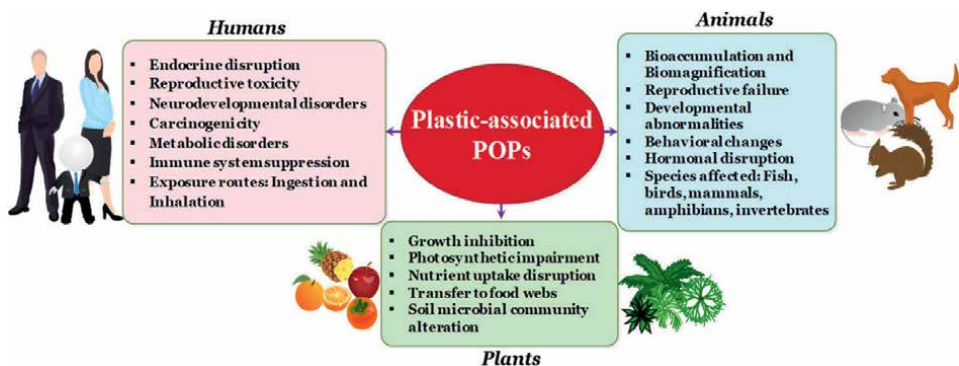


Figure 3.
Effect and toxicity of plastic-associated POPs.

bioaccumulation. This process can lead to toxicants entering the food chain when herbivores consume contaminated plants, ultimately affecting the broader ecosystem.

5.3 Epidemiological evidence and case studies

Epidemiological studies provide strong evidence of the health risks associated with exposure to POPs from plastics. Research has linked prenatal and childhood exposure to chemicals such as BPA and phthalates to neurodevelopmental disorders, including attention deficits, lower IQ levels, and an increased risk of autism spectrum disorders [83]. Long-term exposure to PBDEs has been associated with cognitive impairments, delayed motor development, and attention deficits in children. In terms of reproductive health, epidemiological data show that exposure to phthalates during early development can result in testicular dysgenesis, reduced semen quality, and decreased fertility. Studies from contaminated environments also point to the cumulative effect of exposure to a mixture of POPs, which can lead to endocrine disorders, metabolic diseases, and increased cancer risk.

Case studies further underscore the detrimental impacts of POPs in real-world settings. For instance, the Great Lakes region has seen significant ecological disruptions from PCB contamination, affecting fish populations and human health through the consumption of contaminated fish. Similarly, exposure to plastic-derived POPs in agricultural soils has been linked to crops with elevated pesticide residues and disrupted growth, leading to potential food safety concerns. These case studies highlight the need for integrated approaches to assess the health impacts of POPs from plastics in both environmental and human health contexts.

6. Policy, regulations, and future directions

6.1 International policies on POPs in plastics

The management of POPs from plastics relies on international regulatory frameworks aimed at reducing environmental and health risks. However, effective control also demands strong enforcement and the development of sustainable alternatives. This section explores existing policies, challenges in implementation, and future research directions to mitigate the impact of plastic-associated POPs.

6.1.1 The Stockholm convention on POPs

The Stockholm Convention is one of the most important international accords dedicated to the global management of POPs. It was established in 2001 and entered into force in 2004 with a primary objective to protect human health and the environment by eliminating or restricting the production and use of a defined list of highly hazardous POP chemicals [3].

Plastic-related POPs regulated under the convention include 12 POP compounds known as the dirty dozen, and a further 16 compounds have been added to the list (**Figure 4**).

While the Stockholm Convention has led to the phase-out of numerous legacy POPs, challenges persist, particularly regarding incomplete national implementation, delays in adding emerging POPs to the treaty's annexes, and managing stockpiles and waste containing POPs.

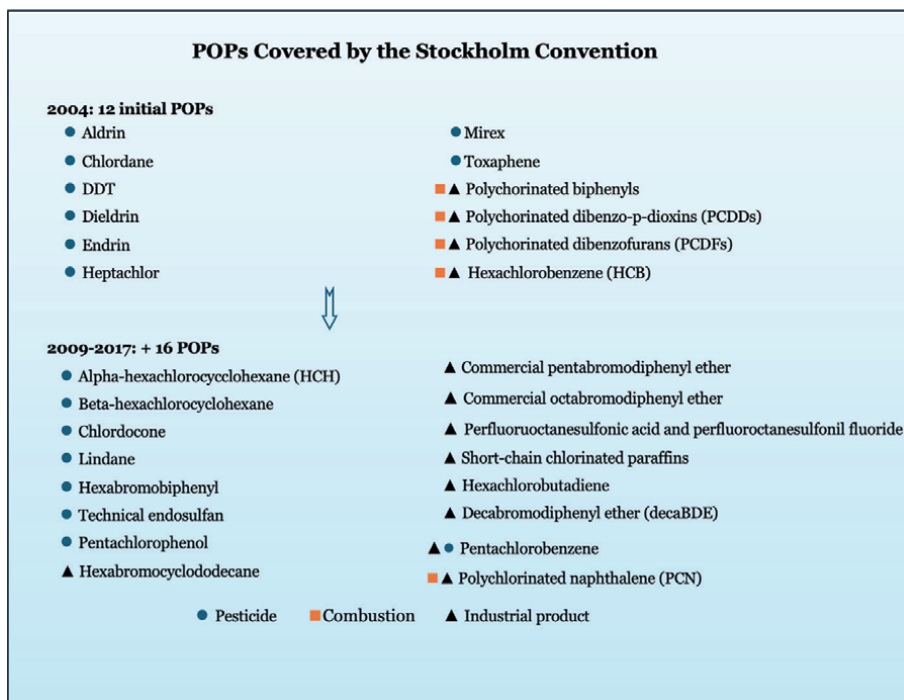


Figure 4.
Persistent organic pollutants regulated by the Stockholm convention (2004–2017).

6.1.2 European Union POPs regulation

The European Union has established a stringent regulatory framework that not only supports the objectives of the Stockholm Convention but also goes beyond by implementing the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) and Regulation (EU) 2019/1021, aimed at limiting POPs in consumer products, waste, and materials [84]. Key elements include:

- Regulation (EU) 2019/1021 on persistent organic pollutants, which sets strict limits on the presence of POPs in waste, consumer products, and materials, ensuring that plastics containing these substances are managed to prevent environmental release [84].
- REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals): This comprehensive chemical regulatory system requires manufacturers and importers to assess and manage risks associated with chemicals used in plastics, including POPs. REACH promotes the substitution of hazardous substances with safer alternatives and supports the circular economy by encouraging sustainable product design and recycling [85].

The EU's approach integrates environmental protection with economic strategies, emphasizing the reduction of plastic waste containing POPs through circular economy initiatives, stricter waste management practices, and innovation in material substitution.

6.1.3 United States environmental protection agency (EPA) standards

In the United States, the regulation of POPs in plastics is governed primarily by:

- The Toxic Substances Control Act (TSCA), which provides the EPA with authority to regulate the manufacturing, processing, and disposal of chemical substances, including those classified as POPs.
- The Clean Air Act and Clean Water Act, which regulate emissions of POPs during plastic production and disposal processes to safeguard air and water.

Despite a robust legal framework, regulatory progress in the United States has been challenged by slow chemical review procedures and industry lobbying efforts that can delay or weaken regulatory actions on hazardous substances in plastics [86].

6.1.4 Other global initiatives

Beyond these major frameworks, several international efforts contribute to the governance of POPs in plastics:

- The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal restricts the international trade and disposal of hazardous plastic waste containing POPs, aiming to prevent dumping in countries with limited waste management infrastructure.
- The United Nations Environment Programme (UNEP) plays a critical role in global environmental governance by supporting the monitoring of POPs, capacity building, and facilitating cooperation among nations to implement POP-related policies [87].

6.2 Challenges in global POPs management

Despite the existence of international regulatory frameworks, effective management of POPs in plastics faces significant challenges. Enforcement gaps, especially in developing countries with inadequate regulatory infrastructure, hinder the full implementation of global regulations. This gap has led to the illegal trade of POP-laden plastic waste, particularly in regions with insufficient waste management systems, undermining the environmental and health benefits of international frameworks like the Stockholm Convention [88].

Additionally, the widespread use of POP-based additives in plastics, such as halogenated flame retardants and phthalate plasticizers, is driven by cost-effectiveness and performance characteristics. However, the lack of scalable, eco-friendly alternatives to these hazardous chemicals remains a major barrier to reducing POPs in plastics. The plastics industry also resists regulatory changes due to economic interests, relying on hazardous additives that perpetuate environmental and health risks. This resistance, coupled with greenwashing tactics, slows down the transition to safer materials and prolongs the environmental and health impacts of plastic production [89, 90].

6.3 Future research and sustainable alternatives

To address the global crisis of plastic-associated POP pollution, breakthroughs in materials science, chemical engineering, and waste management are essential. Key

research areas include the development of biodegradable and nontoxic plastics, as well as safer chemical substitutes. Bio-based polymers like polylactic acid (PLA) and polyhydroxyalkanoates (PHAs) show promise as alternatives to petroleum-based plastics. However, their biodegradability under real-world conditions remains a challenge, as some still form microplastics in certain environments. Future research must focus on improving biodegradation kinetics to minimize the environmental persistence of these [91]. Additionally, transitioning to nontoxic flame retardants and plant-based plasticizers could significantly reduce the hazardous chemical burden in plastics. Chemical recycling offers a viable alternative to traditional recycling methods, enabling closed-loop systems and reducing the need for virgin plastic production. Advanced sorting technologies, such as near-infrared (NIR) spectroscopy and AI-driven systems, are being developed to enhance recycling efficiency, ensuring cleaner recycling streams and reducing contamination from POPs.

6.4 Call for interdisciplinary action

Addressing the persistent issue of POPs in plastics requires a collaborative, multi-stakeholder approach that involves scientists, policymakers, industry leaders, and the public. Scientists and researchers must focus on developing innovative remediation technologies, such as bio-based degradation and green chemistry methods, to break down POPs in plastics. Evidence-based policy recommendations should guide the formulation of regulations that are scientifically sound and implementable. Policymakers must strengthen enforcement of existing regulations and introduce incentives for sustainable plastic production, such as subsidies for eco-friendly materials, alongside stricter penalties for noncompliance. The plastics industry must take responsibility for the environmental and health impacts of its products by investing in safer plastic formulations, nontoxic additives, and closed-loop recycling systems. Public awareness campaigns are essential to educate consumers on reducing plastic waste, supporting sustainable brands, and making responsible consumption choices. By aligning research, policy action, and industry responsibility, the transition to a sustainable, pollution-free future can be accelerated.

7. Conclusion

This chapter has examined the complex issue of POPs associated with plastics, focusing on their sources, environmental behaviors, monitoring techniques, treatment technologies, and health risks. Plastics act both as carriers for POPs and as sources of these pollutants, with additives such as phthalates, BPA, and PBDEs contributing significantly to environmental contamination. Through these mechanisms, POPs enter ecosystems, including marine, terrestrial, and atmospheric environments, where they bioaccumulate and biomagnify across food chains, causing extensive ecological and human health impacts. Significant progress has been made in monitoring POPs, with advanced techniques such as GC-MS and HRMS enabling the sensitive detection of these pollutants in various environmental matrices. These tools are essential for tracking POP distribution and concentrations, providing valuable data for policymaking and public health assessments. However, the remediation of POPs remains challenging. While physical, chemical, and biological treatment methods offer promising solutions, each comes with its limitations. Bioremediation and photodegradation show potential as sustainable

approaches, while AOPs and thermal treatments can offer faster degradation of contaminants. These technologies need further adaptation and scaling for broader application to ensure they are both effective and economically viable. The health risks of plastic-associated POPs are significant, with exposure linked to endocrine disruption, neurotoxicity, reproductive toxicity, and carcinogenicity. Vulnerable populations, especially children, pregnant women, and those in heavily polluted areas, are at increased risk. Chronic low-dose exposure to POPs, particularly during early development, can have lasting and irreversible health consequences, making it critical to address these issues with urgency.

8. Recommendations

Given the persistence and long-range transport of POPs, accelerating advancements in detection and mitigation are critical. Monitoring tools must be refined to detect trace amounts of POPs in environmental samples and human biomarkers. Emerging technologies like nanotechnology-based remediation and sustainable materials show promise but require real-world validation and global collaboration for effective implementation. Regulatory action is also essential. While frameworks like the Stockholm Convention have made progress, enforcement gaps remain, and new harmful chemicals continue to be introduced. Stronger policies are needed to reduce plastic production, improve waste management, and promote sustainable alternatives. A shift toward biodegradable plastics, nontoxic additives, and circular economy models must be prioritized to minimize ecosystem contamination and human exposure. A multidisciplinary approach is necessary, with research focusing on developing advanced monitoring tools for POPs in plastic waste, aquatic ecosystems, and human populations. Innovative remediation methods that combine biological and chemical techniques should be explored, alongside investigating the long-term ecological and health impacts of plastic-derived POPs. Additionally, regulations on toxic additives must be strengthened, and global plastic waste reduction targets must be implemented. Expanding the Stockholm Convention to include more POPs and investing in safer alternatives like biodegradable plastics are key to mitigating the impact of plastic pollution.

Conflict of interest

The authors declare no conflict of interest.

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Section 3

Treatment Technologies

Influence of Biochar Shape on the Microbial Remediation of Chlorpyrifos-Contaminated Soil Using Immobilized Bacteria

Nancy Pino, Luisa Múnera and Juan Fernando Pérez

Abstract

Chlorpyrifos (CP) is a widely used organophosphorus insecticide that poses significant risks to soil health and ecosystem stability due to its persistence and toxicity. While traditional bioremediation using free-living bacteria has shown limitations, the immobilization of microbial consortia in biochar presents a promising solution. This study investigates the influence of biochar shape on CP degradation efficiency in contaminated soil using immobilized bacteria. Biochar in pellet (PL-BC) and chip (CH-BC) forms was used to immobilize two bacterial strains, *Stenotrophomonas maltophilia* (C4) and *Xanthomonas sintii* (C8), known for their CP-degrading capabilities. Results demonstrated that biochar in pellet form significantly enhanced the degradation efficiency, achieving a maximum removal rate of 82.61% when the bacterial consortium was immobilized in PL-BC, compared to 34.55% in CH-BC. The improved performance of the pellet biochar is attributed to its higher surface area and porosity, facilitating better microbial colonization and activity. These findings underscore the importance of biochar morphology in optimizing bioremediation processes and provide insights into sustainable approaches for managing pesticide-contaminated soils.

Keywords: biochar, bioremediation, immobilization, pesticide degradation, organophosphorus insecticide

1. Introduction

Chlorpyrifos (CP; O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate) (**Figure 1**) is a widely used organophosphorus insecticide extensively applied to major crops such as wheat, maize, and rice due to its effectiveness in pest control [1, 2]. However, concerns have emerged regarding its adverse effects on soil ecosystems and human health. Studies have highlighted its toxicity to non-target organisms and its potential for bioaccumulation and biomagnification, contributing to soil and water pollution [3, 4]. The persistence of CP in soil varies from 2 weeks to over a year,

depending on factors such as pH and climatic conditions [5]. Despite these concerns, the global CP market is projected to reach \$576 million by 2025, driven by demand in both agricultural and non-agricultural sectors. The detection of CP residues in various environmental compartments underscores the urgency of addressing this significant environmental and health concern [6].

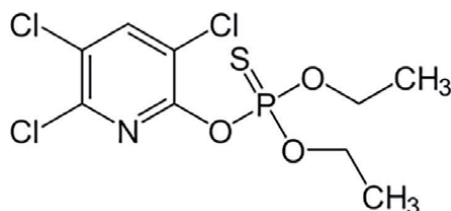


Figure 1.

The chemical structure of chlorpyrifos, which contains a pyridyl ring substituted with three chlorine atoms and a phosphorothioate ester group, making it resistant to degradation under natural conditions.

Soil contamination by CP poses substantial risks to soil health and ecosystem stability [7]. Various remediation methods, including chemical transformation, physical adsorption, and microbial degradation, have been explored [8]. While physical and chemical methods can be effective, they are often associated with high costs and environmental disruption. In contrast, bioremediation, an eco-friendly and cost-effective technology, focuses on degrading contaminants using microorganisms. Several bacterial strains, including *Pseudomonas* sp., *Bacillus* sp., *Enterobacter* sp., and *Sphingomonas* sp., have been identified as effective CP degraders [9, 10]. However, conventional approaches using free-living microorganisms for soil bioremediation face limitations such as susceptibility to washout and reduced viability under harsh environmental conditions [11].

Among CP-degrading bacteria, *Stenotrophomonas maltophilia* and *Xanthomonas sintii* have shown notable promise due to their metabolic versatility and enzymatic capacity. *S. maltophilia* produces a range of hydrolases, including carbaryl hydrolase and TCP hydrolase, which enable efficient cleavage of organophosphorus bonds [12, 13]. *X. sintii* complements this activity through the production of metalloproteases and additional hydrolases, facilitating the breakdown of CP metabolites [10]. These complementary enzymatic pathways suggest that co-immobilization of these strains may enhance biodegradation through synergistic mechanisms.

The use of immobilized bacterial cells has emerged as a promising strategy to overcome these challenges, offering several advantages over free bacterial cells [14]. This approach enhances microbial stability, reusability, and efficiency in contaminant degradation [15]. Biochar, a stable, porous, carbonaceous material derived from biomass through thermochemical conversion, is considered an ideal carrier for microbial immobilization [16, 17]. Its high surface area, internal porosity, and ability to adsorb organic compounds and microorganisms make it a highly effective biocarrier [18]. Additionally, incorporating biochar into soil enhances CP adsorption while maintaining low costs [19]. Despite these promising attributes, the mechanisms involved in CP bioremediation using biochar-immobilized

bacteria and the effects of biochar's physicochemical characteristics remain insufficiently understood.

Various factors influencing the immobilization of microorganisms in biochar and bioremediation efficiency, such as biochar's physicochemical properties, environmental conditions, and microbial characteristics, have been studied. However, limited research has focused on how biochar's shape and structure affect these processes. Biochar shape can significantly influence microbial immobilization and bioremediation due to its impact on surface area, porosity, nutrient accessibility and retention, physicochemical interactions, and structural stability. For instance, biochars with larger surface areas and complex three-dimensional structures provide more sites for microbial colonization [20, 21]. Porosity plays a crucial role, as macropores facilitate the entry of larger microorganisms while micropores enhance the adsorption of small molecules and nutrients [22, 23]. Additionally, biochar shape affects its ability to adsorb organic compounds and maintain favorable conditions for microbial activity [16].

Among the key factors that determine the performance of biochar as a microbial support and adsorbent matrix, pyrolysis temperature plays a critical role in shaping its physicochemical properties. Elevated pyrolysis temperatures—particularly those above 500°C—promote the formation of highly aromatic and carbon-rich structures with increased surface area and well-developed microporosity. These characteristics enhance the adsorption capacity of biochar for organic contaminants and provide a favorable microenvironment for microbial colonization and stability. The resulting improvements in structural stability, porosity, and hydrophobicity contribute directly to the effectiveness of biochar-based systems in soil remediation processes [24].

This study aims to investigate the influence of biochar shape on CP remediation in contaminated soil using immobilized bacteria. Specifically, we evaluate two biochar forms—pellets (PL-BC) and chips (CH-BC)—as immobilization matrices for *Stenotrophomonas maltophilia* (C4) and *Xanthomonas sintii* (C8), bacterial strains known for their CP-degrading capabilities. We hypothesize that biochar in pellet form provides a larger surface area and more stable microhabitats, thereby enhancing microbial colonization and degradation efficiency compared to chip-shaped biochar. By elucidating the role of biochar morphology in microbial bioremediation, this research contributes to the development of optimized strategies for pesticide-contaminated soil remediation.

2. Materials and methods

2.1 Soil

CP-contaminated soil was collected from an agricultural farm in the Antioquia department, Colombia. Five soil samples (1000 g each) were extracted from a depth of approximately 30 cm using a sterile metal shovel. After extraction, the soil samples were sieved to remove large debris, thoroughly mixed, and homogenized. The soil was classified as loamy sand, with a pH of 6.25 and a cation exchange capacity (CEC) of 5.2 meq/100 g. The available phosphorus content was 55.5 mg/kg, and the total nitrogen Kjeldahl content was 0.37%. The CP concentration in the soil was determined to be 139.1 mg/kg.

Although organic matter (OM), calcium carbonate (CaCO_3), and soil texture were not determined in this study, it is recognized that these variables can influence chlorpyrifos adsorption due to their surface activity and interaction with hydrophobic compounds. However, all soil used in the microcosm experiments was homogenized and derived from the same composite sample, which minimized variability across treatments. The relevance of these soil properties has been previously described in studies addressing pesticide behavior in soil matrices [8, 19].

2.2 Consortium isolation

The microbial consortium was obtained from a soil sample through successive enrichment cultures following the method described by Pino and Peñuela [25]. The consortium underwent a 2-month adaptation period, during which the final pesticide concentration was adjusted to 20 mg/L. After adaptation, 0.1 mL of the supernatant was spread onto a solid medium composed of noble agar and minimal salt medium (4.8 g/L K_2HPO_4 , 1.2 g/L KH_2PO_4 , 1.0 g/L NH_4NO_3 , 0.2 g/L $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 0.04 g/L $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, 0.001 g/L $\text{Fe}_2(\text{SO}_4)_3$, and 15 g/L agar-agar), supplemented with CP (10 mg/L) as the sole carbon source. After 1 week of incubation at 30°C, 11 strains (C1–C11) were selected. Each isolated strain was subcultured three times to ensure adaptation to CP as the sole carbon source.

DNA was extracted using the GeneJET Tissue DNA kit (Thermo Scientific, USA). The 16S rRNA gene fragment was amplified using primers 968F and 1492R. PCR was performed with the Taq DNA polymerase kit (Thermo Scientific) in a TM100TM thermal cycler (Bio-Rad, USA), using a final reaction volume of 25 μL containing 1X Taq buffer, 1 mM MgCl_2 , 0.2 μM dNTPs, 0.25 μM of each primer, 0.1 U Taq polymerase, and ~20 ng of DNA. PCR conditions included an initial denaturation at 94°C for 3 minutes, followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 56°C for 1 minute, and extension at 72°C for 1 minute, with a final extension at 72°C for 5 minutes. Amplicon size was verified in a 1.2% agarose gel stained with EZ-Vision® (Amresco®, USA) and visualized in a Labnet EnduroTM photodocumenter (USA). PCR products were purified and sequenced at Macrogen Korea. Basic local alignment search tool (BLAST) analysis was performed against the DDBJ/EMBL/GenBank databases to determine bacterial genus identity based on the highest homology and bit score.

2.3 Immobilization of the consortium on biochar

Biochar pellets (PL-BC) and chips (CH-BC) were derived from *Pinus patula*. The production conditions and physicochemical characterization were described by Gutiérrez et al. [26]. The biochar used in this study was produced *via* slow pyrolysis at 550°C, a temperature known to favor the development of microporosity and surface area [26]. Three to four bacterial colonies were inoculated in 100 mL of *Tryptic Soy Broth* (TSB) and incubated at 37°C and 120 rpm for 4 hours. Optical density (OD600) was measured during the logarithmic phase until reaching 1.6–1.8. The cultures were washed three times with sterile 0.9% saline solution to remove the residual medium. Immobilization was performed following the method described by Wahla et al. [27] for both biochar types. Bacterial suspensions, adjusted to an OD600 of 1, were mixed with sterile biochar at a 5:100 (w/v) ratio and incubated at 30°C for 16 hours at 100 rpm.

Immobilization efficiency was determined by centrifuging the bacteria-biochar mixture at 1000 rpm for 10 minutes and measuring the OD₆₀₀ of the supernatant. The immobilization percentage was calculated using the formula:

$$\% \text{immobilization on biochar} = (\text{OD}_0 - \text{OD}_1) / \text{OD}_0 \times 100 \quad (1)$$

where OD₀ is the initial bacterial suspension OD⁶⁰⁰, and OD₁ is the OD₆₀₀ of the supernatant. The immobilization efficiency was calculated as 50%. The inoculated biochar was stored in resealable plastic bags at 4°C until soil inoculation assays were conducted.

2.4 Soil microcosm experiment

A CP degradation assay was conducted in a greenhouse microcosm. The experiment consisted of 10 treatments: (1) soil + C4 PL-BC immobilized, (2) soil + C4 CH-BC immobilized, (3) soil + C8 PL-BC immobilized, (4) soil + C8 CH-BC immobilized, (5) soil + consortium PL-BC immobilized, (6) soil + consortium CH-BC immobilized, (7) soil + free consortium, (8) soil + PL-BC, (9) soil + CH-BC, and (10) untreated soil. Each treatment was performed in triplicate in a completely randomized design using plastic pots containing 0.5 kg of soil. Biochar was added at 1 g/kg soil, totaling 30 experimental units. Water was added as needed to maintain soil moisture at 7-day intervals. Microcosms were covered with plastic wrap to prevent evaporation and incubated at a *greenhouse temperature of approximately 25–28°C*. After 45 days, 100 g soil samples were collected from each unit to measure CP concentration.

2.5 Chlorpyrifos quantification

Chlorpyrifos extraction and quantification were conducted according to environmental protection agency (EPA) Method 3550C (ultrasonic extraction) and EPA Method 8081B gas chromatography with electron capture detector (GC-ECD detection), respectively. CP was extracted from 10 g of soil using EPA Method 3550C. The ultrasonic extraction was performed with 20 mL of a 1:1 acetone-hexane mixture for 30 minutes, repeated twice. Extracts were concentrated to 1 mL, purified with a silica gel column, and eluted with 10 mL of hexane. The eluate was further concentrated to 1 mL. CP quantification followed EPA Method 8081B using gas chromatography with an electron capture detector (GC-ECD). Calibration standards were used, with 1 µL injections analyzed under specific GC conditions (injector at 250°C, detector at 300°C, and a temperature gradient from 150°C to 250°C). Quality control included method blanks, spiked blanks, and sample duplicates.

2.6 Statistical analysis

Statistical analysis was conducted to evaluate the effects of biochar-immobilized bacteria on CP degradation and to compare the influence of biochar type (pellets vs. chips) and bacterial treatment (individual strains vs. consortium). A two-factor

analysis of variance (ANOVA) was performed to assess the main effects and interactions. Post hoc Tukey honestly significant difference (HSD) tests identified significant differences between treatments. All analyses were conducted using R software (v4.2.2).

3. Results and discussion

3.1 Enrichment and immobilization of the CP-degrading microbial consortium

Eleven bacteria were isolated from soil samples through enrichment culture using CP as the sole source of carbon and energy. Among the strains, C4 and C8 could degrade more than 55% of CP in the liquid culture medium and grow at concentrations exceeding 400 ppm of the pesticide. Various morphological and biochemical analyses revealed that strains C4 and C8 were Gram-negative. The bacteria were further identified through molecular characterization by sequencing the 16S rRNA gene. The nucleotide sequences were compared with other 16S rRNA gene sequences in the NCBI database using ClustalW and BLAST analyses. The search indicated that the 16S rRNA gene sequence of strain C4 showed the highest similarity (100%) with that of *Stenotrophomonas maltophilia* (Accession No. OR775774.1). Strain C8 was found to be most similar to the genus *Xanthomonas*, with the best sequence match to *Xanthomonas sintii* (Accession No. CP049966.7).

3.2 Immobilization efficiency and CP removal in soil microcosms by individual strains and the consortium

The immobilization efficiency observed for strains C4 and C8 on biochar (both PL-BC and CH-BC) demonstrated the adequate performance of the technique. The immobilization percentage exceeded 75% for strain C4 and 65% for strain C8, indicating adequate adherence and colonization on the biochar matrices. These results are noteworthy compared to previous studies, such as the work of [24], which revealed lower or comparable immobilization efficiencies. The high immobilization percentages observed in this study can be attributed to the type of biochar used (PL-BC and CH-BC) and the optimized experimental conditions [28].

Figure 2 shows the degradation capabilities of the immobilized strains in biochar. Strain C8 exhibited the highest individual removal efficiency, with a maximum removal of 55.27% when immobilized in CH-BC. The high CP removal efficiency achieved by strain C4, coupled with its adequate immobilization in biochar, suggests that this genus's metabolic versatility plays a crucial role in bioremediation. *Stenotrophomonas* sp. is known for its ability to degrade various environmental pollutants, and its immobilization in biochar could enhance its stability and activity in contaminated environments. Similarly, the high removal efficiency of *Xanthomonas* strain C8 indicates its potential in bioremediation applications. *Xanthomonas* species are often associated with plant-pathogenic activities, but their metabolic capabilities can also be harnessed for environmental remediation [29]. ANOVA and Tukey HSD tests confirmed statistically significant differences between treatments, with consortium treatments outperforming those with individual strains.

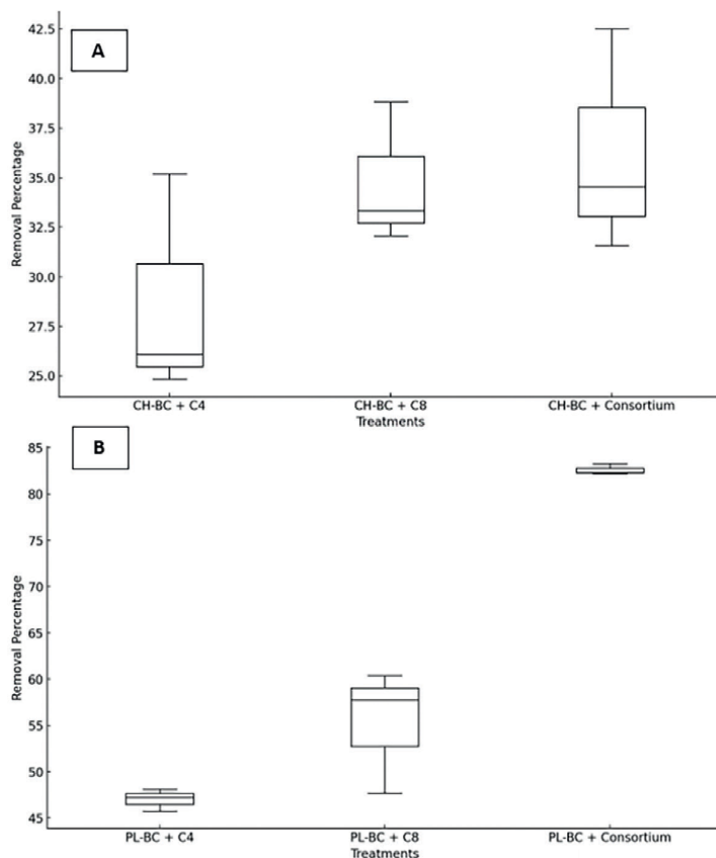


Figure 2.
 CP removal percentage for individual immobilized strains and the consortium in microcosm. A: CH-BC treatment. B: PL-BC treatment.

The consortium immobilized in PL-BC achieved the highest removal efficiency of 82.61%, which is significantly higher than any individual strain treatment. This finding aligns with previous research indicating that microbial consortia often exhibit synergistic interactions that enhance biodegradation efficiency [30]. The improved performance of the consortium could be attributed to several factors. First, consortia can exploit a broader range of metabolic pathways, enhancing the breakdown of complex compounds like CP. Second, consortia can mitigate the toxic effects of CP metabolites by distributing the metabolic burden among different microbial species, reducing its inhibitory impact on individual strains [31, 32].

Stenotrophomonas sp. and *Xanthomonas* sp. possess different but complementary sets of enzymes that can break down CP and its metabolites. While both *Stenotrophomonas* and *Xanthomonas* utilize organophosphorus hydrolase for the initial breakdown of CP, they employ different additional enzymes for further degradation. *Xanthomonas* mainly utilizes metalloprotease and hydrolases for hydroxyproline-rich glycoproteins [12], whereas *Stenotrophomonas* employs a range of hydrolases, including carbaryl hydrolase and TCP hydrolase, exhibiting a broader enzymatic toolkit for organophosphate degradation [12, 13]. The presence of diverse microbial

communities often enhances catabolic pathways that would not be as effective if utilized by a single species, leading to a more efficient degradation process [33].

During the degradation of CP, intermediate metabolites can be toxic and inhibitory to microbial growth. The ability of *Stenotrophomonas* sp. to initiate the breakdown of CP and that of *Xanthomonas* sp. to further degrade the resultant metabolites reduces the accumulation of toxic intermediates, thus maintaining a conducive environment for microbial activity. By distributing the metabolic burden among different microbial species, the overall efficiency of CP degradation is enhanced, allowing each strain to focus on specific metabolic tasks and reducing the overall stress and energy expenditure required for pollutant degradation [10, 12].

The formation of biofilms on biochar provides a stable and protective environment for microorganisms. Biofilms enhance microbial interactions and cooperation, leading to improved pollutant degradation efficiency. Both *Stenotrophomonas* sp. and *Xanthomonas* sp. can form biofilms, which protect them from environmental stresses and promote sustained CP degradation [34]. The combined presence of *Stenotrophomonas* sp. and *Xanthomonas* sp. enhances the consortium's ability to adapt to varying environmental conditions, ensuring that the microbial community remains active and efficient in degrading CP under different soil and environmental conditions. Additionally, their metabolic activities contribute to nutrient cycling within the biochar matrix, supporting microbial growth and activity and further enhancing CP degradation [35–37].

3.3 Effect of biochar shape on CP removal in soil microcosms

Figure 3 illustrates the CP removal efficiencies across different treatments, including the consortium immobilized in two types of biochar (PL-BC and CH-BC), the free consortium, and soil without the addition of microorganisms or biochar. Control treatments with biochar but without microorganisms are also depicted. Significant differences in removal efficiencies were observed when comparing the immobilized consortium treatments to those with free bacteria. Specifically, the immobilized consortium achieved 82.61% CP removal with PL-BC and 34.55% with CH-BC, whereas the free consortium only achieved 22.8% removal. Thus, immobilizing the

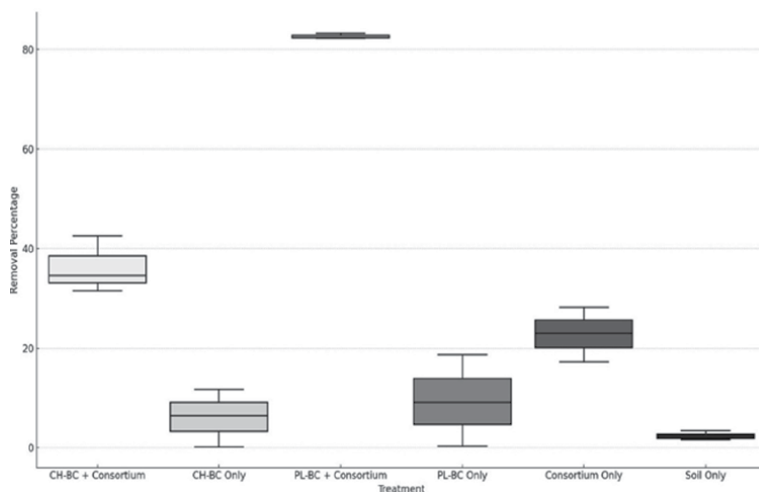


Figure 3. CP removal with different types of biochar and the bacterial consortium.

consortium in biochar significantly enhanced degradation efficiency compared to that of the free consortium, likely due to the stabilization of microbial communities within the biochar matrix, protection from environmental stress, and a continuous supply of nutrients and contaminants for degradation [38]. Treatments without bacteria showed markedly lower removal efficiencies, indicating that microbial activity was the primary driver of CP removal; additionally, the negligible removal in biochar-only controls underscores the limited abiotic adsorption capacity of biochar alone, highlighting the importance of microbial processes.

The ANOVA revealed significant differences between the treatments in terms of CP removal ($p < 0.001$). Tukey's post hoc test indicated that treatments with PL-BC immobilized with the consortium achieved the highest removal efficiencies, significantly outperforming treatments with CH-BC and those without bacteria (**Figure 4**). The t-test comparison between PL-BC and CH-BC also confirmed that PL-BC was more effective ($p < 0.0001$).

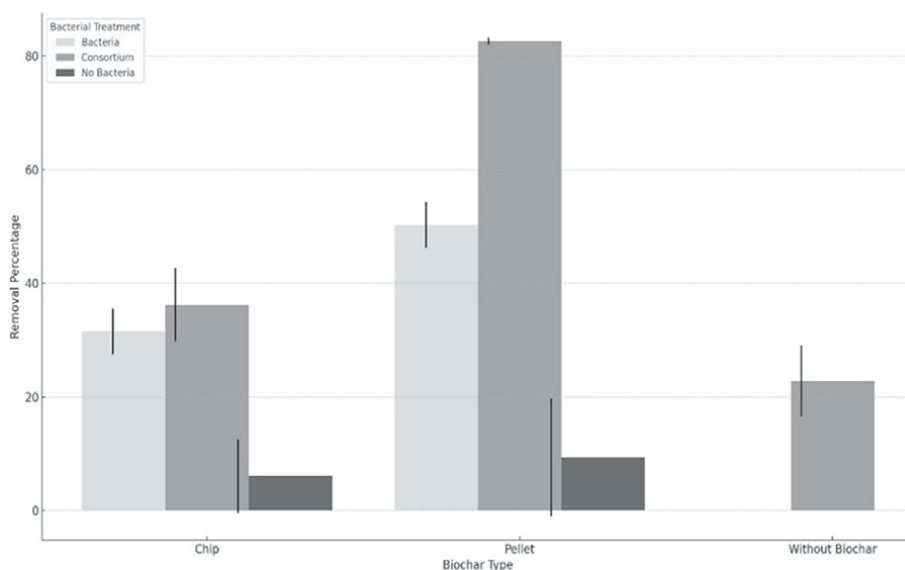


Figure 4.
 Effect of biochar shape on soil CP removal.

The physical properties of biochar, such as pore size and surface area, significantly influence bacterial activity and degradation efficiency, along with chemical characteristics like functional groups and carbon content [39]. Comparing these properties between the two types of biochar revealed that while the mineral composition, pH, CEC, and moisture content were similar, PL-BC exhibited a higher surface area and larger pore size due to its pellet form [26]. This characteristic likely contributed to the metabolic activity of the microbial consortium by facilitating more extensive biofilm development. High porosity and large surface area in biochar provide a conducive microenvironment for the growth of immobilized strains and protect them from soil faunal predators such as protozoans and nematodes.

Furthermore, the pore size of biochar is crucial for determining the extent of adhesion and cell viability of inoculated microorganisms. Biochar with high porosity offers better aeration and hydrology, which is beneficial for the survival and proliferation of

inoculated microbes when amended to the soil [40]. Additionally, biochar with macropores has a stronger adsorption capacity for organic pollutants such as pesticides, aiding immobilized strains in using pesticide molecules as a growth energy source.

Although microbial bioaugmentation is an environmentally friendly strategy for remediating contaminated soils, it has several limitations. It often fails due to the rapid decrease in bacterial viability and abundance after inoculation and the limited dispersal of inoculated bacteria in the soil matrix [41]. Moreover, it can alter the phylogenetic composition and function of the indigenous soil microbiome [42]. Bacterial biochar immobilization can improve soil fertility and mitigate competition between indigenous and inoculated microorganisms for nutrients, thus representing an interesting approach to enhancing pollutant removal from contaminated soils [43].

The physical properties of biochar, particularly its porosity, surface area, and structural stability, can significantly influence soil conditions that support microbial survival and contaminant degradation. High porosity biochars improve aeration and water retention in the soil, reducing desiccation stress and creating favorable conditions for microbial metabolism. These porous structures also act as protective niches, limiting exposure to environmental fluctuations and predation by protozoa and other soil fauna. Additionally, the increase in surface area facilitates biofilm formation, which enhances cell stability and enzymatic activity during pesticide degradation. These attributes, especially in pellet-shaped biochar, contribute to the sustained performance of immobilized bacterial consortia in the remediation of chlorpyrifos-contaminated soils [38].

4. Conclusion

This study's findings suggest that employing biochar, especially in pellet form, can be an effective strategy for enhancing CP bioremediation processes. This approach not only leverages the adsorption capacity of biochar but also capitalizes on its ability to support and stabilize microbial consortia, making it a sustainable solution for soil and water decontamination. The interaction between biochar and bacteria significantly influences the efficiency of CP removal from contaminated soil. The results demonstrated that PL-BC combined with bacterial consortia showed the highest removal efficiency, likely due to the larger surface area and porosity of pellet-shaped biochar, which enhances microbial colonization and activity. This synergy between biochar's physical properties and microbial degradation capabilities underscores its potential as a multifunctional addition to bioremediation strategies. Future research should focus on optimizing biochar properties, exploring long-term stability, and assessing the environmental impacts of biochar-immobilized systems to develop sustainable solutions for soil and water decontamination.

Funding statement

This research was funded by the Committee for the Development of Research (CODI) at the University of Antioquia.

Conflict of interest disclosure

The authors declare no conflict of interest.

Data availability statement

The data supporting the findings of this study are available within the chapter and its supplementary materials. Additional data that support the findings of this study are available from the corresponding author upon reasonable request.

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Pesticides as POPs in Terrestrial and Riverine Ecosystems: Behavior, Effects, Monitoring, and Management Strategies

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Abstract

Modern organic chemistry is capable of synthesizing molecules with incredible structural and functional diversity. Since the Second Industrial Revolution (1870–1914), vast amounts of technogenic organic chemicals have been released into nature, either in waste streams, accidentally, or deliberately as fertilizers and pesticides. The early generation of organic pesticides, including aldrin/dieldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dicofol, lindane, and others, has been recognized as an environmental hazard due to broad-spectrum toxicities, extraordinary persistence in ecosystems, and tendencies for bioaccumulation and biomagnification in higher organisms. First-generation organic pesticides comprise 10 of the original 12 persistent organic pollutants (POPs) governed by the Stockholm Convention (2001). While the phase-out of most POP pesticides has attracted widespread publicity, several risks have not been addressed widely: (1) Residual risk of POP pesticides has diminished but not disappeared across Europe, North America, and Australia; (2) DDT continues to be deployed in areas with high risk of drug-resistant malaria; (3) consistent use of “modern” pesticides may necessitate expansions of the POP list; and (4) as demonstrated by the war in Ukraine, unforeseen events like the destruction of the Kakhovka Dam (6 June 2023) can create a risk of pesticide remobilization, necessitating new solutions. With the expected intensification of agriculture by 2050, pesticide use is foreseen to be a major driver of biodiversity loss and other irreversible environmental damage. The current chapter is a review of the state of the art in the ecotoxicology and monitoring of pesticide contamination in terrestrial and riverine ecosystems, presenting new and little-known information.

Keywords: pesticides, persistent organic pollutants, ecology, ecotoxicology, contamination, nontarget effects, bioaccumulation, biomagnification, riverine ecosystems, monitoring

1. Introduction

1.1 The pesticide problem: Essence and global significance

A pesticide is “any toxic substance used to kill animals, fungi, or plants that cause economic damage to crop or ornamental plants or are hazardous to the health of domestic animals or humans” [1, 2]. Further, pesticides are subdivided by the clade of their target organism into insecticides, targeting class Insecta; acaricides, used against mites, ticks, and other arachnids; fungicides, targeting molds and other fungi; nematicides, specifically designed to kill roundworms; herbicides, employed against weeds; rodenticides; and other classes of toxins intentionally released into the environment with the objectives of controlling or limiting damage caused by organisms that are perceived to be detrimental [1–3]. It is widely understood that most pesticide types used today have the capacity to cause damage extending beyond the target organism(s) and translate into significant harm to ecosystems and health effects in humans [3, 4]. A recent meta-analysis of 1705 publications reports that pesticides of all types affect nontarget organisms negatively (>95% CI) by:

1. *limiting the growth* of invertebrate animals, vertebrate animals, seed plants, spore-producing plants, bacteria, and fungi [3, 4];
2. *interfering with the reproduction* of invertebrate animals, vertebrate animals, seed plants, spore-producing plants, bacteria, and fungi [3, 4];
3. *changing ecosystem productivity by producing detrimental effects on key species* such as honeybees, wild bees, lepidopterans, and other pollinators [3, 4];
4. *changing various processes and biomarkers within ecosystems*, including changes to the soil microbiome, biochemical activity of microbes, and microbial metabolomics profiles, and similar wide-reaching effects [4].

Beyond any reasonable doubt, continuous application of chemical pesticides also tends to undermine its own objectives by leading to the development of biocide resistance in the target organisms, as well as by destroying the pest's natural enemies, for instance, microbial pathogens, parasitic mites, and insectivores [4–6]. This decreases the resilience of ecosystems and, paradoxically, leads to the application of more pesticides, creating an example of a “positive feedback loop” with very detrimental consequences for biodiversity and ecosystem productivity [4–6].

Today, pesticide use is expanding rapidly. In 2020, globally, 3.45 million tons (Mt) of pesticides were utilized, out of which 47.5% were herbicides, 29.5% were insecticides, 17.5% were fungicides, and 5.5% were other types of pesticides [7–9]. Within just two years, in 2022, total pesticide use in agriculture was 3.70 million tons of active ingredients, marking a 4 percent increase with respect to 2021, a 13 percent increase in a decade, and a doubling since 1990; in 2022, herbicide consumption alone reached 1.9 million metric tons [7–9]. In 2020, >51% of all used pesticides were deployed in North and South America, with the United States utilizing a substantial 408 thousand tons (kt), Brazil - 377 kt, and Argentina - 241 kt, respectively [7–9]. The Asia-Pacific region deployed 28.6% of all pesticides used globally, with China peaking at 273 kt; Europe deployed just 12.8% of the global pesticide load [7–9]. Nevertheless, pesticides are still considered a very serious environmental risk across the EU [2, 4–6].

Manufacturing and deployment of pesticides is projected to intensify in the next two decades. The UN Food and Agriculture Organization (UN FAO) projects that, by 2050, feeding a world population of 9.1 billion people would require raising overall food production by some 70 percent between 2005/07 and 2050, with land-based agriculture producing ~95% of the nutrients globally [10]. Simultaneously, intensive farming, often combined with inappropriate farming practices, for example, slash-and-burn agricultural farming, leading to deforestation (e.g., Amazon River basin, Indonesia), and inappropriate fertilization leading to soil exhaustion (often seen in sub-Saharan Africa), leads to soil degradation on an unprecedented scale [11–14]. Alongside deforestation, desertification, soil exhaustion, soil erosion, and climate change, pesticide use is expected to be a major driver for the loss of biodiversity and loss of ecosystem productivity [11–15]. Second only to habitat loss, pesticide use may lead to the extinction of 40% of the world's insect species over the next few decades, which may largely go undetected, since most insect species are limited to small geographical areas in the tropics [15–18]. While the loss of insect biodiversity is an immeasurable loss in itself, it will negatively affect other animal species as well (fish, migratory birds, and bats, *et alia*), leading to further loss of ecosystem resilience [15–18]. Even with regulated application, pesticides will have a detrimental effect on the resilience and natural biological control of ecosystems [4–6, 19]; some of the biocides act as endocrine disruptors, affecting primarily riverine ecosystems, but also the health of many nontarget species, including humans [20, 21]. Organic biocides accumulate in ecosystems through two main processes: bioaccumulation and biomagnification. Each subsequent level in the food chain accumulates a greater concentration of pesticides, affecting apex predators, including humans [19–21]. The main negative consequences of these processes are reduced fertility and hormonal disruptions, reduced strength of eggshells in birds, death or mutations in animals, DNA damage and mutagenesis, etc. The risks to human health are primarily neurological, oncological, and reproductive [4, 7, 19, 20]. With the expected intensification of agriculture by 2050 [10–14], the governance and regulation of pesticide use is now an urgent problem of global significance.

1.2 Pesticides as POPs: World outlook, chemistry, toxicity, and environmental behavior

Today, on a worldwide basis, there are approximately 1000 pesticides consisting of 800 active ingredients in use, and the number of chemical formulations and brand names is still increasing [22]. Individual countries have different restrictions and permissive limits on marketed active ingredients and final products. For example, the Indian government allows the use and marketing of a total of 293 pesticides (as of 01 March 2021), of which 4 are WHO Class Ia pesticides (extremely hazardous, with high risk of acute toxicity), 15 are WHO Class Ib pesticides (classified as highly hazardous), and 23 are WHO Class II molecules (moderate risk), together constituting 40% of the registered biocidal agrochemicals in India [23, 24]. Although dichlorodiphenyltrichloroethane (DDT) is well-known for its environmental persistence and hazards, India still continues to use it, with an annual limit of 10,000 metric tons (mt) *per annum*, with the objective of controlling mosquitoes as disease vectors, although in some localities DDT is already ineffective due to emerging insecticide resistance of mosquitoes and midges [25]. The use of DDT is permissible by the WHO and UNEP in cases of high disease transmission and epidemic risk [25]. There are, in contrast, over 500 active pesticide ingredients registered for agricultural applications

in the USA since 1970, the year the US EPA was founded [26, 27]. Of the 508 pesticide active ingredients that have been FDA- and EPA-approved and used in agriculture in the USA since 1970, 134 have been canceled [26, 27]. Of those 134, 97 have been voluntarily withdrawn by pesticide licensees or had a time-limited approval that expired. For the remaining 37 pesticides, the US EPA took unilateral action to ban an ingredient. Many of these 37 are highly persistent, high-risk pollutants, including aldrin, DDT, dieldrin, chlordane, carbofuran, and toxaphene, all of which can still be detected in river sediments across the USA [26–28]. The European Union has one of the most legally restrictive pesticide control regimes worldwide, with <300 approved active ingredients under Directive 91/414/EEC and monitoring of maximum residue levels (MRLs) in food according to Regulation (EC) No 396/2005 [28, 29]. The EU bans 72 pesticides still permitted in the USA; for example, the updated legislation bans the use of neonicotinoids in order to protect honeybees and other pollinators [28, 29]. Nevertheless, even within the EU pesticides are a reason for extreme concern due to (1) overall high anthropogenic pressure on ecosystems, (2) the almost automatic renewal of licenses for pesticides with disputable safety, (3) the unpredictable effects of mixtures of pesticides on the environment, and (4) the environmental persistence and continued toxicity of already discontinued biocides [15, 30, 31].

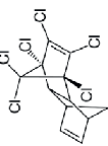
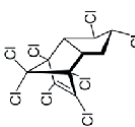
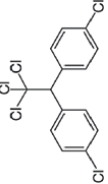
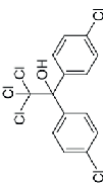
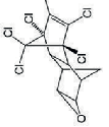
What makes a pesticide a persistent organic pollutant (POP)? There is a range of qualities that make an organic chemical particularly hazardous for the environment and, secondarily, to human health, namely:

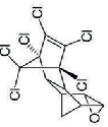
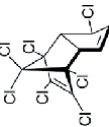
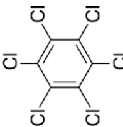
1. *Persistence in the environment.* POPs are, first and foremost, characterized by resistance to photochemical, metabolic, redox, and other chemical reactions leading to the breakdown and inactivation of the molecule. They typically have a long environmental half-life, which enables their long circulation in ecosystems and makes them a global hazard [32–35].
2. *Tendency to accumulate in living matter.* More often than not, POPs are lipophilic, which leads to bioaccumulation within living organisms and *biomagnification*, which is the process of increasing the concentration of a toxicant in the upper levels of food chains. Biomagnification can lead to an increase of a toxin's content beyond permissible limits even if the overall environmental concentration is low [32–35].
3. *Potential for long-range environmental transport.* In many cases, these chemicals can travel long distances from their source via air, water, or migratory species and can be found in regions where they were never used. Notably, organochlorine pesticides are detected globally, including in remote and nonagricultural areas like the Arctic and Antarctica [34, 35].
4. *Substantial ecological risk at low concentrations.* Often, POPs have very low mean lethal doses to wildlife or are characterized by *gene toxicity and mutagenicity*, *reproductive toxicity* or are *endocrine disruptors*, chemicals that disrupt hormone signaling within one or more living species [32–35].
5. *Hidden toxicities leading to higher risks than previously anticipated.* Some organic chemicals are “metabolically activated toxins,” which means that they get converted to a toxic metabolite within living cells; other organic chemicals pose a hazard to humans and animals due to high-temperature activation, which converts them into toxins after processes such as cooking or pasteurization [36–38].

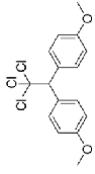
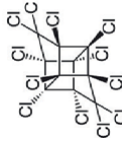
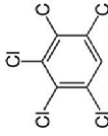
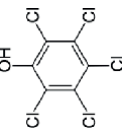
The Stockholm Convention on POPs, which was drafted by the UNEP in 2001 and entered into force on May 17, 2004, initially included a list of 12 initial POPs, of which 9 were pesticides, namely, aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, and toxaphene [39]. Subsequent revisions, the latest in 2023, have added more agrochemicals, namely, chlordecone, dicofol, lindane (the γ -isomer of hexachlorocyclohexane-HCH), as well as α - and β -HCH, methoxychlor, pentachlorophenol (PCP) and its derivatives, and endosulfan [40, 41]. As evident from the list, most of the POP pesticides under the Convention are organochlorine molecules. Chlorpyrifos, an organophosphate, is considered for a ban under the Convention (provisionally listed as a POP in 2025), while other molecules like carbofuran (a very toxic, highly persistent, carbamate-based endocrine disruptor) are *de facto* POPs and are being phased out but are not yet subject to UN restrictions [42, 43]. The chemistry, mode of action, and main characteristics of POP pesticides are presented in **Table 1**.

As evident from the table, most molecules identified as POPs under the Stockholm Convention are organochlorine molecules. This group of compounds mostly belongs to the first generation of organic pesticides, which have been used for at least five decades and are resistant to photochemical lysis, redox processes, and biodegradation, causing widespread nontarget effects and global contamination [44–47]. Sufficient and indisputable peer-reviewed data has been accumulated about their environmental effects; nevertheless, they are not the only organic biocides that should be considered as POPs. For example, carbofuran, widely used and marketed across the world, including the USA, has been demonstrated as the first carbamate compound that is at least as toxic as some molecules on the current POP list [48]; parathion, a first-generation organophosphate, has a “moderate” half-life in the environment, “not exceeding 4 months” (being subject to photochemical degradation), but is nevertheless persistent for much longer in river sediments, when applied indoors, or in dark storage spaces, and extremely toxic to mammals and birds [49]. Other organophosphates like fenitrothion, diazinon, and dimethoate, although less persistent, are endocrine disruptors, acutely neurotoxic in humans, and mobile in the environment [49, 50]. Fungicidal and bactericidal organomercury compounds (e.g., thimerosal, ethylmercuric chloride, *et alia*), formerly widely used in seed pretreatment before planting, have very high toxicity in vertebrates, ranging from aquatic wildlife to humans [51–53]. Perhaps most alarmingly, widespread use of herbicides is a well-known and still very pertinent environmental risk. The massive use of the herbicides “Agent Orange” (50% 2,4-dichlorophenoxyacetic acid (2,4-D) and 50% 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)) and “Agent Blue” (65.6% cacodylic acid (Ansar 138) and sodium cacodylate) over Indochina (1955–1975) has led to well-documented environmental destruction persisting 5+ years after the end of hostilities, as well as acute toxicity, cancer risk, and teratogenesis in humans [54]. Glyphosate (Roundup), extremely widely used today, is now openly claimed to be genotoxic and carcinogenic, making its continued use a multibillion-dollar question [55, 56].

As evident from this information, the need to treat many pesticides as POPs extends beyond the list of chemicals included under the Stockholm Convention and subject to UN-mandated monitoring, elimination, and restrictions. The scale of the chemical biocide problem and the degree of environmental damage it has already caused require urgent rethinking of pesticide deployment, monitoring, and management beyond the current state of the art. This is especially pertinent in the next two decades, considering the anticipated expansion of the human population and associated intensification of agriculture [7–10, 15, 30, 31, 44–56].

Organochlorine molecules				
Name and structure	Use	Environmental persistence	Acute LD50	Toxicity profile WHO classification
Aldrin, C ₁₂ H ₈ Cl ₆ 	insecticide	Moderate. Half-life: 4–7 years	Rat: Oral: 39–60 mg/kg Dermal: 100 mg/kg Mouse: Oral: 44 mg/kg	lipophilic, high bioaccumulation, metabolized to dieldrin; neurotoxic, extremely toxic to fish, with an LC50 of 0.006–0.01 Highly hazardous
Chlordane, C ₁₀ H ₆ Cl ₈ 	insecticide	High persistence. Half-life: 10 years	Rat: Oral: 200–700 mg/kg Dermal: 530–690 mg/kg Mouse: Oral: 145–430 mg/kg Dermal: 153 mg/kg	immunotoxic, neurotoxic, carcinogenic, risk factor for type-2 diabetes, toxic to fish, with an LD50 of 0.022–0.095 mg/kg (oral). Moderately hazardous
Dichlorodiphenyltrichloroethane (DDT), C ₁₄ H ₉ Cl ₅ 	acaricide insecticide	High persistence. Half-life: 2–15+ years	Rat: Oral: 113–130 mg/kg Dermal: 2510 mg/kg Mouse: Oral: 150–300 mg/kg Guinea Pig: Oral: 300 mg/kg	genotoxic, carcinogenic, endocrine disruptor (androgen antagonist), toxic and reproductively toxic to birds, widespread nontarget species effects Moderately hazardous
Dicofol, C ₁₄ H ₉ Cl ₅ O 	acaricide	Moderate persistence. Half-life: 60 days–1 year	Rat: Oral: 684–1495 mg/kg Rabbit: Oral: 1810 mg/kg Dermal: 2.1 g/kg	lipophilic, irritant, high biomagnification, highly toxic in fish, aquatic invertebrates, algae, and birds Moderately hazardous
Dieldrin, C ₁₂ H ₈ Cl ₆ -O 	insecticide	High persistence. Half-life: 9 months	Rat: Oral: 46 mg/kg Dermal: 50–120 mg/kg Mouse: Oral: 38–77 mg/kg	lipophilic, high bioaccumulation, genotoxic, teratogenic, extremely toxic to fish Highly hazardous

Organochlorine molecules				
Name and structure	Use	Environmental persistence	Acute LD50	Toxicity profile WHO classification
Endrin, C ₁₂ H ₈ Cl ₆ -O 	insecticide, avicide	Moderate persistence Half-life: 1 Day–12 Years	Rat: Oral: 3 mg/kg Dermal: 15 mg/kg Mouse: Oral: 1.37 g/kg Intravenous: 2300 g/kg	metabolically activated toxin; neurotoxic, teratogenic, reproductive toxin, very toxic to fish, aquatic invertebrates, and phytoplankton Highly hazardous
Heptachlor, C ₁₀ H ₅ Cl ₇ 	insecticide	High Persistence Half-life: 2 years	Rat: Oral: 40–220 mg/kg Dermal: 119–320 mg/kg Mouse: Oral: 30–68 mg/kg	metabolically activated to heptachlor epoxide; neurotoxic, immunotoxic, teratogenic Highly to moderately hazardous
Hexachlorobenzene, C ₆ Cl ₆ 	fungicide	High persistence. Half-life: 3–9 years	Mouse: Oral: 4000 mg/kg Guinea pig Oral: < 3000 mg/k	genotoxic, carcinogenic, mutagenic, hepatotoxic in humans (causes porphyria) Acute hazard is unlikely
α-hexachlorocyclohexane, β-hexachlorocyclohexane C ₆ H ₆ Cl ₆ 	insecticide	High persistence Half-life: 15 months	Rat: Oral: 88–270 mg/kg Mouse Oral: 59–246 mg/kg	persistent in water in colder regions; bioaccumulates and biomagnifies in biota and arctic food webs Moderately hazardous

Organochlorine molecules					
Name and structure	Use	Environmental persistence	Acute LD50	Toxicity profile	WHO classification
γ -hexachlorocyclohexane, C ₆ H ₆ Cl ₆ , Lindane 	acaricide insecticide rodenticide	High persistence. Half-life: 15 months	Rat: Oral: 88–270 mg/kg Mouse: Oral: 59–246 mg/kg	bioaccumulates easily and biomagnifies rapidly; reproductive toxin and carcinogen	Moderately hazardous
Methoxychlor, C ₁₆ H ₁₅ Cl ₃ O ₂ 	insecticide	High persistence. Half-life: <120 Days	Rat: Oral: 5000–6000 mg/kg Mouse: Oral: 2000 mg/kg Monkey: Oral: 2500 mg/kg	lipophilic, neurotoxic, nephrotoxic, endocrine disruptor (xenoestrogen), growth inhibitor	Acute hazard is unlikely
Mirex, C ₁₀ Cl ₁₂ 	insecticide	High persistence. Half-life: 10 years	Rat Oral: 600–740 mg/kg	toxic to several plant species and to fish and crustaceans; possibly carcinogenic	Acute hazard is unlikely
Pentachlorobenzene (PeCB), C ₆ HCl ₅ 	fungicide, solvent for other pesticides	High persistence. Half-life: 194 days to 3.5 years	Rat: Oral: 1080 mg/kg Mouse: Oral: 1175 mg/kg	metabolically activated to other POPs: polychlorinated dibenzodioxins (“dioxins”) and polychlorinated dibenzofurans. Very toxic to aquatic organisms	Moderately hazardous
Pentachlorophenol (PCP), 	fungicide herbicide insecticide disinfectant	Moderate persistence. Half-life: 45 days	Rat: Oral: 27–211 mg/kg Dermal: 96–330 mg/kg Mouse: Oral: 74–130 mg/kg	hepatotoxic, neurotoxic, nephrotoxic, immunotoxic, probable carcinogen, not significantly biomagnified along food chains	Moderately hazardous

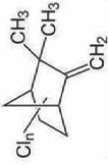
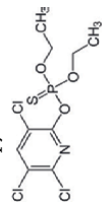
Organochlorine molecules				
Name and structure	Use	Environmental persistence	Acute LD50	Toxicity profile WHO classification
Toxaphene (Camphechlor), 	acaricide, insecticide	High persistence Half-life: 11 years	Rat: Oral: 80–293 mg/kg Dogs: 25 mg/kg	developmental and reproductive toxin; highly toxic to fish; possible carcinogen Slightly hazardous
Organophosphate molecules and combined organochlorine-sulfur compounds				
Chlorpyrifos, C9H11Cl3NO3PS 	insecticide, nematocide	Moderate persistence. Half-life: 10–120 days	Rat: Oral: 135 mg/kg, Dermal: 202 mg/kg	neurotoxic, immunotoxic, leading to developmental defects and growth retardation, very toxic to bees and crustaceans Moderately hazardous
Endosulfan, C9H6Cl6O3S 	insecticide	Moderate persistence Half-life: Alpha Isomer: 35 days Beta Isomer: 150 days	Rat: Oral: 18–220 mg/kg Dermal: 74 mg/kg Rabbit: Dermal: 200–359 mg/kg Duck: Oral: 33 mg/kg	volatile, subject to long-range transport; acutely neurotoxic; endocrine disruptor; xenoestrogen; reproductive toxin and mutagen Highly hazardous

Table 1.
Chemistry, environmental fate, and toxicity profiles of POP pesticides listed under the Stockholm Convention (Annexes A and B); based on Refs. [38–41, 44–47].

2. A brief history of pesticides

2.1 Preindustrial biocides: From ancient Sumeria to the end of the nineteenth century

Contrary to the notion that pesticides are a recent invention, there is evidence and written records that inorganic salts of mercury, copper, and arsenic, as well as elemental sulfur, were often used to combat molds, rodents, and insects in the ancient world, at least as far back as 2000 B.C. [57, 58]. These mixtures and preparations were seldom sprayed on fields due to their rarity and relative expense; they were most often used to combat lice and other phoretic insect parasites in humans and domestic animals or as components of insect poisons and rodent baits in granaries [57, 58]. The ancient Greeks wrote about using sulfur-containing smoke to purge orchards of pests, as well as the use of sulfurous lime in homes [58]. With the advent of modern chemistry, often associated with Antoine Lavoisier, Sir Humphry Davy, and John Dalton in the late eighteenth and early nineteenth centuries, the options at hand for farmers and gardeners increased. More sophisticated methods gave rise to a wider array of compounds, including Paris Green (copper(II) acetate triarsenite), accidentally discovered in 1814 by the paint makers Wilhelm Sattler and Friedrich Russ in Germany [59]. Disease outbreaks in France's vast vineyards during the nineteenth century (different fungal diseases, as well as the aphid *Phylloxera vastatrix*) led to the scientific testing of a wide range of inorganic chemicals. The most potent emerging solution was the fungicidal Bordeaux mixture (copper(II) sulfate (CuSO_4) and quicklime (CaO)), which became a standard treatment of many vineyards well into the twentieth century [59, 60]. Until the end of the nineteenth century, most pesticide formulations were inorganic (or, in rare cases, organomercury compounds) and existed alongside traditional agricultural practices such as mechanical and physical control (e.g., tree-banding with lime), cultural and sanitation controls (like crop rotation), and the use of resistant crop cultivars [61–63]. As a legacy from this period, the Bordeaux mixture is still widely used in viticulture across the globe; due to the presence of copper, it was provisionally banned within the EU-27, with the notable exceptions of Cyprus, Greece, Bulgaria, Hungary, Italy, Malta, Portugal, Romania, and Slovenia [63, 64].

2.2 Industrial poisons: Gestation of the modern organic pesticide (1870–1945)

The period after 1870 was characterized by rapid innovation in three key areas: electricity and electrification, advanced steel smelting, and organic chemistry. William Perkin's serendipitous discovery of "mauveine" (an aniline-based purple dye derived from coal tar) in 1856 launched a frenetic flurry of corporate and academic innovation in organic chemicals; although Friedrich Wöhler was the first to make an "organic" compound in 1828, Perkin's discovery was the catalyst for a vast industrial expansion in carbon-based chemistry [65, 66]. Innovation, mainly conducted in German universities and German companies like Agfa, BASF, Bayer, Griesheim-Elektron, Hoechst, and Weiler-ter-Meer, and, to a lesser extent, in Switzerland by Ciba, Geigy, Sandoz, and Roche, led to the development of a vast array of medicines, synthetic fertilizers, and, in the period leading to World War I, explosives, pesticides, and chemical weapons like hydrogen cyanide (HCN) and phosgene (COCl_2). World War I itself saw the widespread use of poison gases against soldiers on all fronts; nevertheless, serious efforts into pest control started in the interwar period [63, 67]. An entire range of organochlorine compounds, such as hexachlorobenzene

(C₆Cl₆) and DDT, were first synthesized in the 1800s, but their insecticidal effects were not fully appreciated until the late 1930s. Hexachlorobenzene was first produced by Michael Faraday in 1825, but its properties as an insecticide were not identified until 1944. Dichlorodiphenyltrichloroethane (DDT) was first prepared by Othmar Ziedler, an Austrian chemist, in 1825, but DDT's insecticidal properties only became apparent in 1939 due to the work of Swiss chemist Paul Hermann Müller at J. R. Geigy AG [63]. Beginning with the 1940s, an arsenal of thousands of insecticides, herbicides, fungicides, and other pesticides was developed, including organochlorines (Aldrin, HCH, Chlordane, DDT, and others), organophosphates and phosphonates (Malathion, Parathion, Chlorpyrifos, Glyphosate, *et alia*), carbamates (Aldicarb, Carbofuran, Oxamyl, Methomyl) [67], and, later in the 1980s, neonicotinoids (Imidacloprid, Acetamiprid, Clothianidin, Nitenpyram) [52, 57, 59, 63]. The vast majority of these are now considered unsustainable and are subject to bans in various countries.

2.3 Opportunity creates habit: Pesticides unleashed (1945–1970)

The later stage of World War II in the Pacific Theater (1942–1945) was characterized by the massive use of DDT as an airplane-deployed pesticide in all areas of US military action [57, 63, 68]. Following the war, and with DDT production pipelines established across the US by companies such as Dow, DuPont, and Union Carbide, domestic deployment of organochlorines and organophosphates reached epidemic proportions across North America [57, 63, 68]. Meanwhile, the Soviet Union, which had been rapidly industrializing its agriculture since the 1930s, began a process of “chemicalization” (“*khimizatsiya*”) of agriculture during the Cold War; as a legacy of that period, the former Soviet states are still among the world's largest fertilizer and pesticide producers [37, 38, 52, 68, 69]. USSR statistics estimate that the annual use of pesticides increased about tenfold between 1949 and 1956, from 30,000 to 300,000 tons, then continued to increase, peaking at 500,000 tons annually in the early 1980s [69, 70]. The primary targets were the Colorado potato beetle (*Leptinotarsa decemlineata*), various fungi and molds, and grain and cotton pests, with very significant residual contamination of rivers and dams [52, 69, 70]. During the Cold War, research on both sides of the Iron Curtain included chemical weapons, with weapons research often disguised as civilian pesticide development [52, 68–70]. The US widely deployed defoliants like “Agent Orange” and “Agent Blue” over Indochina (1955–1975), perhaps most clearly highlighting the massive environmental damage and health risks of herbicides **Figure 1** [54]. The WHO itself launched a Global Malaria Eradication Programme (GMEP; 1955–1969), deploying DDT and other organochlorines across the globe; while the GMEP completely eliminated malaria from the Balkans and Central Asia, its objectives in Africa and Southeastern Asia were not met, instead resulting in the emergence of pesticide-resistant mosquitoes [74, 75].

2.4 After *silent spring*: Working toward sustainable pest management

Rachel Carson's popular science book *Silent Spring* (1962) [76] served as a warning of the already apparent dangers of widespread pesticide spraying [77, 78]. Although the topic of *Silent Spring* is destruction caused by the US Department of Agriculture, the importance of the book extends beyond pesticides: it is widely believed that *Silent Spring* catalyzed the formation of the Western environmental movement; more than



Figure 1. Pesticides unleashed: The US Army Air Force (USAAF) spraying DDT over Manila in 1945; a Soviet poster cautioning workers against pesticide toxicity (center), and destruction of forests and crops, caused by the massive deployment of Agent Orange in Indochina, 1961-1971 (right). Sources: [71-73].

that, it is a testament to the importance of counterculture and scientific objection in the face of authoritarian decision-making [77-79].

Carson sowed the seed of doubt, and as a result of her work, the world can no longer tolerate environmental destruction. After many years of civil protest, the Nixon administration established the US EPA in 1970, and the United States banned the general use of DDT in 1972 [77-79]. The Soviet Union had outlawed DDT in 1970 and continued to revise its agricultural use of biocides through increasingly harsher regulations in 1972, 1980, and 1989; as a result, the use of pesticides dropped from ~200,000 tons in 1980 Soviet Russia to <97,000 tons in present-day Russia [37, 38, 51].

Today, the world is dealing with an expanding use of pesticides; nevertheless, newer formulations tend to be less persistent [8, 9, 26, 29]. Recent scientific thinking leans towards sustainable practices for crop protection, such as integrative pest management (IPM) [80] and the use of nanoinsecticides [81]. The focus nowadays is shifting toward the development of target-specific biological control organisms, such as varieties of *Bacillus thuringiensis*, *E. coli*, and other bacteria, or highly lethal fungal pathogens like *Beauveria bassiana*, *Metarhizium species*, and *Entomophaga maimaiga*, with *E. maimaiga* being a spectacularly effective, host-specific biocontrol agent against the defoliating spongy moth (*Lymantria dispar*) [82-84].

3. Biological effects of pesticides

The biological effects on nontarget species are discussed at length elsewhere [4-7, 15-21, 41-45, 85, 86]. Nevertheless, it will be beneficial to mention briefly the two main sources of concern, as this is related to the spectrum of damage induced by biocides on nontarget species in terrestrial and riverine ecosystems, as well as to the residual risk of pesticides as POPs.

1. *There is sufficient evidence that many first-generation organic pesticides are genotoxic* [49-53]. Recent studies implicate particularly the organophosphates dimethoate, malathion, parathion, and azinphos, as well as 1960s herbicides, particularly 2,4,5-T and 2,4-D, which form "Agent Orange" [49, 52, 87]. Synthetic pyrethroids like cypermethrin induce DNA damage and developmental abnormalities in experimental animals and are likely human carcinogens [87, 88]. Evidence is mounting that current herbicides, including atrazine, are genotoxic [87, 88].

2. *More alarmingly, in the context of ecosystems, many pesticides act as endocrine disruptors in a range of species, including mammals* [87–89]. More than 120 pesticides have endocrine disruptor properties in nontarget organisms, including notably acephate, aldrin, atrazine, carbofuran, cypermethrin, DDT and its metabolites, dicofol, dieldrin, endosulfan, endrin, fipronil, glyphosate, heptachlor, lindane, malathion, methomyl, mirex, tolclofos-methyl, toxaphene, tributyltin (TBT), and Ziram [88, 89]. These effects are particularly concerning, since they occur at very low dose levels and can affect nontarget species in a manner that is very hard to detect [88, 89].

Both gene toxicity and endocrine disruption are due to a variety of mechanisms, as dictated by the varying molecular structures. Genotoxic pesticides are often weak alkylators or intercalators, with others having indirect mechanisms of action, including the disruption of redox homeostasis: overproduction of ROS during their metabolism, mitochondrial disruption, or inhibition of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [87–90]. Hormonal disruptors often tend to be xenoestrogens, receptor blockers, or thyroid hormone mimetics [87–89]. More often than not, these effects are exacerbated by the tendencies of the majority of POP molecules toward bioaccumulation and biomagnification [37–45, 49, 52, 63].

4. Environmental damage of POP pesticides in terrestrial and riverine ecosystems

Typically, pesticides are deployed in agricultural areas, where they target a particular risk organism or a range of species. Nevertheless, they harm the agroecosystem they are meant to protect by changing the soil microbiome (potentially leading to a degradation of soil quality and productivity), as well as by limiting the ecosystem's capacity for biological control of pests through destruction of the pest's natural enemies, including bacterial and fungal pathogens, parasitic mites and nematodes, and insectivores [4–6, 32–35, 55, 56].

Nevertheless, the environmental persistence of POP pesticides leads to effects extending beyond the immediate geographical area of deployment. Besides absorption by the target, pesticides are also (1) absorbed by crops, which in turn can harm humans and livestock; (2) capable of migration in and out of soils through sorption and leaching, sometimes leading to groundwater contamination; (3) prone to surface runoff into lakes and river drainage basins; and (4) known for the tendency of phoretic or chemical attachment to organic matter (due to their lipophilic structure) and adherence to all forms of organic aggregations, from detritic particles to entire organisms [91]. This leads to an entirely new risk profile for POP molecules, affecting, more often than not, primarily riverine ecosystems, with a very high deposition pattern in river sediments and riparian soils; concentrations of a given POP in sediment can exceed its concentrations in surface waters by a factor exceeding 1000 [92, 93]. This is the main reason why POP pesticides form a looming threat in developing countries and are still a source of residual risk in well-regulated environments such as the EU and most of West Asia [91–94].

The risk profile of POP pesticides makes them particularly hazardous to life in slow-flowing small rivers and intermittent rivers adjacent to agricultural areas, but also for benthic organisms in the estuaries of major rivers; typical pesticide-sensitive

lifeforms are amphibians: crested newts (*Triturus* spp.) and fire-bellied toads (*Bombina variegata*, *Bombina bombina*, etc.) [95–97]. In contrast, more resistant, ubiquitous amphibians like *Bufo viridis*, *Hyla orientalis*, and *Pelophylax ridibundus* can serve as suitable species for monitoring pesticide exposure and gene toxicity in water bodies with high pesticide load [96]. Similarly, some fish characteristic of slow-flowing water bodies, such as the common carp (*Cyprinus carpio* L.), are sensitive to pesticide-induced genetic biomarkers at very low environmental concentrations but are nevertheless resistant to acute lethality [98]. **Figure 2** is an illustration of amphibian and piscine species suitable for environmental indication and monitoring.

Following from the image, “bioindicator species,” which disappear from polluted water bodies, include chemically sensitive species such as crested newts and fire-bellied toads; more resistant, ubiquitous species like marsh frogs and carps are good “monitors” of pesticide loads and biological effects in high-risk environments [95–98].

In Europe, the least-contaminated river ecosystems are in areas without high-intensity farming in Austria, Denmark, Estonia, Lithuania, Malta, Norway, Slovenia, and Sweden [102]. In contrast, rivers with high loads of POP pesticides include the lower Rhine/Meuse, the Schelde, the lower Elbe, the Vistula and Oder basins, the lower Danube, and the Dnieper [102]. Worldwide, high-contamination areas include the Indus River basin [93] and a significant part of the Mississippi, Missouri, and Ohio watersheds in the USA [63, 64, 103]. The residual risk associated with the use of POP pesticides and the excessive deployment of herbicides necessitates consistent ecological monitoring in these river basins. POP pesticides in the river benthos can pose additional risks in case of environmental disasters and damage caused by warfare: an example

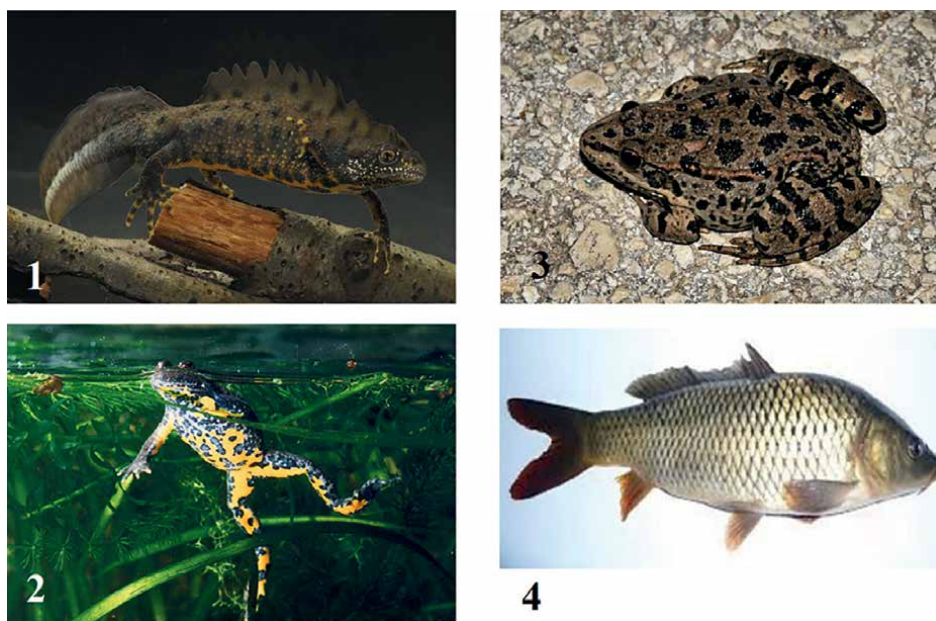


Figure 2. Bioindicator species (left), like *Triturus cristatus* (1) and *Bombina variegata* (2), disappear from heavily contaminated ecosystems. Species suitable for the monitoring of pesticide load and gene toxicity in polluted water bodies tend to be more resistant (right): *Pelophylax ridibundus* (3) and *Cyprinus carpio* (4), image based on Refs. [98–101].

is the military destruction of the Kakhovka Dam (6 June 2023) in the ongoing war between Russia and Ukraine—the breach released POP pollutants that had accumulated in the reservoir sediments, creating a long-term source of contaminants that could be spread by future floods [104, 105]. In a global situation characterized by increasing insecurity, the monitoring of POP pollution requires new techniques and solutions.

5. Monitoring and management of POP pesticides: New and pertinent methods

5.1 Monitoring and impact assessment in terrestrial and riverine ecosystems

The assessment and monitoring of environmental damage due to POP pesticides is a complex and rapidly developing science. Usually, the monitoring of a particular site starts with an analysis of legacy data, followed by an environmental survey, a measurement of total organics in water, and a biotic survey. Legacy data can be obtained from a variety of sources; one convenient source for legacy data on surface waters and groundwaters in Europe is the EEA's Waterbase, which has substantial downloadable datasets [94, 106]. Pesticide load is first estimated via total organic carbon (TOC) content in water, including suspended particulate matter (SPM), by a variety of methods [106, 107]. Particular pesticides and their daughter molecules can be detected by a variety of methods and sensors, including fluorescence, surface-enhanced Raman spectroscopy (SERS), or quantum-dot sensors [108, 109]. A recent meta-analysis of European surface waters found that many surface water samples within the EU exceed the permissible levels: regarding herbicides, 15.6% of water samples exceed the maximum permissible limits (MPLs) for glyphosate and 6.7% for diflufenican (DFF); regarding insecticide levels, 29.2% of samples exceed national MPLs for malathion, 20.7% for heptachlor, 16.4% for dichlorvos, 15.9% for heptachlor epoxide, and 15.5% for imidacloprid [94].

Chemical content assessment alone is not enough to estimate the risk profile of a particular terrestrial or riverine ecosystem [30, 31]. Recent years have seen a resurgence in biomonitoring studies, including monitoring for radionuclides, toxic metals, and pesticides [34, 110–113]. Among the zoomonitors used for the study of contamination effects on terrestrial ecosystems are European wild rodents, including wood mice (*Apodemus* spp.) and different vole species (*Microtus arvalis*, *Myodes glareolus*, *Microtus oeconomus*, *Chionomys nivalis*, and others) [110–114], as well as North American deer mice (*Peromyscus* spp.) and kangaroo rats (*Dipodomys merriami*) [115]. The endpoints measured in rodents include pesticide load, genetic damage (*via* micronucleus test or comet assay), chromosomal damage (*via* cytogenetic methods), hematological parameters, and others.

Riverine ecosystems present a different challenge and risk profile, particularly due to POP accumulation in sediments [91–94, 116]. One emerging system for estimating residual risk is the detection of genotoxic stress and neoplastic lesions in zoobenthic predator organisms, particularly euryhaline flatfish like the European flounder (*Platichthys flesus*), dab (*Limanda limanda*), and turbot (*Scophthalmus maximus*) [116–118]. A good method is to identify oxidative stress, precancerous lesions, and cancer in thin histopathological sections (2–5 μ M) of the livers of estuarine flatfish, where cancer morphology is detected *via* hematoxylin-eosin (HE) [116–118], and focal cellular degradation is highlighted by the lipofuscin/Schmorl stain method [119]. A result of such a study is presented in **Figure 3**.

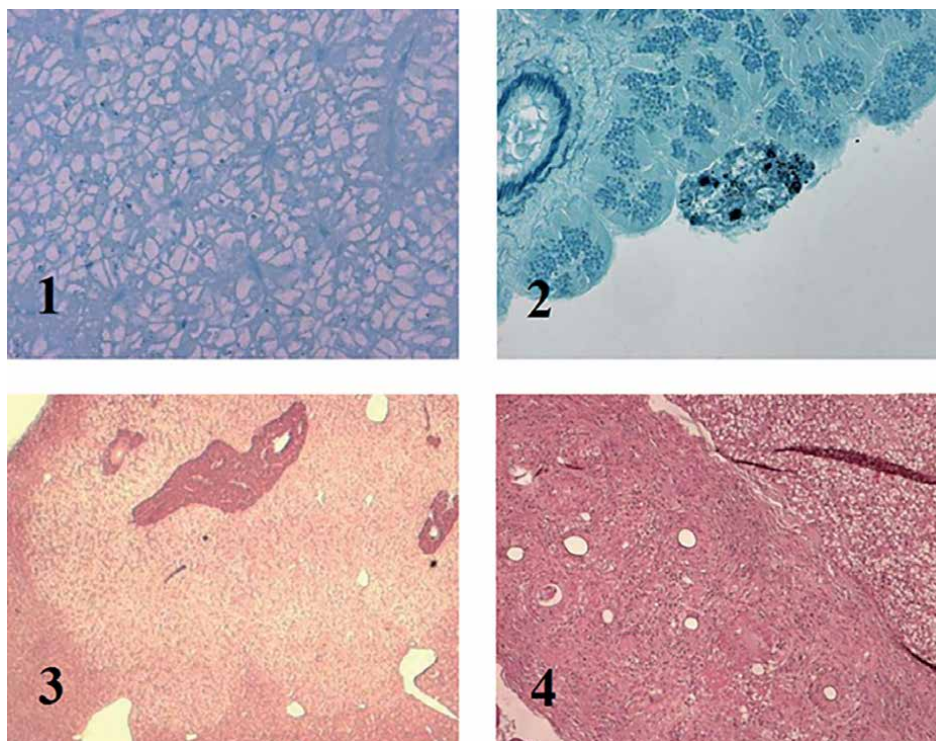


Figure 3. Histopathological lesions in European flounder from the Elbe estuary, Germany. Top: senescence and oxidative damage. Schmorl staining of normal liver parenchyma (1) and Schmorl staining of focal degradation, characterized by lipofuscin accumulation in hepatopancreatic tissue (2), 400x magnification. Source: P. Ostoich personal archive, 2006. Bottom: cancerous lesions. Trabecular clear cell carcinoma, HE stain, 15x magnification (3), and hepatocellular carcinoma, HE stain, 100x magnification (4). Source: P. Ostoich personal archive, 2006.

As seen above, focal oxidative damage and cancerous lesions are readily observable in the livers of *Platichthys flesus* with good microscopy. Both methods are suitable for the detection of complex genotoxic stress resulting from exposure to river sediments in these benthic species [116–118].

5.2 Management and mitigation of environmental pesticide damage

While monitoring techniques are sufficiently advanced, good management and remediation of POP pesticides are challenging; some organic molecules like parathion are subject to photochemical degradation but turn into POPs in the riverine and marine benthos [49]. Various microorganisms, including bacteria and fungi, have been found to help remove or detoxify organochlorine and organophosphate pesticides, as well as degrade polycyclic aromatic hydrocarbons (PAHs) [120, 121]. Notably, the common bacteria *Clostridium sporogenes* and *Escherichia coli* produce benzene and chlorobenzene from lindane and can further metabolize it by producing CO₂. *Pseudomonas putida* and several *Acinetobacter* species can dehalogenate most organochlorines [120]. Major bacterial genera capable of degrading organics include *Acinetobacter*, *Aerobacter*, *Arthrobacter*, *Bacillus*, *Pseudomonas*, *Flavobacterium*, *Moraxella*, *Paracoccus*, and *Sphingomonas*; fungal genera with POP degradation potential include *Aspergillus*, *Fusarium*, *Penicillium*, *Lentinula*, *Lecanicillium*, and

Oxysporum [121]. Other methods for pesticide degradation include chemical catalysis; for instance, P–O and P–S bonds are easily oxidized with TiO₂ as a catalyst [122]. Further, modern synthetic biology can provide novel transgenic strains for the purposes of pesticide degradation; modified *E. coli* strains secrete functional enzymes that cleave carbaryl, λ -cyhalothrin, and paraoxon [122–124]. Despite ongoing progress in the chemical and biological remediation methods, the best strategies for ecosystem preservation are to limit the release and geographical area of pesticide deployment and to use an integrated, science-based approach to pest control, including old techniques like crop rotation and natural approaches like biopesticides.

6. Conclusion

The current chapter reviewed and analyzed the toxicity, environmental behavior, monitoring, and management prospects of pesticides as POPs in terrestrial and riverine ecosystems. Besides an analysis of the state of the art, we mention some little-known aspects of the use of rodent, amphibian, and piscine species, respectively, in the monitoring of terrestrial ecosystems, riverine contamination, and brackish water bodies; it is the authors' belief that monitoring complex pollution patterns in these ecosystems necessitates the use of zoomonitor species, particularly for the accurate estimation of gene toxicity, carcinogenicity, teratogenicity, and hormonal disruption in the terrestrial and aquatic biota. While the intensification of agriculture appears unavoidable in the next 2–3 decades, it is still advisable to keep pesticide deployment to a minimum, particularly keeping in mind the surprising persistence and gene toxicity of modern herbicides. The past use of pesticides has demonstrated the fragility of ecosystems in the face of chemical biocides; both humanity's survival and the need to conserve the Earth's ecosystems depend on the adoption of new, more sustainable methods for crop protection and sanitary control.

Conflict of interest

The authors declare no conflict of interest.

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Mechanochemistry in Organic Synthesis: An Overview

Francesco Basoccu

Abstract

Mechanochemistry is a branch of chemistry that uses mechanical energy to drive chemical reactions, offering a powerful and eco-friendly alternative to conventional solution-based approaches. This method typically employs grinding or milling equipment, such as ball mills, to facilitate reactions by exerting mechanical forces. Unlike traditional methods that rely heavily on toxic organic solvents, mechanochemistry operates in the solid state, significantly reducing the need for harmful organic solvents and minimising waste production. One of the most compelling advantages of mechanochemistry is its environmental sustainability. By eliminating or reducing solvent use, it aligns with the principles of green chemistry, lowering the environmental footprint of chemical processes. Additionally, mechanochemistry enables reactions that are difficult or impossible to achieve through solution-based methods, such as those involving incompatible reactants or highly stable compounds. The ability to activate chemical bonds via mechanical force opens new possibilities for innovation in fields like materials science, catalysis, and pharmaceutical synthesis. Besides, it also promotes efficiency, as it allows for rapid reactions under controlled conditions without the need for high temperatures or pressures. With its unique blend of sustainability, versatility, and efficiency, mechanochemistry is transforming the way chemists approach synthesis, offering a pathway to more sustainable and innovative chemical processes.

Keywords: mechanochemistry, organic synthesis, scale-up, sustainability, green chemistry

1. Introduction

Nowadays, organic chemistry is generally involved in different fields like biotechnology, cosmetics, the industry of raw materials, the pharmaceutical sector, and so on [1, 2]. Consequently, the new requests from all these different fields have led not only to the development of new reaction pathways and more complex synthetic strategies but also to the necessity of lowering the waste and the environmental impact associated with these approaches. This is due to the low sustainability of synthetic methodologies in which it is generally required to dissolution of all reaction components, resulting in huge consumption of organic solvents [3–5]. These will then be treated for extracting or precipitating the product; otherwise, they will be directly distilled from the mixture. In any case, they generally account for the most relevant part of the

waste associated with a specific industrial process due to the difficulty in recovering them with a high degree of purity. Moreover, several industrial processes still rely on the employment of highly toxic reagents and solvents for their processes, leading to a huge concern in terms of pollution and sustainability [6, 7]. Specifically, more than 70% of the waste associated with pharmaceutical production is solvents [7, 8].

In the '90s, the global acceptance of the importance of sustainability has brought to the genesis of a different discipline within chemistry and chemical engineering. Pioneered by a devoted community of experts in the field, this innovative way of conceptualising chemistry focuses on minimising or completely eradicating the production of toxic substances and environmental pollutants from chemical processes [9, 10]. This responsibility represents a profound paradigm shift towards practices that prioritise environmental stewardship. This new way of conceptualising chemistry gave birth to the concept of green chemistry.

Described by 12 principles proposed by Warner and Anastas in 1998, green chemistry aims to redefine chemical processes to be inherently safer and more respectful towards ecological standards. These fundamentals can be summarised into “Reducing Risk” and “Minimizing the Environmental Footprint” [11, 12]. This way of considering chemistry has deeply remodelled ordinary chemical protocols, leading to the advancement of pioneering approaches, such as electrochemical techniques, photochemical methodologies, and flow chemistry. Each of these modifications highlights a remarkable development for improving sustainable protocols, allowing the integration of eco-efficiency and safety into the inner part of chemistry and chemical engineering.

Within the array of groundbreaking techniques that have emerged in the framework of green chemistry, solvent-less techniques distinguish themselves through their peculiar ability to facilitate reactions without the employment of solvents [13–16]. Among these, mechanochemistry surely proved to be one of the most valuable due to its simplicity in setup and remarkable efficiency, which has driven its widespread adoption across the scientific community [17–20]. The International Union of Pure and Applied Chemistry (IUPAC) has honoured mechanochemistry as one of the most significant emerging technologies in 2021, underscoring its transformative potential in steering chemical synthesis towards a more sustainable and environmentally friendly direction [21, 22]. This widespread approval highlights the role of mechanochemistry in giving a new shape to the landscape of chemical research, allowing a cleaner, greener alternative to traditional methods. As mechanochemistry proceeds forward, it is set to become a cornerstone in pursuing more sustainable and eco-conscious scientific practices, embodying the principles of green chemistry and driving innovation towards minimising the environmental impact of chemical processes [23–28].

Mechanochemical experiments involve the use of specific equipment called the ball-grinding device [29, 30]. This innovative instrument utilises the kinetic energy of balls of varying sizes within a jar to drive chemical transformations in solid-state conditions (**Figure 1**). The machine can operate in various dynamic modes, including vertical, horizontal, and planetary movements or even patterns that mimic the shape of a figure-eight [31, 32]. These diverse motions result in applying grinding and shredding pressures on the reactant materials through the balls, facilitating the trigger of chemical transformations [33].

The choice of materials for the grinding balls and the vessels deeply influences the efficacy and nature of these transformations. Commonly used materials for grinding balls and jars include stainless steel, zirconia, and Teflon, as well as less conventional



Figure 1.
Typical setup employed for a mechanochemical reaction is composed of jars made of either stainless steel or zirconia.

choices like tungsten carbide, Erthalite®, and polyacrylamide (PAM) [34, 35]. Each material presents peculiar densities and properties, providing the flexibility to tailor the mechanochemical process to meet specific experimental demands [36]. Apart from these, there are other key parameters such as mechanical energy input, which depends on milling speed, frequency, and impact force; ball-to-powder ratio (BPR), which affects energy transfer and reaction kinetics; and milling time, which determines the extent of conversion. These parameters collectively control reaction yield, selectivity, and mechanochemical product properties, paving the way for innovative discoveries and progress in the field.

With such an advanced and versatile technique, scientists finally succeeded not only in renewing the old organic methodologies reported but also in discovering reaction pathways peculiar to the solid-state approach. For completeness, the most significant organic procedures repropounded under solid-state conditions have been summarised in the following paragraphs.

2. Organometallics

Organometallic chemistry, a field at the intersection of inorganic and organic chemistry, focuses on compounds featuring a direct bond between a metal atom and a carbon atom in an organic group (**Figure 2**) [37, 38]. This branch of chemistry has emerged as one of the most dynamic and influential disciplines due to its broad range of applications in catalysis, materials science, and organic synthesis [39–41]. This field began to take shape in the mid-nineteenth century when Edward Frankland synthesised diethylzinc (C_2H_5)₂Zn in 1849, marking one of the first examples of a

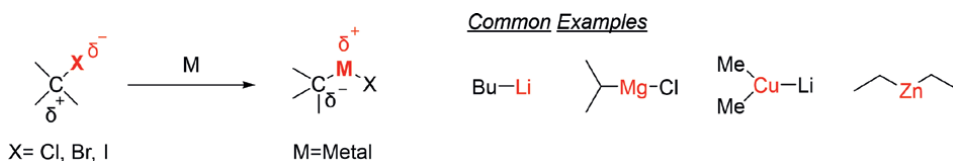


Figure 2.
Common organometallic reagents.

compound featuring a metal-carbon bond [42, 43]. Later, in the twentieth century, the development of Grignard reagents by Victor Grignard in 1900—organomagnesium compounds widely used in organic synthesis—laid the groundwork for the explosive growth of organometallic chemistry [44, 45].

Major advances in the field have been driven by the development of transition metal-based catalysts for important industrial processes, such as hydroformylation and cross-coupling reactions like Suzuki-Miyaura and Heck reactions, which have found applications in pharmaceuticals, fine chemicals, and polymer synthesis [46–48]. Throughout its history, organometallic chemistry has played a pivotal role in shaping modern chemical sciences, offering insights into metal-ligand bonding, facilitating the synthesis of complex organic molecules, and contributing to sustainable technologies in materials and energy [49, 50].

Therefore, its use has been widely documented in mechanochemistry as well, leading to the development of the most relevant procedures through such a solvent-free approach.

2.1 Grignard reagents

Grignard reagents, named after Victor Grignard, are a class of organomagnesium compounds with the general formula R-Mg-X , where R is an organic group (alkyl, aryl, or alkenyl) and X is a halogen (Cl, Br, or I) [44, 51]. Structurally, Grignard reagents feature a polar covalent bond between carbon and magnesium, where the carbon is nucleophilic and reactive towards electrophiles. They are typically prepared by reacting an organic halide (R-X) with magnesium metal in a dry ether solvent such as diethyl ether or tetrahydrofuran (THF), which stabilises the reagent by coordinating with the magnesium atom [52, 53]. Despite their utility as nucleophiles, Grignard reagents are sensitive to moisture and air, reacting violently with water or acidic protons and requiring inert conditions for handling. Additionally, their use is limited to substrates containing functional groups incompatible with their nucleophilicity.

Their necessity of being generated under these strict conditions increased the interest of researchers working in the mechanochemistry field, resulting in the development of Grignard reagents under mechanochemical conditions as pioneered by Harrowfield in 2001 [54]. In his work, he reported the first successful solvent-free preparation of a naphthyl Grignard reagent, followed by its reaction with ketones. Although the approach delivered the desired tertiary alcohol, a mixture of byproducts was detected as well. These were mainly connected to the onset of Wurtz and McMurry couplings and other side processes [55–57]. Interestingly, it was described the physical state and appearance of the crude mixture on the basis of the excess of magnesium employed. From the data collected, it was supposed that the chemical form of the ‘Grignard reagent’ present is different when a specific amount of magnesium is present, though there is no evidence that this led to appreciable differences in reactivity.

It was necessary to wait approximately 20 years for further developments on the synthesis of Grignard reagents under ball-milling conditions. In 2021, Ito and workers finally developed a protocol based on milling magnesium turning with a halo derivative in the presence of a stoichiometric amount of THF or cyclopentylmethyl ether (CPME) (**Figure 3**) [58].

The following refill of the jar with an electrophilic agent, led to the formation of the desired product smoothly eliminating the need for inert environment or dry organic solvents. Notably, common byproducts, including alkanes (RH) or Wurtz-like coupling products (R–R), were barely detected allowing to run these processes without the necessity of a proper moisture exclusion and a controlled addition of the reagents to the reaction medium.

Furthermore, they also reported the preparation of an organomagnesium reagent from a poorly soluble aryl halide—an achievement not possible using conventional solution-based methods. This approach permitted the synthesis of various organic derivatives, even on a gram scale, starting from the reaction of an electrophile with the organomagnesium compound. Further analyses about the formation of organomagnesium compounds concern the stable structures between an RMgBr and THF, which have been investigated by comparing the theoretical calculations run and the experimental Near edge, X-ray absorption fine structure (NEXAFS) spectra collected.

Successive uses of Grignard reagents were reported by Bolm, who documented the carbonatation of these derivatives under ball-milling conditions by exploiting an atmosphere of CO₂ [59]. The specific setup for gaseous reagents allowed firstly the formation of the organomagnesium under an argon atmosphere, for then proceeded with its carbonylation by forming a CO₂ atmosphere or by using sodium methyl carbonate as a solid surrogate of CO₂. Moreover, the addition of a lithium salt to the reaction environment was evaluated on the basis of the reported literature [60, 61]. Notably, it has been seen that the presence of LiOH, instead of the more common LiCl, relevantly increased the yield of the *p*-toluic acid employed for the optimisation process, laying the ground for further future investigations on this specific aspect.

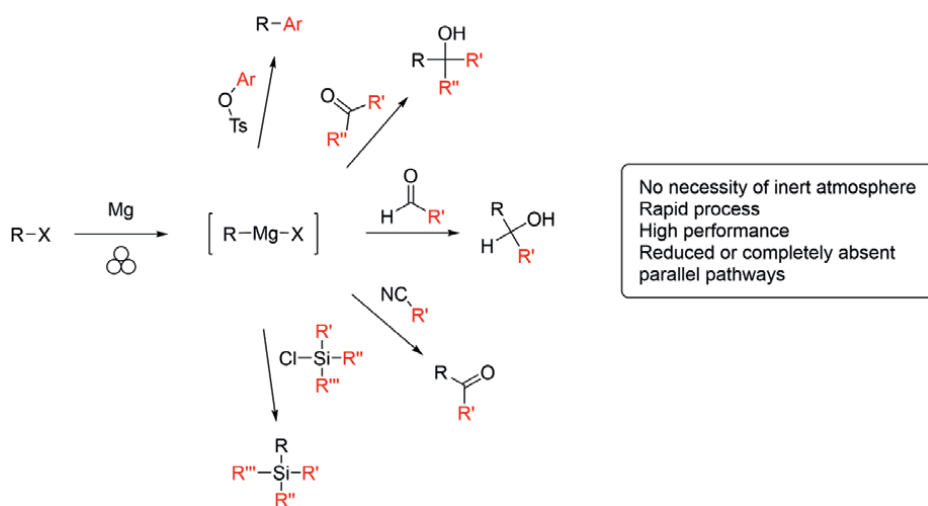


Figure 3.
 Potential application of Grignard reagents under mechanochemical conditions as reported in Ref. [58].

2.2 Cross-coupling reactions

Cross-coupling reactions are a cornerstone of modern organic synthesis, enabling the formation of carbon-carbon and carbon-heteroatom bonds with high precision and efficiency [62, 63]. These reactions involve the catalytic coupling of two precursors, typically an organometallic reagent and an organic halide or pseudohalide, in the presence of a transition metal catalyst, such as palladium, nickel, or copper. Central to the process is the catalytic cycle, which consists of oxidative addition, transmetalation, and reductive elimination steps, facilitating the assembly of complex molecules from simpler components (**Figure 4**) [64–66].

Prominent examples of cross-coupling reactions include the Suzuki-Miyaura coupling, Stille coupling, Heck reaction, Negishi coupling, and Sonogashira coupling, each tailored to specific bond-forming applications.

2.2.1 Suzuki-Miyaura reaction

The Suzuki reaction, also known as the Suzuki-Miyaura coupling, is a powerful and widely used cross-coupling reaction that forms carbon-carbon bonds between an organoboron compound (such as an aryl- or alkyl-boronic acid) and an organic halide or pseudohalide (e.g., aryl halides) [67–69]. Its utility in forming biaryl structures and other complex architectures has made the Suzuki reaction a cornerstone of modern organic synthesis. The first approach to this kind of process was proposed by Axelsson in 2000, where he successfully synthesised various aryl derivatives by combining an aryl bromide, phenylboronic acid, Pd-tetrakis, and potassium carbonate [70]. However, the stickiness of these mixtures did not permit correct milling of the reagents, making the addition of a grinding auxiliary like sodium chloride to allow a correct grinding of the reaction components. Interestingly, the reactivity of substrates characterised by low performance in-solution demonstrated to be rather reactive under solid-state conditions and vice versa, making the procedure somewhat complementary to what was already reported in the literature.

Further developments of catalytic systems for robust C–C bond-forming reactions in the solid-state were reported by Ito [71]. Compared to previous studies, this system broadened the application to various aryl halides, especially inactivated aryl chlorides. The main feature of this approach is the presence of an olefin-additive, which

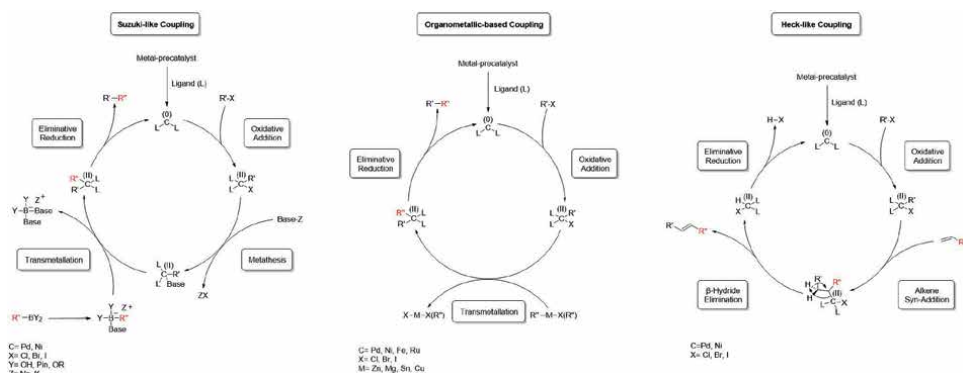


Figure 4.
General scheme of the most common cross-coupling reactions.

acts as a molecular dispersant for the Pd-based catalyst. Remarkably, this addition permitted acceleration the process, resulting even in a quantitative conversion of the starting material when 1,5-COD (1,5-cyclooctadiene) was employed. Additionally, the feasibility of solvent-free solid-state synthesis of large polyaromatic hydrocarbons was demonstrated, including the successful application of this mechanochemical methodology on a gram scale.

The potentiality of the Suzuki coupling was then increased by Browne and collaborators in 2022 when they suggested the replacement of an expensive palladium catalyst with a cheaper and more earth-abundant nickel-based one [72, 73]. This substitution required a different setup compared to a common ball-milling reaction due to the necessity of heating the reaction mixture. For this purpose, a controllable jar-heating apparatus was used, composed of a Proportional-Integral-Derivative (PID) controller and interchangeable band heaters with internal thermocouples. The precise control of the reaction temperature assured not only the performance of the process but also the high reproducibility of the methodology. Lastly, the procedure was even scaled up through a double screw extruder demonstrating how the protocol was highly performing and highly sustainable.

Another relevant breakthrough was described by Iaroshenko when he revisited the Suzuki cross-coupling by running it with a Ru-based catalyst and using a phenol as substrate under solid-state conditions [74]. The synthesis of various biphenyl derivatives was accomplished under mild reaction conditions using both an arylboronic compound and a trialkoxysilane. The latter approach showed a comparable potential of this methodology even for a Hiyama-like coupling [75]. For concluding, the synthesis of benzophenone derivatives was analysed by reacting potassium benzoyl-trifluoroborates with phenols. In this case, it was necessary the presence of ZrN along with a second piezo additive like BaTiO₃ leading to a high-performing protocol for the synthesis of benzophenones.

2.2.2 Negishi reaction

The Negishi coupling is a palladium- or nickel-catalysed cross-coupling reaction that forms carbon-carbon bonds between organozinc reagents and organic halides or pseudohalides [76–79]. This reaction is highly versatile and widely used due to the mild and selective nature of organozinc reagents, which tolerate various functional groups and minimise side reactions [80]. However, performing the Negishi reaction is somewhat under-utilised due to the absence in the commerce of organozinc reagents [80]. Moreover, their preparation is generally tedious, further complicating the applicability of the methodology. All these methods require an inert atmosphere, and those which exploit zinc metal are highly dependent on the physical form of zinc used [81, 82]. Therefore, a mechanochemical approach for these strict requirements has been envisaged by Browne and co-workers, who proposed the use of Zn (20–30 mesh, granular) in the presence of a stoichiometric amount of dimethylacetamide (DMA) for preparing the organozinc compound [83]. This species was then made to interact with a haloaryl derivative to obtain the C-C coupling product. The possibility of running the reaction through a one-step approach was shown to be feasible as well, avoiding the handling of an organozinc derivative.

A variant version of the Negishi reaction was proposed later by Sebesta, who employed organozinc pivalates [84]. These organometallic compounds can be conveniently prepared and handled in air, and they are also suitable partners in Pd and Co-catalysed cross-coupling reactions. Consequently, an entire methodology has been

proposed allowing the straightforward application of the Negishi reaction on these substrates.

2.2.3 Sonogashira reaction

The Sonogashira reaction is a palladium-catalysed cross-coupling reaction that forms C-C bonds between terminal alkynes and aryl or vinyl halides, often using a copper(I) co-catalyst [85–87]. This reaction is widely used for the synthesis of conjugated systems, such as alkynes, enynes, and aromatic compounds, which are important in pharmaceuticals, materials science, and natural products [88, 89]. The first Sonogashira reaction was reported by Mack, who successfully demonstrated its feasibility under high speed ball-milling (HSBM) conditions, allowing the obtainment of a wide range of alkynes [90]. Nonetheless, the reaction worked well only when aryl iodides were employed, whilst bromo, chloro, or fluoro aryl compounds poorly performed. In these specific cases, neither a large excess of acetylene increased the yield. The methodology was then analysed by removing the copper iodide catalyst to verify the robustness of the method. Unfortunately, this modification was revealed to be effective only when copper-made jars and balls were used.

A successful removal of the copper source was presented by the Stolle group, who reported the use of a palladium catalyst combined with a base like 1,4-diazabicyclo[2.2.2]octane (DABCO) [91]. The procedure, based on a planetary ball mill, was successfully applied to both alkynes and bis-ethynyl derivatives. The replacement of DABCO with sterically hindered bases like triphenylamine or tribenzylamine did not make any reaction begin leading to the hypothesis that the base is intermittently coordinated to the catalyst. Nevertheless, an acetylene–DABCO adduct was not detected in the reaction mixture, probably because of the formation of an adduct with HI (DABCO·HI) generated *in situ*. A rather valuable outcome was obtained when the Sonogashira reaction was performed in the presence of copper iodide (I), CuI, as a co-catalyst. Surprisingly, the conversion decreased by 10% due to the increasing formation of the homocoupling product in the reference process (glaser reaction) [92].

The use of the milling material as active catalysts for the Sonogashira reaction was taken again under analysis by Borchardt in 2023 [93]. This concept is referred to as direct mechanocatalysis, and it offers the advantage that the catalyst can be easily separated and, consequently, recovered from the reaction mixture. Precious metals like palladium are scarce and laborious to recycle, so it was proposed to use palladium milling balls as the active catalyst [94]. However, the high cost of this apparatus suggested their replacement with electroplated steel balls, which performance was shown to be almost comparable even after some reaction cycles. Furthermore, it was investigated the role of all the reaction components through powder-X-ray diffraction (*p*XRD), X-ray photoelectron spectroscopy (XPS), and Raman spectroscopy. The data collected permitted description of the complex between DABCO, triphenylphosphine, CuI, and the alkyne, shedding light on the role of the components during the process.

2.2.4 Heck reaction

The Heck reaction is a palladium-catalysed cross-coupling reaction between an aryl or vinyl halide and an alkene, leading to the formation of a substituted alkene [95–98]. This reaction is widely used in organic synthesis due to its ability to construct carbon-carbon bonds in a regioselective and stereoselective manner. The catalytic cycle is a bit different from the ones reported for the other procedures. It involves the

oxidative addition of the aryl or vinyl halide to the palladium catalyst, coordination and insertion of the alkene, and a β -hydride elimination step that regenerates the catalyst and forms the product [99, 100].

The methodology for this kind of coupling usually involves extensive reaction times in hot dimethylformamide (DMF), followed by an extractive workup and a chromatographic separation to remove excess olefin [95]. Therefore, a suitable ball-milling approach was suggested by Frejd in 2004 by functionalising protected aminoacrylates [101]. A key ingredient of this mixture was found in the quaternary ammonium salt Bu_4Cl due to its supposed ability to act as ionic liquids in the molten state, enhancing the stability of the catalyst. Remarkably, the use of sodium formate was rather important, as well for reducing the palladium species to the zero state. Notwithstanding, the most relevant concept of this work is the comparison with the model studies run using in-solution and microwave approaches. Essentially, it is not sufficient to simply heat the reaction mixture in a stirred or unstirred vessel or to apply a static pressure to have comparable results. Instead, it was demonstrated that the combination of pressure, heat, grinding, and stirring provides the conditions necessary for the successful outcome of the reaction.

An interesting application of the power of mechanochemistry was described by Yu, who defined a solvent-free oxidative coupling of phenylboronic acid with olefins using polysaccharides for running a Polymer-assisted grinding (POLAG) procedure under an oxygen atmosphere [102]. These were commercial cyclodextrins (CDs), which were able to influence the selectivity of the Heck reaction by exploiting the interaction between the olefin and the cavity of the CD [103]. The study was, hence, extended to various CDs for understanding the importance of their structure in altering the reaction pathway. From this, it was understood how the reactivity and selectivity of the POLAG reaction are highly connected to the matching of the cavity size of the CD and the substrate. For the peculiar cases analysed in this work, α -CD was the most performing for acting on the small molecules chosen for the scope.

2.3 Metathesis

Metathesis, or olefin metathesis, is a catalytic chemical reaction in which carbon-carbon double bonds are broken and reformed in a rearranged manner, resulting in the exchange of substituents between alkenes [104–106]. This process is mediated by transition metal carbene complexes, with ruthenium-based Grubbs catalysts and molybdenum- or tungsten-based Schrock catalysts being the most notable and widely used examples [107, 108]. Various forms of metathesis reactions have been developed to address different synthetic challenges, including ring-closing metathesis (RCM), cross-metathesis (CM), ring-opening metathesis (ROM), and ring-opening metathesis polymerisation (ROMP) (**Figure 5**). The broad applicability of metathesis is further enhanced by its high atom economy and functional group tolerance, which allow for the efficient synthesis of both small molecules and complex macromolecules.

The first mechanochemical metathesis was reported by Friscic in 2015, who described the potential and general application of mechanochemistry to such a process [109]. Reactions involving the metathesis of neat liquids occurred readily, provided that steel-based equipment was avoided. However, the metathesis of solid substrates posed challenges, which were effectively addressed using straightforward methodologies without requiring modifications to commercial catalysts. Systematic screening of catalytic liquids and solid auxiliaries provided valuable insights into the reactivity of these substrates under solid-state conditions. Importantly, replacing

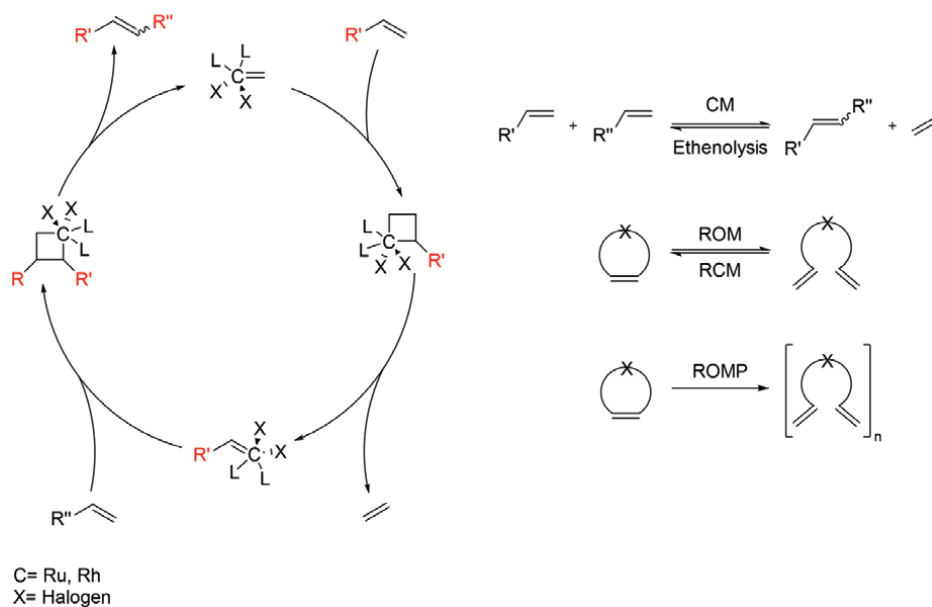


Figure 5.
 General metathesis reaction mechanism along with the typical reactions run.

bulk toxic organic solvents with inert and environmentally benign solid auxiliaries, such as NaCl, significantly enhances the appeal of mechanochemical approaches. This shift holds great promise for minimising the environmental impact of organic processes.

A comprehensive investigation of the Ring-Opening Metathesis Polymerisation (ROMP) approach was carried out by the same research group in 2022 [110]. In their study, Ru-alkylidene catalysts were employed under ball-milling conditions, enabling the successful synthesis of polymers, including those with units that are typically insoluble using conventional synthetic methods. Regarding chain degradation during the grinding process, it was hypothesised that mechanical action predominantly drives the chain scission process. To address this challenge, the potential benefits of Liquid-Assisted Grinding (LAG) were explored. Remarkably, the use of dichloroethane (DCE) not only facilitated chain protection but also enabled rapid polymer initiation. Through a series of control experiments, the researchers demonstrated that LAG not only minimised chain scission but also improved material dispersion, enhancing polymerisation activation driven by the grinding process. This dual effect underscores the significant potential of LAG in optimising ROMP under mechanochemical conditions.

All relevant mechanochemical procedures are compared with analogous methods reported in the literature, as summarized in **Table 1**.

3. Heterocycles synthesis

Heterocycles are an integral class of organic compounds containing at least one atom other than carbon within a cyclic structure, typically nitrogen, oxygen, or sulphur. These compounds are ubiquitous in nature and play a pivotal role in a wide

Reaction	Temperature	Atmosphere	Steps required	Time	EF or PMI	Yield	Purification	Ref.
Grignard ^a	RT	Ambient	2	60 + 60	/	93%	Chromatography	[58]
	60 + 0	Argon	2	180 + 30	/	84%	Chromatography	[53]
Suzuki ^b	RT + 63 + 100	Ambient	1	10 + 10 + 10	18.59	87%	Chromatography	[72]
	180	Argon	2	10	42.77	93%	Chromatography	[69]
Negishi ^c	RT	Ambient	2	240 + 240	/	95%	Chromatography	[83]
	0 + 70	Argon	2	30 + 1200	/	91%	Chromatography	[79]
Sonogashira ^d	RT	Ambient	1	90	/	94%	Filtration	[93]
	120	Ambient	1	960	/	100%	Filtration	[111]
Heck ^e	RT	Oxygen	2	30	4.23	72%	Chromatography	[102]
	RT	Ambient	1	20	/	77%	Chromatography	[98]
Metathesis ^f	RT	Ambient	2	15 + 15	/	97%	Filtration	[109]
	60	Ambient	1	840	/	91%	/	[106]

Each row represents a reaction that was divided into two distinct rows: the upper stands for the mechanochemical procedure, the bottom shows the features of a protocol reported in the literature.

^aValid for the synthesis of diphenyl carbinol.
^bValid for the synthesis of 2-(4-fluorophenyl)naphthalene.
^cValid for the synthesis of [1,1'-biphenyl]-4-carbonitrile.
^dValid for the synthesis of 1,2-diphenylethyne.
^eValid for the synthesis of dodec-1-en-1-ylbenzene.
^fValid for the synthesis of styrene.

Table 1.
Overview of all the reactions described in Section 1.

range of scientific fields, including medicinal chemistry, materials science, and agrochemicals [112–114]. Their unique chemical properties stem from the presence of heteroatoms, which influence the electronic distribution within the ring and offer diverse reactivity patterns [115, 116]. Common examples include pyridine, furan, thiophene, and imidazole, each with distinct chemical and physical characteristics. They also serve as key intermediates in synthetic organic chemistry, enabling the development of more complex molecules. From a structural perspective, heterocycles can be classified as aromatic or non-aromatic, depending on the conjugation and electron distribution in the ring, and as three-, four-, five-, or six-membered based on ring size.

By being so relevant in all these fields, heterocycles have been widely synthesised through various methodologies as listed below.

3.1 Azaheterocycles

Azaheterocycles are a class of heterocyclic compounds containing one or more nitrogen atoms within their ring structure. These nitrogen atoms replace one or more carbon atoms in the ring and contribute to the diverse chemical and biological properties of the compounds [117]. Their importance arises from their roles in forming hydrogen bonds, acting as electron donors or acceptors, and modulating electronic properties, which makes them critical scaffolds in drug design and chemical development.

3.1.1 5-membered rings

One of the most relevant procedures for the synthesis of aza-5-membered rings under mechanochemical conditions was reported by Stolle, who described the obtainment of 1,4-substituted-1H-1,2,3-triazoles through a click reaction [118]. The methodology was based on a planetary mill, which smoothly allowed the onset of the reaction by using an azide and an alkyne in the presence of copper acetate. Moreover, the approach was applied to the polymerisation of a bis-alkyne allowing the successful formation of the polymer under mild reaction conditions.

A following discovery was reported by Rousseau and colleagues, who prepared various pyrroles by using a Paal-Knorr approach under mechanochemical conditions [119]. The novelty in using solid biosourced “green acids” permitted a further increase in the sustainability of the methodology. In this framework, the most eligible acidic source was found in citric acid, which demonstrated to positively influence the reaction outcome even with a loading of 1 mol%.

3.1.2 Fused system

The high versatility of nitrogen in forming heterocycles has been widely analysed in mechanochemistry through the preparation of various fused heterocyclic systems. A relevant contribution to this field has been made by Bolm when he reported the synthesis of indoles through the coupling of acetanilides and alkynes [120]. This has been set-up by using a rhodium-based catalyst, which possesses both the ability to activate specifically acetanilides and the possibility of running an oxidative coupling with alkynes. With such a powerful action, it was possible to straightforwardly obtain the desired products under mild reaction conditions. With regards to the additional modification of the heterocycle formed, it was demonstrated that the possible

removal of the acetyl group from the nitrogen moiety by milling the substrate with only two equivalents of KOH.

Subsequent advancements in the synthesis of indoles were suggested by Porcheddu and co-workers, who established the mechanochemical version of the Fisher synthesis [121]. Effective generation of indole-based compounds employing this reaction usually requires strong acids in organic solvents (toluene, xylene, DMF, THF, etc.) at elevated temperatures (up to 200°C) in the presence of acidic catalysts [122, 123]. Consequently, a more sustainable approach based on a combination of oxalic acid and dimethyl urea in the presence of acetic acid as a liquid additive. Once the conditions were optimised for selectively converting the hydrazine to the corresponding indole, the purification of the mixture was then run by precipitating the heterocycle in water. Besides the preparation of these derivatives, it was also detailed the interrupted Fischer indolisation, that is, the most widely used approach to prepare the indolenine scaffold [124]. In this case, the indolenines generated were successively reduced *in situ* to the corresponding indolines, showcasing the huge potential of mechanochemistry in the synthesis of these backbones.

The progressive interest in the synthesis of aza-heterocycles was then finally established by Porcheddu's group when it proposed the preparation of 2-aryl benzimidazoles under solid-state conditions (**Figure 6**) [125].

For this purpose, it was employed a modified version of aldehydes, such as their bisulphite adducts (also known as Bertagnini's salts) [126, 127]. These derivatives showed significant advances compared to carbonyl compounds due to their higher stability and lower volatility. Moreover, they selectively formed the desired aza-heterocycles without stopping the process at the formation of the intermediate imine, permitting a more performing purification process [128]. Apart from benzimidazoles, the synthesis of tricyclic scaffolds was investigated as well. These were dihydroperimidines, perimidines, and spiroperimidines. Remarkably, the preparation of perimidines was possible only by heating the reaction mixture to 70°C. At this temperature, it was possible to preserve the integrity of Bertagnini's salt, avoiding its decomposition to the corresponding aldehyde. Any other approach based on the employment of an oxidant, instead, failed due to the compromise of both the bisulfite adduct and the 1,8-diamino naphthalene. Lastly, the synthesis of the spiro derivatives was accomplished by reacting 1,8-diaminonaphthalene with the bisulphite adduct of cyclic ketones under mild and sustainable conditions.

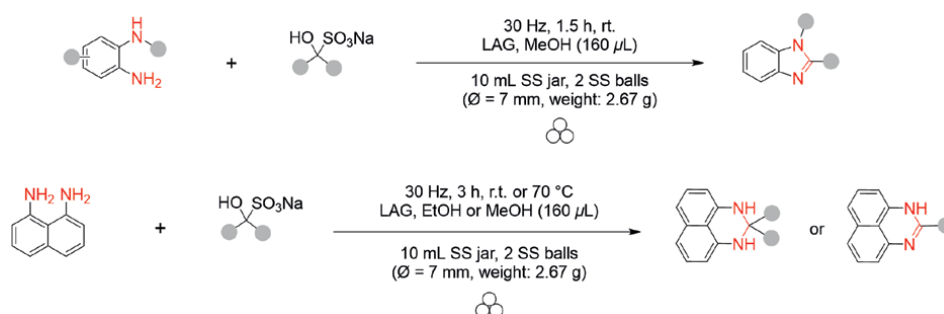


Figure 6.
General procedure reported for the synthesis of aza-heterocycles from bisulphite adducts of carbonyl compounds (Bertagnini's salts) as described in Ref. [125].

Reaction	Temperature	Atmosphere	Steps required	Time	EF or PMI	Yield	Purification	Ref.
Paal-Knorr ^a	RT	Ambient	1	15	/	71%	/	[119]
	70°C	Ambient	1	60	/	100%	Chromatography	[132]
Fisher-Indole synthesis ^b	RT	Ambient	1	100	42.9	90%	Precipitation in water	[121]
	60°C	Ambient	2	240	79.9	96%	Extraction with DCM	[133]
2-Aryl benzimidazole synthesis ^c	RT	Ambient	1	90	30.46	72%	Recrystallisation	[125]
	RT	Ambient	1	240	311.06	99%	Chromatography	[134]
Gewald ^d	RT	Ambient	1	1440	/	41%	Chromatography	[129]
	RT	Ambient	3	2400	/	43%	Chromatography	[131]

Each row represents a reaction that was divided into two distinct rows: the upper stands for the mechanochemical procedure, the bottom shows the features of a protocol reported in the literature.

^aValid for the synthesis of 1-benzyl-2,5-dimethyl-1H-pyrrole.

^bValid for the synthesis of 2,3,4,9-tetrahydro-1H-carbazole.

^cValid for the synthesis of 2-(4-chlorophenyl)-1H-benzo[d]imidazole.

^dValid for the synthesis of ethyl 2-amino-4-phenylthiophene-3-carboxylate.

Table 2.
Overview of all the reactions described in Section 2.

3.2 Sulphur-based heterocycles

Sulphur heterocycles are heterocyclic compounds containing sulphur atoms within their ring structures, which often replace one or more carbon atoms. These compounds exhibit unique chemical, physical, and biological properties due to the sulphur atom's electron-donating and polarizability characteristics. They are key structural motifs in many bioactive molecules, such as antibiotics and anti-inflammatory agents, and are essential for developing pharmaceuticals, agrochemicals, and functional materials.

Following this line, Mack reported in 2014 the mechanochemical Gewald reaction by using high speed ball-milling (HSBM) [129]. The Gewald method involves the reaction of ketones, aldehydes, or 1,3-dicarbonyl species with activated nitriles and elemental sulphur in the presence of an amine base [130, 131]. The employment of mechanochemistry was fundamental in this case for avoiding the low solubility of elemental sulphur in organic solvents. The methodology was also run with the use of an oven set at 120°C and an HSBM approach implemented with a heat gun, permitting comparison of these different conditions among each other. This approach definitely laid the ground for future developments in the implementation of heat into milling techniques.

All relevant mechanochemical procedures are compared with similar procedures reported in the literature in **Table 2**.

4. Enantioselective processes

Enantioselectivity is a fundamental concept in chemistry that refers to the preferential formation of one enantiomer over another in a chemical reaction [135, 136]. Enantiomers are chiral molecules that are non-superimposable mirror images of each other and often exhibit dramatically different biological, physical, and chemical properties. Enantioselectivity is crucial in fields such as pharmaceuticals, agrochemicals, and material sciences, as the activity, efficacy, and safety of chiral compounds can vary significantly between enantiomers [136–138]. The measure of enantioselectivity is typically expressed as the enantiomeric excess (ee), representing the proportion of the desired enantiomer relative to the racemic mixture. Achieving high enantioselectivity often relies on asymmetric synthesis, which involves the use of chiral catalysts, reagents, or auxiliaries to guide the reaction towards the formation of one enantiomer [139, 140]. The development of enantioselective processes is a major focus in modern chemistry, driven by the demand for single-enantiomer drugs and precision in material properties.

The impressive advances achieved in asymmetric organocatalysis made chemists envisioning how these procedures could benefit from the inherent solvent-free conditions of the ball-milling technology. An initial approach was proposed by Bolm in 2006, who analysed the proline-catalysed intermolecular aldol reaction for affording products with high chemo- and stereoselectivity through a C-C coupling (**Figure 7**) [141]. Any problem concerning the solubility of these derivatives (which generally require high polar solvents like dimethylsulfoxide (DMSO)) was smoothly avoided through the employment of a mechanochemical solvent-free approach [142]. By employing this technique, anti-aldol products were synthesised with excellent stereoselectivities (up to >99% ee). Moreover, a comparative study using conventional magnetic stirring revealed the beneficial effect of ball-milling, significantly accelerating the analysed processes.

Another relevant field of enantioselective reactions concerns the preparation of chiral propargylamines due to their high versatility as synthetic intermediates and for their recurrence as important biological substructures [143–145]. Unfortunately, their preparation relies on expensive and air-sensitive Cu(I), and it can be significantly influenced by the solvent chosen. Therefore, Su and his co-workers proposed running this reaction under mechanochemical conditions, showcasing the feasibility of using Cu(OTf)₂ combined with Ph-pybox (a ligand containing a pyridine-oxazolidine scaffold) [143]. Additionally, it was rationalised that its recovery from the reaction mixture as well permit running five consecutive cycles without relevantly affecting the reaction outcome.

A next step towards more performing processes has been reported by Mack in 2019 [146]. By being sensitive to the reaction temperature, enantioselective processes usually require a correct control of the reaction conditions. Running a reaction through a grinding approach might imply the fluctuation of a set of data, therefore, the reinvestigation of these processes through using a Spex8000 apparatus, thermostated, was taken under analysis for a unique control of both temperature and frequency applied [147]. Apart from thoroughly investigating previous procedures, the role of frequency on a Diels-Alder reaction was also studied by demonstrating the exponential frequency effect on the reaction yield.

An advancement in this field was presented by Juaristi in 2019 by analysing the stereoselectivity of an aldol reaction when a dipeptide was employed as a catalyst

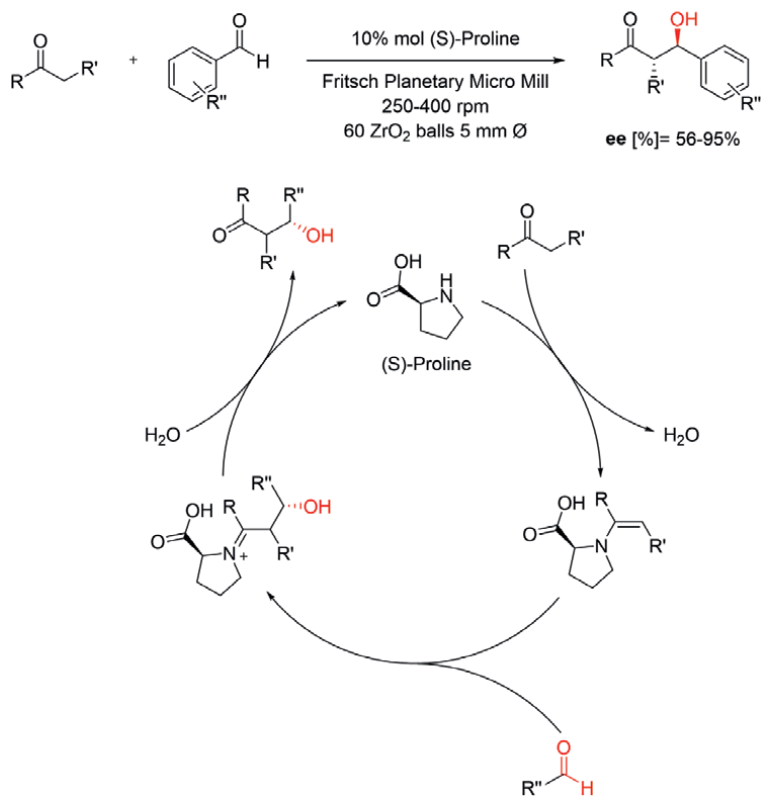


Figure 7.
Overview of the procedure and reaction mechanism adapted from Ref. [141].

Reaction	Temperature	Atmosphere	ee%	Time	EF or PMI	Yield	Purification	Ref.
Proline catalysis ^a	RT	Ambient	94%	330	/	99%	Chromatography	[141]
	RT	Ambient	94%	5760	/	98%	Chromatography	[141]
Chiral Propargylamine ^b	RT	Ambient	99%	30	/	99%	Chromatography	[143]
	RT	Ambient	94%	900	/	98%	Chromatography	[145]
Chiral reduction of carbonyls ^c	RT	Ambient	93%	60	/	98%	Chromatography	[155]
	70°C	Argon	80%	1440	/	97%	Chromatography	[156]

Each row represents a reaction that was divided into two distinct rows: the upper stands for the mechanochemical procedure, the bottom shows the features of a protocol reported in the literature.

^aValid for the synthesis of (S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one.

^bValid for the synthesis of (R)-N-(1,3-diphenylprop-2-yn-1-yl)aniline.

^cValid for the synthesis of (R)-1-phenylethan-1-ol.

Table 3.
Overview of all the reactions described in Section 3.

[148]. The astonishing results collected from this approach permitted to lay the ground for a new cutting-edge concept of mechanoenzymatic reaction. This concept, already investigated by Gross and Bolm, further enhances the sustainability inherent to these approaches by reducing or completely avoiding the use of solvents, preventing waste generation [149, 150]. The current procedures reported are based on Lipases, Proteases, Cellulases, Glucosyl Hydrolases, Cutinases, PET Hydrolases, and Chitinase [151]. Interestingly, some of these were also run on an extruder, laying the ground for future developments of continuous mechanoenzymatic processes.

Ultimately, it was explored the enantioselective reduction of ketones, which are definitely convenient precursors of chiral alcohols [152]. The reactions were run through a transfer hydrogenation process based on sodium formate, avoiding the employment of hazardous gaseous hydrogen and a gas apparatus [153, 154]. Through this approach, the mechanochemical methodology was run by considering the reduction of acetophenone as a control experiment. Relying on a Ru-TsDPEN catalyst and sodium formate as the hydrogen source, the mechanochemical methodology demonstrated a superior performance compared to the process run in-solution, with Turn Over Frequencies (TOFs) of 139.2 and 134.4, respectively [155]. The screening of the various reaction parameters revealed how the enantioselectivity of the method was rather stable when varying the number and size of the balls and the frequency. Contrarily, the amount of water used as a liquid additive appeared to be critical for a correct performance of the reaction. In conclusion, the protocol was also scaled up to the gram scale, retaining its performance both in terms of yield and enantioselectivity.

All relevant mechanochemical procedures are compared with similar procedures reported in the literature in **Table 3**.

5. Redox processes

In organic chemistry, redox reactions involve changes in oxidation states of carbon atoms, often through the addition or removal of oxygen and hydrogen atoms [157]. Oxidation typically increases the oxygen content or decreases the hydrogen content of an organic molecule, while reduction does the opposite [158]. The tendency of a species to gain electrons is defined by its own redox potential (E°) and is expressed in expressed in volts (V) relative to a reference electrode, typically the Standard Hydrogen Electrode (SHE) at 0.00 V (**Figure 8**) [159, 160].

A more positive redox potential indicates a stronger oxidising agent (higher electron affinity), while a more negative redox potential signifies a stronger reducing agent (greater tendency to donate electrons). Under non-standard conditions, it can be calculated through the Nernst equation, allowing a better understanding of oxidation-reduction reactions involving organic molecules [161]. Common oxidation reactions include the conversion of primary alcohols to aldehydes and then to carboxylic acids (e.g., ethanol to acetic acid *via* acetaldehyde) using oxidants like pyridinium chlorochromate (PCC) (for aldehydes) or KMnO_4 and CrO_3 (for carboxylic acids) [162]. Secondary alcohols oxidise to ketones (e.g., isopropanol to acetone), while tertiary alcohols resist oxidation due to the lack of a hydrogen on the carbonyl carbon [163]. Reduction reactions involve reagents like LiAlH_4 and NaBH_4 , which convert carbonyl compounds to alcohols (e.g., ketones to secondary alcohols, aldehydes to primary alcohols). More extreme reductions, such as catalytic hydrogenation (H_2 with Pd, Pt, or Ni), convert alkenes and alkynes to alkanes and

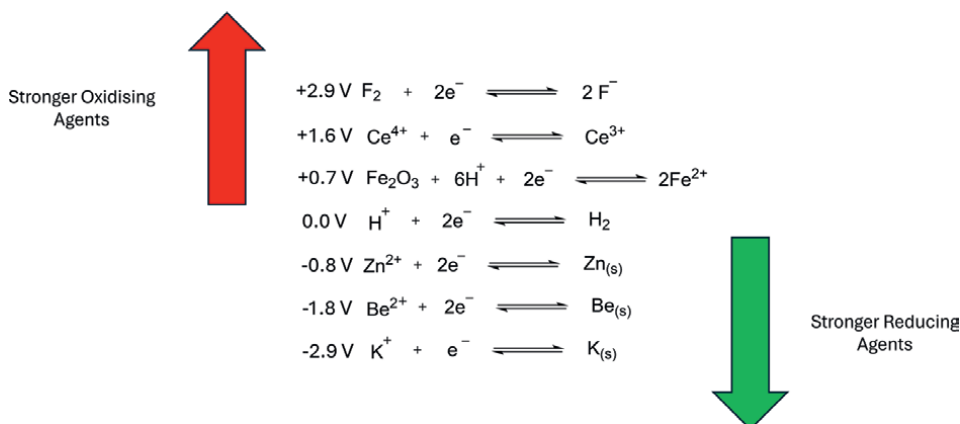


Figure 8.
 Common redox potentials for both reducing and oxidising agents.

nitrobenzenes to anilines [164, 165]. These kinds of processes are also common in biological systems, like in the electron transport chain (ETC) that takes place inside mitochondria or in the metabolic reaction catalysed by the coenzymes NAD^+/NADH and FAD/FADH_2 [166, 167].

5.1 Oxidations

The starting approaches towards oxidative processes run under solid-state conditions commenced with the analysis of potassium permanganate (KMnO_4) reactivity [168]. Its high redox potential (1.70 V) entitles the oxidation of various organic substrates, resulting even in the rupture of the C-C of cycloolefins, yielding dicarboxylic acids [169]. Having tested different starting components, Nuchter and co-workers demonstrated how the presence of water was crucial during the grinding of organic compounds, KMnO_4 and a grinding auxiliary like aluminium oxide. The presence of this latter compound is supposed to contribute to lowering the local pH due to its interaction with aluminium oxide leading to a faster and more performing process as a whole.

Nonetheless, the release of manganese dioxide (MnO_2) as a by-product raises significant concerns in terms of sustainability due to its high toxicity, if inhaled, for human lungs [170]. A safer choice relies on OXONE®, a peroxymonosulfate-based oxidant with a redox potential comparable to KMnO_4 (1.81 V). It is typically available as a triple salt mixture: $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, which stabilises the active peroxymonosulfate species [171, 172]. This inorganic species was employed in the mechanochemistry field to avoid the typical limits concerning its scarce solubility in organic solvents. By using a grinding approach, the necessity of dissolving OXONE® and the organic substrate decays, allowing for to full exploitation of its potential in organic synthesis. These advantages were employed for coupling aldehydes and amines and forming the corresponding amides [173]. Contrarily to traditional synthetic methods based on activating acid derivatives under stringent reaction conditions, this mechanochemical approach permitted the straightforward obtainment of the desired amide rapidly and under mild conditions. It was also proposed a reaction mechanism ascribable to two possible different pathways both based on the initial nucleophilic addition of the amine on the carbonyl moiety.

Subsequent studies on KMnO_4 and OXONE® were run on anilines by chemoselectively oxidising them to the corresponding azo or azoxy homocoupling products using a planetary ball mill [174]. The reaction proved to be tunable towards the formation of all three major oxidation products (azo, azoxy, nitro) by choosing the correct combination of oxidant and grinding auxiliary [175]. Furthermore, the solvent-free method was compared with various in-solution techniques (microwave, in-solution through a round-bottom flask, and ultrasound reactor), displaying superimposable or even more performing results in specific cases. To conclude, the amount of energy required was calculated by several techniques tested for running the model reaction. Surprisingly, the ball-milling methodology needed a lower quantity of electrical supply (expressed in terms of kWh mol^{-1}).

Starting from these concepts, the reactivity of anilines was further investigated for selectively synthesising nitrosobenzenes as reported by Friscic [176]. These were recovered from the crude reaction mixture through sublimation due to their high vapour pressure. The approach was applied to anilines bearing both electron donating groups (EDGs) and electron withdrawing groups (EWGs), with the latter ones being less reactive. Unfortunately, some specific anilines were themselves characterised by high vapour pressure, which resulted in their presence in the recovered sublimate as impurities. With the discoveries reported in this last study, the true potential of OXONE® was finally disclosed as a powerful and performing oxidant under ball-milling conditions.

An interesting application of an oxidative approach based on OXONE® was described by Cravotto in 2012, who applied this optimised procedure to different sulphides for then moving to the desulphurisation of medium to high sulphur content paraffins [177, 178]. The procedure proved to be highly selective towards the formation of the corresponding sulfone without presenting any trace of sulfoxides. Moreover, it was attempted to recycle the excess of oxidant employed, showing how the recovery is feasible up to three consecutive cycles. The approach was also analysed through the employment of Reactive Extrusion (REX) for pushing beyond the limits of a typical ball-milling approach. With its ability to integrate heat and mass transfer with chemical reactions, REX enables the modification of the reacting materials' properties, offering a powerful platform for running challenging chemical transformations.

5.2 Reductions

Initial investigations of reducing approaches were conducted by Mack in 2007, when he established a procedure for converting carbonyl derivatives to primary and secondary alcohols, and esters to primary alcohols, through the use of HSBM [179]. In the first case, aldehydes showed a greater reactivity, allowing the formation of the corresponding alcohols in only 1 hour. Ketones, instead, required a total amount of 6 hours to perform results. In the latter method, it was defined a remarkable approach was defined, based on the formation of a strong reducing agent like LiBH_4 , whose preparation is expensive and cumbersome, by using NaBH_4 and LiCl as precursors [180]. This reducing species enabled the reduction of esters to primary alcohols in moderate to high yields, demonstrating how the use of mechanochemistry effectively circumvented the common drawbacks associated with this transformation. However, the reduction of esters still required long reaction times of approximately 16 hours, highlighting the need for further investigation into both the genesis of LiBH_4 and the overall redox process within the mechanochemical framework.

The following progress was done on the employment of another common reducing agent like NaBH_4 [181, 182]. This reagent is weaker compared to LiAlH_4

and LiBH_4 ; therefore, it is generally employed for the selective reduction of carbonyl moieties in the presence of groups like esters, amides, or nitriles. The tedious workups and low regioselectivity that sometimes affect the in-solution approach were smoothly avoided in the solvent-less procedure presented by Kaupp [183]. This approach revealed a high performance through a neat grinding approach, resulting in the direct synthesis of various alcohols from both aldehydes and ketones. Furthermore, the use of a solvent-less technique permitted to recovery and characterise the sodium tetralkoxyborates generated from the reaction. These showed a relevant stability in a dry box and can also be converted to the corresponding alcohol by decomposing them with water.

In conclusion, it was analysed the reduction of nitrobenzenes by Porcheddu et al. [175]. The purpose of their investigation was the conversion of a nitro aryl moiety to the corresponding amine without employing a metal source [184]. This redox process is generally conducted under acidic conditions due to the high reactivity of the intermediates formed, namely nitrosobenzenes and *N*-phenylhydroxylamine. The acid employed plays a key role because it harshly reduces the nucleophilic of *N*-phenylhydroxylamine, avoiding the coupling between these two species that will lead to the genesis of diazoproducts. Notably, the solvent-less approach was based on a stoichiometric redox reagent like thiourea dioxide (TDO), an oxidised derivative of thiourea generally employed industrially for bleaching processes [185]. Its reducing properties are based on the release of sulfoxylic acid formed from the decomposition of TDO in a strong basic environment due to the addition of sodium hydroxide. Apart from specific cases where the use of this strong base altered the reactivity of the starting material (like in the presence of phenolic moieties), the course of the reaction was not negatively affected, permitting to straightforward synthesise the desired products. Moreover, the possibility of analysing the effect of solvents on the reactivity of TDO was demonstrated by mechanochemistry. When a LAG of water was employed, its conversion to its more reactive tautomer aminoiminomethansulfonic acid (AIMSA) took place, permitting to finally apply the concepts previously proposed to an organic process [186, 187].

All relevant mechanochemical procedures are compared with similar procedures reported in the literature in **Table 4**.

Reaction	Temperature	Atmosphere	Steps required	Time	Yield	Purification	Ref.
Amides synthesis ^a	RT	Ambient	1	90	78%	Chromatography	[173]
	RT	Ambient	4	20	98%	Chromatography	[152]
Reduction of carbonyls ^b	RT	Ambient	2	10	99%	Aqueous workup	[183]
	RT	Hydrogen	1	480	100%	Chromatography	[188]
Thiourea Dioxide reduction ^c	RT	Ambient	1	120	97%	Filtration	[175]
	100°C	Hydrogen	1	90	100%	Chromatography	[184]

Each row represents a reaction that was divided into two distinct rows: the upper stands for the mechanochemical procedure, the bottom shows the features of a protocol reported in the literature.

^aValid for the synthesis of 4-Nitro-*N*-*p*-tolylbenzamide.

^bValid for the synthesis of benzyl alcohol.

^cValid for the synthesis of aniline.

Table 4.
Overview of all the reactions described in Section 4.

6. Biomolecules and drugs

Biomolecules and drugs are fundamentally interconnected, as biomolecules form the basis of life while drugs interact with them to influence biological functions. Biomolecules, including carbohydrates (energy storage like glucose), proteins (enzymes, hormones, structural roles like haemoglobin), lipids (energy reserves, membrane components like phospholipids), and nucleic acids (DNA and RNA, carriers of genetic information), are essential for life processes. Drugs, on the other hand, are formulations of one or more Active Pharmaceutical Ingredients (API) combined with a bulking agent designed to interact with biomolecules to modify physiological processes for therapeutic purposes [189].

The huge interest in preparing these derivatives in a less-impacting manner sparked the interest of several industries bringing them to both establish collaborations with various universities and start their own research in such a field. Part of this relevant topic was investigated through mechanochemistry resulting in the proposal of different solvent-free methodologies.

6.1 Biomolecules

The first approach towards the synthesis of compounds of biomolecular interest was reported by Lamaty in 2009 when he proposed the synthesis of various dipeptides and tripeptides under ball-milling conditions [190]. The method was based on the use of urethane-protected α -amino acid *N*-carboxyanhydride (UNCA) derivatives, and the coupling in the presence of NaHCO_3 during the grinding procedure was demonstrated through infrared (IR) analysis and CP/MAS ^{13}C NMR. Further investigations also showed how the process was characterised by zero-order kinetics along with a complete absence of epimerisation of the aminoacidic chain. In the view to prove the potentiality of their procedure, the dipeptide α -L-aspartyl-L-phenylalanine methyl ester (aspartame) was prepared. This derivative is generally employed as an artificial sweetener, and it is considered safe by global health authorities [191]. Notably, its synthesis as a Boc-protected derivative was accomplished in only 1 hour under ball-milling conditions, demonstrating the possible application of the methodology in preparing such a valuable industrial product.

Recently, it was portrayed by Aav the possibility of using biotin as a starting material for forming a Biotin[6]uril scaffold, a water-soluble receptor for anions useful as a sequestrant of toxins and for the controlled drug delivery [192]. The protocol required a ball-milling step of 1 hour, followed by an ageing process at 60°C , allowing a shorter and more performing process compared to what already reported in the in-solution approach. This was made possible by the higher effect exerted by the anion-binding affinity under solid-state conditions, resulting in a boost of the yield of a + 27% compared to the in-solution approach (this accounts for a 64% yield). This phenomenon is rationalised by the absence of anion-solvent interaction due to the solvent-less environment employed. With the aim of proving the synthesis of this macrocycle, the scale-up procedure of Biotin[6]uril was extensively studied for synthesising this product on a scale of 20 grams. This task was finally achieved by the systematic study of the scale-up approach that required moving from a shaker mill to a planetary ball mill. By using this latter set-up, Aav succeeded not only in scaling up the process (20 grams scale with 92% isolated yield) but also in reducing the milling time to a total of 30 minutes due to the higher energy input of the planetary mill.

6.2 Active pharmaceutical ingredients (APIs)

One of the preliminary purposes for the synthesis of APIs was reported by Lamaty in 2012 by giving an overview of the formation of amide bonds [193]. This kind of chemical interaction usually relies on the activation of a carboxylic acid by converting it to an acyl chloride or an ester, followed by the reaction with the desired secondary or primary amine. However efficient, this double-step methodology suffers from various downsides, such as the necessity of activating the carboxylic acid with toxic agents and harsh reaction conditions [194–196]. Therefore, a more sustainable route was proposed by using *N,N'*-carbonyldiimidazole (CDI) for improving the acid reactivity and making the reaction procedure proceed smoothly to the obtainment of the corresponding amide. The sustainability behind the possibility of recovering the pure product in high yield and without further purification steps spurred the interest in establishing the synthesis of a pharmaceutical scaffold with such a technique. So, it was taken under analysis the preparation of Teriflunomide, a drug promoted by the Food and Drug Administration (FDA) for the treatment of multiple sclerosis [197]. Impressively, the desired amide was rapidly prepared, and it was converted to the Teriflunomide scaffold after treatment with a 1 N solution of aqueous HCl for opening the isoxazole ring.

A methodology proposed in the following years by Friscic and collaborators permitted the synthesis of sulfonylureas under mild reaction conditions [198]. These compounds are commonly used for the treatment of type-2 diabetes and inhibitors of Interleukin-1 β and are generally synthesised by coupling the sulphonamide with an isocyanate either in the presence of a base or through a catalytic approach [199, 200]. This latter methodology requires long reaction times (up to 24 hours) and the use of noxious solvents such as *N*-methyl pyrrolidone. Therefore, the use of a catalyst for coupling the sulphonamide with the isocyanate was proposed under ball-milling conditions, leading to astonishing results even by running the process for only 2 hours [201]. The best results were achieved with a 5% loading of CuCl and by adding nitromethane as a liquid additive. With such an effective procedure, it was also possible to set-up the synthesis of Tolbutamide and Chlorpropamide, which are first generation sulfonylureas. Beyond these scaffolds, it was even possible to prepare Glibenclamide by first synthesising the amidic intermediate that will then undergo the coupling with the isocyanate. All these steps were done under a solid-state environment, showcasing the promising effect exerted by the grinding of the reagents.

Lamaty et al. dedicated part of their research also to the synthesis of hydantoins, drugs for the treatment of seizures [202]. By employing a planetary ball mill, they proved how the ureas deriving from α - and β -amino acids (synthesised from the reaction between the amino acid and potassium cyanate (KOCN) under solid-state conditions) can be easily cyclised to the corresponding 5- and 6-member rings, respectively. In both steps of the procedure, mechanochemistry demonstrated how it could beneficially affect the reaction outcomes by reducing the reaction time, increasing the yields, requiring milder reaction conditions, and lowering the waste associated with the process. After having optimised the reaction conditions, the possible cyclisation of diphenyl glycine was investigated for proposing the synthesis of a compound of pharmaceutical interest, such as phenytoin (also known as Phenytek or Dilantin) [203, 204]. TMS-NCO has been used as a source of isocyanate due to the low reactivity of KNCO in this specific process, permitting the obtainment of urea intermediate that was then cyclised by treating it with caesium carbonate and then ammonium chloride. For completeness, it was analysed the reactivity of benzil as historically reported by Biltz for preparing phenytoin. Unfortunately, the approach was not efficacious for its synthesis, with only a 10% yield recovered.

The necessity of developing more sustainable processes towards the preparation of APIs under ball-milling conditions continued to evolve up to proposing the concept of “Medicinal Mechanochemistry” [36]. With this term, Porcheddu and co-workers introduced the solid-state synthesis of two scaffolds 5,5-disubstituted hydantoin-based: Nitrofurantoin (an antibacterial agent) and Dantrolene (a muscle relaxant) [205, 206]. Both contain an arylhydrazone moiety that generally requires toxic solvents and harsh reaction conditions for preparation in-solution [207]. The mechanochemical set-up, instead, demonstrated a significant improvement of the conditions required, resulting in a quantitative conversion to the desired scaffolds. By exploiting different ball-milling techniques, it was then seen how the use of the SPEX8000 was the most performing with quantitative reactions running between 15 and 120 minutes. Ultimately, the green metrics were calculated for both the reported in-solution approaches and the mechanochemical technique, demonstrating how the process mass intensity (PMI) was massively lower when the latter setup was used. The high performance described in this approach was then further developed in the successful scale-up synthesis of these pharmaceutical derivatives through the employment of the twin-screw extruder [208]. A twin-screw extruder is a high-performance processing machine that consists of two intermeshing, co-rotating or counter-rotating screws housed within a barrel, which facilitate the efficient mixing, compounding, and extrusion of materials [209, 210]. It offers enhanced control over shear, temperature, and pressure, leading to superior material homogeneity and processing flexibility compared to single-screw extruders. Concerning possible issues associated with the preparation of these derivatives, they were thoroughly analysed, and it was demonstrated that they were not relevant for the correct progress of the reaction. One of the most important was the release of gaseous HCl from the reaction environment, which has high corrosivity and toxicity might be a problem on a bigger scale. If a substantial amount of HCl is generated, the extruder is fitted with gas vents along the barrel, allowing the gas to exit through an airtight connection and be directed to a basic aqueous solution for a safe neutralisation of this acidic component.

Another ubiquitous moiety in various pharmaceutical products is surely the amide bond due to its high resistance to hydrolysis and its inner ability to form hydrogen bonds. Apart from the various reported methodologies, the direct amidation of esters is probably one of the most performing in terms of atom economy and generation of waste [211]. This was the object of research of Browne, who successfully described the

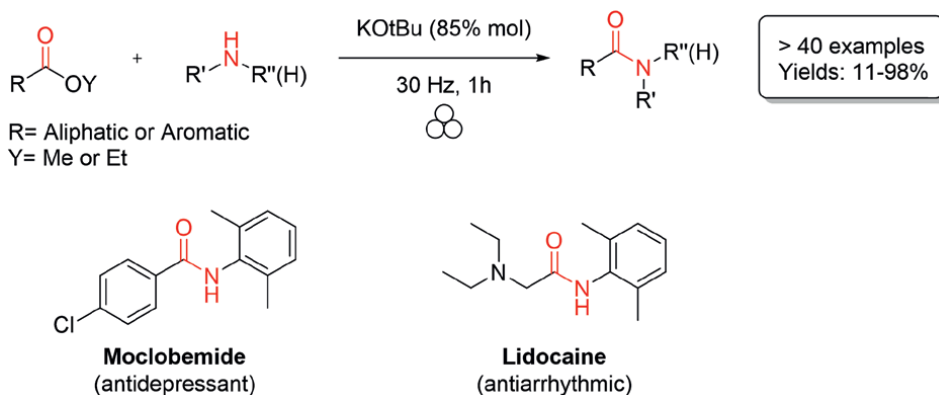


Figure 9.
General overview of the procedure reported in Ref. [212].

Biomolecule or API	Pharmaceutical Class	Temperature	Steps required	Time	EF or PMI	Yield	Purification	Ref.
Teriflunomide ^b	Multiple sclerosis	RT	2	325 + 1440	/	81%	Precipitation	[193]
		35 + 0	2	240 + 240	/	91%	Precipitation	[196]
Tolbutamide	Blood-glucose-lowering drug	RT	1	120	/	92%	Formation of a complex	[198]
Phenytoin ^c	Anti-seizure medication	RT	2	1260	/	85%	Precipitation	[201]
		RT	3	600 + 30	/	84%	Precipitation	[202]
		70	3	120	/	88%	Chromatography	[219]
Dantrolene ^d	Muscle relaxant	RT	1	120	1.30	90%	Filtration	[36]
Moclobemide ^e	Antidepressant	RT	1	60	240	96%	Filtration	[207]
		RT	1	60	/	92%	Chromatography	[212]
Paracetamol ^f	Analgesic	110	1	60	/	100%	Aqueous workup	[211]
		RT	2	75	20	93%	Filtration	[213]
		80 + 50	2	60	43	74%	Filtration	[220]

Each row represents a reaction that was divided into two distinct rows: the upper stands for the mechanochemical procedure, the bottom shows the features of a protocol reported in the literature.

Table 5.
Overview of all the reactions described in Section 5.

synthesis of various amides by reacting esters with amines in the presence of KOtBu under mechanochemical conditions [212]. The mechanochemical set-up was applied to a wide range of esters, enabling the synthesis of Moclobemide (an antidepressant), Lidocaine (an anaesthetic), along with several other amides (**Figure 9**). Moclobemide was also prepared by using the same methodology on bigger jars, resulting in the straightforward 10-scale-up of this derivative.

The peak in terms of scaling up the synthesis of an API was recently reported by Gremaud, who defined the synthesis of paracetamol using the Bead-Milling Technology [213]. A bead mill is a high-energy grinding and dispersing machine used in industries such as coatings, paints, pharmaceuticals, and nanotechnology for reducing particle size and achieving fine dispersion [214, 215]. It operates by agitating small grinding beads within a chamber using a rotating shaft or discs, which generate shear forces that break down particles either under neat conditions or suspended in a liquid medium. This advanced technique has been employed for preparing paracetamol through a neat grinding approach. The process was divided into two steps: the formation of the oxime and the Beckmann rearrangement to the corresponding amide [216]. The first step was easily optimised by screening the rotor speed and the filling degree of the chamber, resulting in a 96% yield of desired oxime in only 20 minutes of grinding (the rotor speed was set to 4000 rpm). The second step showed the best outcome when the rotor speed was increased to 6000 rpm, allowing a 97% yield calculated through $^1\text{H-NMR}$. In both cases it was analysed the relevance of the material that the beads were made of, and it was seen that zirconia ($\text{ZrO}_2/\text{Y}_2\text{O}_3$) beads demonstrated a higher efficiency compared to the zirconium orthosilicate (ZrSiO_4) ones due to their higher hardness and bulk density. Once the synthesis has been scaled up, it was investigated whether any remains of zirconia or yttria were present in the bulk material. Through the employment of Microwave Plasma-Atomic Emission Spectrometer (MP-AES), it was demonstrated how the levels of these two compounds were below the threshold reported in the U.S Food and Drug Administration (FDA) Q3D(R2) elemental impurities guidance for industry [217]. Any possible formation of polymorphs during the process was investigated as well. From the analyses run through Fourier-Transform Infrared spectroscopy (FT-IR); however, it was detected only the monoclinic I form, the most stable and desired form of paracetamol [218].

All relevant mechanochemical procedures are compared with similar procedures reported in the literature in **Table 5**.

7. Conclusion

In conclusion, mechanochemistry has emerged as a powerful and sustainable approach in organic synthesis, offering unprecedented advantages over conventional solution-based methods. By harnessing mechanical force to drive chemical reactions, this technique enables solvent-free or minimal-solvent processes, reducing environmental impact while enhancing reaction efficiency, selectivity, and scalability. The ability to access new reactivity pathways, improve reaction rates, and facilitate challenging transformations highlights the growing significance of mechanochemistry in modern synthetic chemistry. As advancements in equipment design, reaction understanding, and methodology development continue, mechanochemistry is poised to play an increasingly vital role in green chemistry and the future of organic synthesis.

Acknowledgements

We acknowledge financial support under the National Recovery and Resilience Plan (NRRP), Mission 4, Component 2, Investment 1.1, Call for Tender No. 1409 published on 14. 9. 2022 by the Italian Ministry of University and Research (MUR), funded by the European Union – NextGenerationEU- Project Title: The Second Life of Posidonia Oceanica: Sustainability-guided Isolation and Valorization of its Main Constituents – CUP J53D23014680001- Grant Assignment Decree No. 1064 adopted on 18. 07. 2023 by the Italian Ministry of University and Research (MUR). The financial support of the European Union NextGenerationEU under the National Recovery and Resilience Plan (NRRP) of Ministero dell'Università e della Ricerca (MUR) (Project code PE0000021, CUP no. F53 C22000770007, Network 4 Energy Sustainable Transition, NEST) is acknowledged. Fondazione Banco di Sardegna (FDS) also supported the project financially, which had grant number F73C23001600007.

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Edited by Mohamed Nageeb Rashed

Toxic organic compounds known as persistent organic pollutants (POPs) are resistant to breakdown by biological, chemical, and photolytic processes in the environment. Currently, a significant number of POPs are utilized as industrial chemicals, solvents, medications, and insecticides. POPs bioaccumulate and have an impact on the environment and human health globally due to their persistence. It can spread from one nation to another through wind and water, meaning it can have a significant impact on people and wildlife far beyond the areas where it is used and discharged. According to the UN Environment Programme (n. d.), exposure to POPs has the potential to lead to the following health issues: cancer, allergies, nervous system effects, and Immune system effects. This book, *Persistent Organic Pollutants - Monitoring, Treatment Technologies, and Health Effects*, will gather research and contributions from outstanding experts in the field of persistent organic pollutants. It will appeal to a wide readership from universities and industries. Additionally, readers will obtain updated information on all aspects of POPs.

J. Kevin Summers, Environmental Sciences Series Editor

Published in London, UK

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ISSN 2754-6713

ISBN 978-1-83634-021-8

