sustainable chemistry

MDPI

Review

Chemistry and Health: A Multidimensional Approach

Alcione S. de Carvalho, Iva S. de Jesus, Patrícia G. Ferreira, Acácio S. de Souza, Rafael P. R. F. de Oliveira, Debora O. Futuro and Vitor Francisco Ferreira *

Laboratório de Inovação em Química e Tecnologia Farmacêutica, Programa de Pós-Graduação em Ciências Aplicadas a Produtos para a Saúde, Faculdade de Farmácia, Universidade Federal Fluminense, Niterói 24241-000, Brazil; alcionecarvalho@id.uff.br (A.S.d.C.); ivasouza.quimica@gmail.com (I.S.d.J.); patricia.pharma@yahoo.com.br (P.G.F.); acaciosouza@id.uff.br (A.S.d.S.); rrizzo@id.uff.br (R.P.R.F.d.O.); dfuturo@id.uff.br (D.O.F.)

* Correspondence: vitorferreira@id.uff.br

Abstract: This review explores both the positive and negative impacts of chemistry on society, focusing on the intersection between pharmaceutical, natural, and synthetic chemicals. On the one hand, drugs developed through medicinal chemistry have saved lives, improved people's quality of life, and increased longevity. However, they also pose risks, including fatalities and environmental damage. Pharmaceutical chemistry has revolutionized medical practice by enabling the treatment and cure of fatal or debilitating diseases, significantly contributing to the rise in global life expectancy through the research and development of new bioactive substances. This article also highlights the harmful effects of toxic synthetic substances, which negatively impact human health and the environment, affecting plants, animals, air, water, soil, and food.

Keywords: chemistry and health; medicinal chemistry; pharmaceutical chemistry

Academic Editor: Matthew Jones

Received: 7 November 2024
Revised: 31 December 2024
Accepted: 3 January 2025
Published: 9 January 2025

Citation: de Carvalho, A.S.; de Jesus, I.S.; Ferreira, P.G.; de Souza, A.S.; de Oliveira, R.P.R.F.; Futuro, D.O.; Ferreira, V.F. Chemistry and Health: A Multidimensional Approach. *Sustain. Chem.* **2025**, *6*, 2. https://doi.org/10.3390/suschem6010002

1. Introduction

Chemistry plays a fundamental and complex role in human health [1] across multiple sustainable dimensions, both positive and negative. Although this field was recognized as an exact science between the late 17th and early 18th centuries, influenced by fields like metallurgy and pharmacy, chemistry has impacted the entire course of human evolution through traditional medicine, agriculture, health, and environmental interactions. This ancient relationship with chemistry has not only ensured survival but has also improved human quality of life and increased longevity [2]. Much of the knowledge that has advanced human health was originally discovered by indigenous peoples, each tied to their local biomes. In modern times, this knowledge has been exploited by large corporations without proper rights or compensation, while the original knowledge holders have been displaced or even exterminated [3]. However, their understanding of plants for treating diseases, such as medicinal herbs, has been and continues to be used to cure and alleviate pain, significantly contributing to the increased longevity of humanity.

The use of chemicals dates back to the dawn of civilization, beginning with early hunters and gatherers. From the start, humans exploited chemical compounds found in plants, animals, and ores. Many discoveries of their applications took place by chance or by observing animal behavior during food foraging. Though primitive by today's standards, these substances played a crucial role in the survival and success of the human species.

Archeological discoveries indicate that humans have always sought resources to restore health. One of the oldest records of medicine use is the Ebers Papyrus, an Egyptian document from 1550 B.C. that contains information on 7000 medicinal substances in

800 formulas. Another influential work from the Ancient World is Dioscorides' *De Materia Medica*, which shaped medical practice until the 18th century. In this five-volume work, Pedanius Dioscorides compiled knowledge from his military service in the Roman army, documenting about 600 plants, 35 animal-based drugs, and 90 mineral-based substances [4]. Historical records also highlight the pivotal role Arab physicians played by introducing around 400 new drugs into the medicines used in classical antiquity. Arab contributions to the development of techniques such as distillation, sublimation, crystallization, and filtration, and their application in medicine preparation, are also significant [3,5].

The commercial expansion of humanity into new continents and cultures from the 16th century onwards introduced new health products to Europe and broadened knowledge of previously unknown civilizations [6]. During the Renaissance, the invention of the printing press led to the increased production of books, which helped spread knowledge across the known world. Interest in new products sparked a fascination among botanical and therapeutic research, elevating the status of drug traders. Paracelsus (1493–1541) emerged as a key figure in the history of chemistry, pharmacy, and medicine, credited with introducing internal metal salt therapy, advocating for chemical medications, and emphasizing the importance of laboratories in the preparation of drugs [6].

Humanity experienced a period of great scientific excitement during the 17th and 18th centuries, driven by the contributions of prominent thinkers and scientists. This surge of ideas and innovation led to the invention of critical instruments for scientific progress, such as the telescope, barometer, thermometer, and microscope. These advancements laid the foundation for considerable progress in the following centuries, paving the way for the development of microbiology, vaccine production, and public health initiatives through the hygienist movement [7].

In the early 19th century, chemistry emerged as a central science across various fields, uncovering the intricate structures of natural products that had been used for centuries, such as the alkaloids morphine and quinine, which are still employed in clinical medicine today [8,9]. However, despite these advancements, the preparation of chemically pure substances remained a significant challenge throughout the 19th century.

It was only in the mid-20th century that technological advances and the development of analytical and spectroscopic techniques enabled the large-scale separation and preparation of both natural and synthetic substances, as well as their application in the treatment of various diseases. Each molecule tells a unique, centuries-old story of ancestral knowledge, isolation, identification, and, in some cases, synthesis. Even simple molecules like iodine (I_2), introduced in the 19th century as an antiseptic to clean wounds and prevent infections, have played decisive roles [10].

1.1. Examples of Substances That Have Revolutionized Health

The 20th century saw remarkable advancements in the development of chemical-based drugs and therapies, many of which were discovered in nature or developed in laboratories. Chemistry evolved to encompass not only the synthesis of compounds but also the study of their biological interactions and therapeutic effects on the human body. This progress solidified chemistry as a central science, vital to both medical and technological advancements. Beyond creating jobs, chemical science has been instrumental in improving human quality of life, increasing longevity, and shaping modern society.

Some of the substances that have revolutionized health, including quinine (1), aspirin (2), morphine (3), camphor (4), ethanol (5), and penicillin (6), are only some examples, highlighted in Figure 1, among many others. The examples presented in Figure 1 illustrate how chemistry positively influenced human life, even before it was formally recognized as a science.

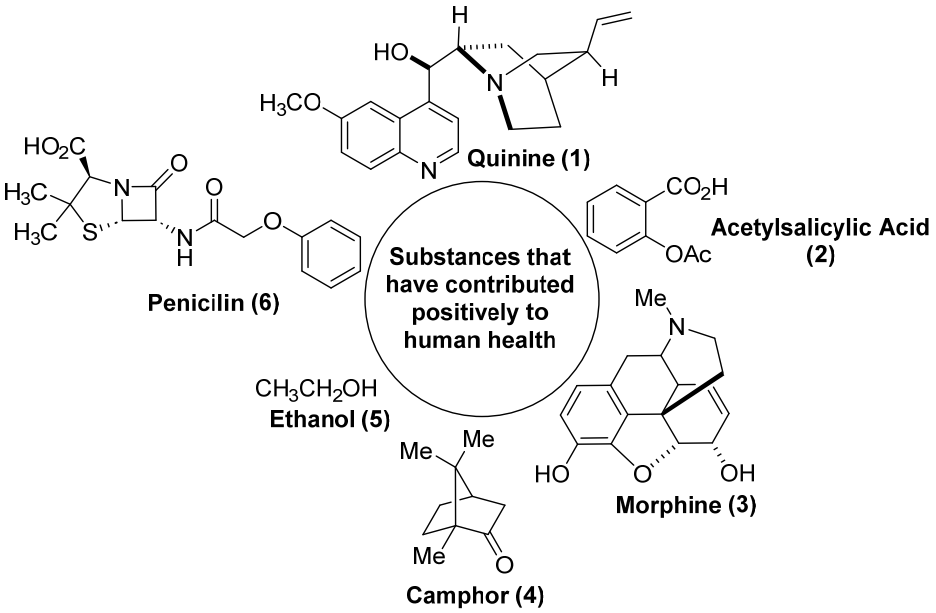


Figure 1. Examples of chemical substances that have had an impact on human health.

Each molecule has a unique and fascinating history. Some began with promise but turned into disasters, while others achieved remarkable success, sparking new fields of study and continue to make valuable contributions. Each trajectory reflects the complexity and profound impact of molecules on science and society.

1.1.1. Quinine

Quinine (1) is one of these fascinating substances. It is an alkaloid extracted from the bark of the Quina or Cinchona tree, found in over 40 species belonging to the *Cinchona* genus (*Rubiaceae*), distributed throughout the tropical forests of South America. The bark arrived in Europe in 1658, with the story of Spanish countess Ana del Chinchón, who was cured of intermittent fevers—likely malaria—during her stay in Peru. At the time, bark powder was the only known treatment for malaria, typically consumed in bitter preparations diluted in water or wine [11,12]. Quinine (1) has saved billions of lives over the past 500 years and has also inspired the synthesis of numerous new drugs. Its use is considered a milestone in the development of antipyretic and antimalarial medications, significantly contributing to the evolution of pharmacology. The isolation of this compound took place in 1820, becoming the standard treatment for malaria. Clinical studies conducted between 1866 and 1868 indicate that quinine, along with four other alkaloids isolated from cinchona bark, was effective in "stopping febrile paroxysms", with cure rates exceeding 98%. However, the low quinine extraction yield from various Cinchona species nearly drove these plants to extinction in South America, prompting specialized cultivation for commercial exploitation [12]. The quest to synthesize quinine led to a dispute among several chemists, culminating in its total synthesis by Paul Rabe and Karl Kindler in 1918, although the synthesis was only fully confirmed in 2008 by Smith and Williams [9].

Quinine remained the primary treatment for malaria until the 1940s, when resistant strains began to emerge, prompting the urgent need for alternative substances. This led to the development of a new class of quinoline compounds derived from quinine (1), i.e., chloroquine (7), mefloquine (8), and amodiaquine (9) (Figure 2) [13]. Mefloquine (8) exhibits a higher structural similarity to quinine (1), featuring a quinolinyl–piperidinoethanol system, a simplified version of the quinine ruban skeleton [14]. This compound was developed at the Walter Reed Army Institute in the USA to be administered in a single daily dose. Chloroquine (7), the leading drug in malaria chemotherapy due to its high

efficacy, low toxicity, safety, and easy synthetic production, is derived from quinine (1), by opening up the ruban ring to form the aliphatic pentane chain. This development involved molecular simplification strategies, such as replacing the ruban nucleus with an aliphatic chain and bioisosterism, substituting the hydroxyl group with an amine group (Figure 2). Discovered by Bayer researchers, chloroquine was the primary drug of choice for 15 years, until its indiscriminate use led to the emergence of resistant strains. Amodiaquine (9), an alternative for chloroquine-resistant strains, is derived from chloroquine (7) and features a phenyl system, a rigidified version of the aliphatic chain (Figure 2). Although it shares a similar mechanism of action with chloroquine (7), amodiaquine displays a shorter half-life of around 3 h. Resistance to amodiaquine has emerged in some areas, which is why it is now used in combination therapies rather than as monotherapy [15].

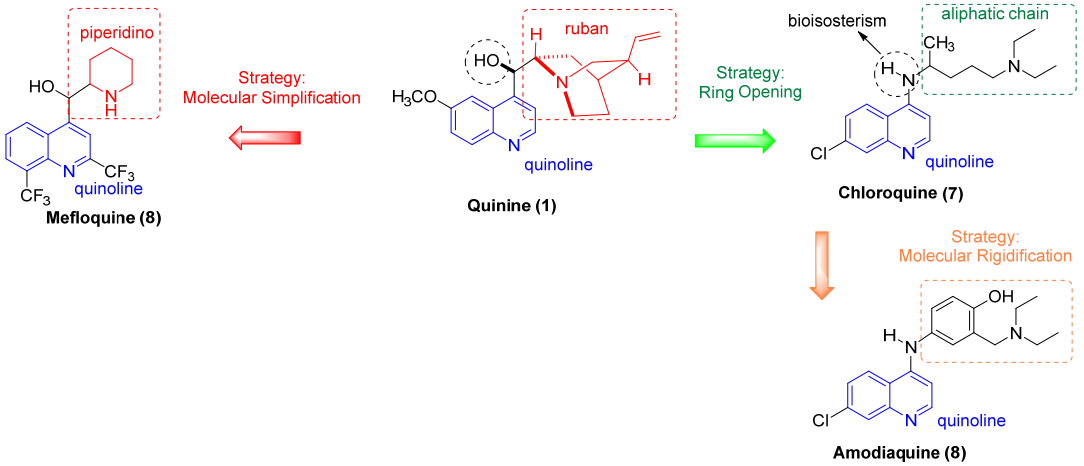


Figure 2. Quinine-derived (1) origin of the antimalarial compounds mefloquine (8), chloroquine (7) and amodiaquine (9).

Despite pharmaceutical advances encompassing new quinine analogs, quinine is still used in combination with other antimalarials in cases where the protozoan *Plasmodium falciparum* is resistant [16]. Beyond its antimalarial use, quinine also exhibits potential applications as an antiarrhythmic and in the treatment of calf cramps, rheumatoid arthritis, colds, gastric issues, and photodermatitis [17].

1.1.2. Acetylsalicylic Acid

Acetylsalicylic acid (2), commonly known as Aspirin® and developed by Bayer, is an acetylated derivative of the natural compound salicin, a glycoside found in the bark of willow trees from the *Salicaceae* family, such as *Salix alba* and *Salix fragilis*. Extracts from willow bark and leaves were known since antiquity by the Sumerians, Egyptians, Greeks, and Romans for their analgesic, anti-inflammatory, and antipyretic properties—a history spanning over 3500 years [18]. Salicin extraction in 1824 enabled its use as an "Indigenous substitute for quinine sulfate". In 1838, the Italian chemist Raffaele Piria made a significant breakthrough by synthesizing salicylic acid (9) through the oxidative hydrolysis of salicin, marking a major milestone in both chemistry and human health. This discovery sparked a race to fully synthesize salicylic acid, eventually leading to the establishment of the first synthetic salicylate production factory in Dresden in 1874. However, the use of salicin and its salicylate derivatives was not successful in therapy due to gastro-irritant properties and an unpleasant taste, a common issue with compounds containing phenolic hydroxyl groups. Continued research on salicylates, primarily at Bayer laboratories, however, led to a breakthrough in August 1897, where German chemist Felix Hoffmann replaced the

phenolic hydroxyl group with an acetyl radical, creating acetylsalicylic acid (2), or Aspirin®, retaining its potent analgesic effects without undesirable side effects (Figure 3).

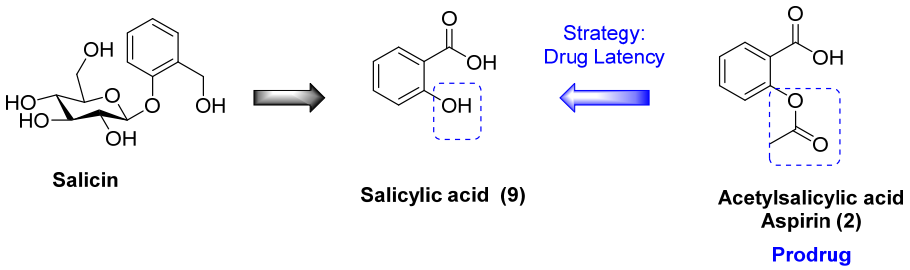


Figure 3. The synthesis of acetylsalicylic acid, Aspirin®, a synthetic prodrug derived from white willow (*Salix alba*).

The transformation of salicylic acid (9) into acetylsalicylic acid (2) (Figure 3) applies the principle of latency [19]. This term was introduced by Harper in 1959, referring to the process of obtaining substances that require prior biotransformation to exert pharmacological effects—also known as prodrugs. The term "prodrug" was first used by Albert in 1958. The enzyme responsible for the biotransformation of acetylsalicylic acid (2) into its active metabolite, salicylic acid (9), is carboxylesterase, which is found in the liver.

Molecular hybridization [20], the combination of bioactive fragments into a single chemical structure, comprises another strategy to develop more active and less toxic compounds derived from salicylic acid (9) and acetylsalicylic acid (2) (Figure 4). One example is the synthesis of benorylate (10), an anti-inflammatory, analgesic, and antipyretic drug, created by combining acetylsalicylic acid (2) and paracetamol (11) (an analgesic and antipyretic). The same strategy has been employed to synthesize acetaminosalol (12), another hybrid with similar pharmacological effects, by combining paracetamol (11) with salicylic acid (9) (Figure 4).

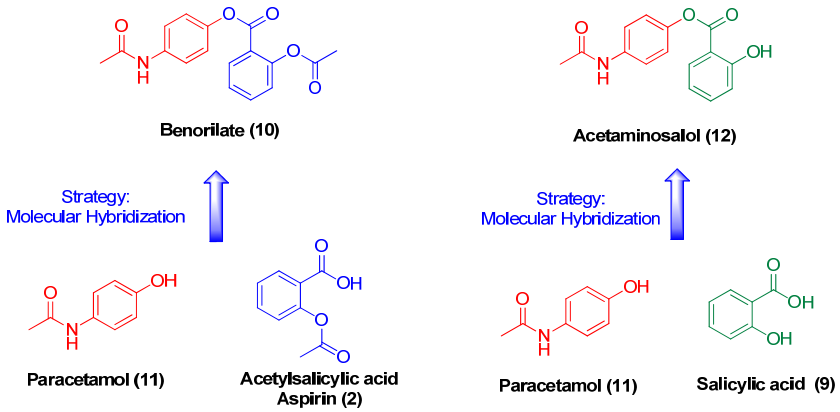


Figure 4. Use of acetylsalicylic acid (Aspirin®) (2) and salicylic acid (9) in the research and development (R&D) of new bioactive molecules, such as 10 and 12, employing the molecular hybridization principle.

Currently, acetylsalicylic acid (2) is the subject of about 1500 scientific studies per year, demonstrating that, over its 125-year history, it has become a cornerstone in medicine. It is widely used for the relief of various types of pain, particularly headaches, as well as fever, preventing and treating cardiovascular [21,22] and cerebrovascular diseases, lowering cancer risks [23,24], and serving as an external antiseptic. Aspirin® is available in different forms and combinations, such as acetylsalicylic acid (2) in 500 mg tablets (ASPIRIN® and MICROACTIVE ASPIRIN®); acetylsalicylic acid combined with caffeine (CAFIASPIRIN®); and with ascorbic acid (vitamin C-ASPIRIN® C) in formats such as

effervescent tablets. Additionally, ASPIRIN® PREVENT was developed following the discovery of acetylsalicylic acid's platelet aggregation inhibition properties, used in the prevention of cardiovascular events such as heart attacks and strokes [25].

1.1.3. Morphine

Morphine (3) is an excellent example of a beneficial substance to humans for at least 5500 years, serving as a prototype for the development of opioid analgesics and anesthetics [26]. This compound belongs to the alkaloid class of substances and is extracted from the resin of immature poppy flower capsules (*Papaver somniferum*). Once dried in the sun, this resin is called opium, a product rich in other alkaloids in addition to morphine [27]. Poppies were used as early as 3000 B.C. by Sumerians, who cultivated them specifically to extract opium [28].

Opium was used for millennia as an analgesic, but not until 1804 did German pharmacist Friedrich Wilhelm Adam Sertürner isolate its main component, morphine (3), named after the Greek god of sleep, Morpheus, due to its sedative effects. By 1853, morphine (3), with its unique chemical structure (Figure 1), had become the most powerful centrally acting analgesic known to society [29]. Its structure was elucidated in 1923 by Robert Robinson and collaborators, but its total synthesis was only achieved in 1952 by organic chemist Marshall D. Gates Jr and collaborator [30,31]. This achievement was a major milestone in organic and pharmaceutical chemistry, although it did not lead to a practical method for the industrial production of morphine, which is still primarily extracted from plants like opium.

Morphine (3) induces tolerance, meaning that progressively higher doses are required to achieve the same therapeutic effect. This tolerance can lead to physical dependence, which is associated with severe withdrawal symptoms in morphine-dependent individuals. Due to these adverse effects, the World Health Organization (WHO) recommends that morphine (3) be used only in specific cases, such as for the relief of severe pain. Despite these limitations, morphine (3) remains one of the most potent and important centrally acting analgesics and is widely used in the treatment of acute pain, particularly in cancer patients [31]. The significance of morphine is reflected in the size of its global market, valued at USD 16.2 billion in 2023. The market is projected to increase from USD 17.27 billion in 2024 to USD 26.8 billion by 2032, with a compound annual growth rate (CAGR) of 6.50% during the forecast period (2024–2032) [32].

Similarly, to salicylic acid (9), many studies have focused on the chemical structure of morphine (3) to develop more selective and easily synthesized substances. The molecular simplification of this compound's structure (3) led to the creation of a safer group of central analgesics, represented by the 4-phenylpiperidine derivative (13). This derivative maintains the pharmacophoric groups responsible for biological activity but features much simpler structures, making their production and application more efficient (Figure 5) [33].

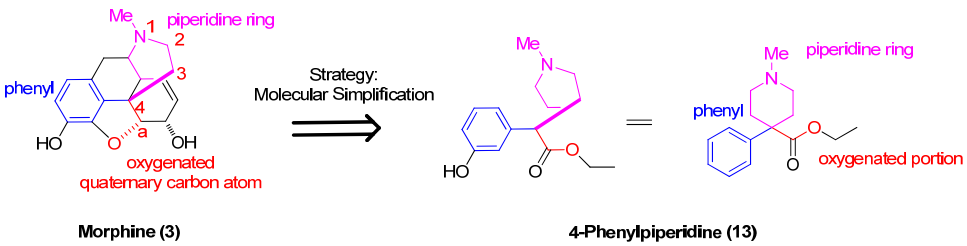


Figure 5. Morphine (3) application in the research and development (R&D) of new classes of bioactive molecules, such as 4-phenylpiperidine (13), utilizing the molecular hybridization principle.

1.1.4. Camphor

Camphor (4) is an organic monoterpene, a white or crystalline compound produced by *Cinnamomum camphora* (L.), a tree native to Asia belonging to the *Lauraceae* family. All parts of this plant emit the characteristic odor of its essential oil, which is associated with a cooling sensation. However, camphor (4) is obtained through steam distillation, purification, and sublimation, primarily from the wood of the tree's branches and bark, where it is present at higher concentrations. The first complete total camphoric acid synthesis was achieved by Finnish chemist Gustaf Komppa in 1903. Today, much of camphor (4) is synthesized from turpentine oil to reduce the need for tree felling in the traditional extraction process [34].

The historical significance of camphor (4) is tied to its extensive and diverse use in the East. Its application as a circulatory stimulant, for example, has been long recognized by the Chinese. During the Black Death in the 14th century, camphor (4) was used as an air purifier, and was even included in perfumes mixed with rose water, which were spread over corpses prior to their burial. In traditional Chinese and Ayurvedic medicine, camphor (4) was used to treat bacterial and fungal infections, inflammation, congestion, muscle aches, irritation, and itching in various parts of the body. The antibacterial, antifungal, and antiviral properties of camphor (4) are currently well-documented in various species. Studies concerning essential oils, in which camphor is a major component, have recognized its effectiveness both in isolated form and in combined with two or three monoterpenes, displaying synergistic activity [35,36]. In medicinal chemistry, camphor (4) holds significance as a chiral starting material in the enantioselective synthesis of various derivatives with broad biological activities, including antimicrobial, antiviral, antioxidant, analgesic, and anticancer properties [37].

1.1.5. Ethanol

Antiseptics and disinfectants are used in hospitals and other environments to eliminate microorganisms through topical application on solid surfaces and hands, as they cause the breakdown of microbial cell membranes [38,39]. A wide variety of chemical agents are used as antiseptics and disinfectants, including alcohols, phenols, iodine, chlorine, quaternary ammonium salts, and polychlorinated compounds, among others. Ethyl alcohol, also known as ethanol or aqua vitae (Latin for "water of life", referring to a concentrated aqueous solution of ethanol) (5), has been used for centuries as an antiseptic and disinfectant for skin asepsis, wound care, and cleaning solid surfaces [40]. During the COVID-19 pandemic, the importance of 70% ethyl alcohol was widely recognized as one of the most effective measures for disinfecting surfaces and sanitizing hands, significantly aiding in reducing the transmission of the SARS-CoV-2 virus. Its easy accessibility, proven effectiveness, and practical application made it an essential tool, particularly in high-traffic areas. Ethyl alcohol (ethanol, 5) at 70% is highly effective against COVID-19 because this concentration allows it to penetrate the virus's lipid membrane, destabilizing and denaturing viral proteins, which leads to virus destruction. The 70% alcohol concentration contains the ideal amount of water to slow its evaporation, ensuring longer contact times with pathogens and enhancing its disinfectant action. In addition to its antiseptic properties, ethanol (5) is also crucial in pharmaceutical chemistry as a solvent in drug synthesis, also used to extract compounds from medicinal plants, and in the purification of bioactive compounds.

Ethanol (5) is an iconic chemical compound that has evolved alongside humanity as one of the most widely consumed substances in history, produced through a simple microbiological fermentation process. Depending on the carbohydrate source, ethanol is used to create various distilled beverages such as cachaça, beer, wine, cognac, whiskey, vodka, and sake. This biological fermentation is the oldest chemical process known for the natural production of alcoholic beverages [41]. In the Middle Ages, alcoholic beverages

were distilled to increase alcohol concentrations and applied topically by physicians as wound antiseptics. More recently, ethanol has been used before injections and as a key component in many hand sanitizers, also becoming a leading renewable fuel [42]. Although its use as a fuel dates back to the early 20th century, it gained significant momentum in Brazil with the launch of the Pro-Alcohol (National Alcohol Program) initiative in 1975. Since then, ethanol's use as a fuel has expanded globally, particularly in flex-fuel vehicles.

1.1.6. Penicillin

Penicillin (6), belonging to the β-lactam antibiotic class, revolutionized the concept of antibiotics in health treatment, providing an efficient way to combat various bacterial infections. This substance was isolated from the fungus *Penicillium notatum* by Alexander Fleming in 1928 and became the first widely employed antibiotic, profoundly impacting the treatment of bacterial infections [43]. Although penicillin (6) was first synthesized in 1957 by Sheehan and collaborators, the product obtained through a total synthesis was not economically viable for commercialization and was, instead, produced via semi-synthetic methods [44]. Penicillin (6) transformed the medical paradigm for treating infections, saving millions of lives and sparking a global scientific search for new antibiotics—a search that continues today due to the growing issue of bacterial resistance due to the overuse and misuse of antibiotics [45]. New penicillin derivatives have been developed through medicinal chemistry techniques, by mapping the relationship between chemical structure and biological activity (Figure 6) [46]. The β-lactam ring is critical for antibacterial activity, along with the presence of a free carboxylic acid. This bicyclic system also plays a key role in optimal β-lactam ring activity. While the sidechain acylamine is typically essential, some exceptions like thienamycin are noted. Sulfur, although common, is not indispensable. Additionally, the stereochemistry of both the bicyclic ring and the acylamine side chain is vital to this molecule's efficacy (Figure 6) [47].

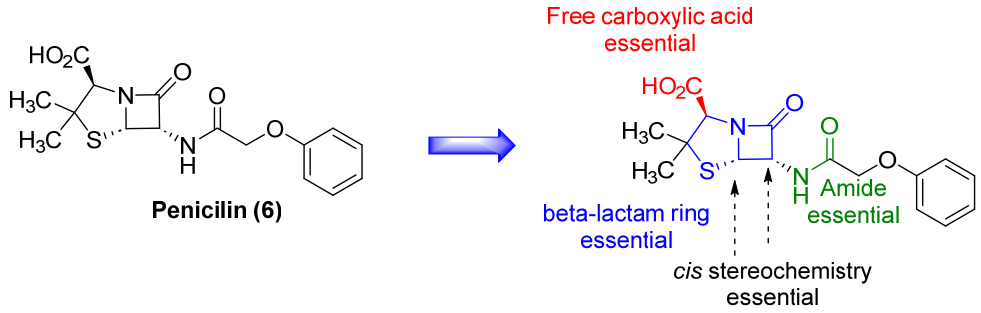


Figure 6. The application of penicillin (6) in the research and development (R&D) of new classes of antibacterial molecules involves mapping its pharmacophoric entities.

1.2. Examples of Harmful Human and/or Environmental Health Substances

The concept of sustainability-driven innovation is excellent and holds significant promise for addressing global challenges. Many substances that were introduced to the market have led to a lack of global sustainability and global climate emergencies. Certain innovative substances, though created with good intentions, have caused more harm than good. Due to serious adverse effects on human health and the environment, many of these substances have been banned in several countries. While some innovations have failed to meet initial promises, others have had disastrous consequences, causing irreversible global damage [48]. Figure 7 highlights what we consider to be the most pressing problems, although this list represents only a small part of reality and does not cover all cases. Most emerging environmental and health issues are associated with chemicals developed in the 1970s and 1980s, whose resolution was often limited to local efforts. These issues have since

escalated into global phenomena, leading to the destruction of rivers and lakes, increased greenhouse gas emissions, ozone layer depletion, ocean acidification, climate change, and air pollution, among others.

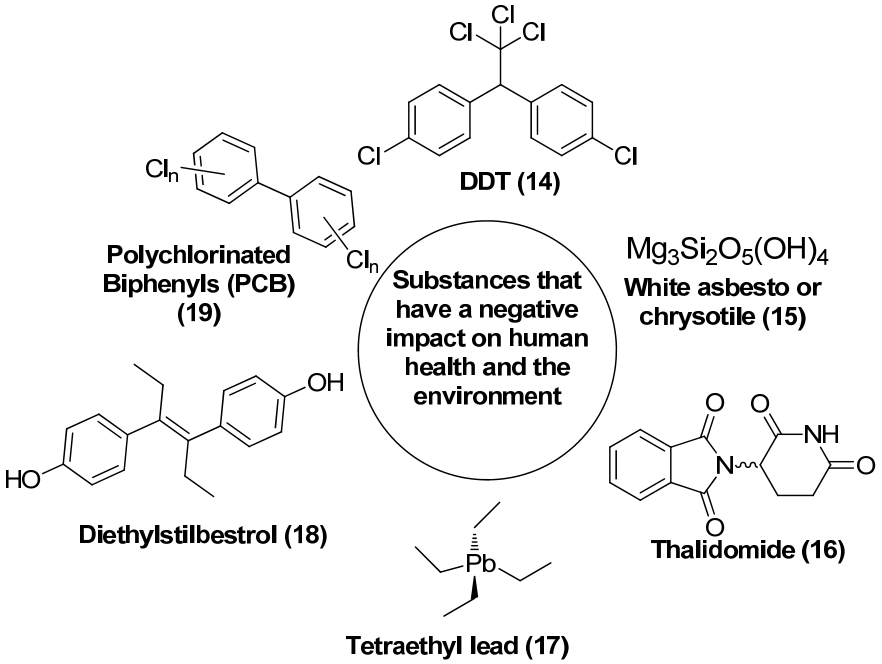


Figure 7. Substances that lead to negative human health and environmental effects.

1.2.1. DDT

1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane, better known as DDT (14), is a pesticide widely used for over 40 years after World War II to combat malaria-carrying mosquitoes and other crop-damaging insects. This compound (14) was first synthesized in 1874 by Viennese pharmacologist Othmar Zeidler. However, it was Swiss chemist Paul Hermann Müller who, in the pursuit of a long-lasting and inexpensive insecticide, discovered DDT's insecticidal properties and chemical stability. The compound is insoluble in water but dissolves well in most organic solvents, fats, and oils. Although effective, DDT (14) is non-selective, killing all types of insects and causing significant environmental damage. It has also been linked to adverse human health effects, including cancer. As a result, its agricultural use was banned in most countries under the Stockholm Convention on Persistent Organic Pollutants in 2001 [49].

1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane (14) was banned due to its toxic and persistent effects, but Paul Hermann Müller was awarded the Nobel Prize in Physiology or Medicine in 1948 for his contributions to pest control, which had a profound impact on agriculture and public health at the time. Despite the numerous problems caused by DDT (14), this compound has played a significant role in human history. Since its discovery in 1939, DDT (14) was instrumental in the eradication of malaria, typhus, and other insect-borne diseases in many countries, particularly between the 1950s and 1970s [50]. Müller's research contributed to understanding how insecticides affect insects, paving the way for the development of new chemicals for pest control. His studies also led to greater awareness of the environmental and health impacts of indiscriminate chemical use, driving further research into safer pesticide alternatives and their interactions with ecosystems.

The uncontrolled use of DDT (14) led to its accumulation and persistence in the environment, food chains, and the adipose tissue of animals, including humans. It is metabolized into DDE (21). Based on toxicological evidence and increasing concerns regarding its harmful effects on birds, DDT was banned in many countries in the 1970s.

It became clear that DDT not only directly harmed wildlife but also caused widespread contamination of water and food sources, affecting ecosystems and human health [51,52].

The product marketed as DDT (14), synthesized from chloral (Cl_3C-CHO), is a mixture of several compounds, including DDT (14), 4,4′-dichloro-diphenyl-dichloroethane (DDD) (20), and 4,4′-dichloro-diphenyl-dichloroethylene (DDE) (21) [52]. One of DDT's defining characteristics is its environmental persistence. However, many fungi are capable of degrading DDT (14) through both aerobic and anaerobic processes. The main byproducts of this microbiological degradation are 4,4′-DDD (20) and 4,4′-DDE (21) (Figure 8).

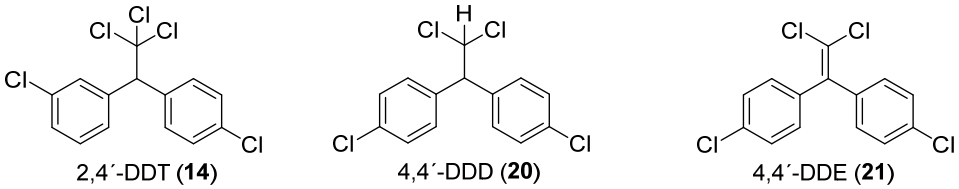


Figure 8. By-products present in commercial DDT (14).

Many books throughout history have had a profound impact on society and shaped the course of historical events. This includes *Silent Spring*, by Rachel L. Carson (1907–1964), which played a key role in the eventual banning of DDT (14) [53]. The book was conceived after Carson received a letter from Olga Owens Huckins of Duxbury, Massachusetts, who reported that DDT (14) was killing local birds. *Silent Spring* is universally recognized as a watershed moment in the history of modern environmentalism, emphasizing the need for political analysis to align with scientific data. In the book's final sentence, Carson wrote, "The control of Nature is a phrase conceived in a spirit of arrogance, born of the Neanderthal age of Biology and Philosophy when it was assumed that Nature existed for the convenience of Man". This book introduced the term "environment" into public policy discourse. However, powerful denialist forces driven by financial interests sought to discredit Carson, both personally and professionally. Chemical companies that manufactured DDT (14) tried to suppress and discredit the book's findings, while newspapers labeled Carson as "hysterical" and "extremist". Time magazine criticized her for "sentimentality", and her scientific credibility was questioned. The industry even funded advertisements aimed at refuting her work. Robert White-Stevens, a biochemist and assistant director of American Cyanamid's Division of Agricultural Research, infamously stated in the 1960s: "If man followed the teachings of Miss Carson, we would return to the Dark Ages, and insects, diseases, and worms would inherit the Earth again" [54]. This is a typical example of scientists acting as denialists in defense of a profit-driven model, prioritizing financial interests over environmental concerns. Current evidence indicates that this approach has collapsed due to its lack of consistency and sustainability. However, the relationship between humans and nature is still largely detrimental to the environment and despite nature being a life provider, it is often viewed as an obstacle to development.

The epigraph of *Silent Spring* was written by German philosopher and physician Albert Schweitzer who won the Nobel Peace Prize in 1952 and remains relevant today: "Man has lost the ability to predict and to forestall. He will end by destroying the Earth—from which he and other living creatures draw their sustenance. Poor bees, poor birds, poor men" [53].

In Brazil, several cases of contamination due to the intensive use of DDT (14) are noted. These include regions in the state of Mato Grosso [55], and the Madeira River basin (Amazon), where DDT (14) was found in the breast milk of local mothers. Other cases include the contamination of marine animals and water in the state of São Paulo by DDT and other organochlorines, as well as soil contamination from DDT (14) and its metabolites in obsolete deposits in the city of Belém, in the state of Pará. In the municipality of Duque de Caxias, in the state of Rio de Janeiro, a DDT (14) factory operated up until 1960 [56–58].

Known as "Boys Town", the site was abandoned with about 350 tons of DDT (14) (borer dust) still present, leading to severe environmental and human contamination. There is suspicion that this DDT (14) exposure contributed to local congenital malformations, miscarriages, early-onset neurological diseases, and certain types of cancer. The soil surrounding the factory remains contaminated with organochlorine insecticides [59,60].

In 2023, it was discovered that pesticides are decimating bird populations across several European countries [61]. In Brazil, the pesticide Menvifos (trade name Phosdrin or Fosdrin) (22) (Figure 9) killed numerous *hyacinth macaws* (*Anodorhynchus hyacinthinus*) in the Pantanal, highlighting the disregard for biodiversity. This class of pesticides is among the most harmful to human health [62]. Bees, *Apis mellifera*, also continue to be decimated by pesticides, causing hive collapses. In January 2019 alone, over 50 million bees were killed in Santa Catarina, with the primary cause comprising the use of the insecticide fipronil (23) (Figure 9) in nearby soybean crops [63,64]. Recently, over 100 million bees were killed in the state of Mato Grosso due to the application of the same pesticide [65].

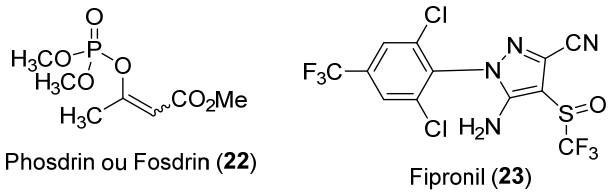


Figure 9. Fosdrin (22) and fipronil (23), two examples of highly toxic pesticides that lack selectivity.

1.2.2. White Asbestos or Chrysotile

Asbestos have become a major global threat to human health. These compounds comprise fibrous silicate minerals that occur naturally and have been widely employed in various commercial products due to their unique properties. The term "asbestos" is often used generically to describe several types of substances, including white asbestos (chrysotile asbestos) (8) and amphiboles such as crocidolite, amosite, and actinolite. More specifically, "asbestos" commonly refers to white asbestos. The most commonly employed type in industrial products is chrysotile, a hydrated magnesium silicate (chemical formula $Mg_3Si_2O_5(OH)_4$) [66].

These fibrous minerals are used in building materials (tiles, water tanks, gloves, thermal wall insulation) and industrial products requiring resistance to heat, fire, and chemicals. Asbestos have been industrially exploited for their insulating properties, fire resistance, electrical resistance, and corrosion resistance. However, they have also been linked to severe respiratory diseases such as pulmonary interstitial fibrosis (asbestosis), lung cancer, and malignant mesothelioma [67], particularly among occupationally exposed workers. The toxicity and carcinogenicity of asbestos in the respiratory tract occur primarily due to their ability to adsorb cell membranes. Due to associated health risks, civil society successfully advocated for the production shutdown and banning of asbestos use in the 1970s in over 50 countries. The pathogenicity of different forms of asbestos varies according to fiber size, with long, thin amphibole fibers being more pathogenic, particularly in causing mesothelioma [68]. Despite over 40 years of research confirming the carcinogenicity of this toxic mineral, which was exploited in alarming quantities worldwide, global asbestos production still hovers around 2 million tons annually [69]. Roughly 90% of the world's asbestos comes from only four countries, namely Russia, China, Brazil, and Kazakhstan [70]. The continued production and use of asbestos remains a significant global health threat.

1.2.3. Thalidomide

Many drugs have entered the pharmaceutical market only to be withdrawn due to dangerous side effects, but none were as catastrophic as thalidomide (16). This drug caused severe deformities in over 10,000 children and is considered the greatest medical-pharmaceutical disaster of the 20th century [71]. Thalidomide (16) was synthesized in 1953 and introduced in various European, Asian, Canadian, and South American countries. By 1957, it became the best-selling drug in West Germany, marketed by the pharmaceutical company Grünenthal GmbH under different brand names such as Kavadon®, Sedalis®, Softenon®, Distaral®, and Contergan®. However, by 1960, thalidomide (16) was being prescribed worldwide as a sedative and anti-nausea agent, particularly to relieve morning sickness in pregnant women. Thalidomide (16) contains an asymmetric carbon in its structure, and it was sold as a racemic mixture, containing equal parts of its two enantiomers. What was not known at the time was that the S-enantiomer displays teratogenic properties (from the Greek terás = monster and gene = origin) (Figure 10), meaning it caused severe congenital malformations, particularly affecting arm and leg development in unborn babies [72]. In December 1961, the scientific journal The Lancet published a letter from Australian obstetrician W. G. McBride, detailing the tragedy of congenital anomalies caused by the use of thalidomide during pregnancy [73]. Frances Kelsey, an American medical officer at the FDA, refused to approve the commercialization of thalidomide in the United States. In 1961, she was awarded the President's Award for Distinguished Federal Civilian Service by President John F. Kennedy, recognizing her as a guardian of public health for her efforts in preventing the drug's distribution and protecting the public from its harmful effects [74,75].

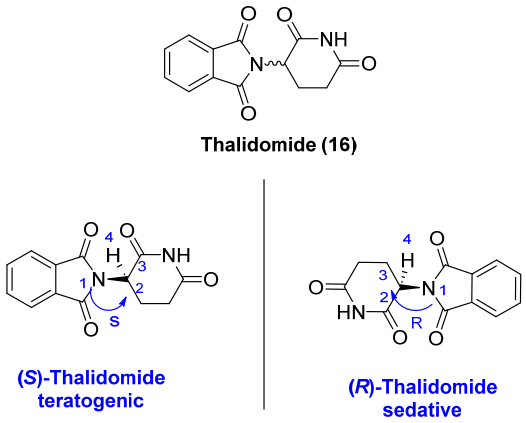


Figure 10. Chemical structure of the racemic drug thalidomide (16), (±)2-(2,6-dioxo-3-piperidinyl)-1*H*-isoindole-1,3-(2*H*)-dione; or (±)-phthalimidoglutarimide.

The observation of the teratogenic effects caused by (±)-thalidomide (16) in pregnant women during their first pregnancy trimester in the early 1960s marked a turning point in recognizing the risks of administering a drug in its racemic form, particularly when the eudysmic ratio (the difference in pharmacological activity between enantiomers) is unknown. This legislative failure led to significant reforms in regulatory agencies, which began to require more rigorous testing for drug approval.

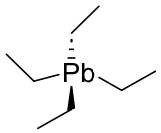
It is important to highlight the importance of thoroughly studying chiral substances intended for pharmaceutical use. In the case of thalidomide (16), subsequent attempts to resolve its enantiomers through chromatographic methods to administer the enantiomerically pure species could not prevent the teratogenic tragedy as, even if the enantiomerically pure form of thalidomide (16) is administered, the (*S*)-enantiomer—responsible for the teratogenic effect—undergoes epimerization in human plasma, converting back to the

racemic mixture in vivo. This configuration inversion phenomenon, or racemization, is also observed in other therapeutic classes, such as non-steroidal anti-inflammatory drugs (NSAIDs) belonging to the 2-arylpropionic acid class [76].

Even with extensive studies to ensure the safety and efficacy of new drugs prior to their market introduction, some instances where approved drugs caused significant harm are noted [77]. This is the case of Vioxx (rofecoxib), a non-steroidal anti-inflammatory drug (NSAID) developed for pain and inflammation relief, particularly in arthritis patients. Manufactured and marketed by Merck & Co. (Rahway, NJ, USA), Vioxx was approved in 1999 but was withdrawn in 2004 after being linked to numerous deaths caused by cardiovascular problems, such as heart attacks and strokes, particularly in patients who used the drug in higher doses or for prolonged periods of time [78].

1.2.4. Tetraethyl Lead

Vehicle fuel additives used in public and private transport are an efficient way to improve engine performance. These additives serve various functions, such as reducing engine wear, preventing engine knock, and inhibiting oxidation. Engine knock, or "ping knock", occurs when the gasoline-air mixture combusts prematurely, before spark plug ignition, causing shock waves. This results in combustion engine power loss, mechanical damage, and overheating. After discovering that the issue was with the fuel, not the engine, researchers began searching for additives to reduce detonation. One such additive is the organometallic compound tetraethyl lead (17) (Figure 11), which was added to gasoline to increase octane ratings since the 1920s, enabling higher compression ratios, preventing engine knock, and improving performance. However, after 75 years of widespread use, tetraethyl lead was banned globally, due to its role in air contamination and the harmful effects of lead exposure.



Tetraethyl lead (17)

Figure 11. The chemical reaction caused by mixing tetraethyl lead (17) to gasoline to obtain higher octane ratings.

The uses and toxic effects of lead on humans have been known since antiquity [79], particularly among the Romans, who were exposed to lead through mining, utensils, and water distribution pipes made from this metal [80]. In one Roman mine, drawings of "butterflies" were found on the walls, suggesting that it was the "butterfly room"—a reference to the hallucinations caused by the toxic effects of lead experienced by miners [81].

Fossil fuels, consisting of aliphatic and aromatic hydrocarbons, including polycyclic aromatic hydrocarbons, are complex mixtures containing varying concentrations of potentially toxic substances. The pursuit of a cheap and efficient chemical compound for use in engines, which would also benefit large corporations, led to the addition of this problematic organometallic compound to fuel mixtures, significantly increased fuel complexity, worsening air pollution, and negatively affecting public health [82]. While improving engine efficiency, these benefits came at the cost of severe environmental damage and air quality deterioration. Particulate lead oxide, released by exhaust gasses (Equations (1) and (2))

$$Pb(C_2H_5)4 + 13\ O_2 \rightarrow 8\ CO_2 + 10\ H_2O + Pb \quad (1)$$

$$2\ Pb + O_2 \rightarrow 2\ PbO \quad (2)$$

became the primary source of lead toxicity, posing a serious threat to both human and environmental health.

The idea of adding tetraethyl lead to gasoline originated from Thomas Midgley Jr. (1889–1944) [83,84], who discovered its anti-knock properties. After testing hundreds of substances, he identified tetraethyl lead as the solution, despite initial misconceptions about its mechanism of action [85]. While Midgley made a significant contribution to the development of tetraethyl lead, the most effective production process—known as the Kraus–Callis process—was developed by Charles August Kraus (1875–1967) [86] and Charles C. Callis (1888–1956) [87]. This process involves combining molten sodium with molten lead at a 1:1 ratio to form a reactive metal alloy, which then reacts with ethyl chloride (CH_3CH_2Cl) to produce tetraethyl lead. The compound is subsequently separated from the mixture using vapor drag distillation (Equation (3)) [88]

$$PbNa + 4\,CH_3CH_2Cl \rightarrow 3\,Pb + 4\,NaCl + Pb(C_2H_5)_4 \quad (3)$$

In the past, gas pumps indicated whether the fuel contained leaded gasoline, leaving the choice to consumers. However, it was not widely known that this additive was highly toxic, both before and after combustion. Studies have demonstrated that tetraethyllead is significantly harmful to humans, particularly affecting workers who handle this substance [89]. Bloodstream levels can cause neurological symptoms and lead to encephalopathy [90,91], cardiovascular diseases [92], cancer [93], hemangiosarcoma [94], and other serious conditions. Exposure to high lead levels can result in a range of illnesses, including intellectual disability, coma, seizures, and death, as well as hyperactivity, impaired growth, learning and reading difficulties, hearing loss, insomnia, and various behavioral health issues [95]. A recent long-term study, which began in 1996, revealed that children born during the "age of leaded gasoline" developed intellectual and cognitive deficits, potentially compromising their performance into adulthood [96]. Importantly, in 1922, before tetraethyllead went into large-scale production and global distribution, Dr. Charles Kraus of Germany warned Thomas Midgley Jr. that the compound was "a treacherous and injurious poison", noting that it had caused the death of a senior scientist at his university. Despite this warning and the fact that companies were already aware of the harmful effects of this product, it was marketed for nearly 100 years before being withdrawn globally, after 1980 [97]. The process was not easy, as it involved powerful corporations and complex dynamics, including industrial, regulatory, judicial, and public health interests, along with public pressure. This collective effort eventually led to a significant reduction in lead exposure [98]. By the 2000s, many countries had completely banned tetraethyl lead in gasoline, driven by the undeniable evidence of its harmful public health effects.

1.2.5. Stilbesterol

Active pharmaceutical ingredients (APIs), initially considered safe and beneficial for treating diseases, can reveal harmful effects over time to both environmental and human health. This can lead to significant changes in their use, regulation, and public perception. One such example is diethylstilbestrol (18), also known as stilbestrol.

Diethylstilbestrol (18) is a synthetic drug that was introduced to the pharmaceutical market in 1940 by Eli Lilly and Company. Prescribed between the 1940s and 1970s, it was developed as an estrogen analog to prevent miscarriages, premature births, and other pregnancy complications. However, serious health risks emerged with its use in pregnant women. One of the most severe problems encompassed the increased risk of clear cell adenocarcinoma of the vagina or cervix in women exposed to the drug in utero, particularly if the exposure occurred during the first pregnancy trimester [99]. An estimated 5 to 10 million Americans either received diethylstilbestrol (18) during pregnancy or were

exposed to it in the womb [100]. In addition, men who had intimate contact with women who used the drug were also affected.

In 1971, Arthurs L. Herbst and colleagues [101,102] were the first to link the drug to a rare and severe form of vaginal cancer in young women. Diethylstilbestrol (18) was later classified as an endocrine disruptor, a substance that interferes with hormonal function in individuals exposed to this compound during development or later in life. After Herbst and his team established its connection to breast cancer, cervical cancer, infertility, and reproductive anomalies, the U.S. federal government banned the use of diethylstilbestrol (**18**) in pregnant women in 1971.

1.2.6. Polychlorinated Biphenyls

Finally, finalizing the descriptions of harmful substances presented in Figure 7, we highlight the problems caused by Polychlorinated Biphenyls (PCBs) (19). This family of compounds consists of two interconnected benzene rings with varying poly substitution patterns which, due to their coplanar structure, can intercalate with DNA. About 209 compounds are classified as PCBs (19), whose physicochemical and toxicological properties are similar to those of dioxins and furans, earning them the label "dioxin-like PCBs". PCBs were introduced to the market in the late 1920s by the Monsanto Company, valued for their chemical stability, electrical insulation properties, and heat resistance [103]. These qualities led to their widespread industrial use in electrical equipment, hydraulic systems, and as additives in paints, sealants, and plastics.

However, the stability that made PCBs useful also lead to their environmental persistence, resulting in increased concentrations over time. This has transformed PCBs into significant health, environmental, and occupational hazards, associated with several health problems [101], including cancer, immune system depression, reduced fertility [104], endocrine disorders (type 2 diabetes, obesity), liver, and neurological issues. Additionally, PCBs are persistent organic pollutants that display the capacity to bioaccumulate in terrestrial and marine organisms, including humans [105]. Human contamination occurs through various exposure pathways, such as through the ingestion of contaminated food and through the inhalation of or dermal contact with dust [106].

The production of PCBs was banned by the U.S. Environmental Protection Agency in 1979 [107] and later restricted by the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2001, which came into effect in 2004. This international treaty aims to protect human and environmental health from POPs, including PCBs. Despite the ban, PCBs continue to contaminate the environment and food sources due to their chemical stability and consequent long-term persistence.

2. Final Thoughts

This article explored the complex relationship between health, the environment, and chemical innovations, highlighting both scientific breakthroughs and some of the worst human and environmental disasters. The widespread use of chemicals in our daily lives has brought numerous health and environmental challenges. The ability of scientists to create new, previously unknown, substances marked a significant chapter in human history, granting humanity immense power over life and nature. While innovative chemicals have saved lives and extended human longevity, they have also caused deaths and deformities when their toxicological risks were inadequately assessed or when they did not perform as expected.

Some synthetic substances have led to poisoning and the contamination of air, soil, and water matrices. We cannot overlook the devastating impacts of harmful pesticides, chemical warfare, and industrial disasters, such as the Bhopal disaster in Madhya Pradesh,

India, in 1984, when a toxic gas leak of methyl isocyanate from a pesticide plant used by Union Carbide India killed between 15,000 and 20,000 people. Over time, regulations have caught up, leading to the banning of substances like DDT, PCBs, and tetraethyl lead—though often belatedly. The fine line between a chemical's efficacy and its toxicity highlights the increasing importance of careful, in-depth research and the development of new compounds.

Author Contributions: A.S.d.C.: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing—original draft, Writing—review and editing. I.S.d.J.: Conceptualization, Writing—original draft, Writing—review. P.G.F.: Conceptualization, Writing—original draft, Writing—review. A.S.d.S.: Conceptualization, Writing—original draft, Writing—review. R.P.R.F.d.O.: Conceptualization, Writing—original draft, Writing—review. D.O.F.: Conceptualization, Writing—original draft, Writing—review. V.F.F.: Conceptualization, Writing—original draft, Writing—review: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: The authors would like to thank the scholarships granted by Faperj CNE E-26/202.800/2017, CNE E-26/200.911/2021, and E26/200.870/2021, CNPq grant 301873/2019–4 and 307736/2023–7, and the FAPERJ projects under number E-26/010.101106/2018, Pensa-Rio E-26/010/00168/2015, and SEI-260003/001178/2020 (Temático).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: All individuals included in this section have consented to the acknowledgement. The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Alcione S. Carvalho, Iva Souza, Patrícia G. Ferreira, Acácio S. de Souza and Rafael P. R. F. de Oliveira gratefully acknowledges their scholarship awarded by Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ). The authors would also like to express their gratitude to FAPERJ for funding the research project. Vitor F. Ferreira acknowledges the grant and fellowships awarded by CNPq.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Aldoshin, S.M. Achievements and innovation prospects of chemical science. *Her. Russ. Acad. Sci.* **2012**, *82*, 143–157. [CrossRef]
2. Ferreira, V.F.; da Rocha, D.R.; da Silva, F.C. Green Chemistry, Sustainable Economy and Quality of Life. *Rev. Virtual Quim.* **2014**, *6*, 85–111. [CrossRef]
3. Posey, D. Intellectual Property Rights: And Just Compensation for Indigenous Knowledge. *Anthropol. Today* **1990**, *6*, 13–16. [CrossRef]
4. Dias, J.P.S. *A Farmácia e a História. Uma Introdução à História da Farmácia, da Farmacologia e da Terapêutica*; Faculdade de Farmácia da Universidade de Lisboa: Lisboa, Portugal, 2005; pp. 5–39.
5. Klein, J.A.; Ragland, E.R. Introduction Analysis and Synthesis in Medieval and Early Modern Europe. *Ambix* **2014**, *61*, 319–326. [CrossRef]
6. Debus, G.A. The Chemical Philosophers: Chemical Medicine from Paracelsus to Van Helmont. *Hist. Sci.* **1974**, *12*, 235–259. [CrossRef]
7. Masic, I. History of Social Medicine and Public Health—A Review. *Int. J. Biomed. Healthc.* **2024**, *12*, 25–52. [CrossRef]
8. Kaboudin, B.; Sohrabi, M. Chemistry and synthesis of major opium alkaloids: A comprehensive review. *J. Iran. Chem. Soc.* **2021**, *18*, 3177–3218. [CrossRef]
9. Bissember, A.C. The Quinine Odyssey: A Barometer of the State of Organic Synthesis Over Centuries. *Chem. Eur. J.* **2024**, *30*, e202403021. [CrossRef]

10. Vermeulen, H.; Westerbos, S.J.; Ubbink, D.T. Benefit and harm of iodine in wound care: A systematic review. *J. Hosp. Infect.* **2010**, *76*, 91–99. [CrossRef]
11. de Oliveira, A.R.M.; Szczerbowski, D. Quinina: 470 anos de história, controvérsias e desenvolvimento. *Quim. Nova* **2009**, *32*, 1971–1974. [CrossRef]
12. Greenwood, D. The quinine connection. *J. Antimicrob. Chem.* **1992**, *30*, 417–427. [CrossRef] [PubMed]
13. Bray, P.G.; Ward, S.A.; O'Neill, P.M. Quinolines and artemisinin: Chemistry, biology and history. *Curr. Top. Microbiol. Immunol.* **2005**, *295*, 33–38. [CrossRef]
14. Barreiro, E.J.; Fraga, C.A.M. *Química Medicinal: As Bases Moleculares da Ação dos Fármacos*, 3rd ed.; Editora Artmed: Porto Alegre, Brazil, 2014; Chapters 9 and 10; pp. 407–476.
15. MMV—Medicines for Malaria Venture. Available online: https://www.mmv.org/malaria-medicines/history-antimalarials (accessed on 8 August 2024).
16. Achan, J.; Talisuna, A.; Erhart, A.; Yeka, A.; Tibenderana, J.; Baliraine, F.; Rosenthal, P.; d'Alessandro, U. Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. *Malar. J.* **2011**, *10*, 144. [CrossRef] [PubMed]
17. Rogóż, W.; Lemańska, O.; Pożycka, J.; Owczarzy, A.; Kulig, K.; Muhammetoglu, T.; Maciążek-Jurczyk, M. Spectroscopic Analysis of an Antimalarial Drug's (Quinine) Influence on Human Serum Albumin Reduction and Antioxidant Potential. *Molecules* **2022**, *27*, 6027. [CrossRef]
18. Montinari, M.; Minelli, S.; Caterina, R. The first 3500 years of aspirin history from its roots—A concise summary. *Vasc. Pharmacol.* **2019**, *113*, 1–8. [CrossRef]
19. Chin, C.H.; Ferreira, E.I. The latency process in drug planning. *Química Nova* **1999**, *22*, 75–84. [CrossRef]
20. Zhang, S.; Zhang, J.; Gao, P.; Sun, J.; Song, Y.; Kang, D.; Liu, X.; Zhan, P. Efficient drug Discovery by rational lead hybridization based on cristallographicoverlay. *Drug Discov. Today* **2019**, *24*, 805–813. [CrossRef]
21. Babu, K.; Salvi, S. Aspirin and asthma. *Chest* **2000**, *118*, 1470–1476. [CrossRef]
22. Bateman, L.; Zaro, B.; Miller, S.; Pratt, M. An alkyne-aspirin chemical reporter for the detection of aspirin-dependent protein modification in living cells. *J. Am. Chem. Soc.* **2013**, *135*, 14568–14573. [CrossRef]
23. Drew, D.; Cao, Y.; Chan, A. Aspirin and colorectal cancer: The promise of precision chemoprevention. *Nat. Rev. Cancer* **2016**, *16*, 173–186. [CrossRef]
24. Hua, H.; Zhang, H.; Kong, Q.; Wang, J.; Jiang, Y. Complex roles of the old drug aspirin in cancer chemoprevention and therapy. *Med. Res. Rev.* **2018**, *39*, 114–145. [CrossRef] [PubMed]
25. Bayer. Available online: https://www.bayer.com.br/pt/midia/aspirina-medicamento-mais-estudado-mundo-celebra-125-anos-inovacao (accessed on 8 August 2024).
26. Tolchin, Z.; Dukes, D.; Gharbaoui, L.; Smith, J. Dearomatize Access to (-)-Thebaine and Derivatives. *Org. Lett.* **2023**, *25*, 8424–8428. [CrossRef] [PubMed]
27. Brook, K.; Bennet, J.; Desai, S.P. The Chemical History of Morphine: An 8000-year Journey, from Resin to de-novo Synthesis. *J. Anesth Hist* **2017**, *3*, 50–55. [CrossRef] [PubMed]
28. Blakemore, P.; White, J. Morphine, the Proteus of organic molecules. *Chem. Commun.* **2002**, *11*, 1159–1168. [CrossRef]
29. Nunes, B.C.; Garcia, J.B.S.; Sakata, R.K. Morphine as first medication for treatment of cancer pain. *Rev. Bras. Anestesiol.* **2014**, *64*, 236–240. [CrossRef]
30. Gulland, J.M.; Robinson, R. CXII.—The morphine group. Part I. A discussion of the constitutional problem. *J. Chem. Soc. Trans.* **1923**, *123*, 980–998. [CrossRef]
31. Stork, G.; Yamashita, A.; Adams, J.; Schulte, G.R.; Chesworth, R.; Miyazaki, Y.; Farmer, J.J. Regiospecific and Stereoselective Syntheses of (±) Morphine, Codeine, and Thebaine via a Highly Stereocontrolled Intramolecular 4 + 2 Cycloaddition Leading to a Phenanthrofuran System. *J. Am. Chem. Soc.* **2009**, *131*, 11402–11406. [CrossRef]
32. Market Research Future. Global Morphine Market Overview. Available online: https://www.marketresearchfuture.com/reports/morphine-market-10643 (accessed on 3 September 2024).
33. Barreiro, E.J. Sobre a química dos remédios, dos fármacos e dos medicamentos. *Cad. Temáticos De Química Nova Na Esc.* **2001**, *3*, 4–9.
34. Lee, S.-H.; Kim, D.-S.; Park, S.-H.; Park, H. Phytochemistry and Applications of *Cinnamomum camphora* Essential Oils. *Molecules* **2022**, *27*, 2695. [CrossRef]
35. Poudel, D.; Rokaya, A.; Ojha, P.; Timsina, S.; Satyal, R.; Dosoky, N.; Satyal, P.; Setzer, W. The Chemical Profiling of Essential Oils from Different Tissues of *Cinnamomum camphora* L. and Their Antimicrobial Activities. *Molecules* **2021**, *26*, 5132. [CrossRef]
36. Chen, W.; Vermaak, I.; Viljoen, A. Camphor-A Fumigant during the Black Death and a Coveted Fragrant Wood in Ancient Egypt and Babylon-A Review. *Molecules* **2013**, *18*, 5434–5454. [CrossRef] [PubMed]
37. Anjaneyulu, B.; Saini, N. A Study on Camphor Derivatives and Its Applications: A Review. *Curr. Org. Chem.* **2021**, *25*, 1404–1428. [CrossRef]
38. Ayliffe, G.; Babb, J.; Quoraishi, A. A test for 'hygienic' hand disinfection. *J. Clin. Pathol.* **1978**, *31*, 923–928. [CrossRef] [PubMed]

39. Otherson, M.J.; Otherson, H.B., Jr. A history of hand washing: Seven hundred years at a snail's pace. *Pharos* **1987**, *23*, 7–10. [PubMed]
40. Verbund für Angewandte Hygiene (VAH) e.V. As a biocidal active substance, ethanol is indispensable for hygienic hand disinfection. *Zentralsterilization* **2020**, *28*, 354–359. Available online: https://vah-online.de/files/download/vah-mitteilungen/VAH_Ethanol_ZT_6_20_354_359_en.pdf (accessed on 3 September 2024).
41. Rasmussen, S.C. From Aqua Vitae to E85: The History of Ethanol as a Fuel. *Substantia* **2019**, *3* (Suppl. S1), 43–55. [CrossRef]
42. Sarathy, S.; Oßwald, P.; Hansen, N.; Kohse-Höinghaus, K. Alcohol combustion chemistry. *Progress in Energy and Combustion, Science* **2014**, *44*, 40–102. [CrossRef]
43. Bédoyère, G. The Discovery of Penicillin. *Br. Med. J.* **1955**, *1*, 711. [CrossRef]
44. Sheehan, J.C.; Henery-Logan, K.R. The total synthesis of penicillin V. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263. [CrossRef]
45. Kardos, N.; Demain, A. Penicillin: The medicine with the greatest impact on therapeutic outcomes. *Appl. Microbiol. Biotechnol.* **2011**, *92*, 677–687. [CrossRef]
46. Ferreira, M.V.C.; Paes, V.R.; Lichtenstein, A. Penicillin: Eighty years. *Rev. Med.* **2008**, *87*, 272–276.
47. Patrick, G.L. *An Introduction to Medicinal Chemistry*, 5th ed.; Oxford University Press: Oxford, UK, 2012; Chapter 19; pp. 427–435. ISBN 978-0-19-969739-7.
48. Nawaz, W.; Bashir, H. Managing the unintended consequences of radical sustainability innovations: The case of catastrophic failure of leaded gasoline industry. *J. Clean. Prod.* **2022**, *375*, 134175. [CrossRef]
49. Chauhan, A.; Singh, J. Biodegradation of DDT. *J. Text. Sci. Eng.* **2015**, *5*, 100183. [CrossRef]
50. Spindler, M. DDT: Health aspects in relation to man and risk/benefit assessment based thereupon. *Residue Rev.* **1983**, *90*, 1–34. [CrossRef]
51. Kim, J.; Sun, Q.; Yue, Y.; Yoon, K.; Whang, K.; Clark, J.; Park, Y. 4,4′-Dichlorodiphenyltrichloroethane (DDT) and 4,4′-dichlorodiphenyldichloroethylene (DDE) promote adipogenesis in 3T3-L1 adipocyte cell culture. *Pestic. Biochem. Physiol.* **2016**, *131*, 40–45. [CrossRef]
52. Lim, B.H. *DDT Chemistry, Metabolism and Toxicity*; United States Environmental Protection Agency: Washington, DC, USA, 1972; pp. 1–119.
53. Carson, R. *Silent Spring*, 1st ed.; Houghton Mifflin: Boston, MA, USA, 1962.
54. McLaughlin, Dorothy. "Fooling with Nature: Silent Spring Revisited". Frontline. PBS. Available online: https://www.pbs.org/wgbh/pages/frontline/shows/nature/disrupt/sspring.html (accessed on 12 August 2024).
55. Villa, R.; Dores, E.; Carbo, L.; Cunha, M. Dissipation of DDT in a heavily contaminated soil in Mato Grosso, Brazil. *Chemosphere* **2006**, *64*, 549–554. [CrossRef]
56. Yogui, G.; Santos, M.; Bertozzi, C.; Montone, R. Levels of persistent organic pollutants and residual pattern of DDTs in small cetaceans from the coast of São Paulo, Brazil. *Mar. Pollut. Bull.* **2010**, *60*, 1862–1867. [CrossRef]
57. Rissato, S.; Galhiane, M.; Ximenes, V.; Andrade, R.; Talamoni, J.; Libânio, M.; Almeida, M.; Apon, B.; Cavalari, A. Organochlorine pesticides and polychlorinated biphenyls in soil and water samples in the Northeastern part of São Paulo State, Brazil. *Chemosphere* **2006**, *65*, 1949–1958. [CrossRef]
58. Rodrigues, A.; Souza, L.; Rocha, C.; Costa, A.; Mendes, R. Assessment of DDT and Metabolites in Soil and Sediment of Potentially Contaminated Areas of Belém, Amazon Region, Brazil. *Bull. Environ. Contam. Toxicol.* **2017**, *99*, 125–130. [CrossRef]
59. Oliveira, R.M. Cidade dos Meninos, Duque de Caxias, RJ, Brazil, Brazil. Ph.D. Thesis, Escola Nacional de Saúde Pública Sérgio Arouca, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil, 2008. 455 f.
60. Bulcão, L. Families Begin to Be Removed After 48 Years of Contamination in Rio de Janeiro. Available online: https://g1.globo.com/rio-de-janeiro/noticia/2013/05/familias-comecam-ser-removidas-apos-48-anos-de-contaminacao-no-rj.html (accessed on 8 August 2024).
61. Camargo, S. Available online: https://conexaoplaneta.com.br/blog/pesticidas-provocam-declinio-assustador-de-aves-na-europa/#fechar (accessed on 8 August 2024).
62. Vicente, E.C.; Guedes, N.M.R. Organophosphate poisoning of Hyacinth Macaws in the Southern Pantanal, Brazil. *Sci. Rep.* **2021**, *11*, 5602. [CrossRef]
63. Agrotóxico Pode ter Causado a Morte de 12 Milhões de Abelhas No Noroeste Gaúcho. Available online: https://www.jornaldocomercio.com/_conteudo/economia/2019/01/664117-agrotoxico-pode-ter-causado-a-morte-de-12-milhoes-de-abelhas-no-noroeste-gaucho.html (accessed on 8 August 2024).
64. Torres, A. The Pesticide That Killed 50 Million Bees in Santa Catarina in a Single Month. Available online: https://www.bbc.com/portuguese/brasil-49657447 (accessed on 8 August 2024).
65. Aplicação Errada de Agrotóxico. Available online: https://g1.globo.com/jornal-hoje/noticia/2023/07/19/cerca-de-600-colmeias-sao-intoxicadas-em-mt-apos-aplicacao-errada-de-agrotoxico.ghtml (accessed on 8 August 2024).

66. Arachi, D.; Soeberg, M.; Chimed-Ochir, O.; Lin, R.T.; Takahashi, K. Trend in the Global Incidence of Mesothelioma: Is There Any Changing Trend After Asbestos Regulation and Ban? In *Malignant Pleural Mesothelioma. Respiratory Disease Series: Diagnostic Tools and Disease Managements*; Nakano, T., Kijima, T., Eds.; Springer: Singapore, 2021. [CrossRef]
67. Mossman, B.; Bignon, J.; Corn, M.; Seaton, A.; Gee, J. Asbestos: Scientific developments and implications for public policy. *Science* **1990**, *247*, 294–301. [CrossRef] [PubMed]
68. Mesothelioma & Asbestos Worldwide. Available online: https://www.asbestos.com/mesothelioma/worldwide/ (accessed on 8 August 2024).
69. Marsili, D.; Terracini, B.; Santana, V.S.; Ramos-Bonilla, J.P.; Pasetto, R.; Mazzeo, A.; Loomis, D.; Comba, P.; Algranti, E. Prevention of Asbestos-Related Disease in Countries Currently Using Asbestos. *Int. J. Environ. Res. Public Health* **2016**, *13*, 494. [CrossRef] [PubMed]
70. Mine Production of Asbestos Worldwide from 2010 to 2023. Available online: https://www.statista.com/statistics/264924/world-mine-production-of-asbestos-since-2007/ (accessed on 8 August 2024).
71. Vargesson, N. Thalidomide-induced teratogenesis: History and mechanisms. *Birth Defects Res. Part C Embryo Today Rev.* **2015**, *105*, 140–156. [CrossRef]
72. Thalidomine org. Available online: http://www.thalidomide.org (accessed on 9 August 2024).
73. Emanuel, M.; Rawlins, M.; Duff, G.; Breckenridge, A. Thalidomide and its sequelae. *Lancet* **2012**, *380*, 781–783. [CrossRef]
74. Ward, S.P. Thalidomide and Congenital Abnormalities. *Br. Med. J.* **1962**, *2*, 646–647. [CrossRef]
75. John, F. Kennedy and People with Intellectual Disabilities. Available online: https://www.jfklibrary.org/learn/about-jfk/jfk-in-history/john-f-kennedy-and-people-with-intellectual-disabilities (accessed on 8 August 2024).
76. Gordon, G.B.; Spielberg, S.P.; Blake, D.A.; Balasubramanian, V. Thalidomide teratogenesis: Evidence for a toxic arene oxide metabolite. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 2545–2548. [CrossRef]
77. Baldwin, H.J.; Droege, M.; Daniel, K.L. A message from the Vioxx case. *Am. J. Health-Syst. Pharm.* **2006**, *63*, 503. [CrossRef]
78. Fielder, J. The Vioxx debacle. IEEE Engineering. *Med. Biol. Mag.* **2005**, *24*, 106–109. [CrossRef]
79. Lead Poisoning and Rome. Available online: https://penelope.uchicago.edu/~grout/encyclopaedia_romana/wine/leadpoisoning.html (accessed on 10 August 2024).
80. History of Lead Poisoning in the World. Dr. Herbert L. Needleman. Available online: https://lead.org.au/history_of_lead_poisoning_in_the_world.htm (accessed on 10 August 2024).
81. Nature's Warnings Lessons Not Learned: The Vital Lead. Available online: https://www.youtube.com/watch?v=qqs4TZx-p1w (accessed on 10 August 2024).
82. Sarkar, C.G. Tetraethyllead (TEL) in Gasoline as a Case of Contentious Science and Delayed Regulation: A Short Review. *Orient. J. Chem.* **2020**, *36*, 86–92. [CrossRef]
83. Junior Midgley, T. Chemistry in the Next Century. *Ind. Eng. Chem.* **1935**, *27*, 494–498. [CrossRef]
84. Viana, H.; Porto, P.; Junior Midgley, T. The Development of New Substances: A Case Study for Chemical Educators. *J. Chem. Educ.* **2013**, *90*, 1632–1638. [CrossRef]
85. Viana, H.E.B.; Porto, P.A. The development of new substances in the first half of the twentieth century: The case of Thomas Midgley, Jr. *Circumscribere Int. J. Hist. Sci.* **2012**, *12*, 16–30. Available online: https://revistas.pucsp.br/index.php/circumhc/article/view/13364/10193 (accessed on 8 October 2024).
86. Fuoss, R.M. *Charles August Kraus 1875–1967*; National Academy of Sciences: Washington, DC, USA, 1971; pp. 119–159.
87. Kraus, C.A.; Callis, C.C. Studies relating to metallo-organic compounds. I. Introduction. II. The equivalent conductance of Trimethylstannyl chloride in ethyl alcohol. *J. Am. Chem. Soc.* **1923**, *45*, 2628. [CrossRef]
88. Nickerson, S.P. Tetraethyllead: A product of American research. *J. Chem. Educ.* **1954**, *31*, 560–571. [CrossRef]
89. Kovarik, W. Ethyl-leaded Gasoline: How a Classic Occupational Disease Became an International Public Health Disaster. *Int. J. Occup. Environ. Health* **2005**, *11*, 384–397. [CrossRef]
90. Tolan, E.; Lingl, F. Model Psychosis Produced by Inhalation of Gasoline Fumes. *Am. J. Psychiatry* **1964**, *120*, 757–761. [CrossRef]
91. Law, W.; Nelson, E. Gasoline-sniffing by an adult. Report of a case with the unusual complication of lead encephalopathy. *JAMA* **1968**, *204*, 1002–1004. [CrossRef]
92. Navas-Acien, A.; Guallar, E.; Silbergeld, E.K.S.; Rothenberg, J. Lead exposure and cardiovascular disease—A systematic review. *Environ. Health Perspect.* **2007**, *115*, 472–482. [CrossRef]
93. Landrigan, P.J.; Boffetta, P.; Apostoli, P. The reproductive toxicity and carcinogenicity of lead: A critical review. *Am. J. Ind. Med.* **2000**, *38*, 231–243. [CrossRef]
94. Bethell, M. Toxic Psychosis Caused by Inhalation of Petrol Fumes. *Br. Med. J.* **1965**, *2*, 276–277. [CrossRef]
95. Tetraethyllead—Toxicity. Available online: https://chem.libretexts.org/Ancillary_Materials/Exemplars_and_Case_Studies/Case_Studies/Tetraethyllead (accessed on 10 August 2024).

96. Reuben, A.; Caspi, A.; Belsky, D.W.; Broadbent, J.; Harrinton, H.; Sugden, K.; Houts, R.M.; Ramrakha, S.; Poulton, R.; Moffit, T.E. Association of Childhood Blood Lead Levels with Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. *JAMA* **2017**, *317*, 1244–1251. [CrossRef] [PubMed]
97. Nriagu, J. The rise and fall of leaded gasoline. *Sci. Total Environ.* **1990**, *92*, 13–28. [CrossRef]
98. Needleman, H. The removal of lead from gasoline: Historical and personal reflections. *Environ. Res.* **2000**, *84*, 20–35. [CrossRef]
99. Hoover, R.N.; Hyer, M.; Pfeiffer, R.M.; Adam, E.; Bond, B.; Cheville, A.L.; Colton, T.; Troisi, R. Adverse Health Outcomes in Women Exposed in Utero to Diethylstilbestrol. *N. Engl. J. Med.* **2011**, *365*, 1304–1314. [CrossRef]
100. Giusti, R.M.; Iwamoto, K.; Hatch, E.E. Diethylstilbestrol Revisited: A Review of the Long-Term Health Effects. *Ann. Intern. Med.* **1995**, *122*, 10. [CrossRef]
101. Herbst, A.; Ulfelder, H.; Poskanzer, D.; Longo, L. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *Am. J. Obstet. Gynecol.* **1999**, *181*, 1574–1575. [CrossRef]
102. Herbst, A.; Kurman, R.; Scully, R. Vaginal and Cervical Abnormalities After Exposure to Stilbestrol in Utero. *Obstet. Gynecol.* **1972**, *40*, 287–298. [CrossRef]
103. James, R.C.; Busch, H.; Tamburro, C.H.; Roberts, S.M.; Schell, J.D.; Harbison, R.D. Polychlorinated Biphenyl Exposure and Human Disease. *J. Occup. Environ. Med.* **1993**, *35*, 136–148. [CrossRef]
104. Montano, L.; Pironti, C.; Pinto, G.; Ricciardi, M.; Buono, A.; Brogna, C.; Venier, M.; Piscopo, M.; Amoresano, A.; Motta, O. Polychlorinated Biphenyls (PCBs) in the Environment: Occupational and Exposure Events, Effects on Human Health and Fertility. *Toxics* **2022**, *10*, 365. [CrossRef]
105. Orlinskiĭ, D.; Priputina, I.; Popova, A.; Shalanda, A.; Tsongas, T.; Hinman, G.; Butcher, W. Influence of Environmental Contamination with PCBs on Human Health. *Environ. Geochem. Health* **2001**, *23*, 313–328. [CrossRef]
106. Schecter, A.; Colacino, J.; Haffner, D.; Patel, K.; Opel, M.; Päpke, O.; Birnbaum, L. Perfluorinated Compounds, Polychlorinated Biphenyls, and Organochlorine Pesticide Contamination in Composite Food Samples from Dallas, Texas, USA. *Environ. Health Perspect.* **2010**, *118*, 796–802. [CrossRef] [PubMed]
107. Ross, G. The public health implications of polychlorinated biphenyls (PCBs) in the environment. *Ecotoxicol. Environ. Saf.* **2004**, *59*, 275–291. [CrossRef] [PubMed]