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Role of the Synergistic Interactions of Environmental Pollutants in the Development of Cancer

Francisco Alejandro Lagunas-Rangel[1], Jenni Viivi Linnea-Niemi[1], Błażej Kudłak[2], Michael J. Williams[1], Jörgen Jönsson[1], and Helgi B. Schiöth[1,3]

[1]Department of Surgical Sciences, Functional Pharmacology and Neuroscience, Uppsala University, Uppsala, Sweden, [2]Faculty of Chemistry, Department of Analytical Chemistry, Gdańsk University of Technology, Gdańsk, Poland, [3]Institute of Translational Medicine and Biotechnology, I. M. Sechenov First Moscow State Medical University, Moscow, Russia

Abstract There is a growing awareness that the large number of environmental pollutants we are exposed to on a daily basis are causing major health problems. Compared to traditional studies that focus on individual pollutants, there are relatively few studies on how pollutants mixtures interact. Several studies have reported a relationship between environmental pollutants and the development of cancer, even when pollutant levels are below toxicity reference values. The possibility of synergistic interactions between different pollutants could explain how even low concentrations can cause major health problems. These intricate that molecular interactions can occur through a wide variety of mechanisms, and our understanding of the physiological effects of mixtures is still limited. The purpose of this paper is to discuss recent reports that address possible synergistic interactions between different types of environmental pollutants that could promote cancer development. Our literature studies suggest that key biological pathways are frequently implicated in such processes. These include increased production of reactive oxygen species, activation by cytochrome P450, and aryl hydrocarbon receptor signaling, among others. We discuss the need to understand individual pathological vulnerability not only in relation to basic genetics and gene expression, but also in terms of measurable exposure to contaminants. We also mention the need for significant improvements in future studies using a multitude of disciplines, such as the development of high-throughput study models, better tools for quantifying pollutants in cancer patients, innovative pharmacological and toxicological studies, and high-efficiency computer analysis, which allow us to analyze the molecular mechanisms of mixtures.

Plain Language Summary In general, every day we are exposed to many pollutants at the same time, and each pollutant can interact with others in different ways. Notably, two or more pollutants can interact and enhance their effects through a phenomenon called synergy and this would explain why, even at low concentrations, pollutants can have important health effects. Several studies have reported a link between environmental pollutants and cancer. Thus, our review of the literature suggests that synergy phenomena between pollutants can alter key points in cells and facilitate cancer development. Similarly, we mention the complications and needs to assess these complex interactions in subsequent studies.

1. Introduction

Humanity has altered the planet in multiple ways. Global warming; biodiversity loss; and pollution of land, water, and air are just a few of the myriad human-caused environmental problems (T. A. Burke et al., 2017). However, these problems have also had an impact on humanity itself, including an increase in health problems related to poor environmental and earth conditions (Martin et al., 2009). Environmental pollutants are compounds that have been released into the ecosystem and can pose a serious threat to the well-being of living things. These compounds have been suggested to be responsible for approximately 9 million deaths per year, which correspond to 16% of all deaths worldwide. Indeed, three times more deaths than AIDS, tuberculosis, and malaria combined (Landrigan et al., 2018). Because of the notable adverse effects in different areas of our lives, it has been suggested that pollution research has not received enough attention by international development and global health programs, and that the effects of environmental pollutants on health are underestimated in the calculations of the global burden of disease (Landrigan et al., 2019). Furthermore, joint exposure to various environmental pollutants is almost always overlooked in the regulatory framework and a harmonized and consistent approach to conducting mixture risk assessments and management is lacking (Bopp et al., 2018).

Key Points:

- There are an increasing number of reports on the synergetic actions of pollutants in cancer
- Mixtures of pollutants can interact (synergy/antagonism) affecting different biological pathways
- Key pathways frequently implicated in synergetic action are reactive oxygen species, cytochrome P450, and aryl hydrocarbon receptor

Correspondence to:
F. A. Lagunas-Rangel and H. B. Schiöth, Francisco.lagunas@neuro.uu.se; Helgi.Schioth@neuro.uu.se

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Author Contributions:
Conceptualization: Francisco Alejandro Lagunas-Rangel, Jenni Viivi Linnea-Niemi, Helgi B. Schiöth
Data curation: Francisco Alejandro Lagunas-Rangel, Jenni Viivi Linnea-Niemi

Formal analysis: Francisco Alejandro Lagunas-Rangel
Funding acquisition: Błażej Kudłak, Helgi B. Schiöth
Investigation: Francisco Alejandro Lagunas-Rangel, Jenni Viivi Linnea-Niemi
Writing – original draft: Francisco Alejandro Lagunas-Rangel, Jenni Viivi Linnea-Niemi
Writing – review & editing: Francisco Alejandro Lagunas-Rangel, Jenni Viivi Linnea-Niemi, Błażej Kudłak, Michael J. Williams, Jörgen Jönsson, Helgi B. Schiöth

Since environmental pollutants are in principle ubiquitous and many of them are quite resistant to degradation, we are exposed to numerous on a daily basis. These include atmospheric air, plastic food and beverage containers, cosmetics, sunscreens, perfumes, cleaning products, and garden products that may contain pollutants or be pollutants themselves. Furthermore, geogenic pollutants (elements and their species occurring naturally in geogenic sources, such as rocks, minerals, and toxic metals) have a strong, often underestimated and permanent influence (Bundschuh et al., 2017). Pollutants can enter our body by different routes, for example, by ingestion, inhalation, or absorption (Iqubal et al., 2020). A growing body of epidemiological evidence as well as a better understanding of the mechanisms that link toxic substances to disease development suggests that exposure to some environmental pollutants may lead to an increased risk cancer development (Goodson et al., 2015; Koual et al., 2020). Several studies have raised the role of exposure to low doses of environmental pollutants in cancer initiation as well as cancer progression, suggesting that these compounds may promote cancer invasion and metastasis (Goodson et al., 2015; Koual et al., 2020; Lagunas-Rangel et al., 2022; Ochieng et al., 2015).

Most environmental pollutants are present only in small amounts in the environment, almost always below threshold values for toxicity and in the form of complex mixtures, where different types of interactions between the components can occur (Goodson et al., 2015). Synergy occurs when the interaction between two or more factors makes the total effect greater than the sum of the individual effects, while additivity describes a situation in which the overall effect caused by a combination of compounds is the sum of the effects of each individual agent. In contrast, antagonism occurs between two or more compounds that cause opposite effects and therefore, the effect is weaker than that of each individual agent (Geary, 2013; J. Niu et al., 2019; Tang et al., 2015). It is important to be aware that pollutant cocktails can arise as premade mixtures that are released from an emitting source or as mixtures that are formed when combined in the same environmental compartment although they are released from different sources. Furthermore, various pollutants can accumulate and interact in our body over time (Boobis et al., 2011). Laboratory and epidemiological studies have shown that there are synergies between pollutants (Cedergreen, 2014; Goodson et al., 2015; Jatkowska et al., 2021; Kudłak et al., 2019; Oliver et al., 2020), and these may occur through a wide variety of mechanisms. For example, two compounds could act in the same step or in different steps in the same mechanistic pathway, the presence of one could influence the ability to mitigate the action of the other, or the presence of one could influence the available fraction/dose of another. These mechanisms are often underestimated and can lead to both a decrease and an increase in the summary toxicity of xenobiotic cocktails in exposed organisms. This could explain how pollutants with low or minute concentrations can promote the development of various diseases and have devastating effects, including death (Lupu et al., 2020; Mauderly & Samet, 2009). Furthermore, as a consequence, there are currently serious doubts that compliance with individual environmental quality standards sufficiently protects against the toxicity of mixtures, and an increasing number of contaminants requires prioritization with respect to monitoring and evaluation (Brack, 2015).

The synergy between different carcinogenic pollutants is a subject that has few published studies, mainly because the effects of mixtures are difficult to investigate for several reasons. The shared number of contaminants in different sources and the exponential number of different combinations that need to be tested are enormous. Furthermore, this problem is compounded by the fact that synergistic or antagonistic effects can be dose dependent and vary widely within different experimental organisms and systems.

2. Aims and Methods

The overall aim of this article is to present those mixtures of environmental pollutants that have shown carcinogenic synergy as well as to try to identify and explain how these interactions occur and the pathways and molecular mechanisms associated with enhancing their effects. This review is based on evidence collected by performing a PubMed query using the words “cancer AND pollutants AND synergy” as search terms. The search strategy was implemented by manually searching the references reported by the most relevant studies on this topic.

3. Mechanisms Linked to Carcinogenesis by Environmental Pollutants

Several studies have shown that environmental pollutants affect cancer development and progression and these have been featured in various reviews (Boffetta, 2006; Brody et al., 2007; Koual et al., 2020; Lagunas-Rangel et al., 2022; Wahlang, 2018). For example, some environmental pollutants can promote sustained growth by

affecting the cell cycle or prevent apoptosis by avoiding activation of the intrinsic and/or extrinsic pathways. Other pollutants have been shown to promote angiogenesis by facilitating the secretion of factors, such as vascular endothelial growth factor, fibroblast growth factor, and tumor necrosis factor-alpha (TNF-α); while others activate invasion and metastasis by stimulating epithelial-to-mesenchymal transition (EMT) and metalloprotease secretion as well as promote genomic instability and chronic inflammation (Boffetta, 2006; Koual et al., 2020; Santibáñez-Andrade et al., 2019).

It is noteworthy that urban air contains a mixture of multiple pollutants that are responsible for nearly 30% of lung cancer that develops each year (Santibáñez-Andrade et al., 2019). Microplastics and their components, such as bisphenol A (BPA) analogs and phthalates, can pose a high risk of different diseases, including cancer, by acting directly on other compounds and allowing their accumulation in the body (Rajmohan et al., 2019; Sharma et al., 2020). Meanwhile, the dietary intake of persistent organic pollutants (POPs) has been linked to obesity and the development of breast cancer (Crouse et al., 2010). Also, among POPs, there is a large group of highly potent xenobiotics, known as endocrine disrupting compounds, which can induce and accelerate the development of hormone-dependent cancers (Lecomte et al., 2017; Wahlang, 2018). Furthermore, heavy metals can also increase the probability of developing cancer through different mechanisms, including increased reactive oxygen species (ROS) generation, inducing DNA breaks and disabling its repair, as well as modifying cellular structure and microenvironment (W. Yuan et al., 2016).

Based on these foundations, we conducted an extensive literature search looking for articles that use the word synergy in the context of environmental pollution and cancer. A list of relevant articles is found in Table 1. The identification of mechanisms suggested in these articles frequently mentions three important general systems related to ROS, metabolism by cytochrome P450, and aryl hydrocarbon receptor (AhR) signaling. Below, we present a more detailed description of these mechanisms and how they relate to cancer development in order to provide an introduction to the next section that addresses the carcinogenic synergy of environmental pollutants.

3.1. Overproduction of Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) are formed as cellular by-products of normal aerobic oxygen metabolism in mitochondria, endoplasmic reticulum (ER), and peroxisomes by enzymatic (NADPH oxidases (NOXs), endothelial nitric oxide synthase, xanthine oxidase, arachidonic acid, lipoxygenase, enzymes of cytochrome P450, and cyclooxygenase), and/or nonenzymatic (mitochondrial respiratory chain) mechanisms. In normal cells, ROS are present at low and stationary levels and play an important role in cell signaling and homeostasis. During various pathological processes, including cardiovascular, neurological, diabetes, and cancer, ROS levels increase (Kirtonia et al., 2020; Lagunas-Rangel, 2020). At high concentrations, ROS readily react with proteins, lipids, carbohydrates, and nucleic acids, causing irreversible functional alterations or even complete destruction. Because of this, cells developed sophisticated strategies to keep ROS concentrations under tight control, and these include antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPxs), peroxiredoxins, and thioredoxins) and antioxidant scavengers (ascorbate, glutathione (GSH), tocopherol, flavonoids, alkaloids, and carotenoids; Brieger et al., 2012). However, natural antioxidant defenses are not always sufficient to maintain proper ROS balance. Exposure to environmental pollutants, mainly xenoestrogens, pesticides, and heavy metals, can cause the overproduction of ROS within cells and their subsequent intercellular transport (Al-Gubory, 2014). The deregulation of ROS balance contributes to the formation of tumors through the activation of several oncogenic signaling pathways, DNA mutations, promoting immunological escape and a tumor microenvironment, metastasis, angiogenesis, and telomere extension (Rodic & Vincent, 2018). It is known that environmental pollutants can induce a greater production of ROS either by producing them directly, by increasing oxidative metabolism, by damaging the mitochondrial structure, or by promoting an inflammatory environment (Figure 1). They can also interfere with antioxidant mechanisms by preventing the expression or activity of the enzymes involved, by consuming the reserves of these enzymes, or by interfering with the metabolic pathways involved in the production of antioxidant scavengers (Al-Gubory, 2014; Drzeżdżon et al., 2018).

3.2. Chemical Activation by Cytochrome P450

Cytochrome P450 is a large and diverse superfamily of hemeproteins that generally participate in the terminal reactions of the electron transfer chain. Cytochrome P450 enzymes have been extensively studied due to their

Table 1
Mixtures of Environmental Pollutants That Have Been Described Presenting Synergistic Carcinogenic Effects and Different Factors That Were Important in the Synergy Mechanisms

Mixtures of environmental pollutants that exhibit synergy		Factors associated with synergy mechanisms								References
		ROS	Cytochrome P450	AhR	GSH levels	Mitochondrial depolarization	Lipid peroxidation	p53 mutations	Anti-apoptotic factors	
Asbestos and cigarette smoke		X			X		X	X		X. Wang et al. (1995)
										Kamp et al. (1998)
										Jung et al. (2000)
POPs mixtures	POPs	X	X	X	X	X	X			Rainey et al. (2017)
										Hansen et al. (2019)
	POPs and AOM	X	X					X	X	Hansen et al. (2019)
TMA and its metabolites		X	X		X	X				Qiu et al. (2021)
Microplastics and heavy metals	PP and cadmium	X			X					Zhou et al. (2020)
	PS nanoplastics and gold ions	X				X				Lee et al. (2019)
	PS, NOM, and copper	X								Qiao et al. (2019)
HANs		X	X		X		X			Lu et al. (2018)
										C. G. Park et al. (2021)
BaP and PAHs	Arsenic and BaP	X		X						Z. Wang et al. (2020)
	BaP and UVA radiation	X					X	X		K. E. Burke and Wei (2009)
										Xia et al. (2015)
	PAHs and HPV		X					X		C. Zhang et al. (2019)
BPA mixtures	BPA and PS	X				X				Q. Wang et al. (2020)
	BPA and 4-CP								X	X. Wang et al. (2020)
Nanoplastics and organochlorides	TMDC nanosheets and organochlorides	X					X			P. Yuan et al. (2020)
Aflatoxins and other fungal toxins	Aflatoxins and hepatitis virus	X	X							Henry et al. (2002)
										Zhao et al. (2021)
										Y. Niu et al. (2021)
	Alternaria alternata toxins		X	X						Hohenbichler et al. (2020)

Note. Apparently, ROS overproduction and metabolism by cytochrome P450 are the mechanisms most involved in mediating carcinogenic synergies between the environmental pollutants described. Note that this table takes only the factors mentioned in the articles although probably many more factors are relevant in the synergy. ROS, Reactive oxygen species; GSH, Glutathione; AhR, Aryl hydrocarbon receptor; POPs, Persistent organic pollutants; AOM, Azoxymethane; TMA, Trimethylamine; PP, Polypropylene; HANs, Haloacetonitriles; PAHs, Polycyclic aromatic hydrocarbons; BaP, Benzo(a)pyrene; UVA, Ultraviolet A; BPA, Bisphenol A; 4-CP, 4-cumylphenol; TMDC, Transition-metal dichalcogenide; HPV, Human papillomavirus; PS, Polystyrene; NOM, Natural organic matter.

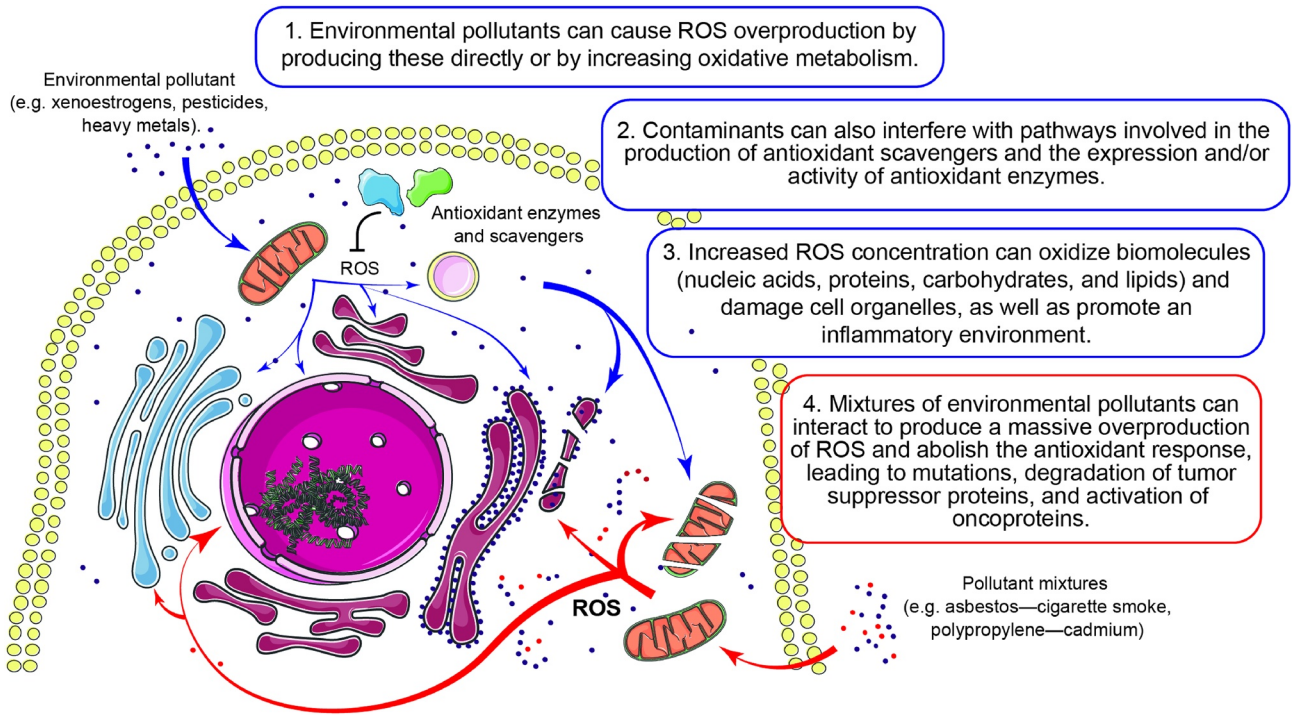

Figure 1. Overproduction of reactive oxygen species (ROS) and effects on antioxidant mechanisms by environmental pollutants. Environmental pollutants such as xenoestrogens, pesticides, and heavy metals can cause ROS overproduction both directly and by increasing oxidative metabolism. They can also prevent the expression or activity of antioxidant enzymes and affect the pathways involved in the production of antioxidant scavengers. Meanwhile, some mixtures of pollutants, such as asbestos and cigarette smoke, propylene and cadmium, and nanoplastics and gold ions can interact in such a way that their effects are potentiated, producing more ROS than with individual pollutants. These ROS subsequently cause damage to biomolecules and organelles as well as promote an inflammatory environment, all of these facilitating the development of cancer.

prominent role in the elimination of drugs (Goodsell, 2001; Nebert & Dalton, 2006; Wahlang et al., 2015). These enzymes play a fundamental role in the oxidative phase of metabolism (phase I) of both endogenous and exogenous substances (Mittal et al., 2015). Some environmental pollutants are strongly hydrophobic in their intrinsic nature and to make them more hydrophilic and easier to remove from the body, they become substrates for some isoforms of P450 (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2E1, and CYP3A4). Therefore, these compounds are oxidized and some of them can become carcinogens or more powerful carcinogens than the parent compounds (Figure 2) as is the case with many polycyclic aromatic hydrocarbons (PAHs) and some persistent organic pollutants (POPs; Croom, 2012). These carcinogenic compounds can bind to DNA forming adducts that subsequently generate DNA breaks and mutations. They can also can cause an increase in ROS or inactivate proteins that prevent carcinogenesis, such as p53 and Rb (Alzahrani & Rajendran, 2020).

3.3. Activation of Aryl Hydrocarbon Receptor (AhR) Signaling

AhR is a ligand-activated transcription factor that influences the expression of a myriad of genes involved in a wide variety of biochemical pathways, including energy metabolism, lipid and cholesterol synthesis, xenobiotic metabolism, and various transport pathways (Paris et al., 2021). Overall, AhR remains in the cytoplasm in complex with HSP90, AhR-interacting protein (AIP), p23, and Src40, but once it interacts with any of its ligands, AhR dissociates from an AIP/Src40 complex and moves to the nucleus, where it then dissociates from HSP90 and p23. Once free in the nucleus, AhR dimerizes with Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) and binds to its consensus aryl hydrocarbon response element. Different sets of genes are activated by different AhR ligands, but they include several cytochrome P450 enzymes, factors that regulate the expression of antioxidant proteins, and cytokines that stimulate cell survival and proliferation, among other direct and indirect factors (Murray et al., 2014). Several environmental pollutants and their metabolites exhibit a high affinity to AhR, mainly represented by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), while others have a medium or low affinity, and some others can indirectly activate this signaling pathway (Figure 3). Regardless of this, chronic activation

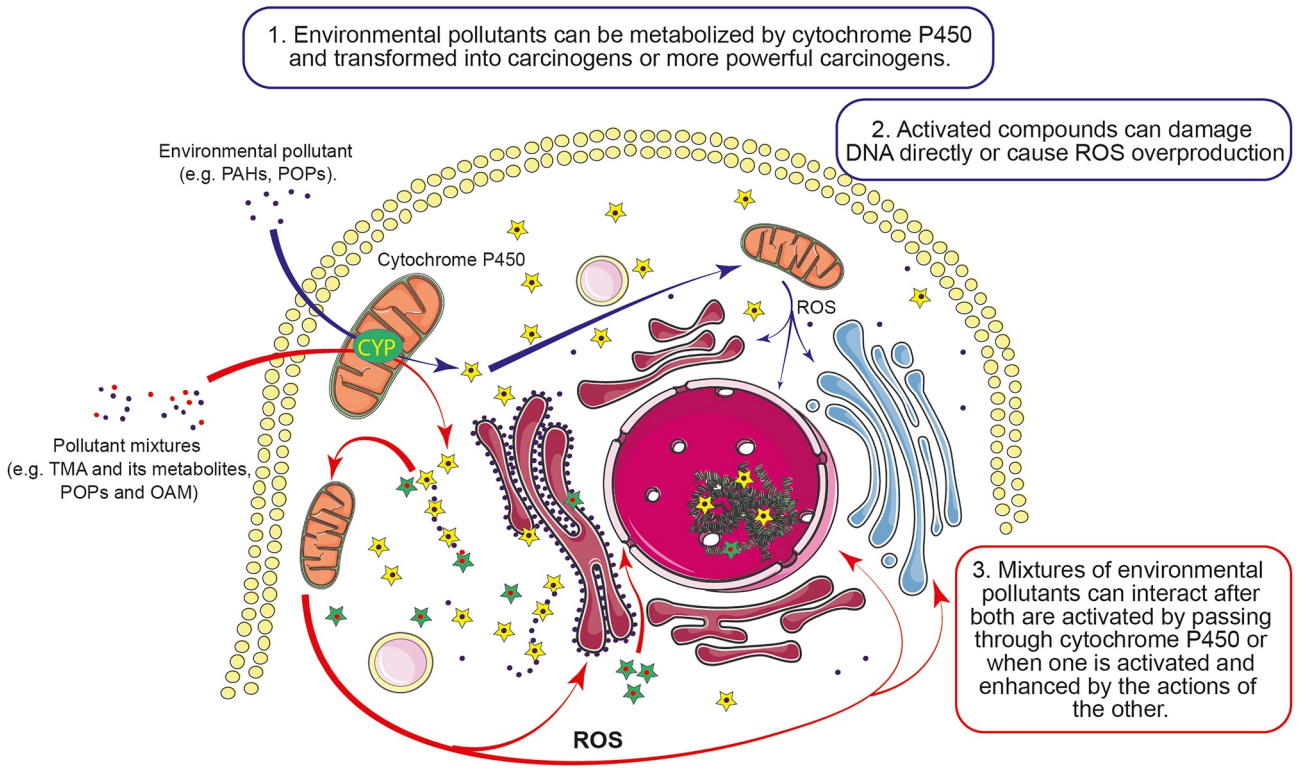

Figure 2. Activation of environmental pollutants by cytochrome P450. By passing through cytochrome P450, environmental pollutants, such as polycyclic aromatic hydrocarbons and persistent organic pollutants (POPs), can become carcinogens or enhance these properties. Now, with mixtures of pollutants, such as TMA and its metabolites, which cross and interact in cytochrome, it is possible to generate more reactive oxygen species (ROS) and consequently more mutations and conditions for the development of cancer. Also, mixtures of pollutants, such as POPs and AOM, can act in two steps, the first to generate ROS that damage DNA, membranes and proteins and the second to promote the production of 6-O methylguanine that later generates DNA breaks.

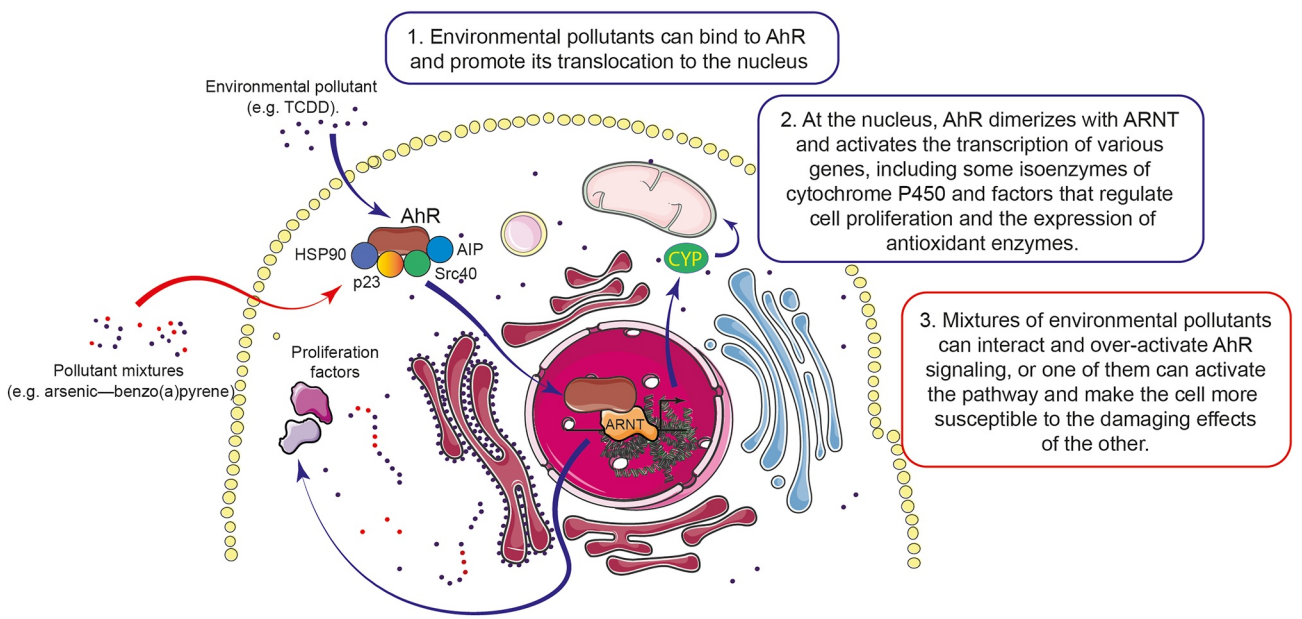

Figure 3. Activation of aryl hydrocarbon receptor (AhR) signaling by environmental pollutants. Environmental pollutants such as the pesticide TCDD can cross the membrane and bind to AhR in the cytoplasm, causing this protein to translocate to the nucleus and dimerize with ARNT. The AhR-ARNT dimer binds to its response elements and promotes transcription of its target genes that include cytochrome P450 isoenzymes. Mixtures of pollutants such as those with different persistent organic pollutants and arsenic and benzo(a)pyrene can cause an overactivation of this metabolic pathway with its consequent stimulation of cell survival and proliferation.

of AhR signaling has been observed in various types of cancers, such as thyroid, breast, lung, and ovary, where it participates in the main stages of carcinogenesis (initiation, promotion, progression, and metastasis). Studies of aggressive tumors and tumor cell lines show increased levels of AhR and constitutive localization of this receptor in the nucleus (Z. Wang et al., 2020).

4. Mixtures of Environmental Pollutants That Have Synergistic Carcinogenic Effects

4.1. Asbestos and Cigarette Smoke

One of the first synergistic interactions described between environmental pollutants was with a mixture of asbestos and cigarette smoke, which promotes the development of lung cancer (Kamp et al., 1998; Ngamwong et al., 2015; Sekhon et al., 1995; X. Wang et al., 1995). This is a very complex mix since cigarette smoke is estimated to contain more than 3,800 chemicals, and more than half of these are considered toxins or potential carcinogens (IARC, 2004). Meanwhile, asbestos is a geogenic contaminant (from mining), but it can also originate from deteriorated, damaged, or altered products, such as insulation, fireproofing, acoustical materials, and floor tiles, which release tiny fibers that remain for a long time and are transported through the air (Bundschuh et al., 2017). It was discovered that cigarette smoke increases the absorption and retention of asbestos fibers in tracheal epithelial cells (Churg et al., 1990; McFadden et al., 1986), but the mechanisms through which these agents interact to promote lung tumorigenesis are still poorly understood. The mixture increases ROS concentrations within the cell and at the same time depletes the antioxidant glutathione (GSH; Kamp et al., 1998), resulting in a large number of DNA breaks and mutations, including in p53 (Inamura et al., 2014; Jung et al., 2000; X. Wang et al., 1995). Likewise, cell proliferation is promoted (Sekhon et al., 1995), innate immune mediators decrease, and impaired inflammatory cell recruitment occurs (Morris et al., 2015).

4.2. Persistent Organic Pollutants (POPs)

POPs, such as 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) or endosulfan, are a group of environmental pollutants that are highly resistant to environmental degradation. Therefore, these can accumulate in the environment and pass from one species to another through the food chain with potential adverse impacts on human health. One study showed that POPs are synergistic with each other, while another study discovered that POPs are synergistic with azoxymethane (AOM), another carcinogenic substance. In both instances, they have been linked to an increased risk of colorectal cancer (Hansen et al., 2019; Rainey et al., 2017). The mixture of different POPs causes a synergy in the production of ROS, which damages DNA and modifies cell membranes through lipid peroxidation. Consequently, mutations occur and the homeostasis of the ER and mitochondria is disturbed, leading to an increase in intracellular calcium levels, a decrease in ATP, and even more ROS production (Hansen et al., 2019; Rainey et al., 2017; Sun et al., 2020). The AhR and Pregnane X receptor (PXR) signaling pathways that are activated by TCDD and endosulfan can induce the expression of cytochrome P450 enzymes within cells, especially CYP1A and CYP1B1 monooxygenases, which convert these compounds into even more toxic epoxy derivatives (Rainey et al., 2017). Epoxy derivatives suppress the activity of p53, requiring a large amount of antioxidant enzymes and scavengers for its detoxification, mainly abundant reserves of GSH (Das et al., 2017; Pizzorno, 2014). It is also possible that a chronotoxicity also occurs since POPs are circadian disruptors (e.g., TCDD; Fader et al., 2019). This chronotoxicity could cause other pollutants to be inadequately removed from the body during the day, which is when we are most exposed to pollutants (Tischkau, 2020). In the case of the mixture of POPs and AOM, AOM initiates carcinogenesis by promoting the production of 6-O methylguanine in DNA, while POPs induce the overproduction of ROS, which also damage DNA and facilitate mutations in key proteins, such as KRAS, p53, and APC. Both compounds are metabolized by the cytochrome P450 system and it is thought that synergistic effects could originate here (Hansen et al., 2019).

4.3. Trimethylamine (TMA) and Its Metabolites

TMA is an organic compound that is widely used in industry for the synthesis of choline, tetramethylammonium hydroxide, plant or herbicide growth regulators, strongly basic anion exchange resins, dye-leveling agents, and various basic dyes. TMA and its metabolites, dimethylamine (DMA) and methylamine (MA), have shown synergistic toxic effects in cells of the respiratory tract that result in decreased cell viability, decreased cell activity, mitochondrial dysfunction, ROS production, and glutathione depletion (Chhibber-Goel et al., 2016; Qiu

et al., 2021). Furthermore, due to the participation of cytochrome P450 enzymes, TMA can also be oxygenated to generate N, N-dimethylformamide (by N-formylation) and N, N'-Bis (2-hydroxyethyl)-1,2-ethanediaminium (by hydroxylation), which are more toxic compounds that stimulate extensive overproduction of ROS in the cytoplasm and mitochondria, and being more hydrophilic cells absorb them more readily (Qiu et al., 2021). If the exposure is through contaminated food, TMA, DMA, and MA are easily converted in the stomach to N-nitrosodimethylamine (NDMA) in the presence of sodium nitrite, a food additive commonly used in cured meat and poultry products. NDMA is also metabolized by cytochrome P450 enzymes, thereby generating the methyldiazonium ion that can generate adducts in DNA and facilitate the appearance of mutations (Chhibber-Goel et al., 2016).

4.4. Microplastics and Heavy Metals

The omnipresence of microplastics in the environment inevitably leads to animal exposure with eventual consequences to human health. An important aspect of microplastics is that they can adsorb (and emit secondarily due to aging degradation) other pollutants, such as heavy metals and hydrophobic organic compounds, causing them to accumulate and their concentration in the environment to increase (Prata et al., 2020; H. Zhang et al., 2020). A study on the earthworm *Eisenia foetida* demonstrated synergy between polypropylene and cadmium that was caused because polypropylene particles were retained in the body and due to their ability to adsorb metals, they can increase the accumulation of cadmium. Both induce oxidative damage in cells and cadmium significantly accelerates the adverse effects (Zhou et al., 2020). Likewise, the effect of polystyrene (PS) nanoplastics on the toxicity of gold ions has been studied and synergistic patterns were also discovered. Synergistic toxicity appears to be related to mitochondrial damage, ROS production, and pro-inflammatory responses (Lee et al., 2019). Synergy was also found in research studying the combined effects of PS and natural organic matter (NOM) on copper toxicity. Apparently, the presence of NOM promoted increased copper adsorption on PS and accumulated in the liver and guts of zebrafish. The aggravated toxicity of copper was reflected by an increase in malonaldehyde and metallothionein levels with a decrease in superoxide dismutase (SOD) levels and was attributed to an inhibition of copper ion transport as well as increased ROS production (Qiao et al., 2019). For all cases, a direct relationship was found between the amount of heavy metals that accumulated and the size of the microplastics (possibly related to the higher specific surface area of nanoplastics; Lee et al., 2019; Qiao et al., 2019; Zhou et al., 2020). These studies only report the effect of a few microplastics on the toxicity of some heavy metals, but similar behavior is likely to occur with other metals and that microplastics act as vectors to transport other xenobiotics into cells.

4.5. Haloacetonitriles (HANs)

HANs exist in drinking water exclusively as by-products of disinfection. It is important to note that HANs appear to fall into the category of activation-independent carcinogens, so they do not require an activation step in order to induce DNA damage (Lipscomb et al., 2009). A study with hepatoma HepG2 cells showed that different HANs, such as chloroacetonitrile (CAN), dichloroacetonitrile (DCAN), trichloroacetonitrile (TCAN), bromoacetonitrile (BAN), and dibromoacetonitrile (DBAN), act synergistically to stimulate ROS production and consequently affect the oxidative state of the cell (Lu et al., 2018). The mechanism behind the synergy is largely unknown, but it is attributed, in part, to HAN-associated reactivity, causing them to covalently bind to proteins and DNA in various organs and tissues. This may lead to the inhibition of endocrine effects mediated by estrogen receptors with other signaling pathways being activated instead (Lipscomb et al., 2009). Coupled with this, Han-induced ROS overproduction increases lipid peroxidation, which causes the cell membrane to become less ordered, allowing for the entry of extracellular ROS, which enhances cytotoxicity (Lu et al., 2018; C. G. Park et al., 2021). GSH stores are a crucial protection against HAN toxicity, and we can speculate that GSH depletion contributes to the synergistic mechanism between various HANs. This would mean that GSH reserves are depleted faster when synergies occur between HANs. Furthermore, HANs inhibit glutathione S-transferase-mediated conjugation although this effect is reversible (Lipscomb et al., 2009; Lu et al., 2018; R. Wang et al., 2020). Notably, there is also evidence that HANs have synergistic effects with ROS. This is expected since ROS contribute to the formation of reactive intermediates from HANs (Lipscomb et al., 2009; Lu et al., 2018). This is interesting because many other xenobiotics also induce ROS production and could have indirect synergistic or additive effects with HANs. The synergy between different xenobiotics and HANs has not been adequately studied, but it could play a crucial role in the development of different cancers. HANs can inhibit CYP2E1, a member of

cytochrome P450, through a covalent interaction with the enzyme and thus may prevent other xenobiotics from being metabolized (Lipscomb et al., 2009).

4.6. Benzo(a)pyrene (BaP) and Other Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are a class of chemicals found naturally in coal, oil and its by-products, wood, and tobacco and are released when they are heated and burned. Several PAHs are known to have adverse health effects and some specific PAH mixtures are considered carcinogenic chemicals (Moorthy et al., 2015). HepG2 cells co-treated with BaP and other PAHs, such as benzo(b)fluoranthene (BbF), dibenzo(a,h)anthracene (DBA), or indeno[1,2,3-cd]pyrene (IP), had synergy in the production of adducts in DNA (Tarantini et al., 2011). Likewise, it has been shown that a mixture of BaP and oxygenated PAH (oxy-PAH) induces more DNA breaks and thus synergized their carcinogenic potential (McCarrick et al., 2019). Meanwhile, arsenic and BaP are among the most common environmental carcinogens that cause lung cancer, but they also showed synergy with each other to induce malignant transformation of bronchial epithelial cells. The importance of this synergy is due to the fact that BaP is one of the most potent carcinogens in cigarette smoke, and arsenic is found in drinking water, so cigarette smokers exposed to arsenic could have a higher risk of developing lung cancer. This mixture does not produce a greater amount of BaP diol epoxide (BPDE)-DNA adducts than BaP alone, but its components synergize to produce epigenetic changes. Specifically, the mixture positively regulates the expression of histone-lysine N-methyltransferase SUV39H1, since both contaminants activate the AhR. There is an increase in the levels of the repressive marker H3K9me2, which hinders the expression of certain genes, including the tumor suppressor SOCS3. SOCS3 inhibition allows an increase in AKT and ERK1/2, signaling that promotes carcinogenesis and inflammation (Z. Wang et al., 2020). PAHs, particularly BaP, DBA, IP, and pyrene (PR), have been reported to exert a synergistic effect with human papillomavirus (HPV) to promote malignant transformation of cervical cells as well as their migration and invasion, especially when there is long-term exposure. The exact mechanism for this is not yet determined, but these PAHs are believed to form adducts with DNA that lead to mutations in RAS and p53. Also, as PAHs are metabolized by cytochrome P450, the ROS produced in this step increase the number of adducts (C. Zhang et al., 2019).

4.7. Bisphenol A (BPA) Mixtures

BPA is a plasticizer used in the production of important plastics, primarily certain polycarbonates and epoxy resins, as well as some polysulfones and certain specialty materials. Because of this, BPA is found in a variety of common products that primarily contaminate food and beverages although there are other sources of exposure. BPA and 4-cumylphenol (4-CP), in low concentrations, have been reported to synergistically induce proliferation of the MCF-7 breast cancer cell line. This is because BPA and 4-CP are estrogen-like chemicals and their co-exposure at low levels causes the cell cycle to progress more rapidly as well as upregulates the anti-apoptotic factors ERα, pS2, and BCL-2 (X. Wang et al., 2020). An in vitro study in Saccharomyces cerevisiae reported that BPA, in concentrations similar to those detected environmentally, exhibited synergy to alter the response to estrogens when mixed with drugs, such as diclofenac, chloramphenicol, oxytetracycline, and fluoxetine (Kudłak et al., 2019). Furthermore, the mixture of BPA, BADGE, and BADGE·2HCl showed toxic synergy in the Microtox assay, and it was suggested that this was due to the three compounds having a similar mode of action (Jatkowska et al., 2021). Meanwhile, a study looked at the synergistic toxicity of BPA and nanoscale PS in Caco-2 colorectal adenocarcinoma cells. It was found that nanoparticles are absorbed more efficiently than microparticles and that nanoscale PS has a large surface area for BPA absorption, leading to higher cytotoxicity. This last finding was probably the result of increased cellular oxidative stress and mitochondrial depolarization (Q. Wang et al., 2020).

4.8. Nanoplastics and Organochlorides

Nanoplastics have been reported to cause severe toxicity and cumulative effects in organisms as well as interact with organic pollutants and influence their potential adverse effects. Synergistic toxicity has been found between transition-metal dichalcogenide nanosheets and some organochlorides, such as triclosan or tris(1,3-dichloro-2-propyl)-phosphate. Interestingly, this synergy had a greater magnitude at low nanoplastic concentrations and decreased with increasing concentrations (P. Yuan et al., 2020). A similar effect was found with nano-sized PS and 2,2′,5-trichlorobiphenyl, 2,2′,5-polychlorinated biphenyl (PCB-18; Lin et al., 2019). Nanoparticle concentrations

in the environment are generally low, which make synergy particularly important. TMDC nanosheets were found to clearly enhance the intracellular accumulation of organochlorides because they cause damage to the plasma membrane and the cytoskeleton through ROS production and lipid peroxidation, resulting in increased permeability. At the same time, nanosheet. also affected the secondary structure of the exit pumps, mainly the ATP-binding cassette transporters (ABC), thus blocking the elimination of these compounds and other xenobiotics (P. Yuan et al., 2020).

4.9. Aflatoxins and Other Fungal Toxins

Aflatoxins are toxic chemicals produced by fungi and are present in food and animal feed. Aflatoxin B1 (AFB1) shows synergy with hepatitis B (HBV) and C (HCV) viruses (Benkerroum, 2020; Henry et al., 2002). This is clearly observed in China, which is a country with a high incidence of chronic foodborne infections due to AFB1 and HBV as well as a high incidence of liver cancer (Benkerroum, 2020). The synergy has also been illustrated by a study investigating the risk of hepatocellular carcinoma associated with AFB1 exposure for hepatitis B- and C-positive or -negative individuals. The test group was followed for 8 years and it was established that people with high exposure to AFB1 and hepatitis C infection had a much higher risk of developing hepatocellular carcinoma than people who only tested positive for one of the factors (Chu et al., 2018). Synergy can be explained as follows: first, chronic HBV infection sensitizes hepatocytes in the liver to the carcinogenic effects of AFB1. Then, HBV interacts with PXR, which is a key regulator of metabolism against xenobiotics, and this leads to increased activation of CYP3A4. CYP3A4 adds a reactive epoxide to AFB1, which converts it to mutagenic AFB1-8,9-epoxide (AFBO; Benkerroum, 2020; Y. Niu et al., 2021; Zhao et al., 2021). AFBO damages DNA by forming an aflatoxin B1-N7-guanosine adduct and in many cases causes a transversion of guanine to thymine at codon 249 of p53, replacing an arginine with a serine (R249S). In this way, p53 stops working properly and consequently, there is an uncontrolled cell cycle, which benefits carcinogenesis (Benkerroum, 2020; Goodsell, 2001; Rushing & Selim, 2019). It is worth noting that DNA damage increases the integration of viral DNA into cellular DNA, which can benefit other viruses in addition to HBV infections. It can be hypothesized that this could lead to additional synergistic patterns in which other viruses can attack susceptible DNA.

On the other hand, a study noted that *Alternaria alternata* mold toxins synergistically activate AhR, which affects cancer cell proliferation and cell migratory abilities. AhR activation led to dose-dependent induction of CYP1A1 activity, believed to be important in the mechanisms that explain the increased risk of breast cancer caused by Alternaria (Hohenbichler et al., 2020).

5. Conclusions and Future Perspective

5.1. Pathways

Our survey of the literature focusing on synergy, environmental pollutants, and cancer (see Table 1) suggests that three important mechanisms are frequently involved. This includes: (a) the overproduction of ROS, (b) the chemical transformation of pollutants into more reactive and carcinogenic compounds when passing through cytochrome P450, and (c) the activation of AhR signaling. While this may not have previously been illustrated in this fashion, it is not surprising for several reasons. First of all, cytochrome P450 is probably the most important system for drug interaction studies and a very important research area within the field of pharmacogenomics (Molenaar-Kuijsten et al., 2021; Nelson et al., 1993; Rao Gajula et al., 2021). ROS signaling is affected by many external factors, and the sophisticated mechanisms to keep ROS under control are prone to being affected by exogenous compounds targeting different proteins that may act synergistically through this mechanism (Apel & Hirt, 2004; Brieger et al., 2012; Rodic & Vincent, 2018). AhR regulates a large number of mechanisms that allow different types of molecules to cause interactions (Lagunas-Rangel et al., 2021; Paris et al., 2021). This review also highlights several important examples of the interactions of these three systems, further reinforcing the suggestion that they could be key targets for future studies within this field.

The synergistic actions we see in this literature are of a different nature considering the type of interactions. We see, for example, that two compounds can produce similar effects that are enhanced, as occur with asbestos and cigarette smoke, where both induce the overproduction of ROS. Meanwhile, these compounds can also act in a complementary way, like POPs and AOMs, where one damages DNA and the other inactivates tumor suppressor proteins (Hansen et al., 2019). Another way in which these interactions can occur is that one of them absorbs the

other, thereby causing it to accumulate and concentrate as in the case of microplastics that mix with heavy metals and organochlorines (Qiao et al., 2019; Zhou et al., 2020). We also see examples where one of the compounds can damage cells and make them more vulnerable to the carcinogenic effects of the other, such as aflatoxins and the hepatitis virus (Chu et al., 2018).

It is important to understand how synergy and antagonism relate not only to pathways but also to specific proteins and protein families. Potential interactions of contaminants with key proteins are important and this relates to well-established target drug families, such as kinases (Attwood et al., 2021), G protein-coupled receptors (Hauser et al., 2017; Lagerström & Schiöth, 2008; Lagunas-Rangel, 2022), ligand-gated ion channels (Rask-Andersen et al., 2011), and other proteins bound to the membrane (Almén et al., 2009). Nonclassical drug targets, such as soluble ligands (Attwood et al., 2020; Lagunas-Rangel & Bermúdez-Cruz, 2020), are becoming an important class of drug family and there is great interest in transcription factors (Bushweller, 2019; Henley & Koehler, 2021), chromatin remodelers (Dawson & Kouzarides, 2012; Lagunas-Rangel, 2019, 2021), among others. Understanding the characteristics of a protein family is important for making predictions of specific points of interactions and for prioritization.

5.2. Methodologies

Although from a historical point of view the methodologies for the general determination of synergies/antagonisms between factors have been known for almost a century, we are still in the initial stage of determining universal guidelines to estimate whether certain complex xenobiotic cocktails represent a threat (which depends on the concentration, the organ, and the exposure time, among others; Wieczerzak et al., 2015). The novel method development has been very important and some of the important discoveries relate to the application and development of isobolograms (Huang et al., 2019), the fractional product method presented by J. L. Webb (1963), the method of Valeriote and Lin (1975), the method of Drewinko et al. (1976), the calculation of the interaction index of Berenbaum (1977), the method of Steel and Peckham (1979), the method of median effect of Chou and Talalay (1984), the method of Berenbaum (1985) and Bliss (1939) independence response surface approach, the method of Prichard and Shipman (1990), nonparametric response surface approaches Facer and Müller (2003), the parametric response surface approach models of Greco et al. (1995) and the models of Weinstein et al. (1990). Among the studies analyzed, the most used methods to determine synergies between environmental pollutants in carcinogenesis are isobolograms, the combination of dose in the scale of effects and concentration addition and independent action approaches, all of them based on the concept of dose equivalence.

The main reason we know little about the interactions between many environmental pollutants is that experiments to determine such interactions are tedious. The process is often complicated and there is a great need for more consistent and high-throughput studies with models that allow analysis on a larger scale. Higher resolution toxicogenomic techniques, such as ToxCast (Toxicity Forecaster) screening assays (Franzosa et al., 2021), liquid chromatography tandem mass spectrometry (LC-MS/MS; Dinamarco et al., 2021), and high-throughput sequencing (House et al., 2017), are also needed to know what changes occur in the cells after exposure to different polluting cocktails. It is important to identify the pollutant mixtures that present synergies, their concentration-dependent ranges, and in general any type of interaction to carry out a systematic prioritization. It is also necessary to keep updated which are the pollutants and combinations to which we are most exposed and the concentrations that we normally find in the environment. There are numerous articles in form of both reviews and original articles that provide compilations of information on contaminants, their speciation, content availability, for example, in food and water matrices (Agathokleous et al., 2021; Dulio et al., 2020; Kantiani et al., 2010; Loos et al., 2013; Picó et al., 2021; Solaun et al., 2021). These reports can be used as an important tool in the candidate preselection stage and in the development of improved methodologies to detect synergies/antagonisms.

5.3. Technologies

This field is complicated by the fact that while many drugs have a well-defined pharmacokinetic profile, there is a greater need for more advanced pharmacokinetic studies on many contaminants and their drug interactions (Fardel et al., 2012). The possible interaction of cocktails of environmental pollutants with pharmacological treatments, considering the interactions of absorption, metabolism, and elimination and changes in the disposition of the coadministered compounds, needs more attention. The development of new computer-aided and artificial

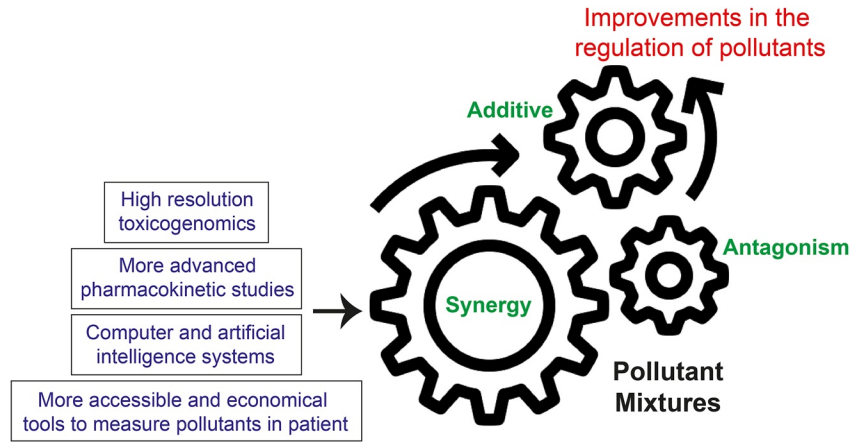

Figure 4. Proposed perspectives in the context of mixtures of environmental pollutants. To make improvements to the current regulations, it is necessary to identify those interactions (additive, synergies, and antagonisms) that occur in mixtures of environmental pollutants. Being of special interest the synergistic interactions that can cause these compounds, even at a low concentration, to have a considerable impact on human health. For which, the use of high-performance tools, such as high-resolution toxicogenomics, advanced pharmacokinetic studies, computer and artificial intelligence systems, and more accessible and economical tools to measure contaminants in patients, has become a necessity.

intelligence systems (S. Webb, 2018) may allow a larger scale approach to the selection of the test mixture in order to reduce the number of actual experimental tests (Chen et al., 2021; Lukashina et al., 2021; Savoca & Pace, 2021).

Currently, there are relatively few studies that measure the actual levels of environmental pollutants in patients with cancer or any other disease (Arrebola et al., 2016; Lim et al., 2017; E. Y. Park et al., 2020). For this reason, it is important to create new, more accessible, and economical tools that allow the levels of different environmental pollutants in blood and/or urine to be measured. In this way, these studies could be carried out in a greater number of people and with greater frequency, establish which levels of each pollutant or mixture of them become a risk factor for the development of diseases, monitor the levels of pollutants, such as chemotherapy and/or advances in radiotherapy, and determine if they are related to the prognosis of patients, among many other things. In this sense, screening tests based on quantitative immunochromatographic methods could be an option in which pools of environmental pollutants, similar to those used for anti-doping tests, could even be managed. In this way, medical personnel could provide a more personalized treatment, predicting the best options based on the type of cancer (or disease), the treatment, and the environmental pollutants to which the patient is exposed.

5.4. Regulations

Current regulatory practice (Clahsen et al., 2019; Drakvik et al., 2020; Lebret, 2015) is largely based on considering individual chemicals, while regulation of combined exposure to multiple chemicals is much less developed (Drakvik et al., 2020). Not accounting for the effects of combined exposures could lead to an underestimation of risk for several different reasons (Kortenkamp & Faust, 2018). In general, regulations have been created to limit the concentrations of environmental pollutants below a certain threshold considered safe and without health effects. However, there is a need for new regulatory principles that take into account environmental pollutants in the form of mixtures that can interact synergistically, thus not requiring high concentrations to cause health consequences. As a result of all of the above (Figure 4), improvements are required in regulations related to exposure to environmental pollutants as well as in strategies and technologies to reduce or eliminate their presence.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

Data were not used nor created for this research.

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