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Article

Threats of nano/microplastics to reproduction and offspring: Potential mechanisms and perspectives

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Abstract: Due to their ubiquitous occurrence in the aquatic environment and terrestrial ecosystem and underlying eco-environmental risks, nano/microplastics (NPs/MPs) have sparked great public concerns. The purpose of this work is aimed to summarize the harmful influence of NPs/MPs on reproduction and offspring health and further explore the potential mechanisms of action, thereby facilitating the more comprehensive understanding of NPs/MPs features. Literature search databases included EMBASE, Web of Science, and PubMed. The study selection and data extraction were implemented according to the inclusion criteria. NPs/MPs could accumulate and trigger reproductive toxic responses and thereafter generate deleterious effects on the offspring's health. Accordingly, the reproductive toxicity of NPs/MPs was characterized as the sperm deformity, decline in sperm count and motility, follicular growth tardiness, ovarian fibrosis, granulosa cell death, disorder of reproductive hormone secretion, as well as the fetal growth restriction, glycolipid metabolism disorder, and inflammatory responses of the next generation. Additionally, mechanism research revealed that NPs/MPs exposure brought about inflammatory responses and oxidative stress and thereafter destroyed the blood-testis barrier (BTB) integrity, motivated spermatogenic cell apoptosis by activating the JNK and p38/MAPK-Nrf2/NF-κB pathways, and induced ovarian granulosa cell pyroptosis and apoptosis and subsequent ovarian fibrosis via the Wnt/β-Catenin and NLRP3/Caspase-1 pathways. Nevertheless, this work also highlighted the imperative requirements for scientific and systematic risk assessments of NPs/MPs, so as to identify feasible risk mitigation strategies.

Keywords: nano/microplastics; reproduction; offspring; adverse effects

1. Introduction

By 2015, more than 5 billion tons of plastic waste had been generated globally. According to the trend during this period, it is expected to produce a total of 40 billion tons by 2050, and approximately 12 billion of that will be disposed of in landfills and the environment [1]. Due to being hardly biodegradable, plastics in landfills are broken down into plastic fragments and then transferred into the soil and the ocean. Microplastics (MPs) are a type of plastic debris with a particle size less than 5 mm and divided into primary MPs and secondary MPs. The former could directly access the environment through various channels, such as personal care or cosmetic product use, accidental losses caused by leaks during production or transportation, wear and tear during washing, and so on [2]. The latter is generated from the deterioration or degradation of larger plastics, which usually occurs when larger plastics suffer from mechanical abrasive actions, biodegradation, UV

radiation, etc. [1]. The components of NPs/MPs are predominantly constituted of polyethylene (PE), polystyrene (PS), polypropylene, polyethylene terephthalate, as well as polyvinyl chloride [3].

From the soil, air, and water source exposure to product usage, NPs/MPs are closely associated with our daily lives. Moreover, NPs/MPs could be transported from the lower nutrient level to the higher nutrient level in the food chain, giving rise to biological accumulation [4]. Therefore, humans could be not only directly exposed to NPs/MPs-contaminated food and water but also indirectly exposed through the food chain. Thus, NPs/MPs are frequently detected in multiple biological samples, such as skin, hair, saliva, placenta, colon, stool, semen, fetal fluid, and so on [5–9]. In general, humans are exposed to NPs/MPs dominantly via ingestion, inhalation, and dermal contact (**Figure 1**). Senathirajah et al. [10] estimated that globally, humans might ingest an average of 0.1–5 g of MPs per week from diverse exposure pathways, while Mohamed Nor et al. [11] calculated that by 18 years of age, the intake of MPs could irreversibly accumulate to 8.32×10^3 particles per person and by 70 years of age to 5.01×10^4 particles per person. Besides, several studies have tested and compared the toxicity of NPs/MPs in different exposure routes. The inhalation of NPs/MPs could exacerbate the toxicity of the lung, while the oral exposure of NPs/MPs could localize in the gut and bioaccumulate in multifarious organs such as the brain, liver, kidney, and reproductive organ, thereby eliciting corresponding detrimental effects. In recent years, growing literature has revealed that NPs/MPs exposure could bring about a series of unfavorable health outcomes, such as the damage of the central nervous system and cerebral function [12], pulmonary injury [13], gut microbiota dysbiosis [14], hepatocellular apoptosis and necroptosis [15], kidney lesion [16], as well as reproductive impairment [17].

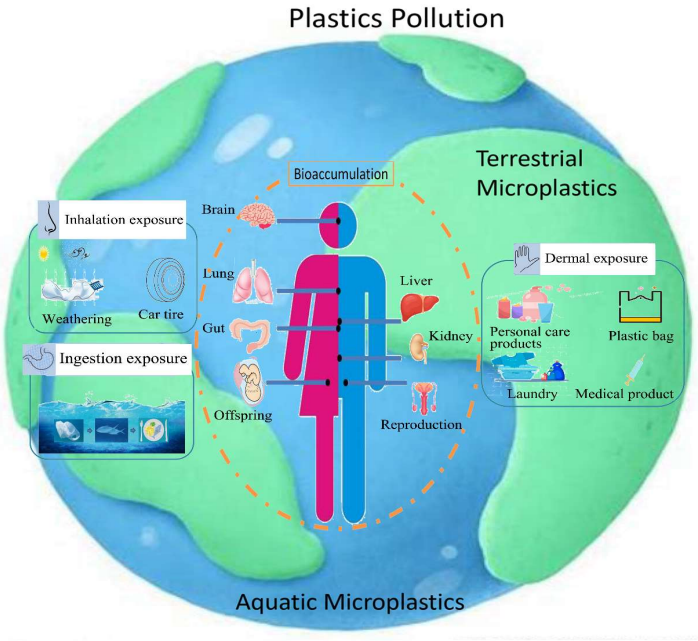

Figure 1. The multiple hazardous influence of plastics pollution on human health though various exposure routes.

Mounting epidemiological evidence has indicated that human fertility displays a

gradually declining trend in recent decades, and approximately 8%–12% of couples of childbearing ages worldwide are affected by infertility [18]. As a result, it is quite necessary and urgent to identify potential risk factors influencing human reproductive health. In recent years, a growing body of literature has suggested the interference effect of NPs/MPs on reproduction and fertility; however, the detailed mechanisms by which NPs/MPs mediate harmful reproductive health effects are still limited and ill-defined. Herein this review retrospected the relevant literature on NPs/MPs exposure to summarize the unfavorable reproductive effects and further explored the underlying molecular mechanisms. A more comprehensive and in-depth understanding of MPs will emerge from these insights.

2. Methodology

2.1. Literature search and relevant study screening

Search databases included EMBASE, Web of Science, Scopus, and PubMed up to September 2023. The two-round search process followed the workflow of PRISMA [19]. Search strategies were optimized using Boolean logical operators. Search terms were as follows: (a) microplastics (MPs), plastic particles, nanoplastics (NPs), or nanoparticles, and (b) reproduction, fertility, testis, ovary, generations, or offspring. Through these searches, studies evaluating the negative effect of NPs/MPs on reproductive health were screened out. Inclusion criteria were as follows: (a) plastic particles were orally administered; (b) the studies were conducted on terrestrial animals or marine animals; and (c) the studies displayed the harmful influence of NPs/MPs on reproductive health or the next generation. The studies were excluded if (a) they only performed the bio-assessment and/or determined the bio-accumulation of NPs/MPs in organisms without evaluating the toxic effects on reproduction, (b) the study tested the co-exposure effects of NPs/MPs and other hazards such as plastic additives, and (c) the unpublished literature or no peer-reviewed literature.

2.2. Literature analysis and data extraction

Two independent authors screened titles and abstracts. Endnote was used to import the full texts if the studies possibly met inclusion criteria. Afterward, a full-text analysis for the eligibility was conducted. Those full texts were examined by three independent authors who carried out the selection using the self-designed eligibility verification checklist, which mainly included research models (species, lineage, age, and sex), research designs (size and type of NPs/MPs, concentration, frequency, and duration), and toxic outcomes (testicular toxicity, ovarian toxicity, reproductive endocrine disturbance, and offspring threats).

2.3. Bias risk assessment

The SYRCLE's tool for bias risk, which was adapted from the Cochrane RoB tool, was employed to evaluate the underlying bias source in selected research, thereby facilitating critical appraisal of evidence [20]. The SYRCLE's tool consisted of ten entries related to the underlying bias source, such as the selection bias,

detection bias, friction bias, etc. Overall and individual data were obtained from SYRCLE's strategy.

3. Results

3.1. Bias risk

Bias analyses revealed that none of the studies selected could fulfill all the standards for methodological quality, suggesting an underlying risk of bias in various aspects of assessment. The aspects of the rational generation of the animal allocation sequence, animal grouping blinded, intervention design blinded for caregivers and/or investigators, as well as the outcome assessor blinded, were not identified in the methodological quality of all studies. Only five researchers selected experimental animals with random data collection (33.33%). Most studies conducted random housing of animals (80.00%). The baseline characteristics, incomplete research data, and selective outcome reporting were adequately addressed in all identified studies. Moreover, other possible sources of bias, such as the particle features and exposure manners, were also clearly described in all investigations. To sum up, the average score for bias risk of the included work was 52.66%, with six investigations (40%) exceeding the average value (**Table 1**).

Table 1. The unfavorable influence of NPs/MPs on male reproductive health.

Hazardous effects	Type of NPs/MPs	Particles size	Dosage	Duration	References
Decrease in sperm count, viable epididymis sperm count, and spermatogenic cell count in the testis	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		0.5 μm	0.015, 0.15, and 1.5 mg/d	For 90 days	[24]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		5.0–5.9 μm	0.1 mg/d	For 30 and 44 days	[26]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Increase in the sperm deformity rate	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	0.1 mg/d	For 30 and 44 days	[26]
		5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		0.5 μm	0.015, 0.15, and 1.5 mg/day	For 90 days	[24]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Triggering oxidative stress in the testicular tissue	PS-MPs	10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		5.0–5.9 μm	100 μg/d	For 30 and 44 days	[26]
Induced inflammatory responses	PS-MPs	5.0–5.9 μm	100 μg/d	For 30 and 44 days	[26]
		5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		0.5, 4, 10 μm	10 mg/mL	For 28 days	[29]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]

Table 1. (*Continued*).

Hazardous effects	Type of NPs/MPs	Particles size	Dosage	Duration	References
Destroyed the integrity of the blood-testis barrier (BTB)	PS-MPs	0.5 μm	0.015, 0.15, and 1.5 mg/day	For 90 days	[24]
		0.5, 4, and 10 μm	10 mg/mL	For 28 days	[29]
		5 μm	0.1, 1, and 10 mg/L	For 35 days	[25]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
Reduced testosterone levels	PS-NPs	50 nm	1, 3, 6, and 10 mg/kg/d	For 5 weeks	[21]
	PS-MPs	5.0–5.9 μm	100 mg/kg/d, 0.01, 0.1, and 1 mg/d	For 6 weeks	[22]
		10 μm	2, 20, 200, and 2000 μg/L	For 60 days	[23]
		5 μm	0.1 and 1 mg/L	For 90 days	[28]
		0.5, 4, and 10 μm	1 and 10 mg/mL	For 180 days	[27]

3.2. Overview of the screened literature

In the current work, 15 preclinical investigations were identified and included. Only one study reported the negative influence of PS-MPs on both male and female reproduction [26]. Among the other included studies, eight studies examined the detrimental impact of PS-NPs/MPs on male reproductive health [21–25,27–29], three on female reproduction [30–32], and three on offspring health [33–35]. Of the 12 studies on male or/and female reproduction, only one work disclosed the hazardous effect of PS-NPs (50 nm) on male reproduction with the dosage ranging from 1 to 10 mg/kg/d for five weeks [33]. The other studies reported that PS-MPs exposure (diameters ranging from 0.5 μm to 10 μm) with distinct doses could also impair reproduction of male and/or female experimental animals. Additionally, male and female reproductive lesions took place after PS-MPs (0.1 mg/d) exposure for 30 days, accompanied by a marked dose-dependent relationship between plastic particle exposure and reproductive damage. PS-NPs were mainly employed to evaluate the harmful effect of plastic particles on offspring health.

3.3. Unfavorable influence of NPs/MPs on male reproductive health

In nine studies on male reproduction, eight studies uncovered that after treatment with PS-NPs/MPs for more than one month, the sperm count, viable epididymis sperm count, and spermatogenic cell count were all decreased [21–28]. Six studies disclosed that PS-MPs exposure could elevate the sperm deformity rate [21,22,25,26,28,29]. Four studies observed that the integrity of BTB was impaired by PS-MPs [24,25,28,29]. Moreover, five investigations revealed that PS-MPs interfered with the hormonal synthesis and secretion and thereby reduced the testosterone level [21–23,27,28] (**Table 1**).

Mechanically, PS-MPs triggered oxidative stress and inflammatory responses [22,23,25,26,28,29]. The abnormal sperm quality and quantity in mice may be attributed to the PS-MPs-induced JNK and p38 MAPK pathways [22,24], or related to the NF-κB pathway caused by Nrf2 suppression [24,25]. Meanwhile, Nrf2 depletion and NF-κB stimulation also destroyed the integrity of BTB and then motivated the spermatogenic cell apoptosis [24,25,28]. Furthermore, PS-MPs could inhibit StAR expression through the LHR/cAMP/PKA signaling pathway mediated

by LH, thereby reducing the testosterone level [27] (**Figure 2**).

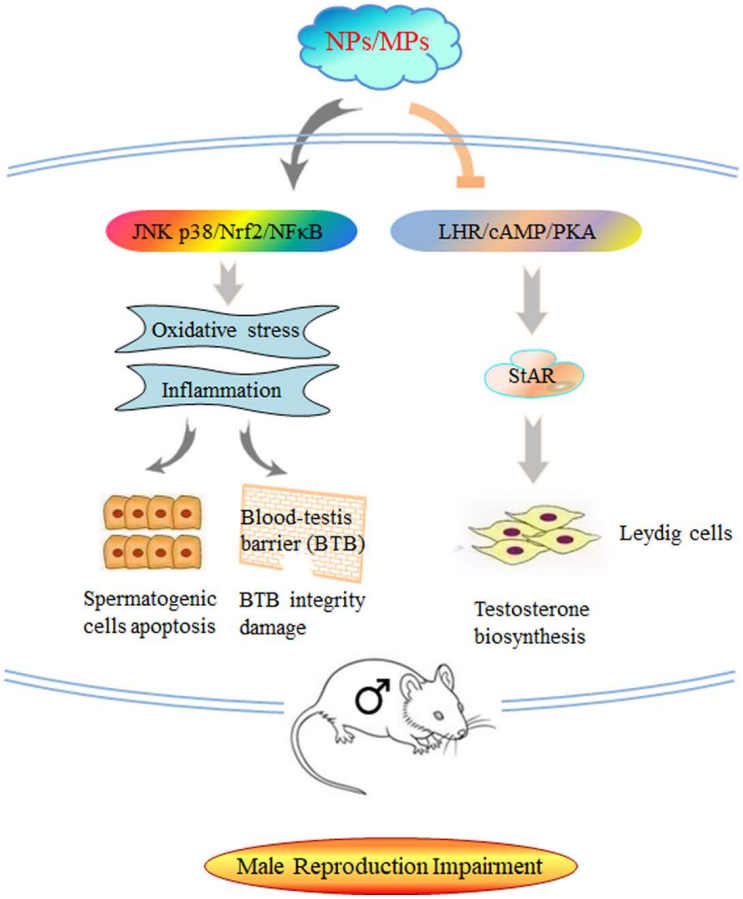

Figure 2. The unfavorable influence of NPs/MPs on male reproductive health and underlying mechanisms.

3.4. Unfavorable influence of NPs/MPs on female reproductive health

PS-MPs exposure could disturb female hormone balance by downregulating levels of estradiol and anti-Müllerian hormone [26,31] and upregulating levels of follicle-stimulating hormone, luteinizing hormone, as well as testosterone in ovarian tissue [26]. Additionally, PS-MPs restrained the survival rate of superovulated oocytes, the first polar body extrusion rate [32], and the growing follicle number [30,31], thereby reducing ovarian reserve capacity as well as the pregnancy rate (**Table 2**). Likewise, it has suggested that inflammatory responses and oxidative stress also contribute to the adverse influence of PS-MPs on female reproduction [26,30–32], such as the study revealing that PS-MPs brought about ovarian fibrosis via triggering oxidative stress and inducing the Wnt/β-Catenin pathway, finally bringing about ovarian granulosa cell apoptosis [30]. Similarly, another study also uncovered that PS-MPs induced the NLRP3/caspase-1 pathway via oxidative imbalance and then mediated ovarian granulosa cell death, including pyroptosis and apoptosis [31] **(Figure 3**).

Table 2. The unfavorable influence of NPs/MPs on female reproductive health.

Authors	Type of NPs/MPs	Particles size & dosage & duration	Species	Unfavorable influence and underlying mechanisms
Wei et al. [26]	PS-MPs	0.1 mg/d PS-MPs with 5.0–5.9 μm diameter administrated by gavage for 44 days	C57BL/6 female mice	**Decreased:** the estradiol levels; GSH levels in ovarian tissue; the corpora lutea count; the pregnancy rate and embryo count. **Increased:** the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone; ROS and MDA contents in ovarian tissue.
An et al. [30]	PS-MPs	0.5 μm PS-MPs at 0, 0.015, 0.15, and 1.5 mg/d for 90 days	Female Wistar rats	PS-MPs entered into granulosa cells (GCs). **Decreased:** the growing follicles number; the anti-Müllerian hormone (AMH) level. **Increased:** oxidative stress, granulosa cell apoptosis, and ovary fibrosis (transforming growth factor-β, fibronectin, α-smooth muscle actin); the protein expression of the Wnt/β-Catenin pathway (Wnt, β-catenin, and p-β-catenin). **Mechanism:** PS-MPs triggered oxidative stress and the Wnt/β-Catenin pathway, then led to apoptosis of GCs and ovary fibrosis, and finally contributed to the decline in ovarian reserve capacity.
Liu et al. [32]	PS-MPs	0.8 μm PS-MPs (1.0% and 2.5% w/v) for 35 days	CD-1 female mice	PS-MPs bioaccumulated in different organs or biological samples of exposed mice, such as the liver, kidney, brain, uterus, ovary, as well as blood. **Decreased:** the rate of the first polar body extrusion and the survival rate of superovulated oocytes; glutathione content; mitochondrial membrane potential (MMP), and endoplasmic reticulum calcium level. **Increased:** the levels of IL-6 and malondialdehyde in mouse ovaries; the ROS level in oocytes.
Hou et al. [31]	PS-MPs	0.5 μm PS-MPs (2.5% w/v) dispersed in deionized drinking water at 0, 0.015, 0.15, 1.5 mg/kg/d for 90 days	Female Wistar rats	**Decreased:** the number of growing follicles; the thickness of the granulosa layer of secondary follicles; the glutathione peroxidase, catalase, and superoxide dismutase activity in ovary tissue; the content of anti-Müllerian hormone (AMH). **Increased:** the ovarian MDA content; the expression of NLRP3 and cleaved caspase-1 in granulosa cells; the level of IL-1β and IL-18; the expression of NLRP3/Caspase-1 pathway-associated factors and cleaved caspase-3. **Mechanism:** PS-MPs activated the NLRP3/Caspase-1 pathway via oxidative stress and then triggered ovarian granulosa cell pyroptosis and apoptosis.

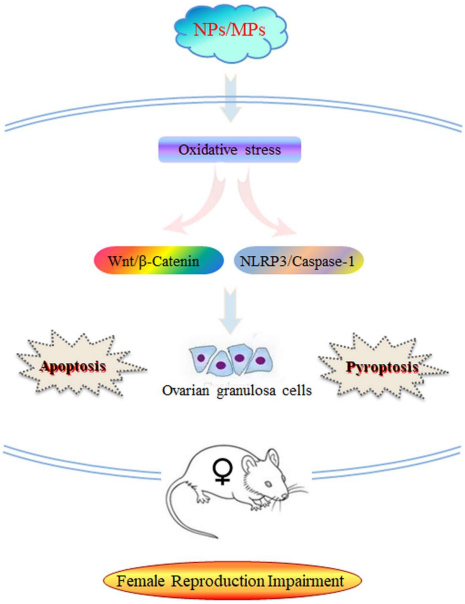

Figure 3. The unfavorable influence of NPs/MPs on female reproductive health and underlying mechanisms.

3.5. Unfavorable influence of NPs/MPs on offspring health

Three studies conducted in rodent models verified that PS-NPs exposure restricted fetal growth to varying degrees [33–35]. The possible reasons for the fetal growth retardation might be the decrease in the feto-placental weight ratio (FPWR) and umbilical cord length, which limited the nutrient transfer capacity and thereby retarded fetal growth [33] **(Table 3)**. Furthermore, previous studies discovered that PS-NPs exposure could elicit inflammatory responses, disorder glycolipid metabolism, perturb testicular development and function of male mouse pups, and impede the normal formation of muscle tissue and skin of fetuses [34,35] (**Figure 4**).

Table 3. The unfavorable influence of NPs/MPs on offspring health.

Authors	Type of NPs/MPs	Particles size & dosage & duration	Species	Unfavorable influence and underlying mechanisms
Chen et al. [34]	PS-NPs	Maternal PS-NP exposure (100 nm; 1 and 10 mg/L) via drinking water for 18 days	C57 BL/6 female mice	**Decreased:** fetal weights to cause fetal growth restriction. **Outcomes:** PS-NPs brought about inflammatory reactions, impeded the formation of muscle tissue and skin, and perturbed cholesterol metabolism of fetuses.
Aghaei et al. [33]	PS-NPs/MPs	Dams treated with 5 μm and 50 nm PS-NPs/MPs in drinking water (0.1, 10, and 1000 μg/L)	Adult CD-1 female mice	**Decreased:** the feto-placental weight ratio (FPWR), suggesting the insufficiency of the nutrient transfer capacity; a 30% decline in the umbilical cord length and a 12% decline in fetal weight in the high concentration group, demonstrating the fetal growth retardation.
Huang et al. [35]	PS-NPs	Maternal PS-NP exposure (100 nm) during gestation and lactation (0.1, 1, and 10 mg/L)	Female Kunming mice	**Decreased**: in birth; the weight of body, liver, and testes; sperm count; testicular CAT and SOD activities of offspring. **Increased:** inflammatory cell infiltration and proinflammatory cytokine expression (Il-1β, IL-6, and TNFα); testicular oxidative damage; testicular MDA content of offspring. **Outcomes:** PS-NPs exposure during gestation and lactation disordered hepatic glycometabolism and gave rise to testicular inflammatory and oxidative impairment of offspring.

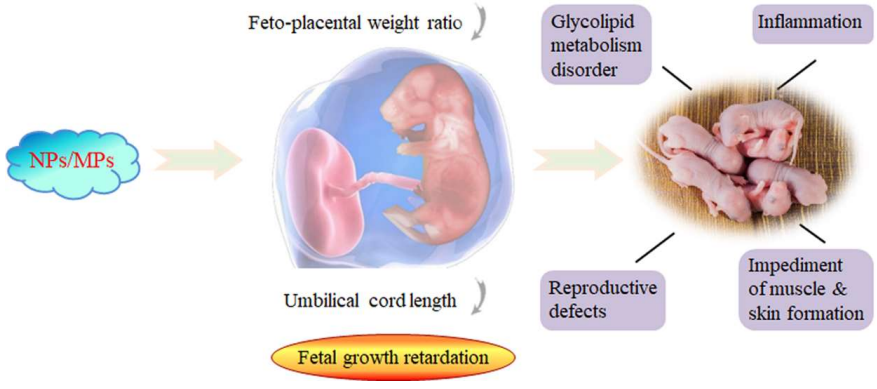

Figure 4. The unfavorable influence of NPs/MPs on offspring health.

4. Discussion

Mounting literature has indicated that reproductive health injury is associated with widespread exposure to environmental contaminants, such as NPs/MPs [21,26,30], which could interfere with reproductive health by regulating steroid hormone biosynthesis, apoptosis, and pyroptosis of germ or granulosa cells, etc. NPs/MPs as an emerging environmental pollutant could contribute to the impairment of male and female reproduction, as well as offspring health.

In male animal models, PS-MPs exposure not only decreased numbers of active

epididymis sperms and spermatogenic cells in testes but also increased the rate of sperm deformity. Meanwhile, serum LH, FSH, and testosterone contents were downregulated, while E2 was upregulated in experimental animals [26]. Another study reported that PS-MPs accumulated in mouse testes and then led to male reproductive dysfunction, abscission and malalignment of spermatogenic cells, decline in sperm quality and T levels, disruption of BTB, and so on [27]. Similar hazardous impacts of PS-MPs on male reproduction were also displayed in the study by Li et al. [24]. Further research has indicated that oxidative stress and subsequent oxidative damage are one of the common mechanisms by which NPs/MPs mediate the detrimental effect on male reproduction, such as the work demonstrating that after treatment with PS-MPs for six weeks, PS-MPs not only inhibited the sperm metabolism-associated enzyme activity, including succinate dehydrogenase and lactate dehydrogenase, but also activated the p38/MAPK pathway via oxidative stress to facilitate sperm damage and testosterone secretion suppression in mice [22]. Nevertheless, these pernicious effects mediated by PS-MPs could be antagonized and alleviated by the antioxidant NAC or p38-specific inhibitor SB203580. Similar findings were uncovered in the investigation, which exhibited that PS-MPs exposure impaired seminiferous tubules, destroyed the integrity of BTB, and brought about spermatogenic cell apoptosis via activating the MAPK-mediated Nrf2 pathway in rat testes [24]. In addition, the inflammatory response is also considered another important mechanism of PS-NPs/MPs-mediated reproductive lesions. In PS-MPs-exposed mice, inflammatory factors were significantly enriched in mouse testes, as evidenced by the increase in mRNA levels of tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), MCP-1, and CXC chemokine ligand 10 (CXCL10), which finally gave rise to reproductive dysfunction in male animals [27]. Furthermore, the alteration of gut microbial abundance, especially the elevation of Bacteroides and Prevotellaceae_UCG-001 abundance, activated the IL-17A signaling pathway, and gut microbial dysregulation was positively correlated with PS-MPs-induced reproductive damage and testicular dysfunction, proposing that gut microbial might be significantly involved in PS-MPs-mediated male reproductive injury [28].

It is well-known that exposure to environmental hazardous factors will give rise to a number of female reproductive diseases and even cause infertility in women [36], but compared with male reproduction, the unfavorable impacts of PS-NPs/MPs on female reproduction and offspring health have received less attention. Nevertheless, growing evidence has suggested that female reproduction is also an underlying target of NPs/MPs, and in comparison with male mice, the female is more vulnerable to NPs/MPs in reproduction [26]. Ovary is an important organ for female reproduction and endocrine regulation, whose predominant roles are to generate oocytes, synthesize, and release related reproductive hormones. In animal studies, PS-MPs restrained ovarian reserve function and interfered with fertility by perturbing sex hormone secretion and reducing follicle number and quality [26,30–32]. Further research revealed that excessive activation and maintenance of inflammatory pathways or their dysregulated resolution may partially account for NPs/MPs-mediated female reproductive disorder or impairment.

With the detection of NPs/MPs fragments in human placentas [37], the underlying unfavorable influence of NPs/MPs on offspring health is receiving

increasing attention and gradually reported. The study conducted in 43 pregnant women declared that in patients with intrauterine growth restriction (IUGR), MPs exposure was significantly negatively associated with the birth outcome in terms of birth weight, height, head circumference, and 1-minute Apgar score, suggesting that plastic particles might interfere with the interaction between the placenta and the fetus [38]. The harmful influence of NPs/MPs on offspring health mainly represented fetal growth restriction [33–35] and the decrease of umbilical cord length [33] in animal models. In humans, maternal NPs/MPs exposure would give rise to fetal growth retardation, which was closely associated with the insufficient transfer of placental nutrition and short umbilical cord [39]. In summary, evidence from population epidemiological studies and experimental research indicates that NPs/MPs have an underlying negative impact on the health of the next generation, which should be paid more attention to in future research.

Because of the mounting concern about the potential reproductive influence of plastic particles, several studies also reviewed the possible impact of NPs/MPs on reproductive health. Marcelino et al. [40] reviewed and synthesized the risk of PS-NPs/MPs on reproductive organs in mammals; however, they were more concerned about the influence of PS-NPs/MPs on offspring health. Another review only confined the concern regarding the impact of PS-NPs/MPs on male reproductive health [1]. Therefore, it is quite necessary to outline the unfavorable influence of PS-NPs/MPs on reproductive health of male and female reproduction and offspring health, as our present work did.

Given the critical interpretation of current evidence, none of the studies met all the methodological standards. Methodological quality assessments indicated that the aspects of animal allocation sequence, intervention design blinded, data collection blinded, and the outcome assessor blinded were critical bias elements in the selected research. Nevertheless, the other aspects such as random housing of animals, baseline features, etc. were eligible. Remarkably, the declaration of the risk of bias could objectively provide clear evidence for the influence of plastic particles on reproduction rather than highlight the flaws in the experimental protocols of the included studies.

5. Conclusion and perspective

With the extensive usage of plastics in production and daily life, humans and animals are ubiquitously exposed to nano/microplastics (NPs/MPs) via inhalation, ingestion, dermal exposure, etc. As the frequent detection of NPs/MPs in a variety of biological samples such as testicular tissue, semen, amniotic fluid, etc., the potential health risk, especially reproductive risk, elicited by NPs/MPs has aroused great public concern and worry. In recent years, a large amount of epidemiological data and toxicological investigations have clearly indicated that NPs/MPs exposure will impair both male and female reproduction and fertility, as well as offspring health, and the underlying modes of action of NPs/MPs-mediated reproductive damage are dominantly consisted of the direct histological injury, oxidative stress, inflammation, immune response, mitochondrial impairment, endoplasmic reticulum stress, apoptosis and pyroptosis of reproductive cells, and so on. Nevertheless, it should be

noted that human studies are relatively sparse in terms of quantity and scale, and even so, the limited population studies have dominantly looked at the correlation between NPs/MPs exposure and negative reproductive health outcomes, lacking in-depth mechanism-based exploration. In addition, the vector-like effect of NPs/MPs implies that further cohort studies and experimental research are warranted to evaluate the cumulative effect of environmental hazardous pollutants carried by NPs/MPs. Furthermore, it is a cruel fact that global accumulation of plastic particles will continuously exacerbate NPs/MPs exposure of ecosystems and organisms. As a result, there is a great need to conduct scientific and systematic risk assessments and then identify the feasible risk mitigation strategies in future work.

Author contributions: Conceptualization, MH and CL; methodology, MH; formal analysis, MH and WT; investigation, MH, WT and JH; data curation, WT and JH; writing—original draft preparation, MH; writing—review and editing, CL; supervision, CL; funding acquisition, CL. All authors have read and agreed to the published version of the manuscript.

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Article

Estimation of microplastics distribution in soil sample from District Una, Himachal Pradesh, India

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Abstract: Plastics have become an indispensable part of our daily lives. Its production and usage are increasing day by day. Our lives have become dependent on plastic-based products, and we are frequently exposed to plastics. The oxidation, fragmentation, and leaching stimulate the formation of small (1 µm–5000 µm) particles termed microplastics. The current study facilitates the assessment and quantification of MPs in soil samples collected from 5 sites (Amb, Gagret, Mubarikpur, Una city, and Tahliwal) in district Una, Himachal Pradesh, India. Soil samples were treated with NaCl for density separation and 30% H_2O_2 for digestion of organic matter. After sample treatment, the obtained supernatant was visualized under a stereomicroscope. In the current study, fragments (81.06%) were the dominant MP type identified, followed by fibers (16.04%) and films (2.89%). Similarly, MPs obtained were of various colours, such as purple (59%), greenish purple (5%), yellow (5%), blue (2%), green (1%) and transparent (28%). The highest microplastics concentration was detected in the soil sample from Tahliwal due to the disposal from small-scale industries and domestic waste, while the lowest microplastics concentration was detected in the soil sample from Una city. However, further research is needed to identify the polymer type and to check the possible source of microplastic examined.

Keywords: health; microplastic; polymers; soil; shape

1. Introduction

Since the creation of plastic in the early 19th century, its production and usage are increasing day by day. Plastics are extensively utilized in daily life and usually preferred in many areas, such as construction sites, textiles, households, offices, the medical field, kitchenware, toys, footwear, and packaging. Globally, the major portion of plastics is utilized for packing (30%), construction work (17%), and transportation (14%). Worldwide production of plastic has increased from 1.7 Mt in 1950 to about 350 Mt in 2021, and only 10% of it is recycled [1].

Plastics are classified in different categories on the basis of their chemical structures and nature (thermoplastic and thermosetting). Thermoplastics are softened plastics that can be deformed easily on heating, like polyethylene, PS, PP, PVC, and polycarbonate. While the thermosetting plastics are non-mouldable, such as epoxy resins, polyester resins, polyurethane, etc. Plastics are cheap, flexible, low-cost, have good moisture resistance, are economical, easy to process, and have electrical and thermal insulating properties [2]. Soil is the world's most abundant environment, the primary habitat for both known and unknown biodiversities [3]. Human life would be impossible without soil. Soil gives plants a place to put their roots and store the nutrients they need to flourish. It also filters rainfall, may store a high amount of organic carbon, and acts as a pollutant buffer.

Microplastics (MPs) can be found in the soil in forms such as primary microplastics, secondary microplastics, and larger plastics, which may be evident due to disposal of waste in soil, accumulation from various sources, and usage of plastic. With the passage of time and environmental actions, tons of plastic leftovers were found in the soil because of mulching procedures converted into MPs. The MPs that arise spread in the soil and interact with other pollutants like heavy metals, insecticides, and POPs, generating cumulative harmful effects on soil flora and fauna. Agricultural water runoff may eventually carry these MPs to rivers, oceans, and other water bodies [4,5]. Consequently, they reach the human body by following different routes from the soil, such as soil microorganisms (through food ingestion), air (construction materials, trash burning, artificial fibers from clothing, and aerosols like dust, fog, forest exudates, and geyser steam), and water (PVC pipes, fishing gear, and water filtering equipment's), etc. [6–8].

Globally, most of the studies reported the presence of MPs in marine water [9], rivers [10], drinking water, and freshwater [11]. Similarly, most of the research in India is limited to coastal areas, but reports addressing the presence of MPs within the soil are very limited [12–14]. MPs presence in soil are responsible for soil structure breakdown and have a negative impression on the water-retaining capacity of the soil [15]. Further, these microplastics can cause various health disorders like miscarriage, infertility, decreased sperm quantity and quality, chromosomal abnormalities in ovum (eggs), inflammations, toxicity, and respiratory and liver diseases in humans [16].

Our research endeavors to address the gap by undertaking a comprehensive study of prevalence, kinds, and distribution of MPs in the soil sample of Una district, Himachal Pradesh (India). Moreover, there is an absence of studies on MP distribution in this region. Our objective is to provide significant insights that are relevant to the local context through a quantitative and qualitative assessment. These insights will influence plans for the regulation and mitigation of MP pollution in this specific area.

2. Material and methods

Study Area: Soil samples (n = 6) were collected from each site of Una district, comprising urban, rural, and agricultural soil. Coordinates of sampling site included Amb (31.6856°, 76.1331°, 478 m), Gagret (31.6868°, 76.0732°, 439 m), Mubarikpur (31.7049°, 76.0949°, 478 m), Una (31.4451°, 76.2548°, 369 m), and Tahliwal (31.3491°, 76.2614°, 389 m) regions of Una district of Himachal Pradesh, India (**Figures 1** and **2**). A control sample was collected from the university campus (32.2253°, 76.1467°, 764 m) because of its regulated environment, minimal industrial influence, and established waste management procedures. Samples (1000 g) were collected as composite samples from four discrete sites of each sampling area targeting the top 30 cm of soil layer, which was combined and homogenized into a single sample. A stainless-steel shovel was used for sample collection and transported to the laboratory in aluminum foil paper. A control sample free from plastic was created by sieving manually and transferred to a hot air oven or ignited at 500 ℃. The temperature attained guaranteed elimination of all plastic particles.

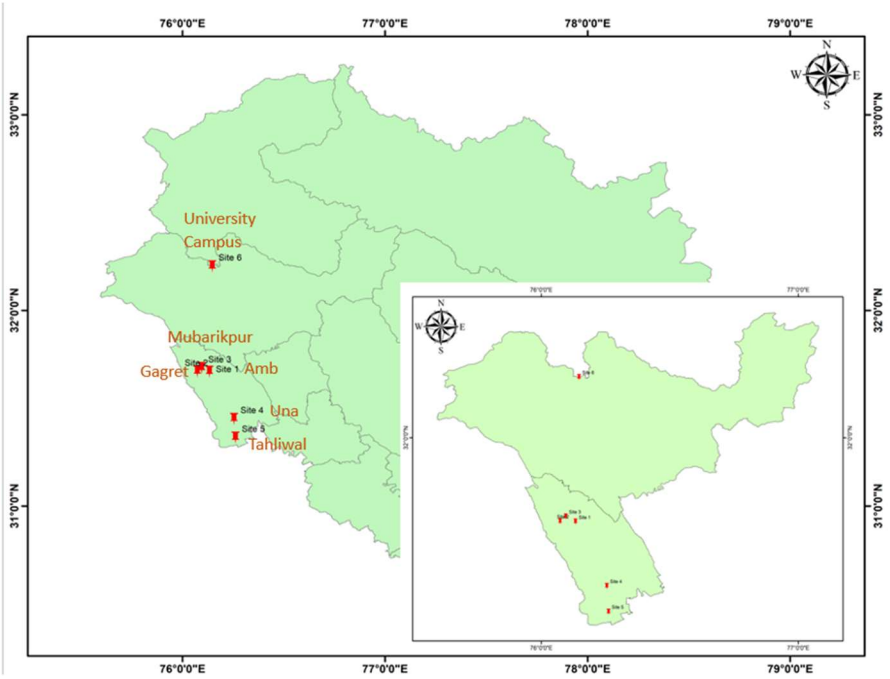

Figure 1. Map locating sampling sites in district Una.

Figure 2. Sampling sites: Urban: **(A)** (Amb), **(B)** (Gagret), Rural: **(C)** (Mubarikpur), **(D)** (Una), Agricultural: **(E)** (Tahliwal) and Control: **(F)** (University Campus).

3. Microplastics extraction

In the laboratory, homogenized and dried soil samples were sieved using stainless steel mesh of pore size 1 mm–5 mm. 50 g of soil sample in triplicates was taken. The density separation method was used for microplastics detection [17]. Distilled water (20 mL) was added to the soil sample (50 g). The soil sample was mixed with 20 mL of saturated NaCl (5 M) solution in a glass beaker. A stir bar was added to the solution, and the solution was continuously stirred at 2200 rpm for 10 minutes. After that, 20

mL of $ZnCl_2$ (5 M) was added to the solution, and the solution was stirred at 2200 rpm for 15 minutes using a magnetic stirrer. The solution was allowed to settle down for 2 hours. The solution was then filtered carefully using Whatman CAT No. 42 (pore size 2.5 μm) filter paper, and the filtrate was collected in a new beaker.

3.1. Removal of the organic matter

Microplastics were separated from organic matter, which is typically present in agricultural soil. Soil organic matter has a density of $\rho < 1.6$ g·cm^{-3} [18], which is similar to that of microplastics $\rho = 0.9–1.6$ g·cm^{-3} [19] and cannot be completely removed by the density separation.

The organic matter present in the filtrate obtained in the previous step was removed by oxidizing the sample using 30% H_2O_2 at 65 °C for 24 h [20]. The digested sample was again filtered with the Whatman CAT No. 42 filter paper, followed by direct observation of the filter paper under the stereomicroscope.

3.2. Microplastics analysis

Visual evaluation was performed to identify the MPs according to the physical characteristics (shape and color) of the particles. The filtered sample were then visualized under stereomicroscope (Magnus CH201) at 10X and 40X magnifications [21].

3.3. Quantitation of MPs

For quantitative estimation of microplastics, the calculation formula was applied in order to check the concentrations of MPs contamination per kg of sample [22].

$$MP_{corr} = (MP_{vis} \times P_{error})/W$$

where, MP_{corr} = Average contamination of MPs per Kg of soil sample.

MP_{vis} = No. of visually identified particles/sample under stereomicroscope.

P_{error} = Theoretical error value (significant value of $P_{error} \leq 0.05$)

W = Weight of sample taken i.e., 50 g.

3.4. Quality control and assurance

Prior to each step, all glasswares and containers were given a three-time cleaning in distilled water, after which they were sealed in aluminum foil. Plastic instruments were avoided throughout the experiment to prevent plastic contamination of the samples. During the entire operation, nitrile gloves and cotton lab coats were worn. The area for stereomicroscopic inspection was meticulously cleansed before the analyses of the sample to avoid any potential contamination.

3.5. Statistical analysis

A t-test was used to compare the difference in the average number of microplastics in the soil samples.

4. Results and discussion

The present study was conducted in five different sites in district Una, Himachal

Pradesh. Five different sites were Amb, Gagret, Mubarikpur, Una, and Tahliwal. Soil samples collected revealed site-specific varied abundance (**Figure 3**). The control sample confirmed the absence of the microplastic contamination through the medium used. Microplastics were counted visually and were categorized into various categories, typically based on their colour and shapes. The microplastics obtained were of various colors, such as green (1%), yellow (5%), blue (2%), purple (59%), and transparent (28%) (**Figure 4**). Concordantly, Feng et al. [23] also found transparent and colourless (49.02%) microplastic dominating in grassland and farmland soil in Tibet.

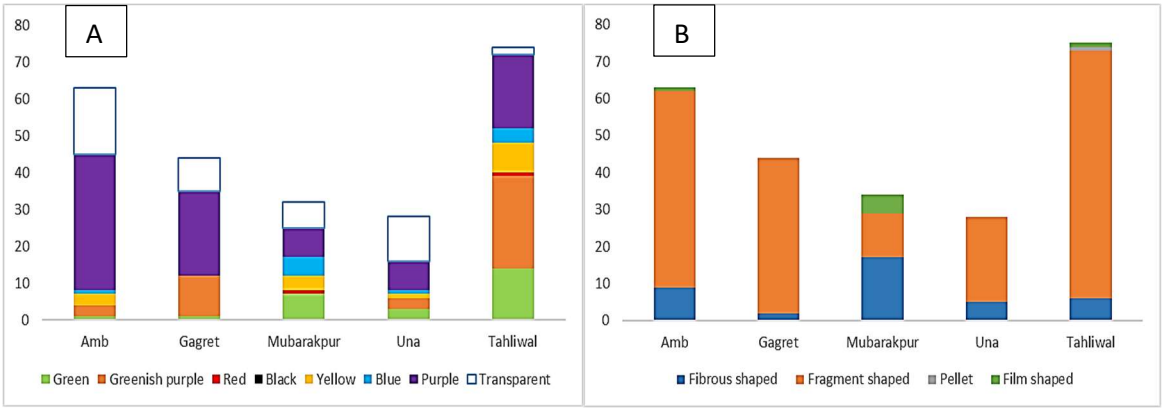

Figure 3. Distribution of microplastics examined in the study sites based on **(A)** Color and **(B)** Shape.

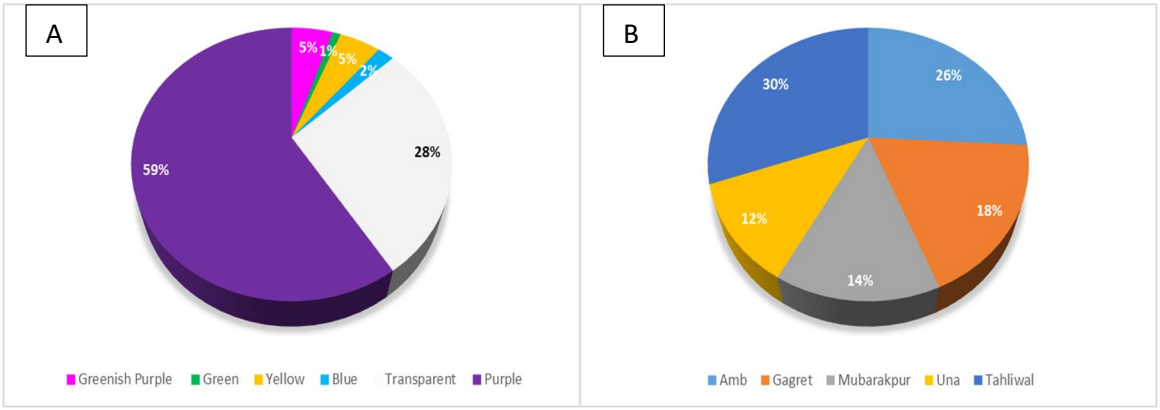

Figure 4. Percentage based **(A)** Color, **(B)** Shape distribution of microplastic in the Una district, Himachal Pradesh.

Similarly, the shape-based microplastics identified were fragmented, fibrous, film, and pellet-shaped. The abundance of MPs identified varied about 81.06% as fragments, followed by fibers (16.04%) and films (2.89%). Zhang and Liu [24] reported 92% fibers, followed by fragments and films (8%) in the soil aggregate fraction in South Western China. In contrast, Karthik et al. [25] reported fragments (50%) in abundance rather than fibers (27%) and foam (19%) in the soil sample. Whereas the present study found fragments to be the most dominant shape, which indicates that the larger fragments of plastic might have broken down into smaller fragments due to various chemical, physical, and biological factors [26]. The study by Lehtiniemi et al. [27] suggested fibers shape as a secondary source of microplastic. The abundance of fibers has been reported in other areas such as Xijin Wetland Park, Nanning, South China [28], Dongting Lake, and Hong Lake, China [29].

Since microplastics size ranges from 1 µm–5 mm [30], the size of microplastic examined varied from 0.44 µm–69 µm (**Figure 5**). The smallest fragment of MP examined was of length 0.44 µm, which was light blue in colour, and the longest particle was of size 69 µm, which was fiber in shape (**Figure 5**). A previous study has reported an almost similar particle size range of 0.1 mm to 2 mm from the sediment samples [31]. In contrast to Chen et al. [32], who reported MPs of size ranging from 3 µm–50 µm in samples.

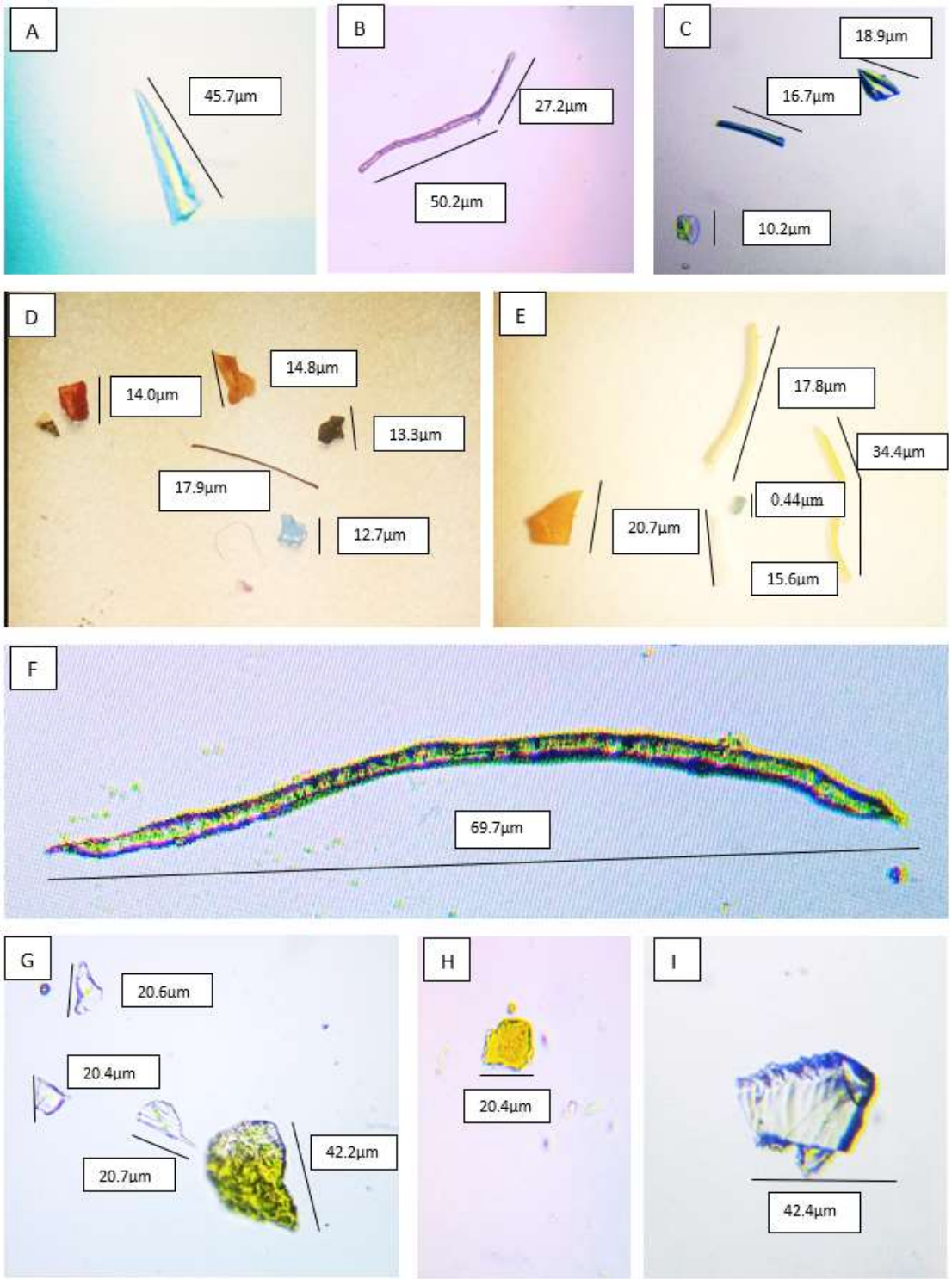

Figure 5. MPs observed in the soil samples **(A, C, D, F, G, H)** (Fragments), **(B** and **E)** (Fibers).

The average concentration of microplastics in diverse sampling sites situated in Distt. Una was 0.021 particles/150 g (Amb) and 0.014 particles/150 g (Gagret) comprising of urban location, while 0.011 particles/150 g (Mubarikpur) and 0.009 particles/150 g (Una) in rural area and 0.024 particles/150 g (Tahliwal) in agricultural land. Significantly higher MPs concentration was observed in all sites except Una and Mubarikpur. A soil sample collected from sampling site 5 (Tahliwal, agricultural land) was reported to be highly contaminated with MPs, which may be accredited to the composition of microplastics in pesticide packaging, regular mulching containing plastic, and environmental deposition [33,34]. The reasons behind rising MPs pollution in this city are industrial effluents, household garbage, and waste dumping in soil. Soil contamination with microplastics alters the physical properties of soil, such as aeration, porosity, and water holding capacity, and affects the microbial community [35,36].

Plastics are complexed materials made up of more than 10,000 chemical components like additives, colorants, dyes, luster additives, processing aids, resins, and other compounds that are used to enhance the rigidity and flexibility of the plastic products, which are known to be toxic to both human health and the atmosphere [29,37,38]. Ingestion and inhalation are two key routes of exposure to plastic additives that may enter the gastrointestinal tract or lungs [39].

5. Conclusion

The smaller the size of plastic, the higher the level of damage. The main reason behind rising MPs pollution in this city is industrial effluents, household garbage, and waste dumping in soil. Considering the negative impact of the contamination, there is a need to create awareness of the consequences of microplastic presence. Even though the government and policymakers have passed several rules and regulations, it is the responsibility of individuals and organizations to guarantee that the policies are followed to preserve ecosystems from the harmful impacts of plastic litter.

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Review

Toxicity of agrochemicals: Impact on environment and human health

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Abstract: Agrochemicals, while essential for increasing agricultural yields and pest control, have unintended consequences. They contaminate soil and water, disrupting ecosystems, reducing biodiversity, and threatening aquatic life. Furthermore, agrochemicals harm non-target organisms, disrupting ecological balance. On the human health front, farmworkers and pesticide applicators face acute poisoning risks, with symptoms ranging from discomfort to severe illness or death. Chronic health effects include links to cancer, neurological disorders, and reproductive problems, raising concerns about food safety and worker well-being. Addressing agrochemical toxicity requires a multifaceted approach. Governments must enforce strict regulations to minimize environmental contamination and ensure safe handling practices. The agricultural industry can adopt sustainable methods like integrated pest management (IPM) and organic farming to reduce reliance on agrochemicals. Innovations such as precision agriculture, biological pest control, nanotechnology, and artificial intelligence for early risk detection are essential. Collaboration among stakeholders is critical for a more sustainable and environmentally friendly agriculture sector, involving regulatory measures like maximum residue limits (MRLs) and sustainable practices like IPM and organic farming. In summary, this review highlights the urgent need to address agrochemical toxicity holistically, balancing agricultural productivity with environmental and health concerns to ensure a sustainable future for agriculture and the planet.

Keywords: acute poisoning; agrochemicals; artificial intelligence; public health; sustainable agriculture

1. Introduction

The toxicity of agrochemicals has profound implications for both the environment and human health. In agriculture, these chemicals are used to boost crop yields and protect against pests, but their unintended consequences are increasingly evident. Agrochemicals can contaminate soil and water, disrupting ecosystems and reducing biodiversity. Soil contamination can lead to long-term fertility issues, while water pollution threatens aquatic life and the quality of drinking water sources. Furthermore, the harm caused to non-target organisms, such as beneficial insects and birds, highlights the intricate interconnections within ecosystems that are disrupted by the use of agrochemicals.

On the human health front, the impact of agrochemicals is equally concerning. Acute poisoning is a risk for farmworkers and pesticide applicators who handle these chemicals, with symptoms ranging from mild discomfort to severe illness or even death [1]. More insidious are the chronic health effects associated with long-term exposure to agrochemical residues. These include links to cancer, neurological

disorders, and reproductive problems, raising concerns about the safety of the food we consume and the well-being of those working in agriculture [2–4].

Addressing the toxicity of agrochemicals requires a multifaceted approach. Governments must enforce strict regulations to minimize environmental contamination and ensure safe handling practices. Meanwhile, the agricultural industry can adopt sustainable methods like integrated pest management (IPM) and organic farming to reduce reliance on these chemicals. It is crucial to strike a balance between agricultural productivity and environmental and human health concerns to build a sustainable future for agriculture and our planet.

2. Environmental impact

Environmental concerns require a shift towards sustainable agricultural practices. Integrated pest management (IPM), organic farming, crop rotation, and reduced chemical usage are some strategies that can mitigate the adverse effects of agrochemicals on the environment while maintaining food production. Additionally, improved education and awareness among farmers about responsible agrochemical use are essential steps toward reducing their environmental footprint.

2.1. Soil contamination

Loss of soil fertility: Agrochemicals, particularly synthetic fertilizers, can lead to soil degradation. Excessive use of fertilizers can disrupt the natural nutrient balance in the soil. Over time, this can lead to nutrient imbalances, making the soil less fertile and reducing crop yields [5].

Microbial disruption: Soil is home to a diverse ecosystem of microorganisms that play a vital role in nutrient cycling and soil health. Agrochemicals, especially pesticides, can harm beneficial soil microorganisms, disrupting these vital processes [6].

Persistence: Some agrochemicals, such as certain herbicides, can persist in the soil for extended periods. This persistence can lead to long-term contamination and potential harm to future crops [7].

2.2. Water pollution

Runoff: When it rains or when fields are irrigated, agrochemicals on the soil's surface can be washed into nearby water bodies. This runoff carries pesticides, herbicides, and fertilizers into rivers, lakes, and streams [8].

Groundwater contamination: Agrochemicals can leach through the soil and contaminate groundwater, which serves as a source of drinking water for many communities. Prolonged exposure to contaminated groundwater can have serious health consequences [9].

Algal blooms: Fertilizer runoff containing excess nutrients like nitrogen and phosphorus can trigger algal blooms in water bodies. These blooms can deplete oxygen levels in the water, harming aquatic life and creating "dead zones" [10].

2.3. Harm to non-target organisms

Insecticides and pollinators: Insecticides, designed to target pest insects, can

inadvertently harm beneficial insects like bees and butterflies, which are essential for pollinating crops. This can disrupt the natural balance in ecosystems and reduce crop yields [11].

Birds and aquatic life: The contamination of water bodies with pesticides can harm aquatic organisms, including fish and amphibians. Birds that feed on contaminated aquatic life can also suffer adverse effects.

2.4. Residue and resistance

Food residue: Agrochemical residues can remain on harvested crops. Consumers may unknowingly ingest these residues, potentially leading to health risks. This is why monitoring and regulating maximum residue limits (MRLs) on food items is crucial.

Pest and weed resistance: Prolonged and widespread use of agrochemicals can lead to the development of resistance in pest insects and weeds. This means that over time, higher concentrations or different chemicals may be needed to achieve the same level of pest control, increasing the overall environmental impact.

3. Human health impact

The human health impact of agrochemicals necessitates stringent safety regulations, proper training, and the use of protective equipment for those handling these chemicals. Additionally, promoting alternative, less toxic agricultural practices, such as organic farming and integrated pest management, can reduce the reliance on hazardous agrochemicals. Monitoring and regulation of agrochemical residue levels on food items are crucial to safeguarding consumer health. Overall, a holistic approach is essential to protect both the environment and human health from the adverse effects of agrochemicals.

3.1. Acute poisoning

Farmworker exposure: Farmworkers and pesticide applicators are at the highest risk of acute poisoning. They work directly with agrochemicals and can be exposed to high concentrations. Symptoms of acute poisoning can range from mild skin or eye irritation to more severe effects like nausea, vomiting, diarrhea, dizziness, and, in extreme cases, respiratory distress or death.

Accidental exposure: Accidental exposure can occur through mishandling of agrochemicals or the lack of proper protective equipment. Inadequate training and safety measures can increase the risk of such incidents.

3.2. Chronic health effects

Cancer: Some agrochemicals, such as certain pesticides and herbicides, have been classified as known or suspected carcinogens. Long-term exposure to these substances, even at low levels, can increase the risk of cancer among agricultural workers [2].

Neurological disorders: Exposure to certain agrochemicals has been linked to neurological disorders. Organophosphate pesticides, for example, have been associated with cognitive and motor deficits, particularly in children [3].

Reproductive problems: Some agrochemicals are endocrine disruptors, which means they can interfere with the hormonal systems of humans. This can lead to reproductive problems, including reduced fertility and developmental issues in children [4].

3.3. Residue on food

Consumer exposure: residues of agrochemicals can remain on food items after harvesting. Consumers who regularly consume these residues may face long-term health risks, especially vulnerable populations such as children, pregnant women, and individuals with compromised immune systems.

Children's health: Children are particularly susceptible to the effects of agrochemicals due to their developing bodies and higher relative food consumption. Prenatal exposure can also have lifelong implications.

3.4. Occupational risks

Farmworkers and their families: Agricultural workers often bring home pesticide residues on their clothing and bodies, which can pose risks to their families. This is known as "take-home exposure" and can affect children and other household members.

Lack of awareness: In many agricultural communities, there may be a lack of awareness about the risks associated with agrochemical exposure. This can lead to inadequate protection and safety measures among farmworkers.

3.5. Psychosocial impact

Stress and mental health: The awareness of the potential health risks associated with agrochemical exposure can lead to stress and mental health issues among agricultural workers and their families. Fear of exposure and its consequences can create a significant psychological burden.

4. Innovations and initiatives to tackle adverse effects of agrochemicals on human and environmental health

4.1. Precision agriculture (PA)

Precision agriculture involves the use of advanced technology to optimize farming practices. GPS-guided machinery, drones and sensor networks help farmers make data-driven decisions regarding the application of agrochemicals. By precisely targeting areas of the field that require fertilizers, pesticides, or herbicides, farmers can minimize overuse, reduce costs, and limit the environmental impact of these chemicals. PA also allows for real-time monitoring of crop health, enabling early detection of issues and prompt action, further reducing the need for chemical interventions [12].

4.2. Biological pest control

Biological pest control utilizes natural predators, parasites, and pathogens to manage pest populations. Beneficial insects like ladybugs and parasitoid wasps, as

well as microorganisms such as nematodes and fungi, are used to control pests without resorting to synthetic pesticides. This approach is environmentally friendly and helps maintain ecological balance in agricultural ecosystems [13].

4.3. Integrated pest management (IPM)

IPM is a holistic approach that combines multiple strategies to manage pests effectively. Farmers monitor pest populations, use biological controls, implement crop rotation, and only resort to chemical pesticides when necessary. By minimizing chemical use and promoting natural pest control methods, IPM reduces the ecological footprint of agriculture [14].

4.4. Nanoencapsulation

Nanoencapsulation involves enclosing agrochemicals in tiny capsules to improve their delivery and release. This technology enhances the efficiency of agrochemicals, reducing the quantity needed while prolonging their effects. This results in reduced environmental contamination and fewer health risks for workers handling these chemicals [15].

4.5. Biodegradable and reduced-risk pesticides

Researchers are developing agrochemicals that break down more quickly in the environment, reducing their persistence and potential harm. These reduced-risk pesticides have lower toxicity to non-target organisms, including humans, wildlife, and beneficial insects. They are designed to be less harmful to ecosystems while still effectively controlling pests.

4.6. Gene editing

Gene editing techniques, such as CRISPR/Cas9, are used to develop crops with enhanced resistance to pests and diseases. By modifying the plant's genetic makeup, farmers can reduce their reliance on chemical pesticides. This innovation offers long-term solutions to pest management while minimizing environmental impacts [16].

4.7. Sustainable farming practices

Sustainable farming practices, such as cover cropping, reduced tillage, and organic farming, focus on reducing agrochemical use. Cover crops enhance soil health and reduce the need for synthetic fertilizers, while reduced tillage prevents soil erosion and retains moisture. Organic farming avoids synthetic chemicals altogether, relying on natural alternatives.

4.8. Remote sensing and data analytics

Remote sensing technologies like satellites and drones provide farmers with valuable data on crop health and pest infestations. Data analytics and machine learning algorithms help interpret this information in real time, allowing farmers to make timely decisions about agrochemical applications. Early detection and targeted responses minimize chemical use and its associated risks.

4.9. Blockchain and transparency

Blockchain technology is used to create transparent supply chains in agriculture. Consumers can trace the origin of their food products and verify the use of sustainable and responsible farming practices. This transparency incentivizes farmers to reduce chemical use, adopt eco-friendly practices, and meet the growing demand for environmentally conscious food production [17].

5. Application of artificial intelligence

Artificial intelligence (AI) stands as one of the most transformative and impactful technological advancements of our era, encompassing a wide spectrum of capabilities that simulate human intelligence. At its core, AI involves the creation of machines, software, and systems that can think, reason, learn, and adapt to various situations, mirroring human cognitive functions. It enables these entities to process large volumes of data, identify patterns, and make decisions based on the insights gathered. One of the fundamental branches of AI is machine learning, which empowers systems to improve their performance over time through exposure to data. Machine learning algorithms, inspired by the neural networks of the human brain, can learn from examples and experiences, iteratively refining their responses. This capability has led to breakthroughs in diverse fields, from medical diagnoses and autonomous vehicles to natural language processing and recommendation systems.

AI's impact is not limited to just machine learning; it encompasses a broader range of techniques. For instance, natural language processing (NLP) enables computers to understand, interpret, and generate human language. This has given rise to virtual assistants and chatbots like ChatGPT that can converse with users in a human-like manner, making interactions with technology more intuitive [18]. Artificial intelligence harnesses data patterns and predictive models to foresee potential disease outbreaks, enabling proactive measures and rapid responses to mitigate their impact on public health. By analyzing diverse data sources, AI aids in early detection and prediction, revolutionizing disease surveillance and prevention strategies [19]. Through the integration of artificial intelligence, digital twins in healthcare, including gene sequencing, facilitate the development of virtual genetic models that mimic individual patients, revolutionizing our comprehension of genetic information and propelling personalized medicine with precisely customized interventions [20].

5.1. Early detection of health risks

AI-driven early detection of health risks associated with agrochemical exposure is a critical component of ensuring the safety and well-being of farmworkers and nearby communities. AI leverages data from various sources, including weather patterns, soil conditions, and historical pesticide usage, to create predictive models. These models can identify high-risk areas where pesticide drift or contamination is likely to occur. By analyzing wind patterns, temperature, and crop characteristics, AI can forecast when and where agrochemicals may disperse beyond their intended target. This early warning system enables farmers and regulatory agencies to take preemptive measures, such as adjusting application methods or temporarily halting

operations, to protect human health.

Additionally, AI can integrate real-time data from sensors placed in fields and on farm equipment. These sensors can monitor factors like pesticide concentration in the air and soil, allowing for immediate alerts if exposure levels exceed safe thresholds. Farmworkers can be equipped with wearable devices that continuously track their exposure levels, providing them with warnings and safety recommendations in real time. This proactive approach to risk management reduces the likelihood of acute and chronic health issues resulting from agrochemical exposure.

Furthermore, AI systems can analyze the historical health data of farmworkers in relation to their work environments. By identifying correlations between specific chemical exposures and health outcomes, AI can assist in establishing evidence-based regulations and safety guidelines. This ensures that policies are informed by data, leading to more effective protection of human health in agriculture.

5.2. Pesticide exposure monitoring

AI-powered pesticide exposure monitoring is a crucial tool in safeguarding the health of farmworkers who handle and apply agrochemicals. AI integrates data from a variety of sources to provide comprehensive and real-time insights into exposure levels. For instance, wearable devices equipped with sensors can continuously measure the concentration of airborne pesticides as well as assess skin contact. These wearables transmit data to AI algorithms, which analyze the information against safety thresholds. By applying machine learning techniques, AI can provide farmworkers with personalized recommendations and alerts based on their unique exposure profiles. For example, if a worker's wearable device detects a spike in pesticide concentration, AI can issue an immediate warning and suggest specific protective measures, such as wearing additional protective gear or moving to a safer area. This real-time feedback empowers farmworkers to make informed decisions to mitigate their exposure.

Moreover, AI-driven exposure monitoring systems can collect and store data over time, creating a comprehensive record of individual exposure histories. This data is invaluable for occupational health assessments, enabling healthcare professionals to evaluate the long-term effects of agrochemical exposure on farmworkers. It also aids in identifying trends and patterns related to exposure, which can inform the development of targeted interventions and safety protocols. In addition to protecting farmworkers, AI-based pesticide exposure monitoring contributes to the overall reduction of chemical risks in agriculture. By pinpointing areas and practices associated with high exposure levels, farmers and regulatory authorities can take measures to optimize application techniques, adopt safer alternatives, or implement buffer zones to minimize the risk to nearby communities and the environment.

6. Regulatory measures and sustainable practices

Balancing the need for agricultural productivity with environmental and health concerns is a complex challenge. Regulatory measures ensure the safe use of

agrochemicals, while sustainable practices aim to reduce their overall impact. Collaboration between governments, farmers, researchers, and consumers is crucial to achieving a more sustainable and environmentally friendly agriculture sector.

6.1. Regulatory measures

Maximum residue limits (MRLs): Governments around the world establish MRLs for pesticides and other agrochemical residues on food products. These limits define the maximum allowable concentration of residues that can remain on or in food items. Regular monitoring and enforcement of MRLs are critical to ensure food safety.

Pesticide registration and approval: Agrochemicals must go through a rigorous registration and approval process before they can be sold and used. This process evaluates the safety and efficacy of these chemicals, taking into account potential risks to the environment, human health, and non-target organisms.

Labeling and safety data sheets: Agrochemical products come with detailed labels and safety data sheets that provide information on proper handling, application, storage, and disposal. These documents also outline safety precautions to minimize risks during use.

Training and certification: Many countries require individuals who handle and apply agrochemicals to undergo training and certification. This training covers safe handling practices, protective equipment usage, and the responsible use of these chemicals.

Buffer zones and restricted application: Regulations may mandate buffer zones around treated fields to reduce the risk of drift and contamination of nearby areas. Additionally, some chemicals may have restrictions on their application during certain times or under specific weather conditions to minimize environmental impact.

6.2. Sustainable practices

Integrated pest management (IPM): IPM is an approach that combines biological, cultural, physical, and chemical strategies to manage pests and diseases. It emphasizes the judicious use of agrochemicals as a last resort after non-chemical methods have been exhausted. IPM aims to minimize the environmental impact while maintaining crop productivity.

Organic farming: Organic farming avoids synthetic agrochemicals and relies on natural alternatives. It prioritizes soil health, crop rotation, and the use of organic fertilizers and pesticides that have a lower environmental impact. Organic certification ensures adherence to these practices.

Crop rotation and diversification: Crop rotation helps break the cycle of pests and diseases, reducing the need for chemical interventions. Diversifying crops in a rotation can also improve soil health and reduce the risk of soil degradation.

Biological control: Beneficial insects, nematodes, and microorganisms can be used to control pest populations. This biological control method is environmentally friendly and minimizes the use of chemical pesticides.

Precision agriculture: Precision agriculture employs technology like GPS-

guided tractors and drones to optimize the use of agrochemicals. By targeting specific areas with pest or nutrient issues, farmers can reduce overall chemical usage and minimize environmental impact.

Cover crops and conservation practices: Planting cover crops and adopting conservation tillage practices can reduce soil erosion, improve soil health, and minimize the need for chemical fertilizers and herbicides.

Research and innovation: Continued research into alternative pest control methods, the development of less toxic agrochemicals, and the promotion of sustainable farming practices are essential for reducing the environmental and health impact of agriculture.

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Review

Sources and toxicological effects of some heavy metals—A mini review

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Abstract: Heavy metals play essential roles in biological activities as enzyme cofactors in trace amounts. However, their significance is overshadowed by potential harm in excess. Bio-accumulation, toxicity, non-biodegradability, and persistence are hallmarks that impact the environment and human health. Bio-accumulation is critical as metals accumulate in organisms, posing risks in ecosystems, especially in the food chain. This leads to elevated metal concentrations in the human food chain. Even at trace levels, heavy metals like lead, mercury, cadmium, chromium, and arsenic exhibit toxicity, causing various health issues, emphasizing the need to regulate exposure. Non-biodegradability distinguishes heavy metals; they persist in the environment, enhancing the risks associated with prolonged exposure and accumulation. Due to their recognized toxicity, heavy metals are a focus of research. Understanding sources, pathways, and effects is crucial for effective mitigation strategies. Researchers explore pollution control, improved industrial practices, and remediation techniques. Anthropogenic activities, such as industrialization, urbanization, waste disposal, and agricultural practices, release heavy metals into the environment. This contaminates air, water, and soil, contributing to environmental and health risks. The present paper discusses the sources and toxicological effects of various heavy metals.

Keywords: heavy metals; sources; toxicology; pollution; environment; biosorption

1. Introduction

The widespread existence of heavy metals in the environment presents a significant risk to human health and ecosystems; hence, efforts must be made to address and reduce their effects. Heavy metals such as mercury (Hg), chromium (Cr), lead (Pb), zinc (Zn), arsenic (As), cadmium (Cd), cobalt (Co), copper (Cu), and nickel (Ni) play essential roles in various biological functions; their excessive accumulation can lead to severe hazards [1]. Heavy metals are necessary for living things to carry out a variety of biological functions, but larger amounts of these elements can be hazardous. Toxic metals (like Hg, Cr, Pb, Zn, Cu, Ni, Cd, As, Co, Sn, etc.), precious metals (like Pd, Pt, Ag, Au, Ru, etc.), and radionuclides (like U, Th, Ra, Am, etc.) are the three main categories of heavy metals [2,3]. Among the group of metals that are classified as toxic, heavy metals such as Pb, Cr, Hg, Zn, As, Cd, Co, Cu, and Ni are released into the environment in unfavorable amounts that are harmful to human health [4]. Through the food chain, humans and other living things may come into contact with heavy metals, which can become extremely toxic when they combine with other environmental variables like water, soil, and air [5]. Heavy metals are toxic, bioaccumulate, and do not biodegrade, which makes their presence in the environment a major cause for concern. These characteristics provide heavy metals with detrimental effects on the environment and human health. The metal ions are generally soluble in an aqueous medium and do not biodegrade [6]. Toxic metals, therefore, quickly accelerate and build up in the human food chain. The detrimental impact of heavy

metals is not confined to environmental degradation alone; it extends to human well-being. Exposure to toxic metals through contaminated food, water, or air can result in a range of health issues, including toxicity and carcinogenicity. The significance of this issue is further magnified by the rapid release of metal-containing wastes into the environment, both directly and indirectly, during various industrial processes. This unchecked release poses a direct threat to ecosystems, contributing significantly to pollution. The detrimental effects of heavy metals are exacerbated when they interact with other environmental factors [7]. Consequently, the urgent need to address this issue arises from the fact that heavy metals, being non-biodegradable and poisonous, have the potential to cause long-lasting and far-reaching consequences [8]. Many researchers have focused their attention on heavy metals because of their toxicity and carcinogenicity [9]. Rapid urbanization, industrialization, and human activity release heavy metals into the environment [10,11]. Metal-containing wastes are either directly or indirectly released into the environment, endangering ecosystems and causing major pollution [12,13]. Therefore, before releasing the solid or watery waste into the environment, these metals must be removed or sequestered.

To safeguard the environment and human health, it becomes imperative to understand the origins and toxicological consequences of these heavy metals. Moreover, strategies for the effective removal or sequestration of these metals from solid or liquid waste before their release into the environment are crucial. This study delves into the multifaceted challenges posed by heavy metals, shedding light on their origins, the toxicological implications of several significant heavy metals present in the environment, and the pressing need for proactive measures to curb their environmental impact.

2. Sources and toxicological effects of heavy metals

Heavy metals, including lead, mercury, and cadmium, are pervasive environmental contaminants with diverse sources, such as industrial discharges and agricultural runoff. Their toxicological effects pose serious health risks, affecting vital organs and causing long-term harm. Understanding and mitigating heavy metal exposure are crucial for safeguarding public health and environmental well-being. The sources and effects of some heavy metals of important heavy metals are presented in **Table 1**.

Table 1. Sources and effects of some heavy metals.

Heavy metals	Sources	Effects	Reference
Arsenic (As)	Industrial effluents, fossil fuel, pesticides, fungicides, paint, dyes textiles industries	Hemolysis, hepatomegaly, pneumonia, and dermatitis are disorders of the nervous system	[14]
Cadmium (Cd)	Nuclear fission reactor, welding, electroplating, fertilizers, insecticides, Cd-Noorul Islam Centre for Higher Education batteries	Renal damage, pneumonia, cancer, gastrointestinal issues, and bone marrow	[15]
Chromium (Cr)	Rubber, textile, tannery, metallurgical, and photographic industries	Quick hair loss and breathing issues	[16]
Cobalt (Co)	Dyes, mining, decomposition of organic matter and minerals	Wilson's illness toxicity to development, reproduction, and nervous system	[17]
Copper (Cu)	Pesticides, mining, electronics trash, electroplating	Failure of the Kidney and Brain Intense anemia and gastrointestinal discomfort	[18]

Table 1. (*Continued*).

Heavy metals	Sources	Effects	Reference
Iron (Fe)	Engineering industries	Anemia	[19]
Lead (Pb)	Vehicle emissions, wastewater, paint, pesticides, mining, and coal burning	Kidney, liver, digestive system damage, and childhood mental impairment	[20]
Mercury (Hg)	Chemical industries, insecticides, batteries, paper industry, contaminated water, scientific instruments	Damage to nervous system	[21]
Nickel (Ni)	Fertilizers, iron-steel, battery, zinc base casting, and electroplating industries	Cancers of the lungs, throat, and stomach; immunotoxin; neurotoxic; genotoxic; hepatotoxic; rapid hair loss	[22]
Zinc (Zn)	Refineries, the production of brass, metal plating, painted idol immersion, and galvanization	Zinc fumes harm nerve membranes and have a corrosive effect on skin	[23]

2.1. Arsenic

Anionic species of arsenate (V) (H_2AsO_4-) at pH 2–6 and arsenite (III) (H_2AsO_3-) at pH 9–12, which exist as oxoanions, are the most prevalent arsenic species found in water bodies. These have varying effects on the biological system [24]. Arsenic pollution can be from man-made and natural sources. Large-scale groundwater and hot spring water contamination with arsenic has been reported in West Bengal, India, as well as in a number of minerals and chemical processes [25,26]. According to WHO estimates, arsenic poisoning alone affects roughly 70 million people in these regions [27].

Naturally occurring processes such as weathering, fire, volcanic eruptions, mineral ores, long-term geochemical changes, etc. lead to the distribution of arsenic. Also, from a variety of industrial effluents, such as those from the metallurgical, ceramic, and smelting sectors; energy generation from fossil fuels; rock sediments; dye; and industries that manufacture fungicides and pesticides, among others. According to Balakumar and Kaur [28], arsenic poisoning can result in bronchitis, cardiovascular failure, gastrointestinal symptoms, abnormalities of the neurological system, bone marrow depression, hemolysis, hepatomegaly, melanosis, polyneuropathy, encephalopathy, and liver tumors. The highest amount of arsenic contamination was 0.050 mg/L [29].

2.2. Cadmium

Natural ore deposits contain cadmium as well as zinc, lead, and copper in common. The main sources of cadmium are released from nickel-cadmium batteries, electroplating, mining, and metallurgy industries. Waste streams from nuclear power plants also contain undesirable levels of $Cd2^+$ ions [30–32]. Other ways to come into contact with cadmium include welding, usage of pesticides and fertilizers, smoking cigarettes, and operating smelters. For example, wheat and rice from Cd-polluted districts of Japan have Cd levels of approximately 1 mg/kg, which is ten times higher than global averages [33]. The maximum amount of lead that the EPA allowed in drinking water was 0.005 mg/L. The WHO determined that a man's daily acceptable consumption of lead was 0.06 mg, while a woman was 0.07 mg.

Cadmium has toxic influence mainly on the respiratory system, bones, and kidneys. It can cause fatal renal failure, osteoporosis, osteomalacia, lung diseases, bone lesions, gastrointestinal disorders, bronchitis, and cancer. The characteristic symptoms of acute Cd poisoning in many patients include the loss of the sense of

smell, weight loss, hypertension, pulmonary edema, headache, nausea, vomiting, and diarrhea [34,35]. Long-term exposure to Cd leads to kidney problems and affects the human bones, resulting in Itai Itai disease [36]. Heavy metals like Cd affect mineral assimilation and physiological and biochemical characteristics of plants; they also retard plant growth [37,38].

2.3. Chromium

One of the most dangerous heavy metals that is frequently discovered in industrial effluent is chromium. The two primary chromium oxidation states found in water are trivalent chromium (Cr (III)) and hexavalent chromium (Cr (VI)). The most poisonous element is thought to be Cr (VI), which is typically found in oxygen as chromate or dichromate ions. Because of its mutagenic and carcinogenic qualities, the hexavalent form of chromium is regarded as a group "A" human carcinogen [39].

Exposure to chromium occurs when human skin comes into contact with chromium or its compounds, as well as when breathing, ingesting, or drinking chromium. Food components that contain chromium (III) are the primary source of chromium absorption because many fruits, vegetables, meats, cereals, yeasts, and vegetables naturally contain chromium (III). The production of dyes, paints, and pigments, film and photography, wood preservatives, galvanometry, steel fabrication, canning, textile dyeing, leather tanning, electroplating, metal cleaning, and finishing industries are among the industries that frequently release Cr (VI) into water bodies through wastewater [40]. Approximately 100 mg/L of Cr (VI) is present in the electroplating industry's untreated effluent; nevertheless, De Filippis and Pallaghy [41] reported that 0.05 to 1 mg/L was the allowable limit. The element chromium is extremely toxic and carcinogenic. Chromium (VI) inhalation might result in nosebleeds and irritations. Trace levels of chromium exposure can result in genetic material changes that can lead to lung tumors and cancer, as well as allergic dermatitis, nausea, vomiting, severe diarrhea, respiratory issues, compromised immune systems, damage to the kidneys and liver, and altered kidney and liver function [42–44].

2.4. Cobalt

Cobalt is a component of vitamin B12, or cobalamin, which is vital to human health. However, cobalt may have a greater impact on human health. Cobalt is a metal that is frequently utilized in radioisotope therapy, turbines, alloys, electronics, and porcelain [45]. Plants that are produced in polluted soil or that receive greater irrigation levels of cobalt acquire the metal, which then finds its way into the food chain that feeds humans. Increased cobalt consumption may result in anemia, cardiac problems, vomiting, nausea, thyroid damage, and visual problems [46].

High copper intake causes severe mucosal irritation, neurotoxicity, toxicity to reproduction and development, upset stomach and ulcer, hepatic irritation, irritation of the central nervous system, followed by depression, gastrointestinal irritation, and potentially necrotic changes in the liver and kidneys [47]. Wilson's disease, which damages the liver and brain, can also be brought on by persistent copper poisoning [48]. It has been reported to accumulate in the liver, pancreas, brain, skin, and myocardium [49,50].

2.5. Iron

There are two forms of iron: ferrous iron (Fe^{2+}), which is soluble, and ferric particulate iron (Fe^{3+}), which is insoluble. Iron is typically found in water in its ferric condition. The disintegration of rocks and minerals, acid mine drainage, landfill leachate sewage, or the engineering industries may be the cause of iron in natural water. When iron concentrations surpass 0.1 mg/L, fish gills will also be harmed. The free radicals have a brief lifespan and are very reactive. The iron on the gill surface produces free radicals that oxidize the surrounding tissue, severely damaging the gill tissue and resulting in anemia [19].

2.6. Lead

Lead is found in nature in three different oxidation states: Pb (0), Pb (II), and Pb (IV). Lead is found in mineral formations. Of them, lead (II) is the most prevalent and readily bioaccumulates via the food chain. It is frequently linked to other heavy metals like zinc, copper, mercury, and zinc. Pb comes from a variety of sources, such as vehicular emissions from vehicles, mining, burning coal and plastics, battery manufacturing industry effluents, gasoline additives, fertilizer, pesticides, paint, pigments, alloys, and sheets, among others. Pb in drinking water was allowed to be as low as 0.015 mg/L [51].

Lead exposure has a lot of negative health impacts, including reduced fertility, cardiovascular disorders, impaired renal function, and neurodevelopmental abnormalities [52]. Kidney illnesses as well as problems with the brain system and circulatory system are the main signs of lead poisoning. This causes anemia, brain damage, anorexia, malaise, loss of appetite, delirium, sleeplessness, convulsions, seizures, gastrointestinal damage, and mental retardation in children [53]. Although lead can be absorbed through the skin, the digestive and respiratory systems absorb the majority of it. Pb exposure can cause oxidative, inflammatory, and immune-modulating illnesses, as well as respiratory, urinary, and cardiovascular problems. Additionally, Pb poisoning has been connected to delayed physical or mental development as well as a lower intelligence quotient (IQ), particularly in children with attention spans and learning deficiencies. According to Jarup [30], further symptoms include encephalopathy, kidney failure, headaches, and stomach pain.

2.7. Mercury

The primary cause of pollution is the process of producing mercury. Mercury was commonly used as a softening agent for various materials. One of the most hazardous elements in the environment and the strongest neurotoxins is mercury. Industries such as paints, paper and pulp, oil refining, volcanic eruptions, spontaneous forest fires, biogenic emissions, burning fossil fuels, mining, metallurgical processes, pharmaceutical and battery manufacturing, rubber processing, thermometers, fluorescent light tubes and high-intensity streetlamps, fertilizer, pesticides, and cosmetics are the main sources of mercury pollution in the environment [54]. Mercury gradually builds up in people and other animals once it enters the food chain. Mercury even has fumes that are easily absorbed by mucous membranes, the skin, and the respiratory system. They can also harm the kidneys, neurological system, circulatory

system, and endocrine system. The tongue, teeth, and gums are also impacted due to the organism's invasion route. According to Boening [55], Manohar et al. [56], and Morel et al. [57], mercury can induce dermatitis, rheumatoid arthritis, deterioration of the skin, eyes, and muscles, dyspnea, pulmonary function impairment, and neurological and renal abnormalities. Prolonged exposure to mercury fumes damages the brain severely and can even be fatal [58,59]. Additionally, genetic abnormalities brought on by Mercury can result in chromosome splitting and disruption during cell division, which can lead to an aberrant distribution of chromosomes. Mercury contamination can reach a maximum of 0.00003 mg/L [29].

2.8. Nickel

As a necessary heavy metal, nickel takes part in a number of metabolic processes, including acidogenisis and ureolysis. According to Akhtar et al. [60] and Farooq et al. [61], the primary sources of Ni (II) released into the environment are industrial discharges from electroplating units, magnets, steel alloys, silver refineries, aircraft industries, coinage, zinc base casting, battery manufacturing plants, paint formulation, porcelain enameling, mining and metallurgy, copper sulphate manufacture, and steam-electric power plants.

The maximum allowable concentration of Ni^{2+} in drinking water, as recommended by the WHO, is 0.07 mg/L. Large-scale nickel consumption has a negative impact on human health, causing birth deformities, a variety of allergic reactions, heart problems, bronchial bleeding, nausea, lethargy, and dizziness. Prolonged exposure to nickel can also cause pulmonary fibrosis, gastrointestinal distress, skin dermatitis, lung and prostate malignancies, neurotoxicity, nephrotoxicity, immunotoxicity, and reproductive toxicity [62]. The most common consequence of nickel exposure, such as coins and jewelry, is dermatitis, which manifests as itching, red skin, and rashes [63].

2.9. Zinc

Zinc is a micronutrient that is vital to bioorganisms. Zinc (II) is the most prevalent oxidation state of zinc found in nature. The production of bronze, zinc-based alloys, stabilizers, thermoplastics, pigment formation, battery manufacturing, municipal wastewater treatment facilities, and galvanization—the process of applying anti-corrosion coatings to steel—are among the main causes of zinc pollution in wastewater. The production of rubber, paints, wood preservatives, dry cell batteries, ointments, glass, ceramics, and coatings for other metals, including steel and iron, are further sources. Zn is also frequently employed as an addition in the paint, plastic, pharmaceutical, and cosmetics sectors. Metal plating, home wastewater, manufacturing of metal, and atmospheric precipitation are the main sources of zinc pollution in water. For men and women, respectively, the Recommended Dietary Allowance (RDA) for zinc is 11 mg/day and 8 mg/day. Zn has the highest permissible level among other heavy metals, 5 mg/L, determined by the EPA as the maximum limit in drinking water. Zinc pollution exposure can result in corrosive effects on skin, damage to nerve membranes, nausea, vomiting, and cramping in the stomach [64].

2.10. Heavy metal removal

Heavy metals were extracted from wastewater and effluents using a variety of techniques. Chemical precipitation, oxidation-reduction [65], filtration, lime coagulation, ionic exchange [65], electrochemical treatment [66], membrane techniques, solvent extraction, adsorption on activated carbon, evaporation, etc. are some of the techniques used to remove the metal ions from an aqueous solution [67]. However, these methods are costly and lead to a partial removal of metal. However, these methods are costly and leave behind some metal [68].

Because of its crucial use, using the biological pathway to control, sequester, and remove metal pollution has received a lot of attention in recent years and is steadily becoming a hot topic in the field of metal pollution control. One such technique is biosorption, which removes hazardous heavy metals from wastewater or effluents by using a variety of naturally occurring materials with a biological origin [69,70]. Low operating costs, environmental friendliness, ease of use, high metal removal efficiency from diluted solutions, minimal chemical and/or biological sludge, no additional nutrient requirements, biosorbent regeneration, and the potential for metal recovery are the main benefits of biosorption over conventional treatment methods [16]. In place of more traditional techniques, biosorption for the removal of heavy metal ions may offer an alluring option [71].

3. Conclusion

Due to rapid industrialization and technological advancements, heavy metals are released into the environment from a variety of sources, endangering both human health and the environment. The study covered the origins, effects, and implications of a few heavy metals. We are currently dealing with a major problem with heavy metal contamination, which can be eliminated by employing organic material. Because of its availability, ability to complete the reaction process, and biodegradability, the technique—known as biosorption—is shown to be effective.

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Review

Chemical health hazards and toxicity of environmental pollutants on humans, animals and others: An overview

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Abstract: Toxicology, rooted in ancient civilizations and evolving through pivotal historical figures like Paracelsus and Alice Hamilton, has become a multidisciplinary field encompassing various branches such as pharmacology, medical, forensic, and environmental toxicology. This exploration embarks on a journey through time and science, unravelling the intricate interplay between chemicals and pollutants and their profound impacts on human, animal, and environmental well-being. Spanning from ancient practices like the use of hemlock in Greek capital punishment to modern-day concerns surrounding industrial chemicals and pesticides, the review delves into the mechanisms by which toxins disrupt biochemical pathways and induce organ dysfunctions. From heavy metals and pesticides persistent effects on the nervous and reproductive systems to the carcinogenic properties of polychlorinated biphenyls (PCBs), hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs). The review highlights the diverse range of toxicants and their widespread impact on human health. Additionally, the review underscores the importance of proactive measures to mitigate exposure to harmful substances, advocating for the development of antidotes, bioremediation techniques, and stricter environmental regulations. By addressing the urgent need for comprehensive strategies to combat toxicological hazards, this review aims to contribute to ongoing efforts to safeguard public health and environmental sustainability in the face of evolving chemical threats.

Keywords: hydrocarbons; pesticides; heavy metals; volatile organic solvents; endocrine disrupting chemicals; environmental pollutants; toxicity

1. Introduction

Ancient toxicology provides a fascinating perspective covered by Elsevier in ancient Egypt: the death of Cleopatra, hemlock (Greek capital punishment), the case against Socrates, poisoning in ancient Rome, the snake as a biological symbol, poisonous medicine in ancient China—aconite (Chinese poison arrow) [1]. The uses of poison vary widely, such as the use of arsenic to achieve the “milk and roses” complexion many women envied and the treatment of syphilis with mercury [2]. Toxicology, or Agada Tantra, is one of the eight clinical specialties of Ayurveda and has been exclusively associated with healing cases of envenomation [3]. In the medieval and Renaissance periods, medicine and toxicology were mostly filled with beliefs in folklore, superstitions, and religion. Subsequently, a new era started with Paracelsus, a Swiss physician alchemist (1493–1541), who is considered the father of toxicology. Paracelsus demonstrated the specific toxicity of chemicals in plants and animals. He also stated that there is nothing that is not poison. The judicious use

of the right dose differentiates poison from remedy and also moots the concept of a dose-response relationship [4]. Georgius Agricola published the book "De Re Metallica" on mining and metallurgy in 1556 [5]. Thereafter, during the mid-19th century, Alice Hamilton carried out pioneering work in the field of industrial toxicology, particularly dealing with industrial chemicals and metals in the USA. Her work largely helped in understanding the occupational diseases associated with mining operations [6]. Henri Becquerel, a French physicist and Nobel laureate, while studying phosphorescence in uranium salt, discovered radioactivity in 1896 [7]. From 1900 to 1930, there was an emergence of chemical elixirs, many chemicals of therapeutic importance, warfare chemicals, and insecticides. During this time, the U.S. Food and Drug Administration and the Drug and Cosmetics Act were developed. Thereafter, many toxicological regulatory bodies were established, including the International Union of Toxicology, the International Society for the Study of Xenobiotics, the Academy of Toxicological Sciences, and the American Board of Toxicology, and many important toxicological books were published [8]. Also, many accidents and disasters of toxicological significance occurred, such as the Bhopal disaster (the release of methyl isocyanate from a Union Carbide production plant), the eruption of a carbon dioxide bubble in Lake Nyos, chemical spillage and fire at the Sandoz Laboratory, which led to tons of chemical spillage into the Rhine river in Basel, and the Chornobyl accident (nuclear power plant meltdown and harmful radioactive waste release), which resulted in atmospheric poisoning to millions of people, and many more events have occurred, causing numerous toxicological and harmful effects on humans and the environment at large [9].

Furthermore, our modern scientific knowledge, advanced analytical methods, and technology helped us to understand how poisons/toxins/toxicants and therapeutic agents act differently on the human body and organ functions and their underlying mechanism(s) of action [10]. Some of the observations on toxicology research helped us to use toxic compounds as a tool for the development of animal models for pharmacological screening (e.g., MPTP, toxins of plant and microbial origin). Modern toxicology helped us in developing research methodologies, including in *vitro* techniques, and move away from the traditional approaches of animal testing to harm-free roots of experimentation [11].

The word toxicology is derived from the Greek word "toxion", and the scientific study "logos" was coined in the 17th century [2]. Today, toxicology encompasses diverse scientific disciplines such as biology, chemistry, pharmacology, medicine, etc., and deals with the study of adverse effects on humans, animals, and other living organisms [12]. Furthermore, it even includes the practice of diagnosis and remedial measures for the treatment of toxin/toxicant effects (in short, management of toxicity). Alternatively, some scientists have defined broadly toxicology as a science of study to characterize the effects of chemicals, gases, pollutants, biologicals, xenobiotics, drugs, and toxins on humans and other living organisms. Thus, definitions of toxicology have undergone many transformations over the years. The term toxicity is the inherent capacity of chemicals or foreign substances to cause injury, harmful effects, and health hazards [13].

The multidisciplinary toxicology has been classified into different branches, all with some similarities but many differences. They are medical toxicology, analytical toxicology, applied toxicology, foreign toxicology, industrial toxicology, immune toxicology, genetic toxicology, environmental toxicology, reproductive toxicology, and investigative and regulatory toxicology (refer **Figure 1**). Each branch of toxicology has been briefly defined and explained in the figure itself. Hence, they will not be discussed or elaborated.

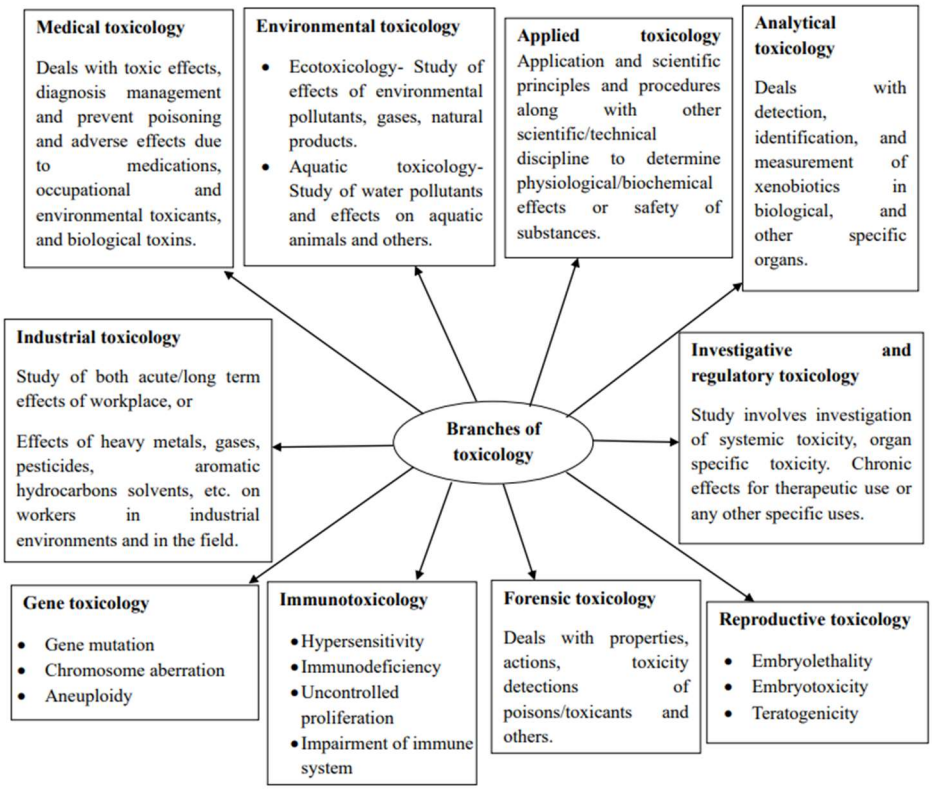

Figure 1. Enumerates various branches of toxicology.

The aim of this review is to elucidate the toxic and adverse effects of various chemicals on the human body and organ functions. Additionally, it seeks to present the state-of-the-art knowledge in the field of toxicology, with special emphasis on toxic manifestations, associated mechanisms, and their outcomes on human health. Furthermore, this review aims to provide an overarching environmental perspective within which humans, animals, and other organisms coexist.

2. Environmental pollutants and their effect on human health, animals, and others

Many chemicals exposure/ingestion leads to biological effects by interfering with functions associated with specific biochemicals or metabolic pathways and/or macromolecules within the tissue (e.g., warfarin inhibits vitamin K-dependent post-translational modifications of clotting factors in hepatic tissue) [14]. In addition, vapor, chemicals, solvents, pure hydrocarbons, containing hydrogen and carbon (chief components of different types of fuels, also exist in the form of gas, liquid, solid, or polymers) to partially oxidized hydrocarbons to organic compounds

containing chlorine, sulphur and nitrogen, polyunsaturated biphenyls (mainly polychlorinated biphenyls and its congeners) used in plastics, fluorescent lighting ballast, transformers, capacitors, organochlorine pesticides, other new generation pesticides, herbicides; asbestos, silica, cigarette smoke all these substances known to induce ill effects/toxic adverse effects on the human body as well as various organ functions and ultimately manifest various disorders or diseases [15] (**Figure 2**).

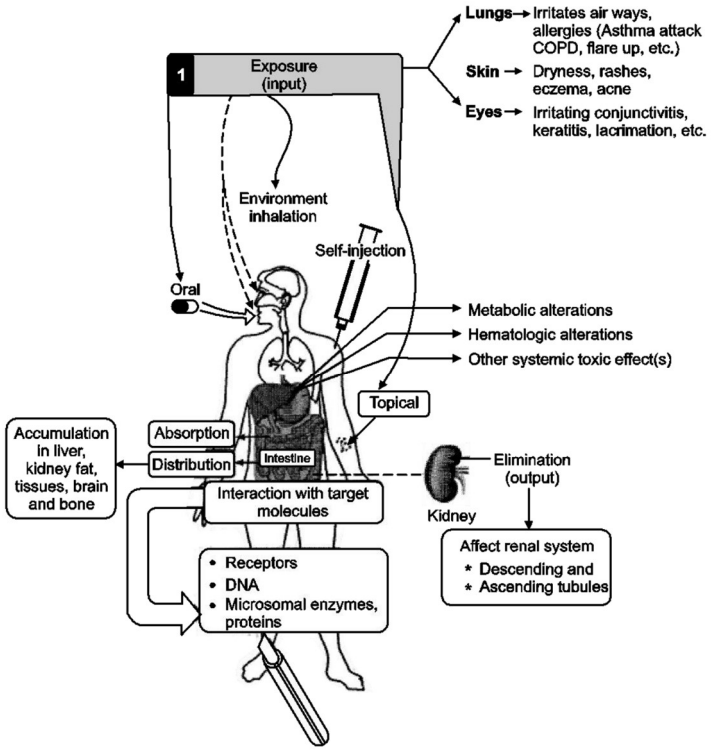

Figure 2. The exposure of environmental chemicals, gases, particles, ingestion including drug treatment, and various aspects on physiological events and general effects on the human body.

2.1. Effects of gases, aerosol, solvents, and chemicals

Environmental pollutants such as gases, dust, aerosols, and volatile organic compounds in the presence of sunlight react with nitrogen oxide emitted from industrial facilities, electric utilities, and motor vehicle exhaust to form ozone, which in turn helps the formation of fine particles. Furthermore, chemicals from the environment include inorganic metals (mercury, arsenic, antimony, lead, cadmium, silicon, zinc, chromium, manganese, etc.), salts of metals (oxide, sulphates of metals, and others), ammonia, nitrates, etc. Organic chemicals like pesticides, herbicides, preservatives, antibiotics, biotoxins, artificial colours, hydrocarbons, organic heavy metals, and carcinogenic compounds also persist in the atmosphere, water, and foods [16,17].

When such pollutants enter the human body via inhalation or skin contact (at the workplace) and reach alveoli, they are absorbed rapidly and then distributed to various organs via the blood stream. The particles retained in the alveoli exert toxic effects locally (refer to **Figure 2**). Furthermore, chemicals or toxins from exogenous sources, when ingested, inhaled, or absorbed in the body either from water, air,

foods, drugs, etc., also produce toxicity either by the parent molecules present or its metabolic products formed by its metabolism in different organs. High blood flow organs (brain, kidney) are also vulnerable to toxic effects of chemicals. Cardiac tissue is more sensitive to toxin-induced alterations of ionic gradients.

Effects of air pollutants such as metal particles (originated from industries, fertilizer usage, burning of fossil fuels, etc.) and water pollutants largely dissolved chemicals, metal salts, and persistence in water and food, when entering the body, cause cellular damages in vital organs (viz., liver, lungs, kidneys) (**Figures 2–5**).

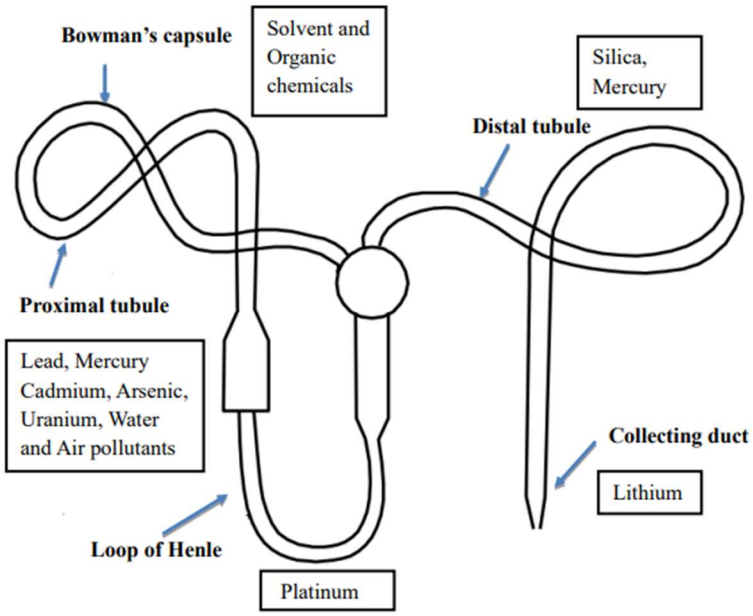

Figure 3. Metals affecting different intricate structural part of kidney.

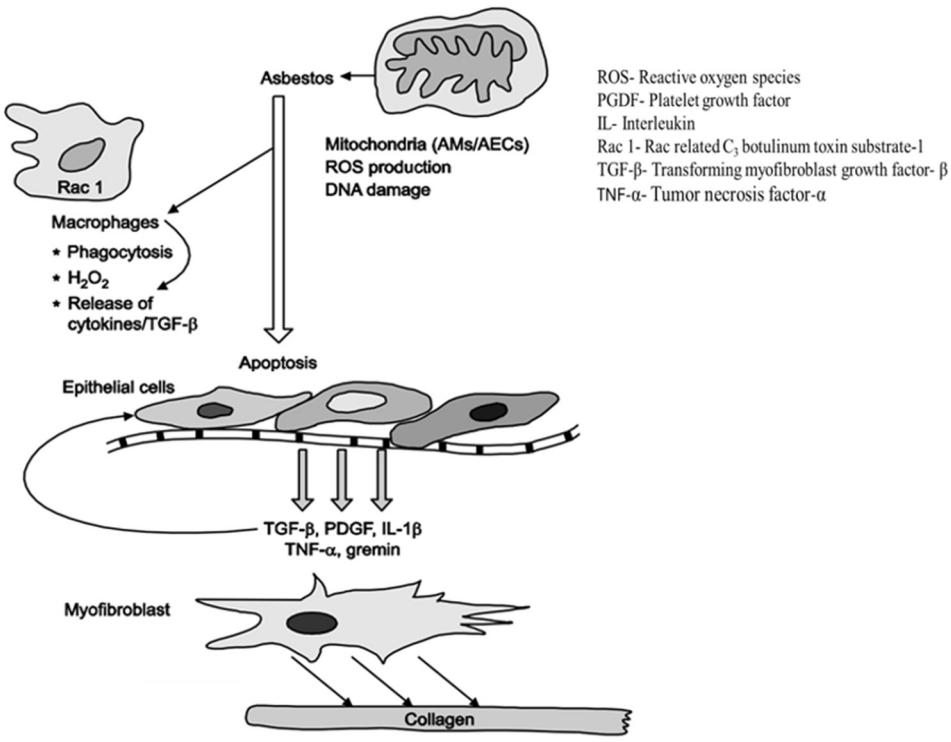

Figure 4. Underlying molecular mechanisms of asbestos induced lung disease.

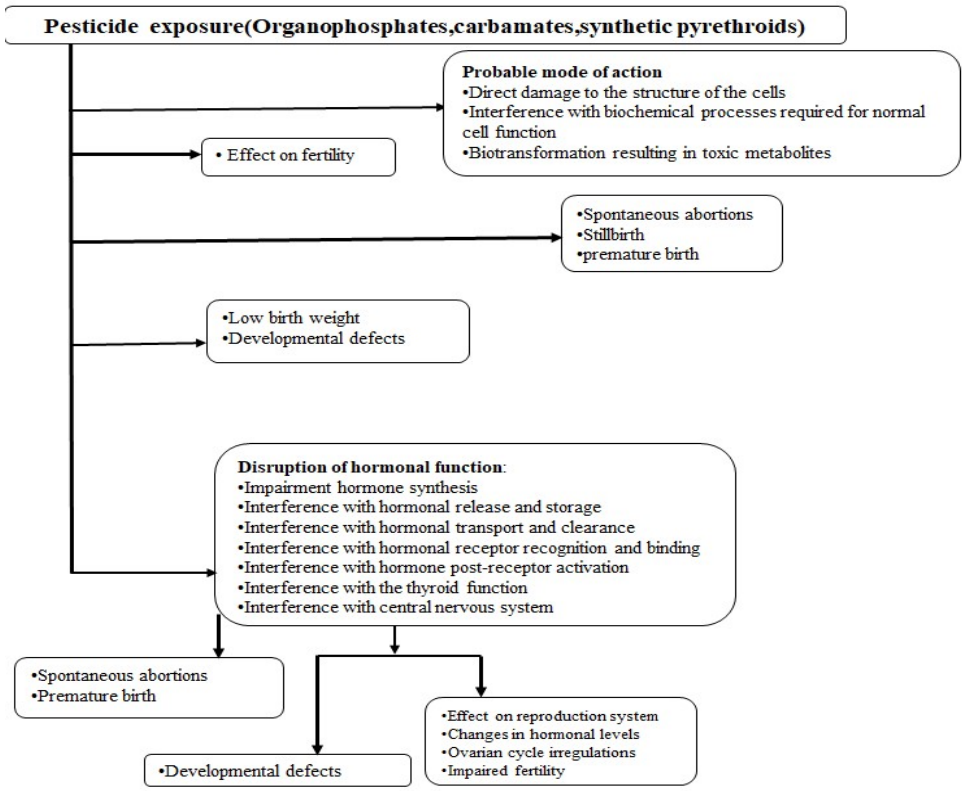

Figure 5. Potential effects of pesticides on developmental and reproduction processes in humans.

Similarly, exposure to corrosive chemicals leads to local irritations/caustic effects at the site of location due to the denaturation of macromolecules (proteins) and cleavage of chemical bonds required for the function of biomolecules, which are often termed non-selective. Heavy metals, which cannot be metabolized, persist in the body and induce toxic effects by combining with one or more reactive groups (ligands) that are essential for physiological functions (particularly –O, S– and N–containing ligands, which are known to form –OH, –COO–, $–OPO_3H$, C=O, –SH, –S–S, $–NH_2$ and –NH) leading to oxidative stress and culminating in impairment of the endogenous antioxidant enzyme defensive system, viz., superoxide dismutase (SOD), glutathione (GSH), glutathione S-transferase (GST), and catalase [18].

2.2. Asbestos

A fibrous silicate mineral used widely in building materials, a range of manufactured goods (automobile clutch, brake, and transmission parts), heat-resistant fabrics, packaging materials, gaskets, and coatings. The chronic exposure of asbestos, especially at the workplace, or inhalation of asbestos fibres can lead to serious lung disorders. Many of them are described below.

Asbestosis is a chronic interstitial lung disease largely caused by the inhalation of asbestos fibers (composed of mineral silicates formed due to damaged and degraded asbestos material in the environment) affecting people working in the shipyard, mining, painting, aerospace, building construction, installation of the asbestos board, sprayer, and asbestos stripping, insulation workers. In addition,

general community exposure to road surfaces, playground material, and chemical paints.

The three diseases that are most commonly associated with asbestos exposure are asbestosis, mesothelioma (a rare type of cancer that occurs in the region of the chest wall), and lung cancer. Asbestosis is caused by the inhalation of asbestos fibres over an extended period. Once these fibres enter the lungs, they can cause inflammation and scarring of the lung tissue. Over time, this scarring is known as fibrosis. Further, the fibre in the lungs leads to the accumulation of macrophages turned into fibroblasts; the other participating biological events are: 1) Reactive oxygen species originating from immune cells and phagocytes in response to asbestos fibres cause oxidative injury (type 1 alveolar cells, development of fibroblast growth factor beta) that results in fibrosis. 2) Macrophages produce tissue necrosis factor, interleukins, and stimulation of the phospholipase C pathway. Such mediators are generated due to the above-mentioned pharmacological events, which play a key role in stimulating lymphocytes and myofibroblasts, leading to the proliferation of fibroblasts and an increase (2-fold) in the number of cells in the matrix. Macrophages-derived fibroblast growth factor, platelet, and insulin-like growth factor also participate in the development of fibrosis, such as biological alterations in the lungs, which leads to a significant combination of fibrosis, pleural thickening, and inflammation, resulting in progressive impairment of lung function [19,20]. The reported major clinical symptoms are shortness of breath, persistent cough with mucus, clubbing of fingers, and inability to perform day-to-day physical activities. It is estimated that there are more than 55,000 deaths per year in the world due to asbestosis [21,22] (**Figure 4**).

Increased levels of ROS, cytokines, and growth factors due to chronic exposure to asbestos may produce harmful effects on the lungs. The pathogenesis of asbestos-induced pulmonary diseases derived from a long-term interplay between constant or persistent free radical production and expression of cytokines, growth factors, and other inflammatory cell products.

2.3. Pesticides and herbicides

Pesticides are synthetic chemical compounds used for plant protection and to kill pests/insects. Pesticides are used to eliminate or control a large spectrum of agricultural pests, including vectors of human and animal disease. Herbicides are chemicals used in agriculture and known as weed killers.

2.3.1. Organophosphates

Organophosphates are comprised of diverse groups of chemical compounds (diazinon, phosmet, malathion, parathion, chlorpyrifos, and many more) and are largely used as pesticides and herbicides, as well as nerve agents in chemical warfare. Organophosphate exerts toxicity in mammals through the inhibition of acetylcholinesterase, which results in the accumulation of excess acetylcholine. The accumulated acetylcholine manifests with cholinergic toxidrome, which includes effects on both nicotinic and muscarinic receptors and CNS. The mortality rates caused by organophosphate insecticides range globally from 2% to 25%. The serious effect is respiratory collapse (bronchospasms), which may be the major cause of

death. Respiratory distress is also accompanied by bradycardia. The onset of clinical symptoms varies based on the type of compound and manifests immediately, and reversal can take many weeks. Most organophosphate compounds are readily absorbed in the body after inhalation or ingestion. However, systemic absorption via dermal exposure is comparatively slow. Overstimulation of nicotinic receptors causes myoclonic jerking, which finally results in flaccid paralysis due to depolarization blockade. The clinical symptoms are hypertension, sweating, tachycardia, miosis-induced blurred vision, diaphoresis, and leucocytosis with the left shift [23–25].

OPs exposure to humans (males) induces adverse effects on semen normal quality and morphology. This effect is mainly due to DNA of spermatozoa and alterations in testicular somatic cell functions [26] (refer **Figures 4** and **6**). Most of the pesticides, including OPs and their metabolites, affect any of the reproductive or developmental end points in multiple mammalian species, including humans (**Table 1**). Chronic sub-lethal doses to birds reduced fertility, suppression of egg formation, and chick rearing behaviour [27]. OPs on chronic exposure are also reported to induce lung, kidney, liver, and breast cancer (**Table 1**).

Table 1. Biochemical and cellular effects of pollutants (of environmental origin) that lead to carcinogenesis*.

Source	Type and nature of carcinogen involved/present	Name of the chemical	The nature of damage at molecular/cellular level	likely occurrence of cancer
Food and dietary constituents	Aflatoxin (food and dietary) Food additives and preservatives	Aspartame (artificial sweetener) Butylated hydroxy-anisole Titanium dioxide Sodium nitrate Sodium nitrite	Formation of DNA adducts Formation of DNA replication Epigenetic modification DNA damage Tumour angiogenesis by up-regulating VEGF	Hepatic cancer Variety of cancer Lung cancer Esophageal cancer
	Chloropropanols		-	-
	Ethylene oxide used for ripening fruits		Disruption of cellular proteins controlling the life cycle of the cells that causes DNA adducts.	Breast cancer
	Potassium bromates (used for baking)		Oxidative DNA damage	Hematopoietic cancer
	Benzene		Deletion of chromosome	Renal tumour
	Bisphenol A (used in coating food containers)		Evasion of apoptosis	Breast cancer
	Heterocyclic amines		DNA damage	Colorectal, breast and lung cancer
	Pesticides (phosphates TBT, DDT, DENP, PCBs, TCDD)		Endocrine disrupting chemicals phosphates causes epigenetic modification	Lung kidney liver and breast cancer
	Plastic materials contain polycyclic aromatic hydrocarbons (PAHs), vinyl chloride		DNA damage ^{53}P mutation and amplification MDM2 gene	Lung-cancer, angiosarcomas, blood vessel tumor, liver, brain, renal and breast cancer
	Cigarette smoke contains (PAHs), N-nitrosamines, volatile organic hydrocarbons, heavy metals		DNA adducts formation, permanent somatic mutations in critical genes, somatic mutations cause clonal growth	Variety of cancers including lung cancer

*Adopted from [17].

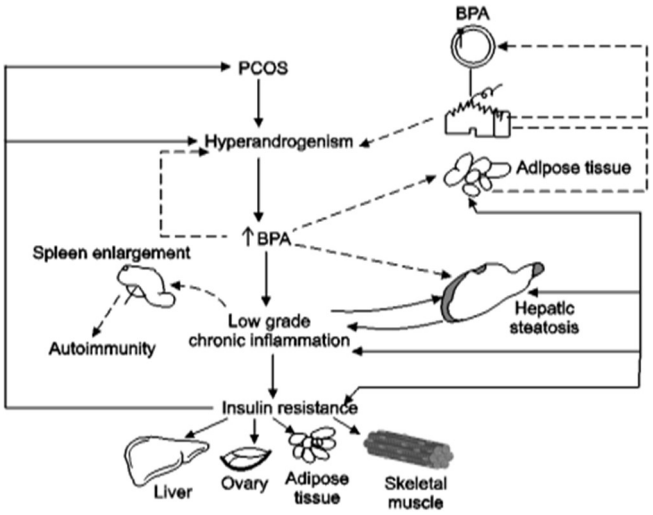

Figure 6. The Pathway Associated Toxicity with BPA and Other EDC (endocrine-disrupting chemicals).

2.3.2. Carbamates

Exposure to carbamates and its derivatives causes inhibition of kisspeptin neurons, which lead to low levels of gonadotropin-releasing hormone (GnRH) in the hypothalamus, which consequently inhibit the synthesis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the anterior pituitary. Such hormonal changes ultimately compromise steroid synthesis in the testis. This effect causes a reduction of epididymal and testicular sperm counts as well as testosterone concentration. Thus, chronic carbamate exposure led to male fertility problems (**Figure 5**).

Carbamates are derived from N-methyl carbamic acid and have been classified as Class II by the Environmental Protection Agency and World Health Organization, indicating they are moderately toxic. Some carbamate derivatives are considered endocrine-disrupting chemicals (EDC) based on their specific adverse effects. (Refer to **Figures 6** and **7**), which depict the profile of action of EDS (endocrine disrupting substances).

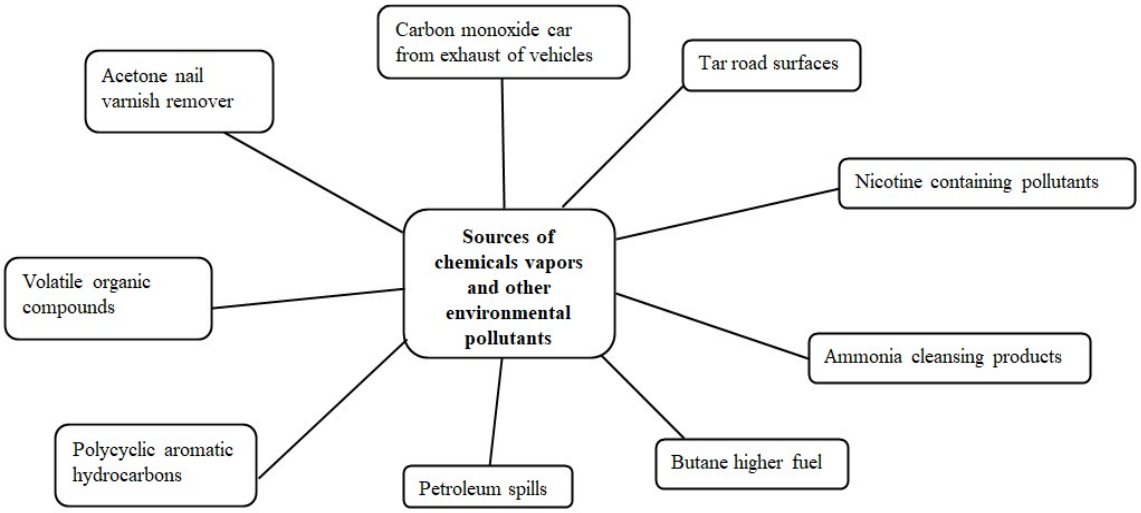

Figure 7. Exposure of chemicals, vapours, and other environment pollutants at workplace.

Carbamates inhibit acetylcholinesterase and melatonin receptors. The clinical symptoms following ingestion inhalation or exposure are tachycardia, hypertension and mydriasis, and flaccid paralysis at a toxic level. Both organophosphates and carbamates induce similar types of toxicity (derived from muscarinic and nicotinic receptors). However, the toxicity symptoms subsided after 24 to 48 h in carbamate-induced intoxication as compared to organophosphates. This is because during the phosphorylation of organophosphates to acetylcholinesterase, carbamate-cholinesterase bonds hydrolyse rapidly within hours [28–30].

Extensive usage of carbamates for increased food production and other purposes; their residual contents are alarmingly high in soil, wastewater effluents, and many food products all over the world [28].

2.3.3. Pyrethroids

Pyrethroids are synthetic insecticides composed of an acid and alcohol derived from pyrethrins and used in controlling insect pests in agricultural production and public and animal health. Pyrethroids exert both mammalian and insect toxicity by modifying voltage-gated sodium channels in neuronal membranes and thereby disrupting the electrical signalling throughout the central and peripheral nervous systems. The major toxicity symptoms include impaired motor coordination, tremors, convulsions, burning, and itching sensations. Pyrethroids act as potential dermal and respiratory allergens, and chronic exposure can result in contact dermatitis or asthma-like clinical conditions. Death occurs in humans largely due to respiratory failure. Pyrethroids are more toxic to insects due to their limited ability to eliminate these compounds. At high concentrations, pyrethroids act on GABA-gated chloride channels, nicotinic Ach receptors, and intracellular gap junctions and induce seizures. They are also reported to be toxic to aquatic organisms, including fish, at an extremely low level (4 parts per million). Beneficial insects such as bees, dragonflies, mayflies, and bottleflies are extremely sensitive and can be eradicated [31].

The recent research reports demonstrated the influence of oxidative stress generated by pyrethroids on the modification of DNA, RNA, proteins, and lipids both in cells and extracellularly [32]. The molecular basis of patho-mechanisms of the pyrethroid effects is detrimental in nature.

2.3.4. Rotenone, a phytoinsecticide

Rotenone, a plant product (isoflavone), is used as a broad-spectrum insecticide in a large number of crops. It mainly acts by inhibiting the oxidation of the reduced form of nicotinamide adenine dinucleotide (interfering with the electron transport chain within the complex system in mitochondria). Thus, creating reactive oxygen species (ROS), which can damage DNA and other components of mitochondria. Rotenone is toxic not only to insects and fish but also to humans and animals.

The rotenone study in animals demonstrated that low doses induce oxidative damage and death of dopaminergic neurons and exhibit symptoms of Parkinson's disease. The dust preparation is highly irritating to the eyes (causing conjunctivitis), skin (causing contact dermatitis), rhinitis, and pharyngitis [33].

Acute poisoning is characterized by respiratory stimulation followed by respiratory depression, ataxia, convulsions, and death due to respiratory arrest. And it is not a human carcinogen.

2.3.5. Herbicides

Herbicides are routinely used to control noxious plants or for falling or inhibiting growth of unwanted plants such as agricultural weed. Bioherbicides are phytotoxins, pathogens, and other microbes used as biologic weed control. Chemical herbicides, mainly chlorophenoxy, glyphosate, and bipyridyl herbicides, are the most widely used for the destruction of weeds or undesirable vegetation. Biosynthetic pathways of amino acids are the major site of action of herbicides. Bipyridyliums and heteropentalenes induce generations of superoxide radicals by energy divergence from photosystem I of photosynthesis [34]. It is also reported that lipid synthesis is the site of action of a broad array of herbicides that are used for controlling monocot weeds. The chemical grouping of dioxins is highly toxic and can cause problems with reproduction development and the immune system. They are also known for disrupting endocrine hormones and leading to cancer. In humans, 2,4-dioxane in large doses can cause coma and muscle hypotonia. In animal experiments, herbicides have demonstrated a fair degree of nephrotoxicity and hepatotoxicity. Occupational hazards, particularly with the chlorophenoxy herbicides, have been implicated in cancer risk. A greater degree of exposure to chlorophenoxy herbicides has been associated with soft tissue sarcoma and non-Hodgkin lymphoma. Glyphosate is reported to be an irritant to the eyes and skin. Female mice treated with tridiphane, a dinitroaniline herbicide, exerted embryotoxicity during early pregnancy [35].

Paraquat and diquat belong to the bipyridyl group and are the most important herbicides reported to cause liver damage in animals and humans. The cytotoxicity of paraquat established by an increase in lipid peroxidation and complete oxidation of both NADPH and NADH occurs at a lower concentration than LC50 level. Furthermore, it also stimulates glucose oxidation at subtoxic doses [36]. The study of paraquat and diquat demonstrated inhibition of microsomal mixed function oxidase (MFO) and NADPH oxidation in lung and kidney microsomal preparations in a concentration- and concentration-dependent manner. It is documented that the degree of NADPH oxidation is an important biological event and is considered to be an important index in the inhibition of xenobiotic metabolism [37]. Its toxicity rating is 4, which places the probable human lethal dosage at 50–500 mg/kg. Paraquat accumulates slowly in the lungs by a special active process, which leads to inflammation, edema, and alveolitis and then develops progressive fibrosis. Paraquat may induce the pathogenesis of dopaminergic neurons via oxidative stress [38]. Symptoms observed after the oral injections are mainly hematemesis and bloody stools. A few days later, delayed toxicity manifests such as respiratory distress and progressive development of congestive haemorrhagic pulmonary edema associated with the widespread cellular proliferation. Death may occur after several weeks of ingestion. No successful method of treatment is available for such toxicity manifestations till today. Organic herbicides (amide compounds) are more toxic to animals. Haemolysis, methemoglobinemia, and immunotoxicity have occurred on experimental exposure [39].

3. Environmental and occupational-specific organic chemicals

3.1. Volatile organic compounds (VOCs)

All halogenated hydrocarbons and aromatic hydrocarbons are volatile solids and liquids and are also known to emit gases. The concentration of many VOCs is consistently higher indoors (ten times) than outdoors. Household products such as paints, varnishes, wax, disinfectants, air fresheners, cosmetics, degreasing and hobby products, pesticides, preservatives, fuels, aerosol sprays, cleansers, and dry clean clothing all have ingredients of organic chemicals and release organic compounds while using them. They can expose themselves, and even stored materials also release very high organic compounds. The elevated concentration can persist in the air for a longer time. Similarly, office equipment (copiers, printers, correction fluids, photographic solutions, graphics) also contains organic compounds. The most common toxic symptoms reported on short/long exposure to these diverse volatile organic chemicals are eye, skin, and throat irritation, headache, allergic skin reactions, emesis, nausea, etc. Excessive exposure may cause liver, kidney, CNS, and visual disorders [40].

Exposure to solvents and organic chemicals of a liquid nature is a major health risk in the workplace. Vapours of solvents accumulate in confined places and persist for a long time. Solvents enter the body by inhalation, swallowing, and skin contact. Solvents and their vapours and mist induce a variety of effects on human health, such as narcotic effects, fatigue, dizziness, and toxic manifestations. Higher levels of these solvents may cause unconsciousness. In addition, they are known to induce skin disorders and dermatitis. Some solvents even enter the blood circulation via the skin [41]. Furthermore, solvents also induce liver, kidney, heart, and blood vessels, bone marrow, and CNS and manifest toxic effects. Benzene, carbon disulfide (CS2), carbon tetrachloride (CCl4), and toluene solvents are excreted mainly via the kidney (urine), skin (sweat), and lungs by exhalation. Ventilation is the most important while handling and using solvents. Personal protective equipment (aprons, gloves, masks, and filters) should be considered and available [42–44].

Major national exposures to benzene occur through tobacco smoking. Low levels of exposure to benzene cause headaches, loss of appetite, gastrointestinal disturbances, and irritation of the nose and throat. Long-term benzene exposure in humans induces hematopoietic toxicities, of which the most alarming effects are agranulocytosis and leukemia (acute myelogenous leukemia). The other path of exposure is non-occupational type to benzene, which occurs due to combustion of fossil fuels, automobile gasoline (petrol pump workers and other oil refinery unit operations, regular vehicular traffic, and consumption of contaminated water) [45].

Other effects of long-term exposure to organic solvents associated with aromatic organic chemicals cause aplastic anaemia which results in erythropoiesis. Also causes respiratory effects (pulmonary inflammation, forced vital capacity, and forced expiratory volume) and thyroid functions (changes in TSH levels, T3, T4) by the toxic substances present solvents and air pollutants via influencing hormones of the hypothalamic-hypophyseal-axis [46–49]. Shoe factory workers who are exposed to organic solvents suffer from chronic airway impairment and non-bronchial hyper-

responsiveness [50]. The carbon monoxide emitted by internal combustion of engines from motor vehicles readily enters the blood through the respiratory system and binds over 200 times more firmly to Hb than oxygen to form carboxy haemoglobin which interferes with blood oxygen transport capability and finally results in hypoxia, consequently stimulating erythropoiesis. Such biochemical events induce the production of a greater number of RBCs and haemoglobin in circulating blood [51] (**Figure 5** and **Table 2**).

Table 2. Gaseous and Solvent based pollutants, their toxicity, and clinical symptoms.

Environmental gaseous pollutants	Nature of toxicity and clinical symptoms
Carbon monoxide	Restrict oxygen supply to tissue/organs via binding to haemoglobin, headache, vomiting, dizziness, seizures, and coma.
Chlorine, ammonia, sulphur dioxide, nitrogen oxide	Local irritant gas-corrosive action leading to cough, wheezing, pneumonia
Cyanide	Restricting cellular oxygen used via binding to cytochrome a3, producing headache, nausea, vomiting, convulsions, and coma
Hydrogen sulphide, ozone	Same as above. Formation of highly reactive free radicals, intermediate produces bronchitis, emphysema and pulmonary fibrosis.
Benzene	Targeting pluripotential bone marrow, stem cells as well as other stem cells, excessive bleeding. Produce bone marrow injury, aplastic anaemia, leucopenia, thrombocytopenia, leukemia, changes in blood vessels of antibodies, myeloma, lymphoma.
Toluene	CNS depression skin and eye irritation. It is fetotoxic.
carbon tetrachloride	Cytochrome P_{450} mediated activation of free radicals (oxidant), produces nausea, vomiting, stupor, convulsions, coma and death. Potent hepatotoxic.

Adopted from [17].

3.2. Polycyclic aromatic hydrocarbons (PAH)

Ubiquitous environmental pollutants are generated during incomplete combustion of organic materials, e.g., coal, oil, petrol, and wood. Some of them originate from open burning, petroleum spillage or coal deposits, and volcanic activities. Other sources of PAHs are the surface of lakes, streams, and oceans, coal gasification and liquefying plants, carbon black, coal tar pitch, coke, and aluminium production petroleum refineries, as well as motor vehicle exhaust. They are used as intermediates in pharmaceuticals, agricultural products, thermosetting plastics, lubricating materials, and other chemical industries [52]. They are lipophilic and hence readily absorbed from the GI tract of mammals and distributed to various tissues, but largely localized in body fat [52,53]. Workplace exposure to high levels of pollutants and mixtures containing PAHs causes irritation, inflammation, nausea, vomiting, and diarrhoea. Anthracene and benzopyrene elicit allergic reactions both in animals and humans. Chronic exposure to PAHs may cause decreased immunity, cataracts, nephrotic and hepatic damage, asthma-like symptoms, and pulmonary function abnormalities [54]. The basic biochemical underlying mechanisms involved the binding of reactive epoxides and dihydrodiols of PAH metabolites to cellular proteins and DNA. Such molecular events result in disruptions and cell damage, which lead to mutations, developmental malformations, tumors, and cancer. PAHs induce moderate to high acute toxicity in fish and birds [52].

Carbon tetrachloride is an important chemical used for multiple purposes. Generally, people are exposed to carbon tetrachloride (CCl4) through consumption of contaminated drinking water. Low-level inhalation produces irritation of the eyes; at higher levels, it produces nausea, vomiting, depression, incoordination, paresthesia, seizures, coma, and death [55].

Non-lethal acute exposure can occur in 7 hours to several days and induce liver and kidney damage. The liver damage is from enhanced lipid peroxidation, largely due to free radical intermediates, which cause intracellular and intramembranous lipid destruction. Also due to the formation of metabolite phosgene, which is also responsible for hepatotoxicity [56,57] (refer to **Table 1** and **Figure 5**).

3.3. Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls, polychlorinated dibenzo-p-dioxin (PCDDs), or die oxides, of which the most important is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In addition, there is a larger group of dioxin-like compounds, including certain polychlorinated dibenzofurans (PCDFs) and co-planer biphenyls [58]. PCBs are oily liquids and solids and stable mixtures that are persistent to extreme temperatures and pressure. Industrial production of PCBs began in 1929; it is estimated that 1.2 to 1.5 million metric tons have been produced. They are used in many products, from lubricants to pesticides, paper adhesives, plastic paint, and flame retardants. Animal studies demonstrated that PCBs could affect the immune, endocrine, and reproductive systems, but such effects are not established in humans [59]. When PCBs are fed to animals in large doses over a shorter period (4 to 6 weeks), they can induce cancer. However, humans exposed to high levels for prolonged periods did not cause cancer. Therefore, they are classified as cancer-causing chemicals [60]. Numerous documented studies indicated environmental and occupational exposure to such chemicals, especially from building construction (refer to an earlier statement on chemicals and pollutants) and waste cycling sites (highest PCB contamination). PCB-contaminated working place, workers often suffer from different health problems such as psychological and neurobehavioral deficits, dementia, impaired immune systems, cardiovascular disorders, and cancer. Furthermore, accumulation can induce adverse effects on the reproductive system, which are manifested in offspring. Despite a ban on their use in the 1970s, their resistance to chemical and thermal degradation results in bioaccumulation in marine animals/organisms and humans. Hence PCBs continue to be a serious problem to the environment and humans at large, and the same has been included in EDS. They have been reported to induce in humans predominantly developmental toxicity, immunotoxicity, metabolic diseases such as type-2 diabetes, thyroid disorders, and impairment of female and male reproductive health [61].

BPA affects the liver-spleen axis, increases androgen activity, and causes low-grade inflammation in the development of polycystic ovarian syndrome (PCOS) (refer to **Figure 8**).

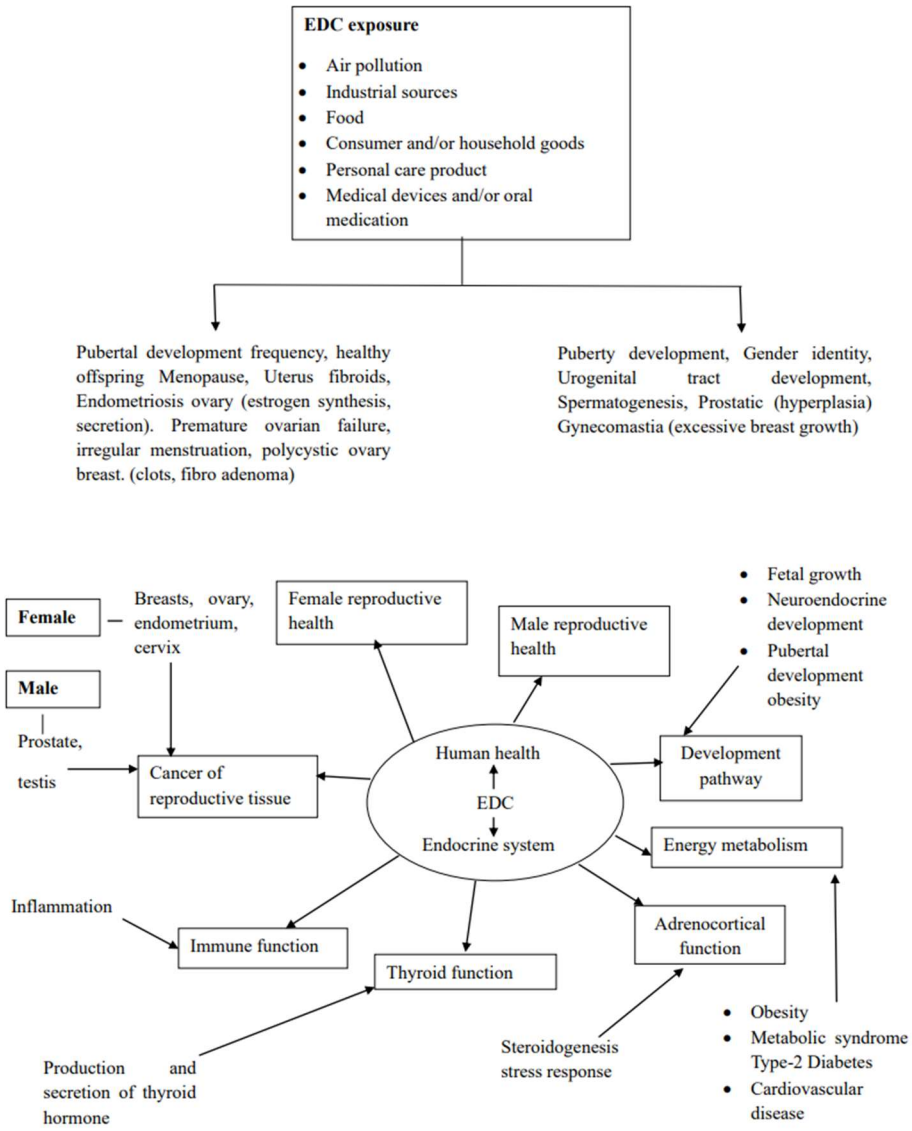

Figure 8. The schematic representation of effects of EDCs (endocrine-disrupting chemicals) on Human Health.

4. Antidotes for chemical and metal poisoning

Some selective chemicals for insecticide acute intoxications are available only in a small number. Some of the chemical antidotes are outlined below:

Atropine is a muscarinic receptor antagonist; hence, it has been used to block the access of increased acetylcholine to muscarinic receptors. It is an important antidote for insecticide intoxication in organophosphates and carbamates. However, the dose of atropine used depends upon the state of intoxication. The second dote is pralidoxime, which is less effective, and its doses used vary very much [62,63].

Penicillamine (D-b, b-dimethyl cysteine)

Penicillamine is an effective chelator of copper, mercury, zinc, and lead and thereby accelerates the excretion of these metals in urine. N-acetylpenicillamine is more effective than penicillamine in protecting, especially from the toxic effects of mercury. Animal studies have demonstrated polycarboxylic acid chelators ($CaNa_2$

EDTA) and calcium trisodium diethylenetriaminepentaacetate EDTA. (Pentate calcium trisodium; Ca-DTPA) can be effective when administered immediately after exposure to cadmium. Dimercaprol and penicillamine are used to treat chronic exposure to arsenic. In methyl mercury poisoning, L-cysteine can be infused into the arterial blood, entering the dialyser to convert methylmercury into diffusible form. This method has been found to be effective in humans [64]. In acute cyanide poisoning, antidotes such as sodium nitrate and sodium thiosulphate are reported to be very effective by intramuscular route in various clinically relevant animal models [65].

Enhancement of detoxification of toxic agents: Some toxic substances are hepatotoxic and metabolised by the liver via cytochrome P450. In such cases, treatment with N-acetylcysteine shall serve as a substitute for glutathione. This will bind and inactivate the reactive metabolite and minimize the hepatic toxicity of the toxicant [66]. Chelators are known to form covalent bonds specifically with cationic metals. The chelators form a metal complex and are then excreted in urine, which may enhance excretion of the heavy metals. However, chelators are not specific to heavy and essential metals, and some of the chelators induce serious adverse effects. Hence, physicians need to outweigh the risks associated with chelation therapy. Dimercaprol is used to chelate mercury and arsenic along with calcium disodium edetate to treat lead intoxication. It is to be administered intramuscularly, as it is not effective by oral route. Since dimercaprol is known to elevate blood pressure and heart rate, physicians should be careful when it is used, especially in hypertensive people [67].

Succimer, a derivative of dimercaprol, is effective by oral route and its lack of effects on blood pressure and heart rate. Today, succimer is approved for the treatment of lead toxicity. Further, it is also found effective in the chelation of other heavy metals. Calcium disodium edetate is used for lead and other heavy metals intoxication intravenous or intramuscularly only. However, it is known to cause kidney damage, but the damage is reversible after the stoppage of treatment [22,68].

5. Summary and conclusion

In the present review, we try to present the impact of chemicals and pollutants on humans, animals, and environmental health. We explained and discussed various pollutants, such as industrial chemicals, pesticides, heavy metals, and air pollutants. Also referred to are the sources, pathways of exposure, and toxic events on physiological and organ functions of the body. These pollutants elicit a large spectrum of toxic effects on CNS, CVS, respiratory system, liver, kidney, etc. by interfering with or impairing biochemical and metabolic pathways, viz., oxidative, mitochondrial electron transfer system, enzyme inhibition, voltage-gated channel(s). Local skin, eye, and mucus membrane irritation are produced by denaturation of macromolecules and/or cleavage of chemical bonds. Clinical symptoms are diverse and related to the specific organ system and the type and nature of chemicals or toxicants. The genetic effects via mutational or larger damage of genetic apparatus led to different types of cancer and also reproduction and developmental-related effects on offspring.

Overall, our review underscores the urgent need for proactive approaches to address the impact of chemicals and pollutants on human, animal, and environmental health. A concerted research work needs to be pursued to develop new generations of antidots and antagonists and bio-remedial measures for minimizing air and water pollution. Exploring isolation of new microbes whose metabolites and enzymes may be helpful in removing chemicals and other harmful pollutants from the environment in eco-friendly ways.

Furthermore, a better understanding of the cellular and molecular mechanism(s) responsible for the developmental effects of air pollution on human body and organ systems is also essential because it may lead to the development of specific therapeutic interventions. It is needless to say that any efforts/approaches towards diminishing emissions and thereby improving air quality would be warranted.

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Review

Toxicity of microplastics in fish: A short review

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Abstract: Microplastic pollution is a growing environmental concern globally, attracting significant attention due to its potential impacts on aquatic ecosystems. This short review aims to provide a comprehensive overview of the research conducted on microplastic pollution in fish, focusing on its occurrence, sources, impacts, and potential mitigation strategies. By analyzing existing studies, this review highlights the urgent need for continued research and increased awareness to address this persistent issue.

Keywords: microplastic; fish; pollution

1. Introduction

In recent years, many efforts have been directed to the discovery and cleaning of pollutants that are called contaminants of emerging concern (CECs), which include any type of chemical substance found in water or the environment, even in small concentrations, or substances that have just been identified.

Microplastics (MP) have all the features mentioned to be in the group of worrisome pollutants, the most important of which is the presence of this pollutant in water environments [1].

According to the National Oceanic and Atmospheric Administration's (NOAA) report, plastic particles with a diameter of less than 5 mm are known as microplastics (MP). While there is no theoretical unity for the dimensions of nanoplastics (NP) in various studies, some researchers define nanoplastics as particles with a diameter of less than 1 micrometer, and some others define them as less than 100 nanometers.

Microplastics, defined as plastic particles smaller than 5 mm in size, have emerged as a pervasive and persistent type of pollution in aquatic environments. These tiny particles often result from the breakdown of larger plastic debris and are now found extensively in marine and freshwater ecosystems worldwide. Concerns surrounding microplastic pollution in fish arise due to their potential adverse effects on both individual organisms and the ecosystem as a whole [2].

Various aquatic environments are contaminated with microplastics; seas close to land and oceans, estuary waters, lakes, reservoirs, freshwater rivers, sewage, and urban and industrial effluents are all contaminated with microplastics [3]. Researchers have shown that oysters, edible crustaceans, and commercial fish are often contaminated with microplastics [4].

Several studies showed MPs contaminations in fish species in different aquatic environments around the world, which is an alarm for paying more attention to this recent known contamination (**Table 1**). Similarly, many studies have described the toxic effects of MPs in different fish species and in different organs (**Table 2**).

Table 1. Reports of MPs contaminations in fish.

S. No	Type of microplastic	Fish	Country/ water bodies	Reference
1	Fibers and fragments	*220 species of marine*	South coast of India	[5]
2	Fibres, pellets, fragments	*Ammodytes personatus*	Yellow Sea	[6]
3	Fibers, fragments, films	*Engraulis encrasicolus*	Med. Sea (east)	[7]
4	Not reported	*Engraulis encrasicolus*	Med. Sea (west)	[8]
5	Fibers	*Engraulis encrasicolus*	Med. Sea (west)	[9]
6	Fibers	*Engraulis encrasicolus*	North East Atlantic	[10]
7	Fragments and beads	*Engraulis japonicus*	North Pacific Ocean	[11]
8	Fibers, fragments and Pellets	*Engraulis japonicus*	Yellow sea	[6]
9	Fibers, fragments, films	*Euthynnus affinis*	Malaysia (fish-market)	[12]

Table 2. Toxic effects of microplastics in fish.

S. No	Type of microplastic	Fish	Organ	Reference
1	Ethylene propylene	*Scophthalmus maximus*	Liver and gills	[13]
2	Polypropylene	*Oreochromis mossambicus*	Liver	[14]
3	Propylene copolymer	*Danio rerio*	Brain, liver	[15]
4	Polystyrene	*Nothobranchius guentheri*	Liver	[16]
5	Polystyrene	*Ctenopharyngodon idella*	Liver	[17]
6	Microfiber types microplastics	*Oryzias latipes*	Liver	[18]
7	Polyethylene	*Pseudobagrus fulvidraco*	Gut, gills and liver	[19]
8	Polystyrene	*Sparus aurata*	Intestine	[20]
9	Polyacrylamide	*Oreochromis niloticus*	Gills, liver and intestine	[21]

2. Occurrence of microplastic pollution in fish

Numerous studies have documented the presence of microplastics in the gastrointestinal tracts of various fish species. For instance, in a study conducted in the Mediterranean Sea, Romeo et al. [22] reported that 18% of the examined fish contained microplastics in their digestive tracts. Abbasi et al. [23] also reported microplastic particles isolated from guts (gastrointestinal tracts), skin, muscle, gills, and liver of demersal and pelagic fish (*Platycephalus indicus*, *Saurida tumbil*, *Sillago sihama,* and *Cynoglossus abbreviatus*) obtained from Musa estuary, Persian Gulf, Iran. **Table 1** shows some of the studies on MPs contamination in fish in several aquatic environments.

The first evidence of the presence of microplastics in marine environments dates back to 1970, when grains with a diameter of 5–2.5 mm were found on the surface of the Sargasso Sea, spherical structures with a diameter of 0.2–0.1 mm in the coastal waters of New England, structures Spheroids and discs with a diameter of 0.9–4.2 mm were observed in the surface waters of the Atlantic Ocean, and grains with a diameter of 1–5 mm were observed in the surface waters of the Pacific Ocean [3].

Since 2004, when Thompson measured the abundance of microplastics in coastal, estuarine, and intertidal sediments of England's coasts, several researchers have investigated the presence of microplastics, their fate, and their transfer in marine environments and beaches across the continent. They have studied small and large islands, the width of the Atlantic Ocean, the Pacific Ocean, the Arctic Ocean, the Adriatic Sea, the Baltic Sea, the Mediterranean Sea, and even the depths of the sea [24].

These findings demonstrate the pervasive nature of microplastic pollution in fish populations and highlight the need for further investigation into its implications.

3. Transfer of microplastics in the food chain

Like many other pollutants in aquatic environments, it's been demonstrated that microplastics could transfer through the food chain, and several organisms in different trophic levels could be contaminated by nutrition. Zooplanktons are one of the lowest trophic levels in aquatic ecosystems susceptible to microplastics through ingestion. Zheng et al. [25] demonstrated microplastic contamination of more than 30 species from 28 taxonomic orders of zooplanktons. Several other studies further described microplastic contamination of crustacean's zooplanktons, such as *Tigriopus fulvus*, *Acartia clausi*, *Centropages typicus*, *Calanus helgolandicus*, *Temora longicornis*, and *Neocalanus cristatus* [26–30]. Moreover, microplastics contamination is also described in gelatinous zooplankton such as jellyfish, tunicates, and salps, which are feeding on crustaceans and fish larvae. These gelatinous zooplanktons are key food sources for higher trophic levels, such as pelagic predators [31–36].

4. Sources of microplastic pollution

There are several sources of microplastic pollution in aquatic environments. One major source is the fragmentation of larger plastic debris, which can occur due to weathering, wave action, and photodegradation. Thompson et al. [37] estimated that the majority of microplastics in the ocean are derived from the breakdown of larger plastic items like bottles and bags. Additionally, microbeads found in personal care products, such as facial scrubs and toothpaste, contribute to microplastic pollution. Synthetic textile fibers, shed during laundering, also play a significant role in microplastic contamination. Šaravanja et al. [38] found that washing a single polyester garment can release up to 1900 microfibers into wastewater.

A small part of the microplastics in the ocean environment are related to marine activities such as the fishing industry (use of plastic equipment), while the majority of them (about 80%), in terms of origin, are plastic waste from land. To be reckless disposal of waste on beaches and coastal areas, rivers that flow into the sea, runoff from storms, passive absorption by marine species, sewage discharge, and deposition of atmospheric microplastics are all factors involved in the presence of microplastics. They are in marine environments.

Microplastic parts are widely transported by oceanic currents over long distances; wind, river, and sea currents are the main factors of microplastics transfer

to distant and unpolluted areas, such as the poles, deep oceans, and interoceanic islands [24].

5. Impact of microplastic pollution on fish

The ingestion of microplastics by fish can have detrimental effects on their physiology and behavior. Studies have shown that microplastic ingestion can lead to reduced feeding efficiency, impaired growth, and altered reproductive success in fish. In addition to physical impacts, microplastics can act as vectors for harmful chemicals. Rochman et al. [39] demonstrated that exposure to microplastics can induce toxic effects and increase susceptibility to diseases in fish species.

Fish can accidentally consume microplastics as they mistake them for food. This can happen because microplastics resemble the size and shape of plankton, which is a common food source for many fish species. Once ingested, microplastics can cause several adverse effects on fish, such as reduced feeding ability, alteration in growth rates, impaired reproduction, and changes in behavior [40].

Moreover, microplastics can also have indirect impacts on fish by acting as carriers for chemicals. Many microplastics have the ability to absorb and accumulate toxic substances from their surrounding environment. These include persistent organic pollutants (POPs) and heavy metals that can adhere to the surface of microplastics. When fish consume these contaminated microplastics, they are essentially ingesting a concentrated dose of these harmful chemicals, which can lead to various health issues and long-term ecological consequences [41,42].

Another concern is the potential transfer of microplastics and associated contaminants up the food chain. Fish that consume microplastics may be preyed upon by larger predators, including humans. This means that the harmful effects of microplastic pollution can eventually be transmitted to humans through the consumption of contaminated fish [43].

6. Mitigation strategies

Efforts to mitigate microplastic pollution in fish should be multifaceted and focus on reducing plastic waste at the source, improving waste management practices, and promoting the development of biodegradable alternatives. Legislation has been enacted in some countries to ban or restrict the use of microbeads in personal care products, which has shown promise in reducing microplastic input into aquatic ecosystems. Innovative strategies, such as the installation of filters in washing machines to capture microfibers, are being researched to address the release of synthetic textile fibers. Public awareness campaigns and educational programs can help minimize the use of single-use plastics and promote responsible waste disposal among individuals and communities [44].

Among other ways to reduce microplastic pollution in water environments, we can refer to the precise treatment of wastewater in order to separate microplastic pollution. In this regard, several scientific ways have been proposed, including biotic degradation of microplastics, bacterial degradation, degradation of microplastics via fungi, removal of microplastics by algae and macrophytes, degradation of

microplastics by periphytic biofilms, removal of microplastics through adsorption, degradation of microplastics by advanced oxidation processes, etc. [45].

7. Conclusion

Microplastic pollution poses a significant threat to fish species, with implications for both ecological health and human food safety. The widespread occurrence of microplastics in fish populations highlights the urgent need for further research to understand the long-term effects of microplastic exposure. Additionally, concerted efforts are required to develop effective mitigation strategies, reduce plastic waste, and promote sustainable practices. It is crucial that we take immediate action to protect our aquatic ecosystems and ensure the well-being of fish populations for future generations.

8. Future directions

Despite enormous studies on microplastic contaminations of aquatic environments and species, many aspects of this subject remained unstudied and needed further investigations. Along with further investigation of the microplastic contamination of the aquatic ecosystems, it is crucial to follow the mitigation strategies to lower the toxic effects of such pollution in aquatic environments.

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Review

Deciphering the mechanisms of carcinogens: Unravelling the pathways of cancer initiation and progression: An insight into DNA damage, genotoxicity, and epigenetic changes

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Abstract: Carcinogens are substances known to induce cancer by altering the genetic material and cellular processes within the human body. Understanding the mode of action of carcinogens is critical for developing effective prevention and intervention strategies against cancer. Cancer remains a significant global health challenge, with carcinogens posing a continuous threat to human well-being. This study explores the intricate mechanisms by which carcinogens induce cancer, focusing on the interplay of DNA damage, genotoxicity, and epigenetic alterations. Through an analysis of direct and indirect-acting carcinogens, the study elucidates how these agents disrupt cellular DNA, leading to mutations and chromosomal abnormalities. Additionally, the role of genotoxicity in driving oncogenesis is explored, highlighting the importance of assessing carcinogenic risk through cytogenetic genotoxicity methods. The study focused on the direct and indirect DNA damage, genotoxicity, epigenetic changes, inflammation, hormonal effects, and immune system suppression induced by different carcinogens. It intends insight on the intricate interplay between environmental factors and the molecular foundation of carcinogenesis by thoroughly investigating these pathways. By comprehensively examining these pathways, which hope to focus on the complex interplay of carcinogenesis. By understanding these mechanisms, this study aims to inform preventive strategies and therapeutic interventions, ultimately mitigating the global burden of cancer.

Keywords: carcinogenesis; genetic erosion; genotoxicity

1. Background

"The measurements make the poison" may be an essential rule of toxicology. Coined by Paracelsus, who was a 15th-century Swiss researcher, doctor, chemist, and secretive mastermind. Known as "the father of toxicology" since of this celebrated state. "The saying implies that any chemical can be harmful in case the dose is past a certain edge; additionally, any harm can be non-toxic on the off chance that the dosage is underneath a certain threshold" [1]. A universal association for the creation of pharmaceutical directions is the Worldwide Committee for Harmonisation (ICH [2]) Specialised Prerequisites for Pharmaceuticals for Human Utilise. The ICH rules known as M7 are utilised to assess and oversee DNA receptive (mutagenic) contaminants in pharmaceuticals in order to decrease the chance of cancer. The center of this rule is on DNA receptive compounds that have the potential to specifically cause DNA harm when displayed at moo levels, coming about to transformations and possibly causing cancer, according to Segment 3 (common standards). The International Council for Harmonisation (ICH), a global organisation, is tasked with establishing regulations that govern the use of pharmaceuticals. The guidelines

outlined in the M7 document aim to mitigate the risk of cancer by assessing and controlling DNA-reactive (mutagenic) impurities in pharmaceuticals. Section 3 of this guideline emphasises its focus on substances capable of inducing DNA damage at minimal concentrations, potentially resulting in mutations and cancer development [2]. Cancer is a complex and multifaceted disease that continues to be a significant global health challenge. The identification of carcinogens and the elucidation of their mechanisms of action are of paramount importance in the field of oncology. Carcinogens can be found in various environmental, dietary, and occupational settings, posing a continuous threat to human health. Understanding the diverse pathways by which these agents initiate and promote cancer is crucial for implementing effective preventive measures and developing targeted therapies.

To lower the chance of getting cancer, it's critical to limit exposure to recognised carcinogens through dietary decisions, environmental safeguards, and workplace safety measures. To guide public health practises and policies, regulatory authorities and research organisations continuously investigate and evaluate potential carcinogens.

Carcinogens are substances that have the potential to cause cancer by destroying DNA and encouraging unchecked cell division. Carcinogens' modes of action might vary based on their chemical and physical characteristics, but generally speaking, they cause cancer by the following mechanisms:

1) Direct DNA damage: Some carcinogens can directly interact with the DNA in cells, causing mutations or chemical changes to the DNA sequence. These alterations can disrupt the normal cellular processes that control cell growth and division, leading to the formation of cancerous cells.

2) Indirect DNA damage: Indirect-acting carcinogens are not inherently cancer-causing but can become carcinogenic once they are metabolised in the body. Enzymes in the body can convert these substances into reactive intermediates that damage DNA. This can happen through processes such as oxidation or chemical modification of the carcinogen.

3) Genotoxicity: Carcinogens that exhibit genotoxicity can cause direct damage to the genetic material (DNA) of cells. This damage can lead to mutations, chromosomal rearrangements, and other genetic abnormalities that may promote cancer development. A genotoxin is a substance or agent that has the potential to damage DNA or chromosomes either directly or indirectly.

4) Epigenetic changes: Some carcinogens can induce epigenetic changes in the cells. Epigenetic modifications do not alter the DNA sequence but can affect gene expression patterns. Altered gene expression can lead to abnormal cellular behaviour and potentially contribute to the development of cancer.

5) Inflammation and chronic irritation: Some carcinogens can cause chronic inflammation or irritation in tissues. Prolonged inflammation can stimulate cell proliferation and create an environment conducive to cancer development.

6) Hormonal effects: Certain carcinogens can disrupt hormonal balance in the body, affecting the regulation of cell growth and potentially promoting the development of hormone-related cancers.

7) Immune system suppression: Some carcinogens can suppress the immune system's ability to detect and eliminate abnormal cells, allowing cancer cells to grow unchecked.

Cancer remains a significant global health challenge, characterised by the accumulation of genetic and epigenetic changes leading to uncontrolled cell growth and tumor formation. Carcinogens, whether natural or synthetic, are pivotal in triggering these alterations. Understanding how carcinogens operate at the molecular level is essential for identifying high-risk exposures, implementing prevention strategies, and developing targeted therapies.

The diverse mechanisms by which carcinogens act on cellular and molecular processes, leading to the initiation and progression of cancer. The distinction between direct and indirect-acting carcinogens and how they impact cellular DNA. Additionally, studies delve into the concept of genotoxicity and its role in causing DNA damage and mutations. Further, epigenetic changes induced by carcinogens will be examined, as they can influence gene expression patterns and contribute to oncogenesis.

Further, this study will explore the link between inflammation and cancer development, as chronic inflammation can provide a conducive environment for tumour growth. The hormonal effects of certain carcinogens will also be discussed, as they can disrupt the delicate balance of hormones and contribute to hormone-related cancers. Lastly, the role of carcinogens in suppressing the immune system's surveillance and defense mechanisms against cancer will be addressed.

1) Direct and indirect-acting carcinogens: Impact on cellular DNA:

Carcinogens can be broadly categorised as direct-acting and indirect-acting agents based on their ability to interact directly with cellular DNA. Direct-acting carcinogens, such as certain alkylating agents and U.V. radiation, directly damage the DNA structure, causing DNA adducts and breaks. Indirect-acting carcinogens, on the other hand, require metabolic activation within the body to become reactive intermediates that can damage DNA. We will delve into the various mechanisms of DNA damage induced by both types of carcinogens and discuss the consequences of such alterations on genomic stability.

2) Genotoxicity: A key driver of carcinogenesis:

"Genotoxicity" describes an agent's capacity to harm DNA, which can result in mutations and chromosomal abnormalities. Alternatively, genotoxicity describes a substance's capacity to contaminate a cell's genetic material. Exposure to chemical and biological substances can cause changes in the epigenome and/or genomic instability, which can lead to a number of disorders, including cancer [3]. A genotoxin refers to a substance or element capable of inducing DNA or chromosomal harm. When such harm occurs in a germ cell, it holds the potential to trigger an inheritable modified characteristic (germline mutation). Conversely, DNA damage within a somatic cell might give rise to a somatic mutation, potentially leading to the development of cancer through malignant transformation [4].

Carcinogens often exhibit genotoxic properties, contributing to their cancer-causing potential. Through this section, we will explore the concept of genotoxicity and its significance in initiating oncogenic events. We will also discuss various assays

and methodologies used to assess genotoxicity and their relevance in identifying potential carcinogens.

3) Epigenetic changes induced by carcinogens: implications for oncogenesis:

Beyond direct DNA damage, carcinogens can induce epigenetic changes that alter gene expression patterns without altering the DNA sequence. These epigenetic alterations, including DNA methylation, histone modifications, and microRNA dysregulation, can significantly impact cellular functions and contribute to tumourigenesis. This section will focus on the epigenetic changes caused by carcinogens and their potential role in cancer initiation and progression. Additionally, we will highlight emerging epigenetic therapies as promising avenues for cancer treatment.

2. Introduction

In our contemporary society, exposure to chemical substances is unavoidable, with certain agents posing risks to human health. The impact of chemical carcinogens is a significant concern globally, prompting the establishment of guidelines by international bodies like the World Health Organisation for their regulation. Carcinogens are presently divided into two groups: genotoxic and non-genotoxic carcinogens, each governed by distinct regulatory measures [1].

2.1. Rationale of the study

Cancer is a significant global health burden, affecting millions of individuals and causing substantial morbidity and mortality worldwide. The identification and understanding of the mechanisms by which carcinogens exert their cancer-causing effects are critical for developing effective prevention strategies and targeted therapeutic interventions. Additionally, unraveling the concept of genotoxicity, a key driver of carcinogenesis, holds immense potential for early detection and risk assessment of cancer.

Despite extensive research on carcinogens and genotoxicity, there are still gaps in our knowledge of the intricate molecular and cellular processes that underlie cancer initiation and progression. Existing studies have highlighted the role of direct and indirect-acting carcinogens, the impact of DNA damage and mutations, and the influence of epigenetic changes on oncogenesis. However, comprehensive and up-to-date insights into the various mechanisms of carcinogens and genotoxicity remain essential for advancing cancer research and clinical practices.

The findings from this study will have significant implications for cancer prevention, early detection, and treatment. By identifying high-risk exposures and understanding the molecular basis of cancer initiation, public health efforts can be better directed towards reducing carcinogenic exposures and improving lifestyle choices. Moreover, this study will contribute to the development of targeted therapies that can disrupt the specific mechanisms utilised by carcinogens and halt tumour growth and progression.

The rationale for this study is to address these gaps and provide a thorough examination of the diverse mechanisms by which carcinogens induce cancer and the role of genotoxicity in the carcinogenic process. By investigating the direct and

indirect-acting carcinogens' distinct pathways and their specific effects on cellular DNA, we aim to uncover the molecular events that drive cancer development. Understanding the complex relationships between environmental variables and cancer pathogenesis will help us to better understand how carcinogens interact with cellular DNA and how these interactions result in genetic changes, abnormal cell activity, and cancer pathogenesis.

2.2. A mechanistic overview of DNA damage

Genotoxic substances directly interact with cellular DNA, inducing stress that, if not managed properly, can lead to mutations [5]. Genotoxic carcinogens are chemicals that cause cancer by inducing mutations [1].

Genotoxic substances can change DNA in a variety of potentially harmful ways. Double-strand breaks (DSBs)—simultaneous breaks on both DNA strands—occur seldom and only when extremely potent DNA-damaging agents are present. DSBs are grave occurrences that split chromosomes and, if left unrepaired, can be fatal. Single-strand breaks (SSBs) are more common and can happen under normal physiological circumstances during transcription and replication processes. However, if these breaks occur at a higher rate than the cell's repair capacity, they can result in detrimental effects [6]. Genotoxic carcinogens are regulated upon the presumption that, even at very low levels, they represent a cancer risk to people. On the other hand, non-genotoxic carcinogens are believed to have a permissible exposure limit or dose, allowing their use in society as long as the exposure or intake remains below this threshold. These carcinogens induce cancer through pathways unrelated to mutations, such as hormonal impacts, cytotoxicity, cell proliferation, or epigenetic alterations [1].

2.3. A study of commonly affecting, well-known carcinogenic compounds

The consensus is that genotoxic carcinogens like benzo[a]pyrene and aflatoxin B1 trigger tumours by causing DNA damage and mutations, whereas non-genotoxic carcinogens like phenobarbital, carbon tetrachloride, or diethylstilbestrol lead to tumour formation through mechanisms that do not involve DNA damage, such as promoting cell proliferation [1].

Benzo[a]pyrene: Found in tobacco smoke, charred food, and exhaust fumes.

Brief information of the carcinogenic substances acting mechanism has been described below:

Benzo[a]pyrene: Benzo[a]pyrene and similar endocrine disruptors impact the growth and behaviour of terrestrial animals, while aquatic species can be affected by the presence of human female urine, which contains residues of oral contraceptives and other substances [7]. The levels of benzo[a]pyrene in sidestream cigarette smoke have been documented to vary from 52 to 95 nanograms per cigarette, surpassing the concentration found in mainstream smoke by over threefold. The primary origins of polycyclic aromatic hydrocarbons (PAHs) in the air, whether indoors or outdoors, encompass residential and commercial activities involving wood, coal, or other biomass combustion for heating purposes. Additionally, indoor sources like cooking and tobacco smoke contribute to PAH levels, while outdoor emissions from motor

vehicles, particularly diesel engines, industrial discharges, and forest fires, also play significant roles.

Mechanism of action: Benzo[a]pyrene is a polycyclic aromatic hydrocarbon (PAH) found in tobacco smoke, charred food, and exhaust fumes [8–10]. PAHs are classified as procarcinogens, implying that they need metabolic activation to become carcinogenic. Occupational exposure to PAHs predominantly happens through inhalation and skin contact. Following entry into the body, enzymes metabolise benzo[a]pyrene into reactive compounds, like epoxides, which can attach to DNA, forming DNA adducts. These adducts have the potential to cause mutations in crucial genes, including tumor suppressor genes and oncogenes. The modified DNA can disrupt typical cellular functions, resulting in unregulated cell proliferation and the onset of cancer [8].

Diolepoxide mechanism: The metabolic pathway of benzo[a]pyrene involving diolepoxide comprises several stages: benzo[a]pyrene undergoes transformation into benzo[a]pyrene-7,8-oxide through the action of enzymes CYP1A1 and CYP1B1, then further converts into benzo[a]pyrene-7,8-diol by epoxide hydrolase. Finally, this compound is metabolised into benzo[a]pyrene-7,8-diol-9,10-epoxides by enzymes CYP1A1 and CYP1B1. Each category of metabolic intermediate has been demonstrated to possess genotoxic and carcinogenic properties [10].

Radical-cation mechanism: The radical-cation mechanism of benzo[a]pyrene has been studied primarily concerning tumorigenesis in mouse skin. When benzo[a]pyrene undergoes one-electron oxidation by enzymes like CYPs or peroxidases, it generates a radical cation primarily localised at carbon 6 due to its geometric arrangement and ionisation potential. The radical cation results in the creation of covalent bonds with guanine (at the C8 carbon and N7 nitrogen) and adenine (at the N7 nitrogen) in the skin of mice. These adducts, which are unstable, are believed to induce the formation of apurinic sites in mouse skin. However, no studies have yet shown an increase in apurinic sites in lung tissues treated with benzo[a]pyrene, and only minimal levels of apurinic sites were observed in the epidermis of mice treated with the compound. Two in vivo studies demonstrated the excretion of 7-(benzo[a]pyrene-6-yl)-N7-guanine in the urine and feces of rats treated with benzo[a]pyrene, while the same adduct was detected in the lung tissue of mice. Additionally, alterations were observed at guanine and/or adenine in codons 12, 13, and 61 of the Ha-Ras oncogene in skin papillomas from mice treated topically with benzo[a]pyrene [10].

Synonyms: BaP; benzo[def]chrysene; 3,4-benzopyrene*; 6,7-benzopyrene*; benz[a]pyrene; 3,4-benz[a]pyrene*; 3,4-benzpyrene*; 4,5-benzpyrene* (*alternative numbering conventions). $C_{20}H_{12}$

Description: Yellowish plates, needles from benzene/methanol; crystals may be monoclinic or orthorhombic [8,10].

Study of carcinogenic activity: Following the administration of benzo[a]pyrene either through gavage or dietary intake to mice of various strains, elevated tumour responses were observed in lymphoid and hematopoietic tissues, as well as in multiple organs including the lung, forestomach, liver, oesophagus, and tongue. When benzo[a]pyrene was orally administered to XPA–/– mice, a significantly higher incidence of lymphomas was observed compared to XPA+/– and XPA+/+ mice under similar treatment conditions. Moreover, in XPA–/–/p53+/– double-transgenic mice,

tumours (mainly splenic lymphomas and forestomach tumours) occurred earlier and at higher rates when benzo[a]pyrene was administered via gavage compared to their single transgenic and wild-type counterparts. These cancer-prone XPA–/– or XPA–/–/p53+/– mice also developed a high frequency of tumours (mainly in the forestomach) when benzo[a]pyrene was included in their diet. Additionally, oral gavage of benzo[a]pyrene in rats led to an increased occurrence of mammary gland adenocarcinomas [8]. The IARC Monograph Volume 3 revealed that exposure to benzo[a]pyrene through various routes (oral, dermal, inhalation, intratracheal, intrabronchial, subcutaneous, intraperitoneal, and intravenous) led to tumour formation across all tested species, including mice, rats, hamsters, guinea pigs, rabbits, ducks, newts, and monkeys. Prenatal and transplacental exposure to benzo[a]pyrene resulted in both local and systemic carcinogenic effects in single-dose studies. Moreover, it induced skin cancer in mice. Repeatedly applying benzo[a]pyrene to the buccal pouch mucosa of male hamsters resulted in a notable increase in forestomach papilloma occurrence. In mice, intravaginal application of benzo[a]pyrene resulted in invasive cervical carcinoma, a phenomenon not observed in control groups [10]. Benzo[a]pyrene, a prototypical polycyclic aromatic hydrocarbon, belongs to the category of human genotoxic carcinogens (classified as IARC Group 1), demonstrating tumorigenic potential across various in vivo experimental animal models. Its carcinogenic activity is linked to the induction of interconnected genotoxic and nongenotoxic epigenetic changes. Specifically, exposure to benzo[a]pyrene leads to the extensive and selective formation of anti-7β, 8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE) adducts at key mutation sites, namely codons 157, 248 and 273 in the human tumour suppressor P53 gene, and at codon 14 in the human KRAS oncogene. CpG methylation at these sites significantly enhances the formation of these genotoxic benzo[a]pyrene-DNA adducts. The presence of BPDE-DNA adducts disrupts both global and gene-specific DNA methylation by impeding the activity of DNA methyltransferases. Consequently, hypermethylation of critical cancer-related genes such as cyclin-dependent kinase inhibitor 2A (CDKN2A; p16INK4A), retinoic acid receptor β2 (RARβ2), hypermethylated in cancer 1 (HIC1), and glutathione-S-transferase genes is frequently observed following exposure to benzo[a]pyrene [11] (**Figures 1–3**).

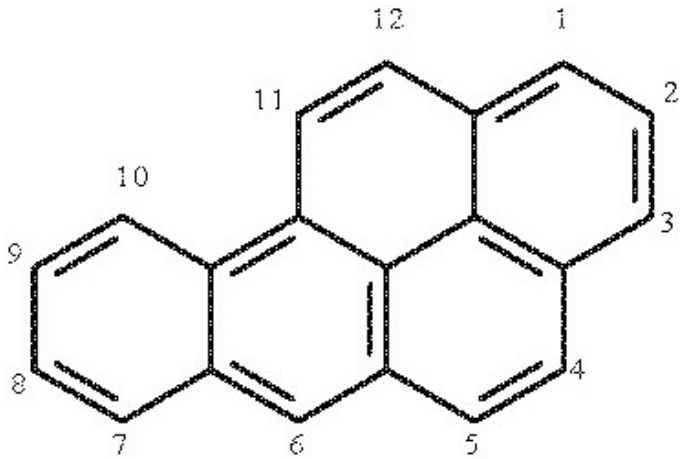

Figure 1. Benzo[a]pyrene structure [8–10].

Carcinogenesis:

Radical cation pathway:

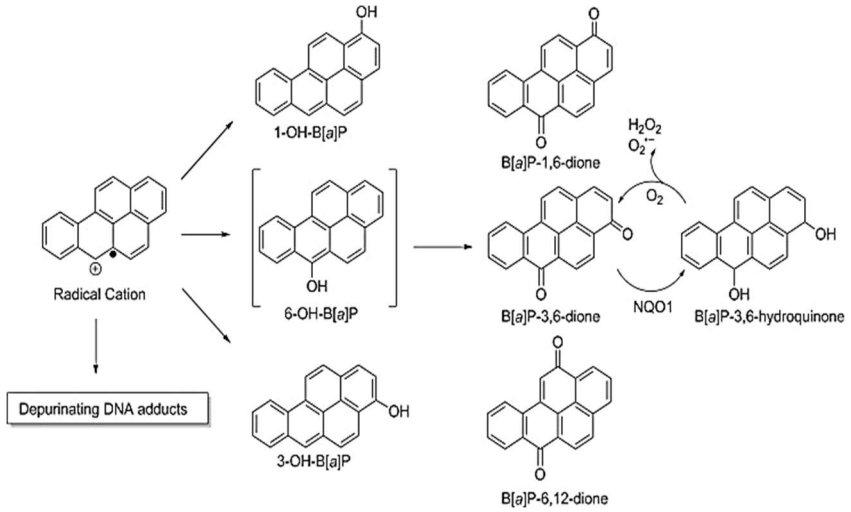

Figure 2. The radical cation mechanism of polycyclic aromatic hydrocarbon (PAH) activation, specifically with benzo[a]pyrene (B[a]P) [12].

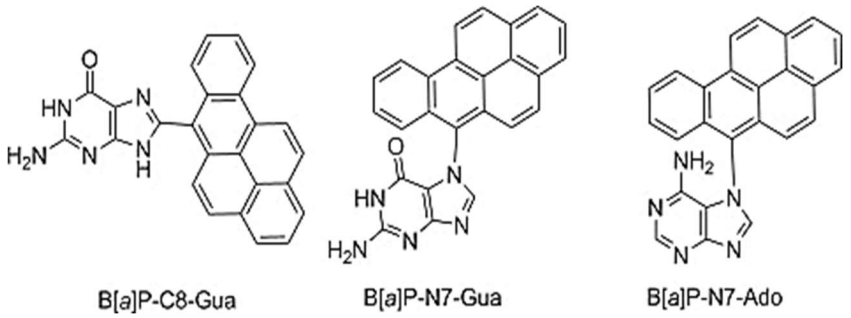

Figure 3. Depurinating B[a]P adducts derived from radical cation pathway [12].

B[a]P undergoes metabolic activation through the action of P450 peroxidase, acting as a co-reductant of Complex 1 $[Fe^{4+} = O]^{+\bullet}$, similar to perferryl-oxygen ($FeV^{+} = O$). In this process, Complex 1 returns to its resting state (Fe^{3+}) by extracting electrons from the C6 atom of B[a]P. Cavalieri proposed that B[a]P's relatively low ionisation potential enables the formation of a relatively stable radical cation capable of traveling to the nucleus and binding to DNA. Cavalieri and colleagues also identified peroxidases within the nucleus, suggesting that the radical cation may be formed locally. Other peroxidases, like horseradish peroxidase, prostaglandin H synthase (PHS), or myeloperoxidase, could generate the radical cation through a similar mechanism. This radical cation pathway also generates hydroxylated metabolites. Oxygen transfer in the peroxidase reaction to C6, the most electron-deficient carbon, produces 6-hydroxy-B[a]P (6-OH-B[a]P), which is highly unstable but can be detected by measuring the formation of stable polynuclear quinones like B[a]P-1,6-dione, -3,6-dione, and -6,12-dione. Oxygen may also transfer to C1 or C3, leading to the formation of 1-OH-B[a]P and 3-OH-B[a]P. Reactive metabolites like polynuclear quinones, such as B[a]P-1,6-dione, B[a]P-3,6-dione, and B[a]P-6,12-dione, are formed. Quinones are highly reactive and can be enzymatically reduced to hydroquinones via a two-electron reduction catalysed by NAD(P)H:quinone

oxidoreductase (NQO1) or two one-electron reductions catalysed by NADPH P450 oxidoreductase, or non-enzymatically by reductants like NAD(P)H and glutathione. The hydroquinones then undergo rapid autoxidation to form semiquinone anion radicals and regenerate the quinones. These futile cycles are linked to molecular oxygen, generating superoxide anion radicals ($O_2^{-}\bullet$) and hydrogen peroxide (H_2O_2) [12].

Genotoxicity assays play a crucial role in differentiating between the two categories of carcinogens. Nevertheless, certain carcinogens may produce negative outcomes in in vitro bacterial mutation tests but show positive results in in vivo transgenic rodent gene mutation assays [1]. Typically, the test employs four strains of Salmonella typhimurium and one strain of Escherichia coli to identify various point mutations. Named after its developer, Dr. Bruce N. Ames, the assay is commonly referred to as the Ames test, which initially utilised Salmonella strains [13]. Following positive findings in transgenic assays, methyleugenol, estragole, and madder colour were identified as genotoxic carcinogens. Conversely, citrinin, flumequine, ginkgo biloba extract, and 3-monochloropropane-1,2-diol esters exhibited unfavourable results in the organs targeted for carcinogenicity and were thus categorised as non-genotoxic carcinogens [14–17] (**Figure 4**).

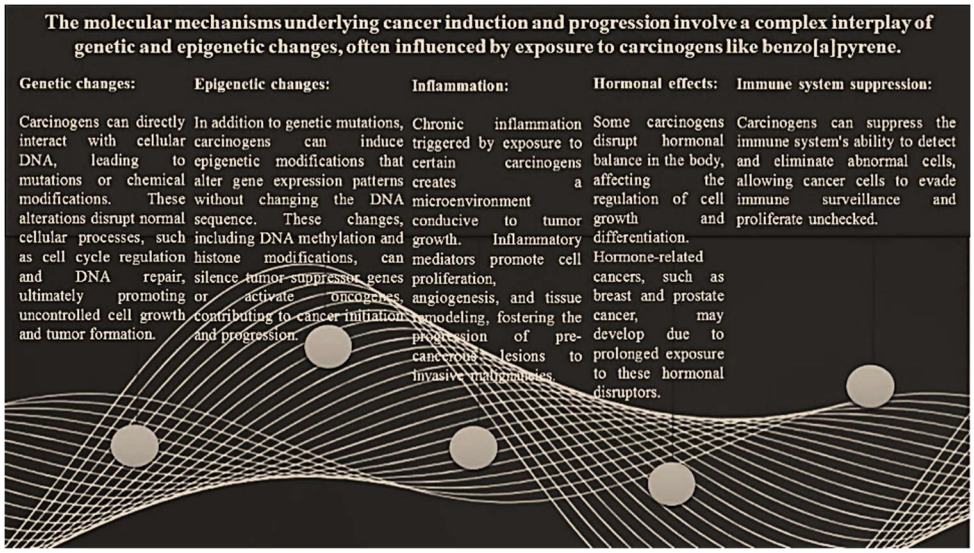

Figure 4. Mechanism of action of carcinogens.

3. Conclusion

To safeguard the public during acute chemical occurrences, it is crucial to provide credible, authoritative, evidence-based, and timely scientific advice that carefully considers the toxicological aspects of dangerous compounds.

The quality of the final response will be influenced by partnership functioning and expert input, among other important considerations. The mode of action of carcinogens encompasses a complex interplay of various cellular and molecular processes that lead to cancer development. From direct DNA damage to epigenetic modifications, inflammation, and immune system suppression, carcinogens utilise diverse mechanisms to induce oncogenesis. Understanding these pathways is vital for

implementing effective preventive strategies and developing targeted therapies against cancer.

By identifying high-risk exposures and adopting stringent environmental and occupational safety measures, we can significantly reduce the burden of cancer caused by carcinogens. Moreover, advancements in research, including genomics, epigenomics, and proteomics, will pave the way for personalised approaches to cancer prevention and treatment.

In conclusion, the study highlights the intricate mechanisms by which carcinogens exert their cancer-causing effects. Continued research into the mode of action of carcinogens is essential for improving cancer risk assessment, management, and overall public health.

The mechanisms of carcinogens encompass a complex interplay of cellular and molecular events that drive cancer initiation and progression. The distinction between direct and indirect-acting carcinogens, the role of genotoxicity in promoting mutations, and the influence of epigenetic changes on oncogenesis are fundamental aspects of understanding cancer development. This comprehensive study focused on these mechanisms and their significance in cancer research and public health. Continued research in this field is vital for advancing cancer prevention, diagnosis, and treatment, ultimately alleviating the global burden of cancer. Cytogenetic genotoxicity methods like the chromosome aberration assay or the micronucleus assay often yield positive outcomes even in the presence of non-DNA-damaging agents like spindle poisons or topoisomerase inhibitors. To discern between genotoxic and non-genotoxic carcinogens, researchers rely on mechanistic analyses of tumour formation derived from the findings of these genotoxicity tests.

Conflict of interest: The author declares no conflict of interest.

Abbreviations

RARβ2	The retinoic acid receptor beta 2 (RARβ2)
BPDE	benzo[a]pyrene diol epoxide
CDKN2A	CDKN2A, also known as cyclin-dependent kinase inhibitor 2A, is a gene which in humans is located at chromosome 9, band p21.3.
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
CYP1B1	gene provides instructions for producing an enzyme that is a member of the cytochrome P450 family of enzymes.
CYPs	Cytochromes P450 (P450s or CYPs)
IARC	International Agency for Research on Cancer
KRAS	Kirsten rat sarcoma virus
p16(INK4A)	proteins
p14(ARF)	proteins
PAH	Benzo[a]pyrene.
XPA	DNA repair protein complementing XP-A cells is a protein that in humans is encoded by the XPA gene.

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