Environment International 156 (2021) 106616

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Chemical pollution: A growing peril and potential catastrophic risk to humanity

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Chemical pollution
Environmental contamination
Toxicity
Endocrine disruptors
Environmental awareness

ABSTRACT

Anthropogenic chemical pollution has the potential to pose one of the largest environmental threats to humanity, but global understanding of the issue remains fragmented. This article presents a comprehensive perspective of the threat of chemical pollution to humanity, emphasising male fertility, cognitive health and food security. There are serious gaps in our understanding of the scale of the threat and the risks posed by the dispersal, mixture and recombination of chemicals in the wider environment. Although some pollution control measures exist they are often not being adopted at the rate needed to avoid chronic and acute effects on human health now and in coming decades. There is an urgent need for enhanced global awareness and scientific scrutiny of the overall scale of risk posed by chemical usage, dispersal and disposal.

1. Introduction

The benefits of synthetic chemicals to everyday life are undeniable but their deliberate and unintentional release into the wider environment is a direct consequence of economic development. Chemical pollutants have been released since the Industrial Revolution but their release and dispersal has accelerated markedly in the last half-century. Emissions of carbon dioxide (CO_2), with their long-term effects on the climate, atmosphere and oceans, are a striking example, but many other substances have been released in the form of industrial and agricultural emissions. Trillions of tonnes of chemically active material are discharged into the environment by mining, mineral processing, farming, construction and energy production (Cribb 2021; Pure Earth and Green Cross Switzerland 2016). In addition to the anthropogenic dispersal of geogenic chemicals, humans have synthesised more than 140,000 chemicals and mixtures of chemicals (UNEP 2019), most of which did not exist previously. Indeed, recent analysis of global inventories of chemicals estimates this figure could be over 350,000, which is many times larger than previously reported (Wang et al. 2020). New synthetic chemicals are constantly being developed: recently, the USA alone produced an average of 1500 new substances a year (GAO 2019). Many of these substances are known to be toxic in small doses, sometimes in combination with other pollutants, or as breakdown products after release into the biosphere and geosphere.

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https://doi.org/10.1016/j.envint.2021.106616
Received 8 November 2020; Received in revised form 26 April 2021; Accepted 2 May 2021

The scale of chemical release is estimated to be as high as 220 billion tonnes per annum – of which greenhouse emissions constitute only 20% – and may, indeed, be greater still (Fig. 1) (Cribb 2017). Furthermore, chemical releases are to a large degree cumulative. The chemical signature of humans is now ubiquitous and has been detected in the upper atmosphere, on the highest mountains, in the deepest oceans, from pole to pole and in the most remote, uninhabited regions, in soil, water, air, and in the human food chain (Gruber 2018). There are more than 700 known 'dead zones' in oceans and lakes, and pollution by fertilisers, agrochemicals and sediments is one of the factors most strongly associated with these habitat collapses (Diaz and Rosenberg 2008; Laffoley and Baxter 2019). Industrial chemicals, including known carcinogens and their residues, have been detected in the blood and tissues of all populations, including the unborn and infants (Mathiesen et al. 2021; Soleman et al. 2020), and in mother's milk (Hu et al. 2021; van den Berg et al. 2017). They are found in aquatic biota, plants and wild animals, as well as foodstuffs (Gruber 2018). Life is a function of genetics, metabolism, nutrition and the environment, and chemical toxicity can impair each of these functions; the combined and cumulative effects of all anthropogenic chemicals, acting together, can potentially impair human life itself.

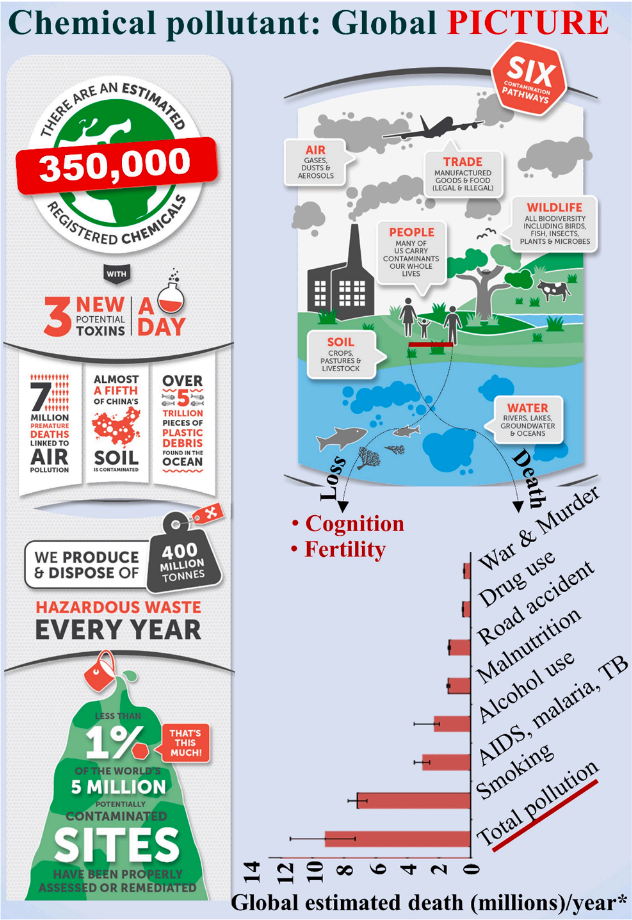

Fig. 1. An overview of global sources and pathways of chemical pollution and its potential impacts on the environment and human health. Six major pathways of chemical pollutants have been identified involving soil, air, water, wildlife, people and trade, as displayed in Fig. 1. The number of estimated chemicals is from Wang et al. (2020). The number of "silent" deaths caused by environmental pollution exceeds any other widely recognised risk factor. *The graphical component of the schematic in Fig. 1 shows estimated deaths reported for the year 2015 (after Landrigan et al. 2018), and may vary from year to year. It also shows the relative importance of environmental pollution as a major cause of human deaths per year. For comparison, pollution-related deaths are now around 9–10 million a year compared, for example, with 2 million deaths from COVID-19 in the first year of the pandemic (WHO 2021). Indeed, the toll may be even higher, if deaths from cancers and other non-communicable diseases are included.

Rockström et al. (2009) warned that chemical pollution is one of the planetary boundaries that ought not to be crossed to safeguard humanity. Altogether more than nine million humans are dying prematurely each year – one in six deaths – due to contamination of their air, water, food, homes, workplaces, or consumer goods (Landrigan et al. 2018). To place this in perspective, the chemical-related annual death toll is significantly greater than that of World War II and today constitutes the greatest preventable form of mortality. Furthermore, it inflicts catastrophic losses on wildlife, notably insects and animals that depend on them, ecosystems and their services, such as pollination or clean water, on which humans depend for our own existence. This underlines the role of chemical pollution in potential planet-wide ecological breakdown (Dave 2013). There is increasing evidence in recent decades of cognitive, reproductive and developmental disorders and premature deaths caused by chemical contamination of the human living environment (Diamanti-Kandarakis et al. 2009).

A thorough and state-of-the-art literature and global database search was made to support the perspective developed here. We present a global picture of chemical pollutants from many sources affecting human wellbeing in general, and humanity's long-term survival prospects in particular. This analysis is in addition to the effects of greenhouse gases and their effects on climate and humanity, which are considered elsewhere (Cavicchioli et al. 2019). Emphasis is given to chronic toxicity from exposure to low levels of pollutants on human reproductive capability, cognitive and foetal health, and food security. We identify priority issues and propose potential solutions to reduce impacts on human civilisation.

2. Production and consumption of chemicals

In *Man in a Chemical World* Abraham Cressy Morrison outlined the importance of chemistry, not only in contemporary post-industrial times, but also during earlier periods of traditional lifestyles (Morrison 1937). Chemical processes and innovations have been a cornerstone of civilisation, which probably started ca. 17,000 years during the transition of humans from hunters to civil societies, and will continue to be so for the foreseeable future (Rasmussen 2015). In 2017, approximately 2.3 billion tonnes of synthetic chemicals were produced globally – double the amount produced in 2000 (Cayuela and Hagan 2019). The majority of the chemicals were petroleum compounds (expressed as 25.7% of sales), speciality chemicals (26.2% of sales) and polymers (19.2% of sales) (CEFIC 2021). The use of chemicals other than pharmaceuticals is projected to increase by 70% by 2030, with China and the European Union (EU) remaining the largest consumers (see such projections in Supplementary Information, Fig. S1a,b). In 2019, world sales of chemicals were estimated at $4,363 billion, equivalent to the production of more than 2.3 billion tonnes of chemicals (excluding pharmaceuticals), which is approximately 300 kg per year for every man, woman, and child in the world (CEFIC 2021; UNEP 2019).

Since the 1970s there has been strong growth in the development and production of industrial chemicals that has introduced thousands of novel substances to daily use. According to the European Chemical Industry Council, the major sectors other than pharmaceuticals that utilise synthetic chemicals are agriculture, health, mining, services, rubber and plastic manufacturing, construction, and other industrial production (CEFIC 2021). New chemicals are often released with insufficient risk assessment (Sala and Goralczyk 2013; Wang et al. 2020), and their mixtures are creating new chemical environments with very uncertain toxicity. Chemical intensification is a feature of almost all major industries: in modern agriculture, for example, the intensive production of crops and livestock to feed much of the world now relies on the annual application of some 5 million tonnes of pesticides and 200 million tonnes of concentrated nitrogen, phosphorus and potassium (NPK) fertilisers. According to the Food and Agriculture Organization of the United Nations (FAO) database, the total volume of pesticides was 3,835,826 tonnes in 2008, which increased by ca. 7% in the next decade (See comparative statistics in Supplementary Information, Fig. S1c) (FAOSTAT 2019). In the USA alone, the number of active chemical components in various pesticides stands at more than 400 (USGS 2017). Agrichemical use is also increasing in newly industrialising countries, such as China, which is now the world's largest producer and user of industrial chemicals, itself accounting for 36% and 25% of world demand for chemical fertilisers and pesticides, respectively (Guo et al. 2010).

3. Chemicals as global pollutants

Although anthropogenic and synthetic chemicals have delivered enormous benefits to human civilisation, including disease control and food productivity, their benefits are now being offset by equally large-scale negative impacts resulting from unintentional human and environmental exposure, and insidious toxicity (Fig. 1) (ECHA 2018; NPI 2017; US-EPA 2017).

Well-known harmful pollutants such as arsenic (As), lead (Pb), cadmium (Cd) and mercury (Hg), as well as smog and air-borne particulate pollutant in large cities, have been documented since ancient Rome and Athens, whose citizens suffered from contaminated water supplies, air, cooking and eating utensils, and food (Patterson et al. 1987). The Agency for Toxic Substances and Disease Registry (ATSDR) lists 275 priority chemicals as pollutants, based on their frequency, toxicity and potential for human exposure. However, this is likely to be a significant underestimate given the difficulties in tracking novel or 'unknown' chemicals in the environment after they have been released (Anna et al. 2016). To overcome this uncertainty, science is attempting to define 'emerging contaminants' that are yet to be regulated, in order to anticipate future problems (Richardson and Kimura 2017).

Many chemicals now considered pollutants were beneficial at the time of their discovery (Kerr 2017). For example, when organochlorine insecticides were developed in the 1950s their main application was to control agricultural and disease-carrying insect pests, and they were successful in the short term. However, with the publication of Rachel Carson's *Silent Spring* in 1962 (Carson 1962), the world began to recognise it was facing severe problems due to the persistence of organic pesticides in the environment and the resulting cumulative exposure of wildlife and humans. Although some persistent organic pesticides have since been banned, humanity is still dealing with their legacy. Dichlorodiphenyl-trichloroethane (DDT), which was used widely in the 1950s, is a well-known example. Continuing illicit pesticide manufacture and use, and lasting residues, remain a problem in some countries.

The lag between discovering a chemical's benefits and understanding its potential harms has resulted in a pattern of new chemical synthesis, licensing, production and use, followed by concerns over potential effects, bans and restrictions, followed by an urgent search for replacement chemicals – frequently with other negative effects. This has led to 'pulses' of new chemicals being released into the environment and food chain in recent decades, followed by frequent detection of negative side-effects.

So, while chemical toxicity is not new, it is the phenomenal 40-fold increase in the production of chemicals and resource extraction during the last 100 years that now poses a serious risk to humanity (see Table 1 for an estimate of combined anthropogenic chemical emissions) (Cribb 2014, 2017, 2021). Emissions of pollutants can be continuous but they are often under-reported and there is great variability in reported values (Supplementary Information, S2).

The emission, dispersal and exposure of dangerous chemical pollutants and their mixtures are often sporadic and not confined in time or space. This is the main reason for increasing chronic exposure of humans to them. There is compelling evidence of their global migration in the form of air-borne particles, gases and aerosols, water-borne suspended particles, and dissolved pollutants (Aneja et al. 2008; Tukker et al. 2014). Chemicals are also distributed by vectors such as contaminated wildlife and people, discarded materials (e.g. plastics and electronics), and nano- and micro-scale synthetic particles (e.g. micro-plastics). International trade in food, minerals, energy, chemicals and manufactured goods, in concert with interconnected waterbodies, is often linked to major shifts in the burden of chemical exposure (Tukker et al. 2014; Zhang et al. 2017).

Table 1
Estimated chemical pollutants emitted by human activities on earth (Cribb 2014; 2017; 2021).

Consortia of pollutants		Released by humanity (million tonnes per year, approx.)
Total disposed waste		10,000–11,000
	Household waste	2,000
	E-waste	50
	Hazardous waste	400
	Food Waste	730
Manufactured/synthetic chemicals		2,500
	Pesticides	5
	Fertilisers	250
	Plastics	400
Food output		5,000
Forest output		5,800
Total mining output		17,000
	Gas	4,000 (cubic metre)
	Petroleum	4,500
	Coal	7,500
	All metals	5,000
	Cement	4,100
	Steel	1,800
	Uranium oxide	0.063
Mining wastes		36,000–84,000 (overburden)
		5000–10,000 (tailings)
Carbon (all sources)		37,000
Soil, eroded by farming and land development		36,000–75,000
Total human chemical emissions		120,000–220,000

4. Global attempts to control chemical pollutants

International attempts to regulate the global release and flow of toxic chemicals began with agreements, such as the Vienna Convention for the Protection of the Ozone Layer (22 March 1985) and the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal (22 March 1989). They were followed by the adoption of the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2001, and the Minamata Convention on Mercury in 2013. Since it became effective in 2004, the Stockholm Convention has managed to examine and ban only 26 out of potentially 350,000 synthetic chemicals ($<0.01\%$), with nine more under review in Annex B (restriction) and C (unintentional production) (Secretariat of the Stockholm Convention 2019). There are success stories of preventing or cleaning up chemical pollution using international, national and regional initiatives and instruments, such as those of the Montreal Protocol amendments for controlling ozone-depleting substances (e.g. chlorofluorocarbons, carbon tetrachloride) (US-EPA 2018), the United States Environmental Protection Agency (US-EPA) (US-EPA 2018), and the European Chemicals Agency (ECHA) (ECHA 2016). However, at current rates of progress, it will take over 100,000 years to evaluate all existing synthetic chemicals for human and environmental safety, and an additional 2,000 years to evaluate each year's new products (Cribb 2017). These estimates strongly suggest that current international regulation of the worldwide effusion of toxic chemicals has failed. Furthermore, it is far from clear whether international bans are being universally observed, especially in countries where regulation of the manufacture, use and disposal of chemicals is weak or corrupt (UNEP 2019). In June 2016, The Frank R. Lautenberg Chemical Safety for the 21st Century Act was signed to amend the USA Toxic Substance Control Act (TSCA) (US-EPA 2020). The amendments included significant changes, such as the obligation of EPA to evaluate existing chemicals with clear and enforceable time frame, and the application of risk-based chemical assessments. The Lautenberg TSCA stated that EPA is to determine the “unreasonable risk” caused by a chemical to ensure that it does not pose “unreasonable risk” to vulnerable populations. Koman et al. (2019) argued that the Lautenberg amendment of the TSCA improved the existing TSCA but failed to incorporate several vital aspects of population susceptibility to chemical pollutants, including defining “unreasonable risk” for specific groups of exposed populations such as children, pregnant women, workers and elderly people. Indeed, the United Nations’ Sustainable Development Goals (SDGs) specified 17 key issues for 2018, among which at least four highlighted environmental pollution as one of the factors causing critical global problems (Supplementary Information, Box S1). Moreover, long-range transport of many chemicals via air, groundwater, soil or international trade, and the constant introduction of novel chemicals are also challenging the capacity of the biosphere to absorb and deal with the present and future impact of chemical pollution (Aneja et al. 2008).

5. Chemical threats to human health

The quantity, residence time and mobility of environmental pollutants combine to create a long-lasting ‘chemical footprint’ (Sala and Goralczyk 2013) (Fig. 1). The exposure of all humans to pollutants from both point and widely dispersed sources is presently unavoidable due to their extensive and ubiquitous release, dispersal and disposal. (Fig. 2).

In 2012 alone, the exposure of people to pollutants via soil, water and air (both indoor and outdoor) resulted in an estimated 8.4 million deaths in lower and middle per capita income countries (Blacksmith-Institute 2014). A subsequent estimate by The Lancet Commission on Pollution and Health put the toll at 9 million premature deaths, while the US National Institutes of Health placed the figure as high as 13 million per year (Hou et al. 2012). Irrespective of the group conducting such surveys, it is clear that exposure to chemical pollutants is killing millions of people each year, and causing damage to the health of many tens of millions worldwide, and costing billions of dollars in lost economic activity (Nøst et al. 2017). The mass emissions of dangerous compounds are mostly estimated by analogy and/or guesswork, but evidence of their impacts grows (Table 2) (Pure Earth and Green Cross Switzerland 2016). Reports indicate that particular pollutants, such as chemical dyes, may cause the loss of 220,000–430,000 years of productive working life annually. Such losses are expressed as Disability-Adjusted Life Years (DALY) and are used to quantify the disease burden attributed to the impacts of various forms of pollution (Gao et al. 2015).

Damage to human health by pollutants has been well documented in fine detail over the past sixty years, and includes both acute and chronic disease of the central nervous, cardiovascular, renal, dermal, and reproductive systems, as well as causing non-communicable diseases

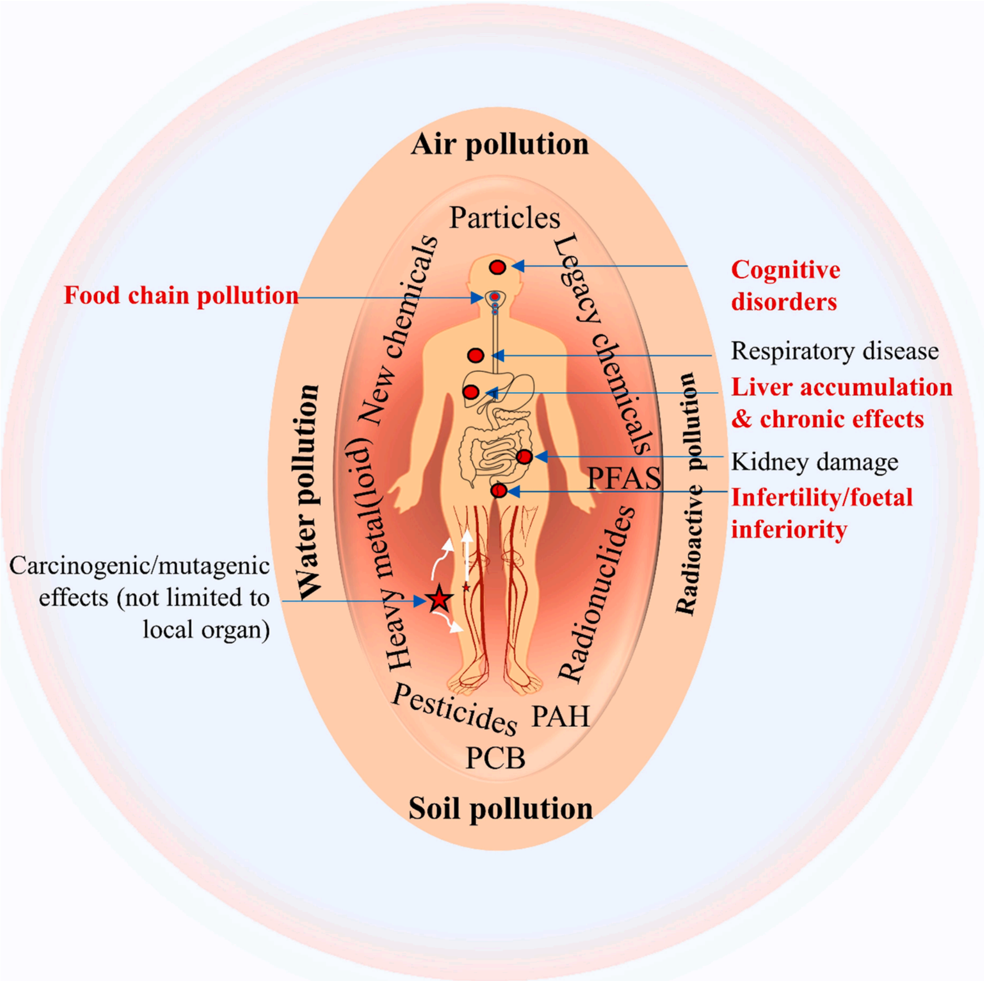

Fig. 2. With the current lifestyles of human civilisation it is almost impossible to avoid exposure to chemical pollutants, even for people attempting to lead healthy lives. Humans are exposed to chemical pollutants throughout their lives through several routes. These include (i) the direct use of chemicals in known or unknown unsafe ways (e.g. workplace chemicals, food additives and preservatives), (ii) living in a point-source polluted environment, or an area impacted by diffuse pollutants (e.g. near old industrial sites or in big cities), and (iii) consumption of foodstuffs harvested from contaminated environments. PFAS = per- and poly-fluoroalkyl substances,), PCB = polychlorinated biphenyls, PAH = polycyclic aromatic hydrocarbons.

Table 2
The top ten polluters and potential impacts on human life (as proposed by Pure Earth/Blacksmith Institute ((Pure Earth and Green Cross Switzerland 2016)).

Rank	Industries	DALYs*	Potential pollutants
1	Used lead acid batteries	2,000,000–4,800,000	Pb
2	Mining and ore processing	450,000–2,600,000	Pb, As, Cd, Hg, hexavalent chromium (Cr(VI))
3	Lead smelting	1,000,000–2,500,000	Pb, Cd, Hg
4	Tanneries	1,200,000–2,000,000	Cr(VI)
5	Artisanal small-scale gold mining	600,000–1,600,000	Hg
6	Industrial dumpsites	370,000–1,200,000	Pb, Cr(VI)
7	Industrial estates	370,000–1,200,000	Pb, Cr(VI)
8	Chemical manufacturing	300,000–750,000	Pesticide, volatile organic compounds (VOCs), heavy metal(loid)s
9	Product manufacturing	400,000–700,000	Pb, Hg, Cr(VI), dioxins, VOCs, sulphur dioxide
10	Dye industry	220,000–430,000	Pb, Hg, Cd, chlorine compounds

* Disability-Adjusted Life Years - a measure of human disease burden attributed to pollution. The more DALY, the more burden it causes.

such as cancer (Kataria et al. 2015; Messerlian et al. 2017; Virtanen et al. 2017; Wu et al. 2018). Acute respiratory inflammation can be triggered by the inhalation of toxic particles (Kim et al. 2011), while chemical deposition in the liver, kidneys or body fat can initiate chronic health issues (Kataria et al. 2015). For example, most hydrophobic chemicals accumulate in body fat, whence they may be remobilised during later life or sudden weight loss, and cause harm to other vital organs (Jandacek and Genuis 2013). Furthermore, many chemical pollutants, even at low doses – particularly POPs, such as DDT, dichloro-diphenyl-dichloro-ethylene (DDE), hexachlorocyclohexane (HCH, also known as lindane), and chlordane, brominated flame retardants (BFRs) such as polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and other organochloride pesticides – are endocrine disrupting chemicals (EDCs) that interfere with the synthesis, secretion, transport, binding or elimination of natural blood-borne hormones (Rusiecki et al. 2008).

5.1. Pollution impacts on cognitive health

Recent studies have revealed significant impacts of various industrial pollutants on the human brain and central nervous system (Underwood 2017). Fine particles, designated PM_{10}, $PM_{2.5}$, or ultrafine $PM_{0.1}$, which commonly arise from industrial waste, ash and the combustion products of fossil fuel, can migrate into the brain through the olfactory bulb, the neural structure responsible for the sense of smell. Ultrafine particles also produce cytokines that inflame the lungs or the nasal epithelium and further attack brain cells (Underwood 2017). Seaton et al. (2020) proposed that exposure of such particles, and particle-borne chemicals, to the blood vessels of the brain could cause inflammation and micro-haemorrhages in the brain-blood barrier wall. Roberts et al. (2013) investigated associations between US-EPA–modelled levels of hazardous air pollutants at the time and place of birth of babies and the subsequent incidence of autism spectrum disorder (ASD) in the children of participants in the Nurses' Health Study II (325 cases, 22,101 controls). Focusing on pollutants associated with ASD in prior research, they found that elevated perinatal exposures to diesel, lead (Pb), manganese (Mn), and cadmium (Cd) were significantly associated with the incidence of ASD, and that the incidence rate doubled among children of women exposed to air pollution during pregnancy. A survey of residents in Canada showed that exposure to $PM_{2.5}$ and PM_{10}, along with NO_2, increased the risk of dementia in inhabitants living near major roads (<50 m distance) in comparison with those living more than 150 m away (Chen et al. 2017b). Lead associated with urban roadways was linked to reduced human cerebral ability (Laidlaw et al. 2017).

Other neurotoxins in the environment, such as arsenic, methylmercury, PCBs, trichloroethylene (TCE), toluene, organophosphate, and fluoride have also proven detrimental to human intellectual ability (Grandjean and Landrigan 2014), and are associated with attention-deficit hyperactivity disorder (ADHD) (Braun 2016). In the USA, a simulation study of office workers concluded that volatile organic compounds (VOCs), such as 2-propanol, heptane, dichloro-ethene and aldehydes, are associated with reduced cognitive ability (Allen et al. 2016). They reported that people working in premises with low concentrations of VOCs (<50 μg/m^3) performed significantly better (av. 61%) than those exposed to high VOC concentrations (506–666 μg/m^3). Similar impacts of VOCs on cognitive ability were reported by several other studies (Li et al., 2021 review article and its cited relevant references), including that by Chen et al. (2017b), who reported the increased incidence of dementia, Parkinson's disease and multiple sclerosis of residents living near major roads in Ontario, Canada. Although the US-EPA has yet to set standards or guidelines for VOCs for non-industrial facilities, the VOC concentrations reported in several studies exceeded the World Health Organization's (WHO) Indoor Air Quality Standard for a reference equivalent individual compound, such as formaldehyde (100 μg/m^3) (Allen et al. 2016), or TCE (1 μg/m^3) (Chen et al. 2017b; Roberts et al. 2013).

Exposure of children to Pb can cause serious cognitive impairment in both the short and long term (Bihaqi and Zawia 2013; Dong et al. 2015). Other metal(loid)s, such as Hg, Cd, and As, as well as fluoride and pesticides, may also cause neurodegenerative disorders (Li et al. 2018; Tang et al. 2008) and the expression of genes attributed to Alzheimer's disease may also be linked to exposure to such contaminants (Wright et al. 2018). A 20-year *meta*-data study on fluoride exposure of young children in endemic fluorosis areas with fluoride-contaminated drinking water in China found five times greater incidence of impaired cognitive performance than in children not exposed to fluoride (Tang et al. 2008). *In vivo* studies revealed that per- and poly-fluoroalkyl substances (PFAS) are potentially neurotoxic to human neuroblastoma cells and can alter methylation regulation in the brain-derived neurotrophic factor, which may be associated with behavioural problems (Guo et al. 2017).

5.2. Impact of pollution on fertility and foetal health

Chemical pollutants have well-established detrimental impacts on human fertility (Aitken et al. 2004; Leiser et al. 2019). For example, male reproductive systems were reported to be adversely affected by some frequently used or emitted pollutants, such as dioxins, polycyclic aromatic hydrocarbons, BFRs and nonylphenol (Guo et al. 2017; Hales and Robaire 2020), and male fertility has been reported in several studies to have declined by half or more globally. A recent comprehensive review on the effects of BFRs on male reproductive health concluded from various animal model and human studies that these compounds are endocrine disrupting chemicals; depending on the types of compounds and degree of the exposure to them they could cause permanent damage to male reproduction systems (Hales and Robaire 2020). Similarly, a single ingestion of tributyltin as low as 10 μg/kg bodyweight can damage and kill mammalian testicular cells, particularly Sertoli cells, leading to male infertility in rodent models (Mitra et al. 2017). Many other known environmental chemicals cause oxidative stress to male reproductive cells, such as POPs, VOCs in polluted air, metals, chemicals used in the plasticising industry (e.g. phthalates), preservatives (e.g. parabens) (Samarasinghe et al. 2018), radionuclides and some unidentified toxicants (Bisht et al. 2017). Research with mice also showed that PFAS, another emerging persistent chemical in the environment, disturbs the testicular lipid profile in the male offspring of exposed mothers, resulting in significantly lower sperm counts and testosterone in the later stage of their lives (Lai et al. 2017). In males of Inuit and European populations, exposure to organochlorines may be causing reproductive damage; however, whether this equates with a significant loss of fertility has yet to be determined (Bonde et al. 2008). Overall, the past 50 years has seen a 50% reduction in sperm counts in both Western and Asian populations (Sengupta et al. 2017). The rate at which this change in semen quality is occurring is too fast to be genetically determined and is thought to reflect the build-up of toxicants in the environment since the Second World War (Levine et al. 2017). A recent book titled “count down” compiled the findings related to the male fertility and sperm quality and analysed the trend of decline of sperm count, where exposure to everyday chemicals, including EDCs was identified as the prime cause of such health risk that is linked to the human generation (Swan and Colino 2021). One of the mechanisms of such impacts is thought to be through exposure of pregnant mothers to chemicals that interfere with the normal differentiation of the male reproductive system *in utero*. The result is a testicular dysgenesis syndrome where a reduced capacity to generate spermatozoa is accompanied by other reproductive tract abnormalities such as cryptorchidism, hypospadias and testicular cancer, all of which are rapidly increasing in incidence in concert with the global decline in sperm counts (Lymperi and Giwercman 2018).

Endocrine disruptive chemicals interfere with reproduction in humans, and advances in molecular technologies are providing insight into the causative mechanisms, which include gene mutation, DNA methylation, chromatin accessibility and mitochondrial damage (Messerlian et al. 2017). There is compelling evidence that frequent exposure to environmental pollutants has large potential to reduce overall fertility (Selvaraju et al. 2021; Xue and Zhang 2018) by DNA methylation (Gonzalez-Cortes et al. 2017), apoptosis (Clemente et al. 2016) and chromatin/DNA fragmentation (Gaspari et al. 2003).

Exposure of future mothers or pregnant women to chemicals, or substances borne with ultrafine particulate matter, could be responsible for teratogenic damage to foetuses (Bashash et al. 2017; Rychlik et al. 2019), even at the mitochondrial level (Clemente et al. 2016). Exposure of pregnant women to neurotoxic metals (As, Pb and Hg) may also lower cognitive ability, or cause ADHD, in their offspring (Braun 2016). However, the impact may be dose, time-of-exposure and metal-specific. For example, the total Hg concentration (1.50–2.44 pg/L) present in the blood of first trimester women living in Avon, UK (1991–1992) did not reduce the cognitive ability of their children (Hibbeln et al. 2018). However, the presence of other metals (e.g. Pb) in human embryonic stem cells (1 μM) impaired the oxidative stress response system through the alteration of the responsible genes. Evidence of compromised birth conditions (e.g. low birth weight and premature parturition) potentially caused by prenatal exposure to volatile and air-borne chemicals has also been reported (Clemente et al. 2016; Stock and Clemens 2017).

Prenatal exposure of women in Mexico City to excessive fluoride caused residual concentrations in maternal urine of 0.90 mg/L and had detrimental consequences on child behaviour (Bashash et al. 2017). This epidemiological study tested participants who were exposed to fluoridated salt at 250 mg/kg and drinking water containing 0.15–1.38 mg/L fluoride. It was estimated that a concentration of 0.5 mg/L of fluoride in maternal urine was associated with a reduced intellectual ability in children of 3.2% as measured by the general cognitive index, and 2.5% when measured by intelligent quotient (IQ) scores (Bashash et al. 2017). Widely used synthetic fluorine compounds, such as PFAS, are also a potential threat to human health through exposure from contaminated soil and groundwater (Graber et al. 2019). Whether there is a link between prenatal exposure to PFAS and the intellectual ability of offspring remains to be established (Lyall et al. 2018). However, PFAS and related compounds may compromise placental health or other obstetric systems (Chen et al. 2017a), which, in turn, may affect the intellectual health of offspring. A significant concentration of total PFAS in cord serum (1.23–3.87 ng/mL as median value) is a warning that these persistent organic compounds are finding their way into succeeding generations (Manzano-Salgado et al. 2015).

6. Contamination of the food chain

6.1. Food chain pollution

According to the American Academy of Paediatrics more than 10,000 chemicals are used or find their way into the modern food supply (Trasande et al. 2018). Food chain pollution poses direct risks to humans from ingestion of contaminated food (Fig. 3). The risk may be passed on to the next generation as pollutants were detected in human breast milk (van den Berg et al. 2017) and were associated with cognitive and other health disorders, or by epigenetic means (Baccarelli and Bollati 2009). The adverse effects of pollutants on the human gut microbiome are also a warning about potential long-term impacts on immunity and metabolism (Jin et al. 2017).

Food can be contaminated at several stages before consumption - during crop or forage or animal production and harvesting, or post-harvest during storage, processing, transport and processing. Heavy metal(loid)s, pesticides, dioxin, PCBs, antibiotics, growth-promoting substances, packaging residues, preservatives and excess nutrients (e.g. nitrate) have all been found to contaminate food at higher than acceptable levels (Awata et al. 2017; EFSA 2018; Islam et al. 2017; Licata et al. 2004). This affects vegetables, grains, fish, and livestock via soil, surface water, groundwater or aerial deposition (Zhong et al. 2015) (Fig. 3). For example, Cd concentrations of various foodstuffs in China, including vegetables, rice, and seafood, were as high as 0.93 mg/kg and contributed 1.007 μg/kg bodyweight to the daily intake for children, which is 1.2 times higher than the acceptable limit recommended by WHO and the FAO (Zhong et al. 2015). Dioxin and PCB-like contaminants in food are also a concern to human health according to a report commissioned by the European Food Safety Authority (EFSA). Similarly, human exposure to pesticides can occur from residues in food or from legacy or inadvertent contamination during production and processing. Such contamination of food products can have chronic impacts on human health (The Gurdian 2004). A recent study of pesticide pollution at global scale reported that 64% of agricultural land was at risk of pollution caused by multiple active ingredients of pesticides. The risk includes adverse effects on food and water quality, biodiversity and human health (Tang et al. 2021).

Post-harvest protection of food can also result in contamination by fumigants, formalin and other insecticides and preservatives (e.g. calcium carbide, cyanide, sodium cyclamate, urea, melamine, aflatoxin and detergents), especially when they are used incorrectly, illegally or accidentally. Serious examples have been reported from numerous countries, including China, India, and Brazil (Handford et al. 2016). Even in countries with well-defined and established regulatory systems, such as those of the EU, chemical contamination in food and animal feed can occur to an extent sufficient to cause concern, due to intentional and unintentional use of post-harvest chemicals (Silano and Silano 2017).

6.2. Loss of soil productivity

Healthy soils are essential for safe, healthy food, ecosystem service delivery, climate change abatement, abundant food and fibre production, pollutant attenuation and freshwater storage, all of which are key to the sustainability of the world food supply. Reduced food availability and security in less-developed countries can occur when productive land is lost due to chemical contamination (Fig. 3). In the last 40 years nearly one-third of the Earth’s total arable land has been lost to soil erosion, desertification, urban expansion, and contamination (Cameron et al. 2015). Soils contaminated with heavy metals and pesticides cause loss of productive agricultural land and compromise food production and quality (Fig. 3). There is no global estimate of the areal losses of arable land attributed to chemical pollution, but regional reports indicate significant loss or potential loss. For example in Europe, 137,000 km^2 of agricultural lands are at risk of being abandoned due to heavy metal (loid)s pollution (Tóth et al. 2016). This situation is exacerbated in

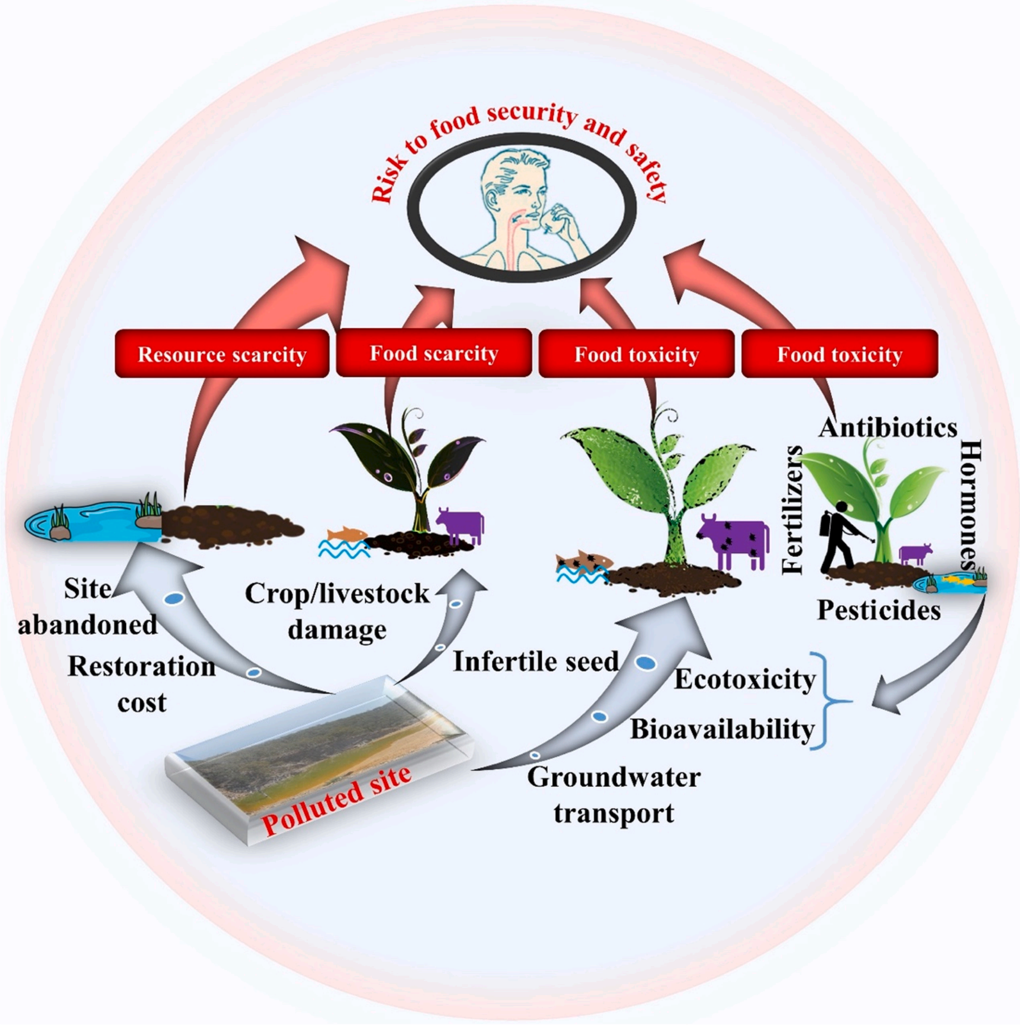

Fig. 3. The food security and safety risks caused by chemical pollutants. The details of each pathway of risks to food security and safety caused by potential chemical pollutants are presented in the main text under the section "contamination of the food chain".

developing countries by inadequate waste treatment and uncontrolled exploitation of natural resources (Lu et al. 2015; Tóth et al. 2016). China lost 0.13% of its total arable land due to chromium (Cr) pollution during 2005–2013 and 1.3% remains at risk (Lu et al. 2015; Tóth et al. 2016). Yet, key policy instruments and initiatives for sustainable development rarely recognise that contaminated soils compromise food and water security.

6.3. *Biodiversity loss and damage to crops and livestock*

Biodiversity in the Earth's surface layer from bedrock to the vegetation canopy provides the primary source of services for the support of life on Earth (Banwart et al. 2019; Cardinale et al. 2012). The acute and chronic impact of excessive current and historical use of agrichemicals and other industrial pollutants is contributing to a substantial loss of Earth's biodiversity. The global loss of honeybee communities due to neonicotinoid pesticides has caused an international crisis for crop pollination (Dave 2013), for example. There are reports of pesticide pollutants causing the loss of more than 40% of the total taxonomic pools of stream invertebrates in some regions (Beketov et al. 2013). Residues of more persistent chemicals, including many pesticides, may have long-term ecological impacts, especially in highly contaminated areas (Gevao et al. 2000) with significant threats of pollution of groundwater and marine water (Arias-Estévez et al. 2008; Jamieson et al. 2017). Losses of up to 78% of insect species have been reported from 290 sites in Germany (Seibold et al. 2019). Such ecological impacts and their persistence may profoundly alter biological processes such as decomposition and soil formation in natural environments, leading to unfavourable or challenging settings for human food production.

Reactive nitrogen pollution of the atmosphere and its deposition are responsible for declining biodiversity at regional (Hernández et al. 2016) and global scales (Condé et al. 2015). For example, assessing more than 15,000 sites, including forest, shrubland, woodland and grassland in the USA, Simkin et al. (2016) found that 24% of the sites had losses of vulnerability of species as a result of atmospheric nitrogen deposition, in particular when the disposition was above 8.7 kg N/ha/yr. A similar study in the UK also revealed that species richness had declined with increases of nitrogen deposition in the range of 5.9 to 32.4 kg N/ha/yr (Southon et al. 2013). Excess loading of nutrient pollutants by human activities affects hundreds of coastal and marine ecosystems and has been linked to a 'missing' biomass of flora and fauna (Diaz and Rosenberg 2008).

At a global scale there is also evidence that low crop yields may be caused by surface (tropospheric) ozone (O_3) pollution (Tai et al. 2014); elevated O_3 levels are also linked to chemical pollutants. It was projected that by 2030 that O_3 precursors could cause crop yield losses for wheat (4–26%), soybeans (9.5–19%) and maize (2.5–8.7%) globally (Avnery et al. 2011). Reduction of crop yield due to the O_3 exposure has also been reported by several regional experimental and model studies (Debaje 2014; Hollaway et al. 2012; Kumari et al. 2020). The yield losses occur as a result of plant physiological interference with the O_3 molecules such as the production of reactive oxygen species mainly through the diffusion of O_3 into the intercellular air space of plant leaves (Ainsworth 2017).

7. The chemical pollutant challenge for humanity: Discussion and questions

From a toxicological point of view, exposure to the vast array of modern chemicals and their billions of mixtures might cause acute or chronic toxicity but also not pose any toxic risk to humans. This wide range of threats can be addressed using a risk-based approach (Siegrist and Bearth 2019). Due to methodological constraints and the varying susceptibility to toxins among humans, there are only a few reports showing direct quantitative, whole life-span analyses of fatalities attributed to environmental pollutants (*section 2–6*). Nevertheless, compilation of the substantial evidence of the health burden caused by chemical pollution both show and predict the impairment of normal human life expectancy by direct exposure to pollutants, food contamination and fertility decline (Fig. 4) (Aitken et al. 2004; Hou and Ok 2019; Rabl 2006).

Rockström et al. (2009) described nine planetary boundaries that humans ought not to breach for our own safety: climate change, ocean acidification, stratospheric ozone, global phosphorus and nitrogen cycles, atmospheric aerosol loading, freshwater use, land-use change, biodiversity loss, and chemical pollution. Later, ‘chemical pollution’ was not considered as a single entry (Condé et al. 2015) as they also cause climate change (e.g. emissions of CO_2, methane and other greenhouse gases), ocean acidification due to elevated CO_2, depletion of stratospheric ozone due to released halocarbons, and interruption of P and N cycles. As pointed out here, atmospheric aerosol loading is another aspect of anthropogenic chemical pollution (Singh et al. 2017), and ambient air pollutants are responsible for millions of premature deaths and cost many billions of dollars (West et al. 2016).

Every year thousands of new chemicals are produced and most of them remain beyond current risk assessment regulations (Sala and Goralczyk 2013; Wang et al. 2020). The effects of mixed pollutants are especially unclear (Heys et al. 2016; Konkel 2017). This due to inadequate methodology to assess the interaction of chemical mixtures and the risk factors for human health (Heys et al. 2016), although the effects of mixed pollutants on human health are probably physiologically more relevant than that of any single pollutant (Carpenter David et al. 2002). Global climate change, including warming and extreme climatic conditions, will exacerbate human exposure to chemical pollutants present in soil and water (Biswas et al. 2018). Erosion and aerial transport of polluted soil or acidification of soil and water causing mobilisation of toxic heavy metal(loid)s are two mechanisms by which this can occur. There is in general far too long a delay between scientific discovery of pollution problems and their effects, and regulations and actions to abate them.

It is likely humanity is approaching a dangerous tipping point due to our release of geogenic, anthropogenic synthetic chemicals (Table 1, 2 and SI Box S1). This raises the issue that, as yet, no scientifically credible estimate has been made of humanity’s combined chemical impact on the Earth and on human health. This gap was highlighted by Rockström et al. (2009) whose popular ‘global boundaries’ chart was unable to include a boundary for chemical emissions because of a lack of data and suitable methodology. Public awareness is constrained by several issues, including the fact that toxic chemicals are now so widely dispersed throughout the Earth’s biosphere that their origins are untraceable, that cases of poisoning may take decades to be officially noticed, researched and proven, that the polluters may not be aware of or well-equipped to curb the pollution, that consumers and many professionals may be insufficiently educated in the risks. There are several local incidents that the aftermath analysis could reveal the insufficiency of knowledge regarding the effect of synthetic chemicals. For instance, the Bhopal Union Carbide gas disaster of 1984 of such categories where gaseous contaminant levels were so high that people died immediately following exposure.

Consequently, humanity is unaware of how near or far it is from exceeding the Earth’s capacity to ‘absorb’ or safely process our total chemical releases, which grows by many billions of tonnes with each passing year. This represents a potential catastrophic risk to the human future and merits global scientific scrutiny on the same scale and urgency as the effort devoted to climate change.

8. Addressing potential catastrophic chemical risk

The evidence submitted here using a thorough search to collate literature and pollution databases points to humanity unleashing a global crisis due to large-scale chemical contamination of the Earth’s atmosphere, hydrosphere, land and biosphere as grave as climate change, but more immediately lethal and devastating to health and nature than is commonly understood. While the full extent of pollution and toxicity remains to be precisely defined, a number of positive measures are being proposed to tackle it. Clean energy and energy efficiency projects across the globe and growing renewable energy markets, for example, are notable improvements in our efforts to tackle the emissions of fossil fuels, including their toxic impacts (UNEP 2017).

The United Nations Environment Programme (UNEP) tentatively

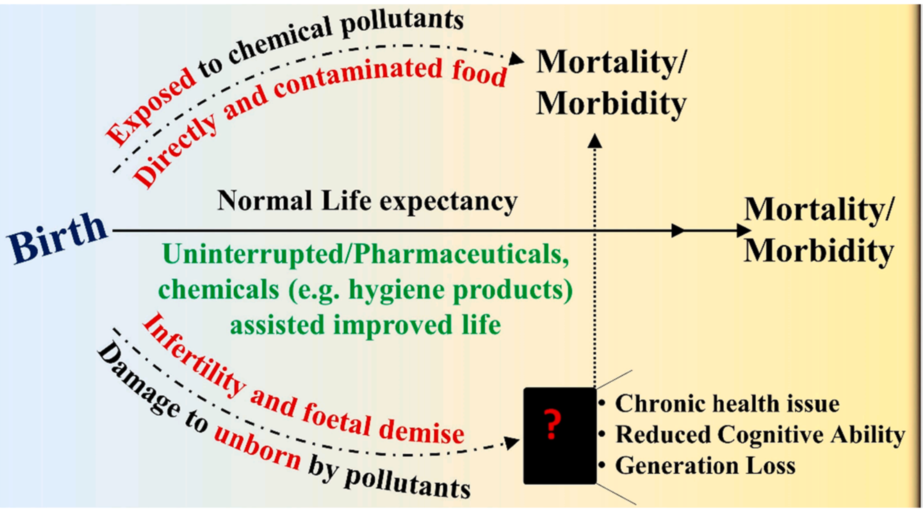

Fig. 4. Human mortality or morbidity as attributed to acute and chronic toxicity of chemical pollutants and reduced normal life expectancy. Damage to the foetus, sperm and embryos induces early mortality as well as causing long-term harm to humanity, such as reduced intellectual ability and the increased infertility. This schematic recognises that normal life expectancy cannot exclude the enormous benefits of pharmaceuticals or other chemicals in the quality of human life. The length of the straight solid line represents lifespan as normal with/without chemicals-assisted improvement; the length of the upper curved dash-dotted line represents potentially the shorter lifespans than normal; the length of the lower dash-dotted line symbolises the pollutant-impacted chronic health issue which causes significant poor quality of lifespan, while it could also lead a shorter lifespan than normal (see round dotted line).

calls for “a comprehensive multi-stakeholder preventative strategy” in its Global Chemical Outlook Report (UNEP 2019). Key aspects of their strategies are a set of responses to address identified challenges related to chemical exposure and sound chemical management at “country and regional level”, “corporate level and civil society” and “international level”. The strategies are often collaborative among stakeholders. In the case of EDCs, an international body, the Endocrine Society, argues for policies that are grounded in science and guided by evidence. One proposal to implement such a strategy is the globalCARE Alliance™, a scientific initiative to define, quantify, set limits to, help clean up, and devise new ways to curb the growing impact of chemical contamination on human health and the environment (globalCARE 2021).

We propose here a number of priority strategies for curbing the dispersal of chemicals known to be harmful to our genes, nutrition and habitat:

A. **Citizen or end-users’ attitudes**
   i. Exploit internet technology to raise awareness and spread knowledge that empowers peoples to transition from indifferent consumers to ‘clean agents’ of a global economy based on ‘green’ production
   ii. Press for prevention of disease, as opposed to chemical ‘cures’ for diseases caused by chemicals
   iii. Disseminate trusted toxicity information that is readily available to the global public
   iv. Monitor environments more closely, measure toxicant levels and take action such as containment and clean-up of polluted sites or industrial processes.

B. **Producer efforts**
   i. Conduct risk–benefit analysis of using chemicals in the food chain, identify health impacts and eliminate toxic substances, including nanoparticles and pharmaceuticals from the food chain, water supplies, personal care products and household goods
   ii. Replace coal, gas, oil and other fossil fuels with clean energy. Replace plastics with natural substances. Replace petrochemicals with ‘green chemicals’.

C. **Regulatory and policy implementation**
   i. Implement mandatory toxicity testing of all new chemicals, industrial substances and major waste streams along the lines of the EU Registration, Evaluations, Authorisation and Restriction of Chemicals (REACH) and US Toxic Substances Control Act (TSCA), their amendments and scientific discussions.
   ii. Implement mandates of the third session of the United Nations Environmental Assembly (UNEA3) concerning the chemical pollution to achieve the sustainable development goals (SDGs) with the collaboration of UN organisations, such as the Food and Agriculture Organisation of the United Nations (FAO), Global Soil Partnership (GSP) and World Health Organisation (WHO)
   iii. Train scientists, medical and legal professionals, technologists, engineers, and other key professions (e.g. economists, social scientists, arts and humanities) in their social and ethical responsibility to ‘first, do no harm’ to the environment or human health
   iv. Use progressive taxes and market measures to drive industries to make profits by producing safe products that do no harm, and promote ‘green chemistry’
   v. In collaboration with consumers and producers, conduct audits of the Earth’s biodiversity, ecosystem services and natural capital and how they are affected by pollutants
   vi. Establish as a Universal Human Right protection against poisoning
   vii. Define a ‘reasonable’ planetary ecological footprint and establish a ban against the exceedance of a specified multiplier of a reasonable planetary ecological footprint by sovereign states

The dramatic increase in the release of chemicals suggests that regulation alone cannot reduce or control the level of harm they cause. A risk-based approach for the assessment of all chemicals and mixtures could make a valuable contribution towards international policy to curb chemical exposure (Siegrist and Bearth 2019). However, the problem lies in the capacity of doing that for all the individual chemicals of concern. Therefore, economic and social pressures are needed to drive industry and consumers to change practices. UNEP advocates a consensus approach of “voluntary and legally binding frameworks for promoting the sound management of chemicals”, despite evidence that the problem is getting worse, not better. The question remains how quickly and effectively such frameworks can control the growing release of chemicals globally, especially in countries where regulation is weak, officialdom corrupt and industry has little or no concern for human health and environmental safety. Indeed, a 2015 report of the Rockefeller Foundation-Lancet commission on planetary health identified that the “environmental threats to human and human civilisation will be characterised by surprise and uncertainty” (Whitmee et al. 2015) while the 2017 commission reiterated that pollution was the largest preventable cause of death in the world (Landrigan et al. 2018).

Unless industry worldwide receives strong, clear economic and regulatory signals to produce clean, safe and healthy products it will continue with business as usual (Hou and Ok 2019). Coordinated action on a global scale is required to make a change in this regard. We propose that a global consensus process similar to that now operating for climate change be introduced as quickly as possible. This will be a multinational initiative underpinned by science and government, to define, quantify, set limits to, recommend clean up approaches, and devise new ways to curb the growing efflux of chemical contamination on human health and the environment.

As with climate change and clean energy, the key lies in changing the behaviour of billions of people so that they, in turn, can change the behaviour of their governments, industry and fellow citizens – a ‘virtuous circle of life’.

CRediT authorship contribution statement

Ravi Naidu: Conceptualization, Writing - original draft, Writing - review & editing. **Bhabananda Biswas:** Writing - original draft, Writing - review & editing, Visualization. **Ian R. Willett:** Writing - review & editing. **Julian Cribb:** Writing - review & editing. **Brajesh Kumar Singh:** Writing - review & editing. **C. Paul Nathanail:** Writing - review & editing. **Frederic Coulon:** Writing - review & editing. **Kirk T. Semple:** Writing - review & editing. **Kevin C. Jones:** Writing - review & editing. **Adam Barclay:** Writing - review & editing. **Robert John Aitken:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank the Cooperative Research Centre for Contamination Assessment and Remediation of the Environment (CRC CARE) for funding this research. Part of figure 1 was taken from The globalCARE Alliance^{TM} – contact Laureate Professor Ravi Naidu at ravi.naidu@newcastle.edu.au for more information.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106616.

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