

CHAPTER 6

Priority Environmental Contaminants: Understanding Their Sources of Exposure, Biological Mechanisms, and Impacts on Health

Sloane K. Tilley, Rebecca C. Fry

Contents

Introduction	118
Selection of Contaminants	118
Top 10 Compounds from the ATSDR 2013 Priority List of Hazardous Substances	119
Arsenic: Background	119
<i>Exposure Sources of Arsenic</i>	120
<i>Health Effects of Inorganic Arsenic Exposure and Potential Biological Mechanisms</i>	121
Lead: Background	122
<i>Exposure Sources of Lead</i>	122
<i>Health Effects of Lead Exposure and Potential Biological Mechanisms</i>	124
Mercury: Background	125
<i>Exposure Sources of Mercury</i>	125
<i>Health Effects of Mercury Exposure and Potential Biological Mechanisms</i>	126
Vinyl Chloride: Background	128
<i>Exposure Sources of Vinyl Chloride</i>	128
<i>Health Effects of Vinyl Chloride Exposure and Potential Biological Mechanisms</i>	128
Polychlorinated Biphenyls: Background	129
<i>Exposure Sources of Polychlorinated Biphenyls</i>	129
<i>Health Effects of Polychlorinated Biphenyl Exposure and Potential Biological Mechanisms</i>	130
Benzene: Background	131
<i>Exposure Sources of Benzene</i>	131
<i>Health Effects of Benzene Exposure and Potential Biological Mechanisms</i>	132
Cadmium: Background	133
<i>Exposure Sources of Cadmium</i>	133
<i>Health Effects of Cadmium Exposure and Potential Biological Mechanisms</i>	134
Polycyclic Aromatic Hydrocarbons: Background	136
<i>Exposure Sources of Polycyclic Aromatic Hydrocarbons</i>	136
<i>Health Effects of Polycyclic Aromatic Hydrocarbon Exposure and Potential Biological Mechanisms</i>	137
Carcinogenic, Organic Hazardous Air Pollutants	138
1,3-Butadiene: Background	138
<i>Exposure Sources of 1,3-Butadiene</i>	138

<i>Health Effects of 1,3-Butadiene Exposure and Potential Biological Mechanisms</i>	138
Formaldehyde: Background	139
<i>Exposure Sources of Formaldehyde</i>	139
<i>Health Effects of Formaldehyde Exposure and Potential Biological Mechanisms</i>	140
Dioxins: Background	141
<i>Exposure Sources of Dioxins</i>	141
<i>Health Effects of Dioxin Exposure and Potential Biological Mechanisms</i>	142
Chloroform: Background	143
<i>Exposure Sources of Chloroform</i>	143
<i>Health Effects of Chloroform Exposure and Potential Biological Mechanisms</i>	144
Environmental Contaminants of Emerging Concern	145
Flame Retardants: Background	145
<i>Exposure Sources of Flame Retardants</i>	145
<i>Health Effects of Flame Retardant Exposure and Potential Biological Mechanisms</i>	146
Perfluorinated Chemicals: Background	147
<i>Exposure Sources of Perfluorinated Chemicals</i>	147
<i>Health Effects of Perfluorinated Chemical Exposure and Potential Biological Mechanisms</i>	147
Siloxanes: Background	148
<i>Exposure Sources of Siloxanes</i>	148
<i>Health Effects of Siloxane Exposure and Potential Biological Mechanisms</i>	149
Conclusions	150
References	155

INTRODUCTION

The World Health Organization (WHO) has acknowledged that the prevention of environmentally related disease constitutes a tangible and effective way to significantly decrease disability-adjusted-life-years (DALYs) around the globe [1]. DALYs are measurements that estimate the global burden of disease by assessing years of life lost as a result of both premature mortality and years lived in decreased states of health. The WHO concluded that environmental factors contribute to 24% of the global DALYs lost [1]. There are many sources of environmental exposures that contribute to adverse health effects, including industry-related sources, burning/incineration, cigarette smoke, commercial products, natural occurrence, geological sources, and automobile exhaust [2]. Likewise, environmental exposures have been extensively linked to numerous diseases and adverse human health outcomes [2]. This chapter aims to provide information on priority chemicals in the environment, including exposure sources, health effects, susceptible populations to exposure and exposure-induced effects, and mechanisms of action. An understanding of these factors is critical in order to develop effective strategies to reduce the global burden of disease attributable to environmental exposures.

Selection of Contaminants

This chapter focuses on contaminants with high relevance to human health and disease and those highly ranked by regulating agencies. The top 10 substances from the Agency

for Toxic Substances and Disease Registry (ATSDR) 2013 Substance Priority List were selected for discussion in this chapter, as the ATSDR compiles their priority listing based on the frequency of occurrence at National Priority List sites in multiple environmental media, toxicity, and potential for human exposure [3]. The top 10 substances ranked by ATSDR, in descending order, were arsenic, lead, mercury, vinyl chloride, polychlorinated biphenyls, benzene, cadmium, benzo[a]pyrene, polycyclic aromatic hydrocarbons, and benzo[b]fluoranthene [4].

It was also important to include high-priority environmental contaminants of emerging concern in this chapter. The Organization for Economic Co-operation and Development has predicted that air pollution will be the top environmental cause of mortality in the world by 2050, surpassing deaths due to contaminated water and other chemical exposures [5]. Therefore, the five organic, hazardous air pollutants associated with the highest risk for cancer in the United States identified by Loh et al., were included for analysis—namely, 1,3-butadiene, benzene, formaldehyde, dioxin, and chloroform [6]. In order to provide a comprehensive analysis of contaminants of emerging concern, three other environmental contaminants were selected for inclusion—flame retardants, perfluorinated chemicals, and siloxanes. These contaminants are highlighted in Ela et al. [7] as future priority contaminants at superfund and hazardous waste sites.

TOP 10 COMPOUNDS FROM THE ATSDR 2013 PRIORITY LIST OF HAZARDOUS SUBSTANCES

Arsenic: Background

Arsenic is a naturally occurring, environmental metalloid that is present in many areas throughout the world [8–10]. Arsenic can exist in many different forms, but is most commonly found as a white or colorless solid that is both odorless and tasteless. There are both organic and inorganic arsenic compounds. Inorganic arsenic (iAs) is the more predominant form of naturally occurring arsenic and is the major form of arsenic in drinking water. iAs compounds are potent human carcinogens and thus more toxic than organic arsenic compounds [8–10].

iAs compounds exist in trivalent and pentavalent forms [8–10]. Pentavalent forms of iAs metabolites are generally considered to be less toxic than trivalent iAs metabolites [11,12]. The proposed explanation for this observation is twofold. First, pentavalent iAs metabolites are negatively charged at the biological pH, and trivalent iAs metabolites are neutral at the biological pH. Therefore, pentavalent forms are less readily transported across the amphipathic cell membrane than trivalent forms. Second, trivalent arsenicals are generally more reactive with sulfhydryl groups than pentavalent arsenicals [11,12]. Thus, trivalent arsenicals can better bind to sulfur-containing proteins, which, in turn, can result in disturbance of biological pathways and homeostasis and cause toxicity [13]. However, the pentavalent arsenical (DMMTA^V) has been found to be comparable in

toxicity to trivalent monomethylated arsenic, incongruous with the general trend of arsenic metabolite toxicity [11]. When it was discovered that DDMTA^V is also very reactive with thiol compounds [14], increased binding with sulfur-containing proteins became the leading hypothesis for the potent toxicity of DDMTA^V [11].

Biomethylation of iAs during metabolism also greatly impacts the toxicity of iAs and thus the risk of iAs-induced health effects in humans [15]. The metabolism of iAs into trivalent and pentavalent monomethylated and dimethylated arsenicals (MMAs and DMAs, respectively) differs among individuals, affecting the relative amounts of excreted iAs, MMAs, and DMAs, as measured in individuals' urine [15]. In the 2011 and 2013 ATSDR rankings, iAs was ranked as the highest priority substance hazardous to human health [4].

Exposure Sources of Arsenic

While arsenic levels exceeding the WHO standards have been recorded all over the world, affecting over 100 million people [16], arsenic found in drinking water in Bangladesh may account for the largest arsenic poisoning in history [17]. Tube-wells were first installed in Bangladesh in efforts to eradicate another public health problem—namely microorganism contamination of surface water used for drinking and bathing. This stagnant surface water accounted for extremely high mortality rates from diarrheal disease, especially among Bangladeshi children and infants. As a result, in the 1970s the United Nations Children's Fund (UNICEF) provided funding to install tube-wells across Bangladesh. The private sector continued to install large numbers of tube-wells throughout the 1980s, resulting in the presence of millions of tube-wells across the country. In 1993, there was an initial report of arsenic in the drinking water originating from tube-wells in one district of Bangladesh. By 1997, however, UNICEF reported that over 80% of the Bangladeshi population had access to “safe” drinking water from tube-wells. Almost simultaneous with the release of this statement, results from studies undertaken in response to the discovery of arsenic in the drinking water emerged in 1996, confirming that an estimated 21 million Bangladeshi people were exposed to arsenic levels over 50 parts per billion (ppb) in their drinking water [17]. Over 40,000 cases of skin lesions from arsenic poisoning have been documented in Bangladesh [18]. While UNICEF has implemented tube-well screening programs, arsenic poisoning through drinking water continues to plague the Bangladeshi people [18].

Humans are primarily exposed to arsenic through food and drinking water consumption [9,10]. Specifically, it is estimated that the total daily average intake of arsenic is 40 µg, and rice, seafood, and poultry are foods that have been demonstrated to contain the largest amounts of arsenic [8]. Other sources of arsenic exposure include inhalation of arsenic compounds produced from glass and pesticide manufacturing facilities, cigarette smoking, and burning of fossil fuels [19]. Arsenic production was banned in the United States in 1985 [19]. In the past, iAs compounds were heavily used as pesticides from the mid-1800s

to the mid-1900s, and some arsenic compounds continue to be used in agriculture today as pesticides and as an ingredient in one chicken food additive [19–21].

As exemplified by the mass arsenic poisoning through drinking groundwater in Bangladesh, arsenic seeps into water supplies through natural processes [9,19]. The WHO recognizes that arsenic is present in the geologic composition of the Earth's crust, and thus is likely to be found in groundwater in places where arsenic occurs naturally in the terrain. However, the WHO has set the guideline limit for the arsenic concentration in drinking water at 10 ppb [22]. Yet, in many places this limit continues to be egregiously exceeded. For example, in Nepal, Vietnam, and Mexico, arsenic levels in drinking water as high as 1072, 3050, and 236 ppb, respectively, have been recorded [23–25]. In addition, arsenic exposure via drinking water is not only a problem in developing countries, but is also, in fact, a priority public health concern in the United States. Specifically, arsenic levels as high as 800 ppb have been observed in North Carolina drinking water [18], and levels reaching 180 ppb have been detected in New Hampshire drinking water [26,27].

While exposure to high concentrations of arsenic is not beneficial to the health of any population, certain demographic groups are at increased risk for iAs toxicity. These include pregnant women and their developing fetuses, children, and workers who are exposed to iAs occupationally [8,19]. iAs exposure in pregnant women can be especially harmful, as iAs can cross the placental barrier and is a possible human teratogen [28]. Furthermore, prenatal iAs exposure has been associated with impairment of fetal growth and increased rates of infant mortality, spontaneous abortion, stillbirth, and preterm birth rates [28]. In China, geographical correlation studies in areas known to contain high amounts of arsenic in soil have demonstrated a relationship between increased rates of birth defects and residency in an arsenic-contaminated area [29,30], and animal studies have demonstrated that arsenic induces birth defects *in ovo* [31,32]. In addition, epigenomic and genomic changes have been observed in infants exposed in utero to arsenic [25,33,34]. Children are at greater risk of iAs exposure due to their higher hand-to-mouth activity [8]. In addition, environmental toxicants, such as arsenic, can be more harmful to children because of their high rates of growth and developmental immaturity [35]. Postnatal arsenic exposure has been shown to be correlated with decreased weight and height in girls in the first two years of life [36]. Workers in the smelting, wood preservation, and electronic and agrochemical production industries have a higher chance of occupational exposure through both dermal contact and inhalation [8,10].

Health Effects of Inorganic Arsenic Exposure and Potential Biological Mechanisms

Acute exposure to high levels of iAs (above 60,000 ppb in drinking water) can result in death, while short-term exposure at lower concentrations (300–30,000 ppb in drinking water) can result in nausea, vomiting, diarrhea, cardiac arrhythmias, fatigue, and vascular bruising [8]. Acute inhalation of As results in throat and lung irritation [8].

Chronic iAs exposure is known to cause many harmful health effects to humans. The International Agency for Research on Cancer (IARC) classifies arsenic and iAs

compounds as Group 1 human carcinogens, and the United States Environmental Protection Agency (USEPA) and the National Toxicology Program (NTP) rank arsenic and its inorganic compounds as known human carcinogens [19,37]. The skin, lung, and urinary bladder are the primary target sites of iAs-induced carcinogenesis, though iAs exposure has also been associated with cancers of the liver, kidney, digestive tract, and lymphatic and hematopoietic systems [10,12]. Numerous epidemiological studies have confirmed iAs carcinogenicity, and evidence of an exposure–response relationship has been found between iAs and different cancers, as reviewed by Cohen et al. [12]. Noncancerous health outcomes associated with iAs include diabetes, immunotoxicity, neurotoxicity, teratogenicity, and cardiovascular disease [28,38–40].

The mechanism of action of arsenic toxicity is multi-factorial, as arsenic is known to induce oxidative stress, inhibit DNA repair, promote chromosomal deletions and rearrangements, and alter gene expression, enzymatic function, the epigenome, cell cycle progression, and telomere length [15]. Mechanisms of action of arsenic-induced toxicity and carcinogenesis have been studied at the epigenomic, genomic, transcriptomic, proteomic, and metabolomic level [41]. Specifically, studies have highlighted arsenic's epigenetic effects, including arsenic-associated altered DNA methylation [42–46], miRNA changes [25], and histone modifications [47,48]. These studies have been important to increase the understanding of mechanism of action as arsenic has not been found to directly damage DNA [49], yet altered transcript and protein profiles have been associated with arsenic exposure [33,50–53]. As reviewed by Bhattacharjee et al., arsenic metabolism generates reactive oxygen species that, in turn, induce genomic instability via DNA damage and disruption of various biological processes, including DNA repair and apoptosis [54]. In addition, the metabolism of arsenic has been demonstrated to play a role in its mechanism of toxicity [15]. Specifically, low methylation capacity of iAs into DMA metabolites and resulting high proportions of MMA metabolites in the urine has been associated with detrimental health outcomes, such as lung cancer, breast cancer, and diabetes [55–57].

Lead: Background

Lead (Pb) is a heavy metal that originally enters the environment through the mining of ore [58]. It exists in many forms, both soluble and insoluble, as well as organic and inorganic, that have broad ranges of colors, melting points, and other physical properties [58,59]. The ATSDR ranked lead as the second highest priority substance hazardous to human health in both 2011 and 2013, and environmental lead exposure remains a risk to human health in both developed and developing nations [4].

Exposure Sources of Lead

Lead compounds have been found dating back to 6400 BCE [60]. Civilizations ranging from the Romans to ancient Indians mined, refined, and used lead [61,62]. Lead compounds continue to be produced in vast quantities (millions of pounds) annually in the

United States [19,59]. Humans are most often exposed to lead through inhalation and ingestion, though inhaling lead results in a larger percentage of lead entering into the blood stream [19]. While lead compounds do occur naturally, most of the lead-related environmental exposures come from anthropogenic sources [58,59].

In the past, lead was used in gasoline in order to improve octane ratings and to increase engine performance [63]. The United States required the removal of lead from gasoline in 1986, as a consequence of the introduction of the catalytic converter and of public health concerns about exposure to lead [63]. Prior to the removal of lead in gasoline, automobile emissions were the primary route of exposure for humans to lead, constituting 90% of the total man-made lead combustion products [19]. In fact, the average blood lead levels of Americans plummeted 78% from 1978 to 1991, following the trend of declining lead levels in gasoline [58].

Still, lead continues to be released into the environment through many industrial operations, including lead smelting itself [19,59]. These exposures to lead occur through food, drinking water, cigarette smoke, and occupational exposures in many industries, including construction, mining, and battery operations [19,59]. The National Institute for Occupational Safety and Health (NIOSH) estimates that over 3 million Americans are exposed to lead in their working environment and sets the occupational exposure limit at less than 0.1 mg/m^3 [59,64]. Particularly, individuals working in the battery and lead smelting industries have a significant risk of increased occupational lead exposure [19,58,59]. Workers in similar industries in developing countries are often exposed to even greater amounts of lead, as a result of less stringent safety procedures and a lack of education regarding the hazardous risks associated with certain occupations [65]. Environmental lead exposure poses a significant threat to human health, contributing \$43.4 billion to health care costs in the United States alone [66], and often cooccurs with other toxic metal exposures [29,67].

Lead poisoning also poses a great threat to children, pregnant women, and the developing fetus [19,59]. Children, particularly, are at risk for lead exposure due to an increased propensity to ingest dust or soil containing lead [68]. Furthermore, children show a higher relative gastrointestinal absorption of lead [69]. Exposure to lead, a known neurotoxicant that can cross the blood-brain barrier, is of particular concern in young children, as the developing nervous system is especially susceptible to adverse toxic effects [35,58,59]. Wigle et al. compiled evidence from numerous epidemiologic studies investigating the relationships between environmental exposures and reproductive and child health outcomes, concluding that there was sufficient evidence for childhood lead exposure and cognitive deficits and renal tubular failure in children [70]. They also found that there was evidence for relationships between parental lead exposure and spontaneous abortion at less than 20 weeks gestation, maternal lead exposure and preterm birth, fetal growth deficit, problem behaviors, sensory function, and prenatal or childhood lead exposure and developmental delays, height, dental

cavities, and delayed onset of menarche [70]. The mobilization of lead stored in bones is known to increase during pregnancy, and lead from the mother's bloodstream can cross the placental barrier [59].

Health Effects of Lead Exposure and Potential Biological Mechanisms

Lead poisoning is associated with adverse immediate and long-term health effects [19,58,59]. Acute exposure to high concentrations of lead has been demonstrated to cause several detrimental health effects including constipation, abdominal pain, nausea, vomiting, encephalopathy, and in some severe cases, coma, and even death [19,58,59]. As reviewed in the ATSDR toxicological profile of lead, numerous studies have reported various ranges in which these symptoms of acute lead poisoning occur [58]. It is generally concluded that blood lead levels above 60 ppb can induce gastrointestinal symptoms, while encephalopathy is most commonly observed when blood lead levels reach approximately 200 ppb. Coma and death usually only occur when blood lead levels exceed 300 ppb [58]. For reference, the Center for Disease Control and Prevention (CDC) blood lead level of concern is 5 ppb in children up to 5 years of age and 10 ppb in adults, and the blood lead level of medical intervention is 45 ppb [71].

While lead is a potent, acute toxicant, the long-term health effects of lead exposure are also a public health concern. One of the most alarming and well-studied effects of chronic lead exposure is neurotoxicity [72]. Lead is particularly detrimental to children's neurodevelopment [73]. Children exposed to lead prenatally and during early childhood have been found to have lower measures of cognitive function [74,75], including decreased intelligence quotient (IQ) [76,77]. Specifically, Grosse et al. [78] reported that a 1.9–3.2 decrease in IQ was associated with a 10 µg/dL average increase in children's blood lead concentration.

Lead and lead compounds are also currently classified by the NTP in the 12th Annual Report on Human Carcinogens to be “reasonably anticipated to be human carcinogens” [19]. Similarly, the IARC ranks inorganic lead compounds as Group 2A human carcinogens [59], while the USEPA reports that lead and lead compounds are “reasonably anticipated to be human carcinogens” [79]. Lead exposure has been consistently, but weakly, associated with an increased risk of lung, stomach, and urinary bladder cancers in human populations [19,58,59]. A dose–response relationship has not been established, and confounding factors, especially the frequent coexposure to other heavy metals in conjunction with lead exposure, have not been accounted for. Lending support to the limited epidemiological studies of lead exposure, many animal studies have reported lead-induced tumorigenesis at different tissue sites including the kidney, brain, lung, and hematopoietic system [19,58,59].

Several mechanisms of action of lead toxicity have been proposed [72]. Evidence suggests that lead does not damage DNA directly, but rather acts through mechanisms of oxidative stress and inhibited DNA synthesis and repair, which, in turn, can lead to lead-associated disease [80]. There is also evidence that the neurotoxic effects of lead are

mediated by increases in proinflammatory cytokine signaling and neuroglial cell activation [81–83]. Although the adverse health effects have been known and studied for decades, environmental exposure to lead continues to threaten the health of people around the globe; public health interventions regarding lead exposure ought to continue to be prioritized.

Mercury: Background

Mercury is a naturally occurring metal that exists in elemental, organic, and inorganic forms [84]. Mercury is the only metal which is a liquid at room temperature. Metallic mercury is shimmery silver–white in color and odorless [85]. Mercury compounds most commonly exist as white crystals or powders [85]. The ATSDR ranked mercury as the third highest priority substance hazardous to human health in both 2011 and 2013, and environmental exposure to mercury continues to threaten human health around the globe [4,85].

Exposure Sources of Mercury

“Mad as a hatter” is a familiar term, but its obscure origin relates to mercury use and toxicity. Beginning in the seventeenth century, mercury began to be used in the making of hats in France and Britain [86]. Consequently, hat makers began to exhibit bizarre behavior ranging from extreme anxiety and shyness to volatile outbursts of temper [86]. While mercury is no longer used in the hat industry, people are ubiquitously exposed to extremely low levels (10–20 ppb) of mercury through inhalation, dermal contact, and ingestion [85]. Inhalation of contaminated air or handling of contaminated soil at hazardous waste sites can result in exposure to mercury [85].

Individuals with diets high in seafood, particularly larger aquatic animals from waters containing large amounts of methylmercury are also at risk for exposure, as metabolic processes concentrate methylmercury in the tissues of animals at the top of the food chain [84]. A meta-analysis by Visnjavec et al. [87] found that fish consumption was the primary source of mercury exposure in European populations across 50 studies.

Mercury is also present in common household items and various medicinal and chemical products [84]. Perhaps the most familiar source of potential mercury exposure is a broken or cracked thermometer, which will release metallic mercury fumes into the surrounding air at dangerous concentrations. Other common household items that pose a threat of mercury exposure include thermostats, fluorescent light bulbs, and electrical switches. Another common possible source of mercury exposure is dental amalgam fillings, which are approximately 50% metallic mercury [84]. While the amount of mercury released daily from an amalgam varies by the individual, dental amalgams have been significantly associated with higher mercury body burdens in children [88]. In addition, some fungicides, topical antiseptics or disinfectants, and beauty products contain mercury at levels dangerous to human health [84].

Exposure to mercury presents a greater risk of harmful health effects in children and pregnant or breastfeeding women [84]. Wigle et al. found that prenatal exposure to methylmercury was significantly associated with delayed development, and cognitive, motor, auditory, and visual deficits in a review of epidemiologic literature and that childhood exposure was associated with visual deficits [70]. Mercury stored in a mother's body can be transferred to a fetus transplacentally or to an infant through breast milk [84,85]. Mercury-induced neurotoxicity poses a threat to children and fetuses due to the critical development of the nervous system that occurs during these stages [35,89]. As the nervous system is not fully developed in children, infants, and fetuses, mercury is better able to cross the blood–brain barrier and adversely affect development of the central nervous system [89–91].

There have been two documented mass exposures to methylmercury in history, and severe health outcomes including seizures, intellectual disabilities, decreased brain mass, and death were reported in children exposed prenatally [89]. In the 1950s, large quantities of dead fish began to appear in the Minamata Bay in southern Japan [92]. Next, cats began to exhibit strange behavior and also die in droves. Humans began to demonstrate symptoms of a damaged central nervous system, often resulting in death. In 1959, the Minamata Disease Research Group of Kumamoto University identified the cause of Minamata disease as methylmercury poisoning. Since the etiology of the disease was discovered, 2200 people were officially diagnosed with Minamata disease, but it is suspected that more people suffered undiagnosed [92]. Unfortunately, approximately 10 years later another, larger incident of exposure to methylmercury occurred in Iraq [93]. In 1972, 6530 cases of methylmercury poisoning, including 459 fatalities, were reported throughout the country. The poisoning was traced back to bread made with seeds treated with a fungicide-containing methylmercury. Patients were recorded having methylmercury blood concentrations greater than 4000 ppb [93]. Severe detrimental health effects including mental, motor, audio and visual impairment were observed in children and in infants exposed prenatally in both the Japanese and Iraqi methylmercury-exposed populations [92,94,95].

In addition, workers in the dental, electrical, battery, and laboratory industries are at risk of mercury exposure [85]. Mercury and mercury compounds have not been established as human carcinogens [96]; however, other severe, detrimental, systemic health effects resulting from mercury exposure necessitate the continued attention of public health research and interventions.

Health Effects of Mercury Exposure and Potential Biological Mechanisms

Metallic/elemental mercury and organic and inorganic mercury compounds have differing effects on human health, as they are metabolized by the human body through different biological processes [85]. Elemental and organic mercury tend to be characterized as neurotoxic compounds, whereas inorganic mercury compounds are identified as

nephrotoxic, though these categorizations are not exclusive [97]. Methylmercury, a form of organic mercury, has been the most relevant form of mercury in mass environmental exposures [97]. It also is the most toxic form of organic mercury [97]. Acute effects of metallic mercury exposure through inhalation include difficulty breathing, lung and eye irritation, coughing, nausea, vomiting, diarrhea, increased blood pressure, and tachycardia [84]. Ingestion of high levels of metallic or organic mercury has caused permanent damage to the central nervous system, while ingestion of large amounts of inorganic mercury causes kidney and gastrointestinal damage [97]. Acute exposure to extremely high levels of mercury (>1 g) has been reported to result in renal failure and necrosis, and, in some cases, death [85].

Long-term exposure to mercury has primarily been associated with neurotoxic effects, including diminished cognitive function, increased risk for autism and attention hyper deficit disorder [97,98]. Mercury exposure has also been associated with immunotoxicity, and is speculated to be involved in the pathology of the childhood immune disease, Kawasaki disease [99]. In addition, mercury has been reported to act as an endocrine system disruptor [100]. While there is some evidence that inorganic mercury can be mutagenic and genotoxic [101,102], the NTP does not classify any form of mercury to be a “likely” or “reasonably anticipated human carcinogen” [19]. However, the USEPA and the IARC classify methylmercury compounds as “possible human carcinogens” [96,103]. Both mercuric chloride, a form of inorganic mercury, and methylmercury have been demonstrated to induce renal tumorigenesis in rodents [104,105], though noncancer endpoints of mercury toxicity are considered to be a higher global public health priority by the WHO [84].

Mechanistic studies of mercury-induced toxicity have implicated various mechanisms. Three primary mechanisms of methylmercury neurotoxicity have been described – namely by increasing cellular levels of calcium ions (Ca^{2+}), inducing oxidative stress, and forming complexes with sulfhydryl groups [106,107]. Mercury’s ability to bind thiol-containing compounds is known to affect biological homeostasis via sequestration of the thiol-containing compound glutathione (GSH) [97,107]. As GSH is an endogenous antioxidant and important compound in xenobiotic detoxification pathways, the resulting decreased levels of GSH can lead to a greater level of oxidative stress [97,107]. Additionally, mercury is suspected to increase extracellular glutamate levels [107]. Glutamate is a nonessential amino acid that also functions as an excitatory neurotransmitter of the central nervous system. However, an overabundance of glutamate leads to neurotoxicity via a signaling cascade for Ca^{2+} ions to enter neurons, activating pathways related to cytotoxicity and generating mitochondrial oxidative stress [107]. Comprehensive toxicogenomic approaches have been suggested for studies of the neurotoxicity, immunotoxicity, and potential carcinogenicity of mercury and other heavy metals and are of high priority in order to understand how exposure can lead to adverse health outcomes [108].

Vinyl Chloride: Background

Vinyl chloride, or chloroethene, is a hazardous air and water pollutant [109]. Vinyl chloride does not exist naturally in the environment, but enters the environment either as a by-product from the plastics industry or through bacterial degradation of chlorinated solvents [110]. It was first produced in the United States in the 1920s, though its potential human toxicity was not recognized until the 1970s [9,19]. Despite its classification as a known carcinogen, vinyl chloride continues to be produced in mass quantities today (>10 billion pounds/year) [19]. It is a colorless organic compound that exists as a gas at room temperature, but is usually stored as a liquid under high pressure [110]. The USEPA has set the maximum contaminant limit of vinyl chloride in drinking water at 2 ppb [111], while the Occupational Safety and Health Administration (OSHA) mandates that vinyl chloride levels must not exceed a 1 ppm average over an 8-hour period or a 5 ppm average over any period greater than 15 minutes in occupational settings [110]. The ATSDR ranked vinyl chloride as the fourth highest priority hazardous substance in both 2011 and 2013 [4].

Exposure Sources of Vinyl Chloride

Almost all vinyl chloride is produced to make polyvinyl chloride products including pipes, wires, and packaging materials [109]. While most vinyl chloride evaporates into the atmosphere upon emission into the environment, groundwater surrounding industrial operations, landfills, and other hazardous waste sites has been reported to contain vinyl chloride [109]. Therefore, humans can be exposed to vinyl chloride through inhalation of contaminated air or ingestion of drinking water containing vinyl chloride. Small amounts of vinyl chloride have also been found in both primary and secondhand tobacco smoke [109].

Workers in the plastics industry may have an increased risk of exposure to high levels of vinyl chloride and accompanying health effects [109]. Additionally, although industrial emissions of vinyl chloride into the environment have decreased, individuals in the areas surrounding plastic industrial operations are likely exposed to higher daily average levels of vinyl chloride than the rest of the population [110]. Much of the concern about environmental exposures to vinyl chloride results not only from its demonstrated carcinogenicity at higher levels of exposure, but also from the unknown health effects of chronic, low-dose exposure that is ubiquitous throughout the world [110]. As vinyl chloride continues to be heavily used in the plastic industry, steps should be taken to mitigate the severe health effects that could result from these occupational exposures.

Health Effects of Vinyl Chloride Exposure and Potential Biological Mechanisms

Acute inhalation exposure of very high levels of vinyl chloride (10,000 ppm) can cause dizziness, possible fainting, and even death, in extreme cases [110]. Skin will blister and become numb upon acute dermatological exposure to vinyl chloride. The acute health effects of ingesting vinyl chloride are currently unknown [110].

Vinyl chloride is classified as a “known human carcinogen” by the NTP and the USEPA, and as a Group 1 human carcinogen by the IARC, with known target sites

including the liver, lung, and connective tissues [19,109,112]. The health effects of vinyl chloride exposure through inhalation have been more extensively studied than those of exposure through ingestion [109]. Early toxicity studies revealed that ingestion of vinyl chloride was associated with adverse health effects in rats, including increased mortality, liver angiosarcoma, and necrosis [113–115]. Vinyl chloride is metabolized by the liver whether it is inhaled or ingested [116], and, unsurprisingly, the liver is the principal site of vinyl chloride-induced toxicity [117]. Vinyl chloride exposure is known to increase the risk of angiosarcoma of the liver in humans [118], and there has been some evidence that exposure is also associated with increased cirrhosis and hepatocellular carcinoma, though these reports remain controversial [118–121].

Vinyl chloride is quickly metabolized via oxidation reactions within the body into reactive electrophilic species [122]. Specifically, the chief Phase I oxidation enzyme is CYP2E1 and the main Phase I metabolite is chloroethylene oxide. These reactive metabolites form DNA adducts with cytosine, adenine, and guanine nucleotide bases. An estimated 98% of the total DNA adducts formed by vinyl chloride metabolites are 7-(2-oxoethyl)-guanine, which itself is not a mutagenic adduct. It is the promutagenic etheno(ϵ)-adducts, which constitute the remaining 2% of the DNA adducts formed by vinyl chloride metabolites, that are responsible for vinyl chloride-induced carcinogenicity. These ϵ -adducts have been found to induce base pair substitutions, deletions, and rearrangements in vitro. It is suspected that these coding changes in specific regions of DNA are potential mediators of vinyl chloride carcinogenicity [122]. Supporting this hypothesis, polymorphisms in metabolism and DNA repair genes have been identified in multiple populations occupationally exposed to vinyl chloride [123–125]. Though the mechanism of action of vinyl chloride is well understood [109], assessment and mitigation of exposure to this potent human carcinogen continues to be of high priority in the field of public health [3,4].

Polychlorinated Biphenyls: Background

Polychlorinated biphenyls (PCBs) are organic mixtures of chlorinated compounds that are dangerous air, water, and soil contaminants [126]. There are no natural sources of PCBs, but they have been produced and heavily used in the electric industry in the United States since the 1930s [127]. While PCB production was banned in the United States in 1977, PCBs are extremely stable and thus persist in the environment for a long time [126]. The ATSDR ranked PCBs as the fifth highest priority hazardous substance in both 2011 and 2013 [4].

Exposure Sources of Polychlorinated Biphenyls

Large amounts of PCBs entered the environment during their time of use through spills, leaks, and fires of products containing PCBs [126]. Two particularly deplorable PCB exposure events occurred in the United States in the Hudson River and in the Great

Lakes regions [128,129]. The USEPA reports that from 1947 to 1977, two General Electric capacitor manufacturing factories discharged approximately 1.3 million pounds of PCBs into the Hudson River in New York and New Jersey, polluting an estimated 200 miles of the river [129]. In a similar manner, mills, chemical and paper factories, and city sewage all contributed to high levels of PCBs in multiple areas of the Great Lakes [128]. Ingestion of seafood from both of these bodies of water remains a potential source for PCB exposure today [129,130].

PCBs continue to be released into the environment from incinerators and power plants [126,131]. Once in the environment, PCBs can exist in all three states of matter and have been found in well water [126]. Additionally, fish and other small organisms that live in PCB contaminated water take up PCBs, which are then concentrated up the food chain [19,126]. Consuming such seafood poses a potential risk of high PCB exposure to humans [19,126].

Children may suffer more health impacts from PCB exposure due to their smaller body mass [126]. In addition, PCBs can pass the blood–brain barrier, and their potential neurotoxicity in children is of great concern [126]. Similarly, PCBs can cross the placental and lactational barriers, and reviews of prenatal exposures to PCBs have been associated with impeded psychomotor development, adverse effects on immune and respiratory system development, and low birth weight [126,132–135]. Although PCBs are no longer produced in the United States, occupational exposure to PCBs through the repair, maintenance, and disposal of PCB-containing transformers and capacitors persists as a public health concern. Furthermore, they continue to endure in the environment and pose a threat to human health through oral, dermal, and inhalation exposures [126].

Health Effects of Polychlorinated Biphenyl Exposure and Potential Biological Mechanisms

Acute health effects of exposure to high concentrations of PCBs include chloracne and other skin lesions, nose, lung, and gastrointestinal tract irritation, and fatigue [126]. However, such health effects have only been documented as results of concentrated occupational exposures. Of greater concern are the human health effects of the low-level, long-term exposure of the general population to PCBs [126]. Chronic PCB exposure has been associated with adverse noncancerous health outcomes, such as immune and endocrine dysregulation [136–139].

In addition, PCBs were reclassified by the IARC from Group 2A human carcinogens to Group 1 human carcinogens in 2013 [140], but remain listed only as “probable human carcinogens” by the NTP and the USEPA [19,141]. Various cancers have been associated with PCB exposure, including those of the kidney, liver, pancreas, brain, and skin [136,142–144].

At a mechanistic level, there is evidence that PCBs induce genomic damage via numerous processes, including direct and indirect genotoxic effects [140,145]. Specifically, PCBs are known to be oxidized by cytochrome P450 enzymes to electrophilic

reactive metabolites, which can then form adducts with DNA, induce telomere shortening, or increase oxidative stress within the cell. These DNA adducts can then result in gene mutations and chromosomal breaks and losses [145]. These types of exposure-induced effects may lead to downstream health consequences, including carcinogenesis [140]. Studying the mechanisms by which PCBs enact their numerous harmful health effects is of critical importance, as these persistent organic pollutants will likely remain a widespread environmental contaminant for years to come [126].

Benzene: Background

Benzene is one of the most common organic compounds and an air pollutant of concern [19,146,147]. It is extremely stable due to its aromatic structure, is only slightly soluble in water, and is highly flammable. At room temperature, benzene is a clear, colorless liquid with a slightly sweet odor. There are both biogenic and industrial sources of benzene, although the quantity of benzene produced from industry far exceeds that of benzene produced naturally. Benzene has been made in the United States since 1849 and is primarily used in gasoline and the chemical and pharmaceutical industries [19,146,147]. Benzene has a relatively short half-life in air, persisting only a few days before being broken down [146,147]. Benzene was ranked by the ATSDR as the sixth highest priority hazardous substance in both 2011 and 2013 [4].

Exposure Sources of Benzene

Humans are chronically exposed to low levels of benzene within the atmospheric environment [19,146,147]. Natural sources of benzene include forest fires and oil seeps, while anthropogenic sources include various industrial operations, automobile exhaust, and tobacco smoke [19,146,147]. The ATSDR estimated that cigarette smoke constitutes approximately half of the United States' exposure to benzene [146]. Ambient outdoor air concentrations of benzene in the United States are reported to range from approximately 0.02–112 ppb, where higher levels of benzene are commonly present in urban environments [19,146,147]. The difference in benzene levels between rural and urban areas is thought to reflect the greater amount of automobile emissions in cities in comparison to those in the country. Oral exposure to benzene can occur through ingestion of contaminated food and drinking water, though inhalation is the primary route of exposure for benzene [19,146,147].

Occupational exposure to benzene can occur in a variety of industries, including the chemical, pharmaceutical, textile, and oil industries [146,147]. The National Occupational Exposure Survey estimated that almost 300,000 workers were exposed to benzene occupationally in the United States between 1981 and 1983 [148]. In 2003, van Wijngaarden and Stewart found that levels of occupational exposure to benzene averaged 0.33 ppm [149]. Although this average exposure was well below the 1 ppm limit for an 8-h workday in a 40-h workweek instituted by OSHA

[19,147,149], chronic exposure to low levels of benzene is still concerning to public health [146].

Occupational exposure and cigarette smoking both present greater risks of exposure to high concentrations of benzene [146]. Benzene exposure is also suspected to pose greater health risks to pregnant women. Benzene can cross the placental barrier, though it is not known what specific effects benzene may have on the developing fetus [146]. A limited number of animal studies demonstrate an association between benzene inhalation during pregnancy and low birth weight, delayed bone formation, and bone marrow damage [150–153].

Occupations that threaten to expose workers to high levels of benzene include taxi or bus driving and employment at gas stations, as well as working in the chemical, pharmaceutical, and oil refining industries [136,137]. Benzene remains a public health concern, as it is consistently released into the atmosphere at low concentrations [146]. While benzene is known to be severely harmful to human health at higher concentrations, the undetermined specific health effects of chronic low-dose exposures continue to be high-priority issues for human health worldwide [19,146,147].

Health Effects of Benzene Exposure and Potential Biological Mechanisms

Acute inhalation exposure to very high concentrations of benzene (>10,000 ppm) can lead to death [146]. At lower levels (700–3000 ppm), benzene exposure can result in eye irritation, confusion, tachycardia, headaches, drowsiness, dizziness, and fainting [146]. These health effects related to acute benzene exposure subside after exposure ceases. Vomiting, gastrointestinal irritation, tachycardia, coma, drowsiness, and death can all be effects of acute or long-term oral exposure to high levels of benzene. Dermal exposure to benzene has been reported to cause red sores [146].

Chronic exposure to benzene has been associated with adverse health effects on the hematopoietic, immune, and reproductive systems [146]. Most notably, benzene is classified as a “known human carcinogen” by the NTP and the USEPA, and as a Group 1 human carcinogen by the IARC [19,137,146]. The association between benzene exposure and leukemia, specifically acute myelogenous leukemia, is well established [137,154,155]. Other types of other lymphatic and hematopoietic cancers among benzene-exposed populations have also been reported [147,156–159]. A dose–response relationship between benzene and leukemia was established by an extensive meta-analysis of 32 benzene exposure epidemiological studies by Savitz and Andrews in 1997 [160]. Additionally, exposure to benzene has been associated with anemia and some adverse effects on female reproductive organs including irregular menstruation and decreased ovary size [146].

Benzene is suspected to induce leukemia and cancers of the lymphatic system via two distinct mechanisms [147]. Particular to benzene’s mode of action as a leukomogen, benzene has been found to induce DNA damage in bone marrow [161]. However, the

mechanism of benzene-associated lymphatic carcinogenesis is less clear, as benzene has been found to disrupt many biological functions, including circulating levels of immune cells and cellular apoptosis and proliferation [162,163].

Cadmium: Background

Cadmium is a naturally occurring, odorless metal, but is only found in complexes with various other elements in nature [19,164]. Pure cadmium, which exists as either soft, silver-white metal or light gray powder, is only produced commercially [19,164]. Pure cadmium is characterized by certain physical properties that make it very useful in industrial settings, namely malleability, corrosion resistance, a low melting point, and higher electrical and thermal conductivity [165]. Cadmium is also produced commercially in a broad range of compounds that have varying physical properties, but tend to be fairly reactive [19]. Natural cadmium is most often found as cadmium sulfide in zinc ore [19]. Cadmium has an oxidation state of +2 and is insoluble in water [19]. The ATSDR ranked cadmium as the seventh highest priority hazardous substance in both 2011 and 2013 [4].

Exposure Sources of Cadmium

Cadmium and cadmium compounds have been used in various commercial and industrial applications since the early 1900s [19,164,165]. Today, cadmium is primarily used in batteries, though other cadmium-containing products include pigments, electroplates and coatings, and plastic stabilizers. However, humans are primarily exposed to cadmium through food and cigarette smoke [19,164,165]. The ATSDR estimates that smoking cigarettes approximately doubles one's body burden of cadmium [164]. The ATSDR further notes that smoking one pack of cigarettes per day leads to the absorption of 1–3 µg of cadmium per day [164], while the NTP reports that smokers are exposed to an average of 1.7 µg of cadmium per cigarette [11]. Food can also contribute substantially to the body burden of cadmium. Legumes, green, leafy vegetables, potatoes, and grains are foods that contain the highest amounts of cadmium, and the estimated daily intake of cadmium from food for a United States adult ranges from 18.9 to 30 µg/day [19,165].

In the early 1900s, a massive outbreak of cadmium poisoning occurred in the Jinzu River region of Japan due to contamination of rice paddies via contaminated irrigation waters [166]. The suspected source of the cadmium was a zinc mine upstream on the Jinzu River. Residents in the area began to develop symptoms of intense bone pain, bone softening, and renal tubular failure that were summed into a diagnosis of “Itai–Itai disease,” or “Ouch–ouch disease,” when translated from Japanese [166]. Less than 200 deaths resulting directly from cases of Itai–Itai disease were documented [167], but subsequent studies of populations in affected areas revealed thousands of victims of higher cadmium body burdens, and increased rates of mortality and renal disease/dysfunction were found in affected areas [168–170].

Workers in industries that use or produce cadmium and cadmium compounds, such as the battery, pigment, plastics, construction, and electroplating industries are at risk for increased cadmium exposure [19,164,165]. The OSHA mandates that the levels of cadmium in workplace air not exceed an average of 5 ppm over an 8-h workday [164]. The workers who are at greatest risk for cadmium exposure are those whose jobs involve the heating of cadmium and cadmium compounds, as these substances release harmful vapors when their temperature is increased [11,122]. The National Occupational Exposure Survey reported that workers in the United States were occupationally exposed to 19 different cadmium compounds and isotopes between 1981 and 1983 [148]. The cadmium compounds that posed a risk to the greatest number of workers from 1981 to 1983 were cadmium sulfide, cadmium mercury sulfide, cadmium selenide, cadmium selenide sulfide, and cadmium oxide [148]. Estimates of total workers exposed to cadmium and cadmium compounds at any level range from 150,000 to greater than 500,000 [11,164].

Cadmium is known to be able to cross the placental barrier [171], and is known to have teratogenic effects [172]. Although cadmium cannot cross the blood–brain barrier in mature adults, it is suspected that a fetus' or neonates' immature central nervous system may be susceptible to neurotoxic effects of cadmium via prenatal or early life exposure [171]. Additionally, neonates can be further exposed to cadmium through lactation [164]. There is some evidence that children absorb more cadmium than adults, so infants and youth may also constitute at-risk populations of cadmium-induced health effects [164].

Health Effects of Cadmium Exposure and Potential Biological Mechanisms

Chronic exposure to cadmium is a more pressing and relevant public health concern than short-term exposures, though such acute exposures do occur [164]. Oral exposure to cadmium in humans is more common than inhalation exposure [19,164,165]. Acute inhalation exposure leads to lung and nasal cavity damage, while acute oral exposure to cadmium results in stomach irritation, vomiting, and diarrhea [164]. In severe cases of either route of exposure, death can occur [164].

Cadmium has an extremely long half-life in human body tissue, with estimates typically ranging between 10 and 30 years [164,171,173,174]. Cadmium is a systemic toxicant in the human body, though its primary target site is the kidney [164,173,174]. Long-term exposure to cadmium can lead to accumulation of cadmium in the kidney [175]. Specifically, cadmium targets the proximal tubules in the kidney, which can result in kidney disease [175,176]. Other toxic effects of cadmium include neurotoxicity, carcinogenicity, teratogenicity, decreased bone health, and endocrine and reproductive system disruption [173,177]. Additionally, there is an established association between cadmium exposure and cardiovascular disease [178].

Although cadmium is known to target the kidneys, reviews have highlighted nonrenal health effects of cadmium exposure. For instance, low-level cadmium exposures have

been associated with decreased bone mineral density and increased risk of osteoporotic fractures [174], and other research has found an association between cadmium exposure and osteoporosis occurrence in a review of seven articles [179]. A meta-analysis found that cadmium has toxic effects on both the central and peripheral nervous systems, and that the olfactory neuron is a primary target for cadmium. Neurological health effects associated with cadmium exposure include learning disabilities, behavioral disorders, decreased attention and memory, brain atrophy, and Parkinsonism [171]. Cadmium has also been demonstrated to have adverse health outcomes on paternal, maternal, and embryonic health, including sperm maturation disruption, suppressed oocyte maturation, implantation failure, and higher risks of birth defects [172]. Evidence also suggests a relationship between cadmium exposure and preeclampsia [180,181].

Cadmium and cadmium compounds are classified as “known human carcinogens” by the NTP, as Group 1 human carcinogens by the IARC, but only as “probable human carcinogens” by the USEPA [19,165,182]. Cadmium exposure has been associated with multiple cancer target tissue sites including the lung, prostate, pancreas, kidney, urinary bladder, and breast tissue [165].

Several mechanisms of cadmium-induced disease have been investigated. For both cancer and noncancer endpoints, cadmium is suspected to generate oxidative stress via induction of reactive oxygen species, and to disrupt apoptotic pathways and cellular tight junctions [173,175,176,183]. Mechanisms of action of cadmium-induced carcinogenesis also include altered gene expression, inhibition of DNA repair, altered DNA methylation, endocrine disruption, and cellular proliferation, but cadmium does not directly damage DNA [184,185]. The family of the metallothionein (MT) genes expresses proteins that are known to have roles in binding and sequestering cadmium in the body [171,184,186]. Specifically, increases in expression of MT genes have consistently been found to be associated with cadmium exposure, and are speculated to be a protective mechanism of cadmium-induced carcinogenesis and toxicity [171,184]. In addition, systems biology approaches to investigating cadmium toxicity have revealed the possible importance of epigenetics in the mechanism of cadmium toxicity [187]. Changes in DNA methylation, histone modification, and miRNA expression have all been associated with cadmium exposure [187].

Four out of the top 10 toxic substances of the ATSDR Substance Priority List are metals [4]. An additional manner by which these metals continue to threaten human health around the globe is their capacity for molecular and ionic mimicry of essential metals [188,189]. Toxic metals often follow the same metabolic pathways and transport pathways for cellular entry as essential metals, such as copper (Cu), iron (Fe), calcium (Ca), and zinc (Zn) [188,189]. Cadmium is a particularly relevant example of this mechanism of metal toxicity [190]. As described previously cadmium is essentially an “opportunistic evil twin of other divalent essential metals such as Ca^{2+} , Fe^{2+} , and Zn^{2+} ” [190]. Recognition of the ability of toxic metals to mimic essential metals is crucial not only

in understanding the mechanisms by which these toxicants act [189], but also in designing therapies to mitigate or prevent their effects, as therapies designed to target toxic metals, such as chelators, can have harmful side effects as a result of also affecting metabolism and uptake of essential metals [191].

Polycyclic Aromatic Hydrocarbons: Background

The ATSDR eighth, ninth, and tenth top priority substances on both the 2011 and 2013 hazardous substance priority lists were benzo[a]pyrene (B[a]P), polycyclic aromatic hydrocarbons (PAHs), and benzo[b]fluoranthene (B[b]F), respectively [4]. Organic chemical compounds consisting of two or more aromatic fused rings are considered to be polycyclic aromatic hydrocarbons [19,192,193]. Both B[a]P and B[b]F consist of five fused aromatic rings, and are, therefore, considered to be PAHs [19]. Therefore, these compounds will be discussed under the broader term of PAHs.

PAHs are slightly water- and ethanol-soluble, and most are soluble in benzene [19]. They are lipophilic, which enables them to cross biological membranes with relative ease [192]. Some PAHs have heteroatoms, such as nitrogen or sulfur, contained in their rings [19]. PAHs exist at room temperature as plate, needle, prism, or crystal solids. PAHs can be colorless or orange, yellow, green, or blue, and most are fluorescent. Specifically, B[a]P exists as pale yellow needles at room temperature, while B[b]F consists of colorless needles [19].

The physical state in which a PAH is present in the environment is largely dependent on its various physical properties [192,193]. For example, lower molecular weight PAHs, often classified as those compounds with fewer than four rings, are more volatile and thus exist mainly in the gas phase. Higher weight PAHs are usually found in complexes with air particulate matter and are also less soluble in water, as each additional aromatic ring decreases solubility in water [192,193].

Exposure Sources of Polycyclic Aromatic Hydrocarbons

All humans are exposed to a baseline level of PAHs via inhalation, oral, and dermal routes [19,192,193]. While pure PAHs are not produced in the United States, PAHs are ingredients in coal tar, creosote, bitumens, asphalt, and mineral oils—various products used in construction and paving. Biogenic sources of PAHs include forest fires and volcanic eruptions. However, most PAHs enter the environment through anthropogenic means; specifically, incomplete combustion of fossil fuels [19,192,193]. Mean ambient air concentrations of singular PAHs range from 1 to 30 ppb in urban settings [194], but those that are used in residential heating units show wide season variation and are considerably higher in the winter months when heating units are run consistently [19,192].

For the general population, major sources of PAH exposure are tobacco smoke and food, though PAHs are also found at low concentrations in water [19,193]. The NTP states that PAHs in cigarette smoke total 1–1.6 µg/cigarette [19]. PAHs can accumulate in the soil and

contaminate food, though PAHs do not tend to bioaccumulate in the food chain [19]. However, PAHs are often generated on the surface of grilled or barbecued meat, so both plant matter and meat present exposure sources to PAHs [192,193]. Dermal contact with PAH-contaminated soil or use of pharmaceutical products containing coal tar also represent potential exposure routes of PAHs [192,193]. PAHs are also known to be able to cross the placental membrane, making prenatal exposure to PAHs an additional public health concern [192].

Workers in the coal melting, combustion, and coal product combustion industries can be exposed to high levels of PAHs through inhalation or dermal contact [19,192,193]. The OSHA set the permissible exposure limit for carbon black, a substance produced in the partial combustion of hydrocarbons, and thus the compound used to assess general PAH exposure, at 3.5 mg/m³ per 8-h workday [195]. The NIOSH expanded this mandate to a recommended exposure limit for carbon black for a 10-h workday during a 40-h workweek of 0.1 mg PAHs/m³ [195]. The number of workers exposed to PAHs was not estimated in the 1981 to 1983 National Occupational Exposure Survey [148]. While exposure to B[b]F was not assessed, the survey reported only 896 United States workers were estimated to be exposed to B[a]P [148].

Health Effects of Polycyclic Aromatic Hydrocarbon Exposure and Potential Biological Mechanisms

Although the long-term health effects of exposure to low levels of PAHs in ambient air are a greater public health concern, concentrated exposure to certain PAHs or mixtures of PAHs can result in lung, skin, and eye irritation, difficulty with breathing, nausea, vomiting, diarrhea, and, in extreme cases, death [192,193,196]. In cases of sustained exposure to PAHs, noncancer health outcomes include immunosuppression, teratogenicity, cytotoxicity, and genotoxicity [192,193].

National registries such as the NTP, the IARC, and the USEPA classify PAHs individually in terms of their carcinogenicity to humans. The NTP lists 15 individual PAHs that are “reasonably anticipated to be human carcinogens,” including B[a]P and B[b]F. The IARC classifies B[a]P as a Group 1 human carcinogen, while the USEPA ranks it as a “probable human carcinogen” [193,197]. Likewise, the IARC classifies B[b]F as a Group 2B human carcinogen, and the USEPA ranks it as a “probable human carcinogen” [193,198]. Carcinogenicity of PAHs has been suggested to increase with increasing molecular weight [192,193]. Cancer target sites of PAHs include the skin, lungs, bladder, and gastrointestinal tract, and often the site of cancer development is correlated with the route of exposure [192].

It is known that many PAHs are metabolized to become reactive species that then can bind with DNA to generate DNA adducts, induce DNA damage, or cause mutations [192,193,199]. The bioaccessibility of PAHs—which itself varies widely and is dependent on numerous factors, including PAH molecular weight, mode of entry to the body, body fat composition, fast or fed condition, and gut microflora population—also plays an important role in PAH-induced toxicity and carcinogenesis [200]. In the interest

of investigating the downstream effects of PAH entry to the body and genotoxic effects, Verma et al. reviewed the existing proteomic data of B[a]P toxicity [201]. This study highlighted the importance of a systems biology approach to studying toxicological mechanisms, as it enables researchers to understand how epigenomic, genomic, and metabolic changes translate to differences in activity at the protein level [201]. PAHs remain an urgent area of environmental health research not only because of widespread exposure, but also due to systemic detrimental health effects [192].

CARCINOGENIC, ORGANIC HAZARDOUS AIR POLLUTANTS

1,3-Butadiene: Background

1,3-Butadiene is an alkene with the chemical formula C_4H_6 [19,202,203]. It is insoluble in water, and exists as a colorless gas at room temperature with a gasoline-like odor [19,104,105]. 1,3-Butadiene has been emitted as an industry-related air pollutant in the United States since the 1930s as a by-product of ethylene manufacture [19,104]. It is used in the synthesis of many polymers and chemicals and is most commonly used during the production of synthetic rubber [19,202,203]. Furthermore, 1,3-Butadiene has been classified as a “known human carcinogen” by the NTP and the USEPA, and as a Group 1 human carcinogen by the IARC [19,203,204].

Exposure Sources of 1,3-Butadiene

Low levels of 1,3-butadiene are present in urban atmospheres [205], as it is emitted into the environment from industrial applications [202]. In addition, 1,3-butadiene is present in cigarette smoke and automobile gasoline and exhaust [19,202,203]. According to the ATSDR Toxicological Profile for 1,3-butadiene, the mean concentration of 1,3-butadiene in outdoor air can range from 0.04–0.09 ppb in urban settings [202]. The OSHA mandates that levels of 1,3-butadiene not exceed an average of 1 ppm over an 8-h workday [19,202]. The primary biogenic source of 1,3-butadiene is forest fires [202].

Only limited animal studies have indicated that 1,3-butadiene has adverse effects on the developing fetus, including low birth weight and skeletal defects [202,203,206]. It is also unknown whether children are more sensitive to potential health effects induced by exposure to 1,3-butadiene [202]. Workers in the polymer industry, forest firefighters, and smokers may be at higher risk for exposure to 1,3-butadiene [202,203]. The 1981 to 1983 National Occupational Exposure Survey estimated that 52,000 people were exposed to 1,3-butadiene in the occupational setting [148].

Health Effects of 1,3-Butadiene Exposure and Potential Biological Mechanisms

There are limited human studies investigating noncancerous health effects of 1,3-butadiene [202]. Acute and chronic exposure to 1,3-butadiene has been associated with irritation

and inflammation of respiratory tissue in humans and rodents. Some rodent studies have shown that very high levels of 1,3-butadiene (>1000 ppm) can cause other health effects, including increased intrauterine death, decreased fetal growth, anemia, and increased mortality. However, it is important to note that such high exposures do not represent environmentally relevant conditions, as the highest reported 1,3-butadiene emission from a polymer plant was under 500 ppm [202].

Numerous epidemiological studies have established 1,3-butadiene as a human carcinogen with primary target sites of the blood and the lymphatic system [19,202–204]. A dose–response relationship between 1,3-butadiene exposure and increased rates of leukemia has been observed among a population of employees of the synthetic rubber industry [207]. Notably, this study used an exposure-monitoring program to correlate 1,3-butadiene exposure levels with specific jobs within the manufacturing plant itself and found that workers with tasks that exposed them to higher levels of 1,3-butadiene had a significantly increased occurrence of leukemia [207–210].

Like many environmental contaminants, the speculated mechanism of 1,3-butadiene carcinogenesis involves its metabolism to epoxide species [202–204]. These toxic metabolites then can induce point mutations, other DNA damage, or micronucleus formation [211]. This damage and mutagenicity is thought to culminate in the silencing of tumor suppressor genes and activation of oncogenes, thus leading to cancer [212,213]. Loh et al. identified 1,3-butadiene as an organic air pollutant of top concern in the United States due to its high exposure risk and carcinogenic properties [6].

Formaldehyde: Background

Formaldehyde is a simple aldehyde with the chemical formula CH_2O [19,214,215]. It exists as a colorless, flammable gas at room temperature, and, at high levels, formaldehyde can be recognized by an acrid odor [19,214,216]. Formaldehyde is soluble in water and has a half-life of a maximum of seven days in surface water and 14 days in groundwater [216]. Therefore, formaldehyde does not bioaccumulate to large amounts in water sources [216]. Similarly, the half-life of formaldehyde in air is estimated between 7 h and 3 days, though it varies widely depending on sunlight, temperature, and other environmental conditions [216]. Formaldehyde enters the environment through both biogenic and anthropogenic sources and is commonly present throughout indoor and outdoor atmospheres [19,214,215]. Formaldehyde has been associated with many adverse health effects in humans and is classified as a “known human carcinogen” by the NTP and as a Group 1 human carcinogen by the IARC [19,215].

Exposure Sources of Formaldehyde

The general population is potentially exposed to formaldehyde through air, food, and water, though the most common exposure route is inhalation [19,214,215]. Formaldehyde enters the air through emissions from industrial and automobile combustion sources. Individuals are

also exposed to formaldehyde by means of many commercial products, including cigarettes, wood and paper products, cosmetics, household cleaning products, paint, and furniture. Formaldehyde is even formed endogenously in mammals via oxidative metabolism [11,117,215]. Ambient outdoor air usually contains less than 10 ppb formaldehyde [215], though indoor levels of formaldehyde tend to be greater, resulting in an estimated range of 0.5–2.0 mg of formaldehyde exposure daily [19]. The OSHA's maximum limit for formaldehyde in the workplace is 0.75 ppm for an 8-h workday in a 40-h workweek, and toxic acute exposure can occur when formaldehyde air concentrations reach 20 ppm [19,214].

Embalmers, paper workers, and pathologists face a higher risk of occupational formaldehyde exposure due to the presence of formaldehyde in the reagents with which they work [19,214,215]. It is unknown whether formaldehyde has a greater effect on children compared with adults [214]; however, childhood asthma has been associated with chronic formaldehyde inhalation exposure [217]. The health effects of chronic exposure to formaldehyde and its potential mechanism of carcinogenesis at sites distal to exposure contact sites are currently topics on the leading edge of environmental health research [218–220]. In fact, the Integrated Risk Information System report for formaldehyde is currently under review at the USEPA [221].

Health Effects of Formaldehyde Exposure and Potential Biological Mechanisms

Acute exposure to formaldehyde has been associated with respiratory tract inflammation and irritation of the eyes and skin [214]. The effects of long-term formaldehyde exposure at levels commonly found in the environment are also of great concern in the field of environmental public health. Chronic exposure to formaldehyde through inhalation has been associated with increased risk of childhood asthma [217], upper respiratory tract inflammation [222], nasopharyngeal cancer [223], and possibly leukemia [224].

The classification of formaldehyde as a leukemogen is controversial, as inhaled formaldehyde does not reach the circulating blood or sites distal to the respiratory tract [218,225,226]. Furthermore, many toxicological findings do not provide *in vivo* evidence supporting potential mechanisms underlying formaldehyde-induced leukemogenesis [219,227–229]. It is, therefore, important to increase the understanding of formaldehyde-associated health effects and mechanisms of action linking formaldehyde exposure to disease.

Many molecular events have been shown to associate formaldehyde inhalation exposure and nasopharyngeal carcinogenesis [215]. Specifically, toxicological studies have shown clear associations between formaldehyde exposure and tissue damage [230,231], increases in cell proliferation [230,231], DNA damage [219,227], inflammation [232], changes in microRNA expression patterns [220], and changes in mRNA expression patterns [220,232] in proximal target regions of exposure. These effects may mechanistically link formaldehyde inhalation exposure to effects in the respiratory tract, including

upper respiratory tract inflammation/irritation and nasopharyngeal carcinoma [215]. Particularly when considering the high occurrence of human exposure, formaldehyde continues to be one of the highest prioritized environmental air pollutants [6,19,215].

Dioxins: Background

Dioxins are a family of compounds encompassing seven polychlorinated dibenzo dioxins (PCDD), 10 polychlorinated dibenzo furans (PCDFs), and 12 PCBs [233]. Dioxins affect harm through similar biological pathways and share common structures. Most dioxins are lipophilic and tend to bioaccumulate and thus persist in the environment and the human body for long periods of time [19,234,235]. The PCDD 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) is a particularly toxic tetra-chlorinated dibenzo dioxin on which much toxicological research has been conducted, though it is expected that exposure to 2,3,7,8-TCDD accounts for only 10% of total risk exposure to dioxins [233].

Exposure Sources of Dioxins

Dioxins are released into the environment by many industries, including the paper, chemical, and agricultural industries, and the primary sources of environmental dioxin are combustion and incineration processes [19,234,235]. Almost all humans are regularly exposed to low-levels of dioxins through inhalation, ingestion, or dermal contact. Ingestion of food containing dioxins accounts for 90% of the daily exposure to dioxin for the average population. Meat, dairy products, and fish contain particularly high levels of dioxins, as dioxins bioaccumulate up the food chain. Likewise, dioxins amass in the human body in the liver and fat tissue, extending the effects of exposure [19,234,235]. Therefore, the classification of dioxins as high priority air pollutants may seem misleading, but massive historical exposures to dioxins that have continuing effects today occurred primarily through inhalation [19,234].

Although dioxins were used as an ingredient in several herbicides in the United States in the 1960 and 1970s, 2,3,7,8-TCDD is infamously known as a component of the infamous herbicide, Agent Orange [19,234,235]. Agent Orange was sprayed over huge stretches of the Vietnamese countryside by the United States in the Vietnam War as part of Operation Ranch Hand in order to defoliate the landscape on which the Viet Cong relied for guerilla warfare tactics and to decrease the Vietnamese food supply [236]. Veterans of the United States Air Force who sprayed Agent Orange had 2,3,7,8-TCDD levels up to 55 parts per trillion (ppt) in their adipose tissue several years after the end of the Vietnam War, in contrast to average levels of 6–10 ppt in the average United States population [237,238]. Likewise, 2,3,7,8-TCDD levels of individuals living in the southern part of Vietnam, where 2,3,7,8-TCDD was most heavily used, averaged 28 ppt in a study conducted more than 10 years after exposure to Agent Orange [239].

There have been three other chemical disasters leading to extremely high exposures to dioxins among human populations—two of which occurred in the United States. In

the Love Canal neighborhood in Niagara Falls, New York, 21,000 tons of toxic waste, including large amounts of dioxins, were deposited by Hooker Chemical Research Company in the 1940 and 1950s [240]. In Times Beach, Missouri, oil containing dioxins was sprayed on all the roads in the town from 1972 to 1976 to prevent dust rising from the road [241]. Levels of dioxins in the soil of these two sites were found to range up to 672 ppm and 1200 ppb, respectively, in studies conducted in the 1980s [242,243]. The third chemical disaster involving dioxins occurred in 1976 in Seveso, Italy, a small town north of Milan. Approximately 45,000 people were acutely exposed to high concentrations of 2,3,7,8-TCDD when a chemical reactor released a cloud of at least 1.2 kg of 2,3,7,8-TCDD into the air [244,245]. Levels of 2,3,7,8-TCDD as high as 20,000 ppm in the soil surrounding the reaction site were documented [246]. For comparison, the CDC's level of concern for 2,3,7,8-TCDD in residential soil is 1 ppb [234]. Adverse health effects resulting from these mass exposures were observed in all three sites [247–250].

There is evidence that dioxins are endocrine disruptors and teratogens, and thus exposure to dioxins poses a health threat to potential fathers, pregnant women, and the developing fetus [251]. It is currently unknown if children are more susceptible to induced health effects from dioxins [234]. Individuals with increased risk for high-level exposure to dioxins include those who eat large amounts of meat, seafood, and dairy products [19,234,235]. Employees of the waste incineration, paper and pulp, and chemical production industries are at risk of occupational exposure to dioxins [19,234,235]. Historically, dioxins have caused extensive harm to global human health, and these contaminants continue to threaten millions of people worldwide through their persistence in the environment [19,235].

Health Effects of Dioxin Exposure and Potential Biological Mechanisms

Many detrimental health effects have been observed in the individuals exposed to dioxins in Vietnam, the Love Canal, Times Beach, and Seveso [247–250,252,253]. Chloracne is the most typical immediate side effect of exposure to dioxins, though other dermal disfigurements such as rashes, changes in pigmentation, and growth of excess body hair have been reported to occur [234].

It is of great concern that the half-lives of dioxins in the human body tend to be long with many compounds persisting in the body for over 5 years and some ranging up to 22 years [254]. Specifically, the half life of 2,3,7,8-TCDD is estimated to be 7.2 years [255]. Extended exposure to dioxins has been associated with immune system disruption [244,256], and reproductive and carcinogenic adverse health effects [251,257]. Altered sperm count and motility and increased rates of birth defects, miscarriages, and preterm births have all been related to exposure to dioxins [249,252,258,259]. Additionally, 2,3,7,8-TCDD is recognized as a “known human carcinogen” by the NTP and IARC, while the USEPA has yet to release their latest cancer assessment for 2,3,7,8-TCDD

[19,235,260]. The USEPA has previously characterized the entire family of dioxin compounds as “likely human carcinogens” [233]. A long-term study of inhabitants exposed to dioxins in Seveso, Italy, found a 1.3 rate ratio of overall deaths from any cancer [247]. The IARC reported a similar relative risk of mortality from all cancers in dioxin-exposed populations of 1.4 from a metaanalysis of cohort studies [235]. However, many studies have demonstrated greater mortality rates from cancers of the rectum, lung, and prostate, in addition to soft tissue sarcomas and nonHodgkin lymphomas [247,261–263]. Furthermore, a dose–response relationship of dioxin exposure and overall cancer mortality was found in an occupationally exposed cohort in Germany [262].

Extensive research has suggested that the mechanism of toxicity and carcinogenicity of dioxins primarily involves the transcription factor family of aryl hydrocarbon receptors (AhRs) [256,264]. In general, it is thought that dioxins bind to AhRs in the cytoplasm and induce a signaling cascade which results in altered gene transcription in the nucleus [264]. Downstream targets of this signaling cascade are numerous and include cellular functions of apoptosis, cell growth, cell cycle progression, hormone response, and intracellular signaling [264]. Chopra and Schrenk highlighted the ability of dioxins, particularly 2,3,7,8-TCDD, to inhibit and promote apoptotic signaling within various cell types, contributing various adverse health effects [256]. However, the mechanism of action of dioxins is not yet fully understood, as AhR activation does not fully account for the toxicity of dioxins [265]. Elucidation of this mechanism at a systems biology level could identify new biomarkers of dioxin exposure for clinical use and valuable insight into how to mediate dioxin toxicity [265].

Chloroform: Background

Chloroform is a trichlorinated organic substance with the chemical formula of CHCl_3 [19,266,267]. It is a clear liquid at room temperature and has a pleasant, sweet odor. Chloroform is only slightly soluble in water and evaporates quickly into surrounding air, increasing the risk of inhalation exposure [19,266,267]. In addition, chloroform persists for a long time in both water and air [266]. There are no natural sources of chloroform, but this contaminant enters the environment through a variety of industrial operations, including the chlorination of water [19,266,267]. Humans can be exposed to chloroform through inhalation, ingestion, and dermal contact [19,266,267].

Exposure Sources of Chloroform

Humans are potentially exposed to low levels of chloroform daily through drinking water and contaminated air [19,266,267]. The USEPA mandates that drinking water concentrations of chloroform do not exceed 100 $\mu\text{g/L}$, and the WHO recommends a maximum limit of 200 $\mu\text{g/L}$ of chloroform in drinking water [140,141]. However, the ATSDR estimates that drinking water, with the exception of water located near hazardous waste sites, does not usually exceed 44 $\mu\text{g/L}$ in the United States [266].

Similarly, OSHA set a maximum limit of chloroform in workplace air for an 8-h day at 50 ppm, while ambient air concentrations typically do not exceed 1 ppm [266].

Chloroform was first produced in the United States in 1903, and exports of chloroform continue to number in the millions of pounds [19,266,267]. Until 2010, chloroform was primarily made during the production of the refrigerant, chlorodifluoromethane [19,266]. Presently, the most common exposure source of chloroform is chlorinated water, both treated drinking water and chlorinated swimming pools [19,266,267].

People at the highest risk for chloroform exposure include employees of swimming pools, water treatment plants, pulp and paper factories, and sites of chemical production of chloroform [266]. According to the 1981 to 1983 National Occupational Exposure Survey, approximately 96,000 workers in the United States could have been exposed to chloroform in this time frame [148]. It is of great concern that humans are consistently exposed to low levels of chloroform, especially as limited epidemiological data exist on the chronic health effects of this persistent environmental contaminant [266].

Health Effects of Chloroform Exposure and Potential Biological Mechanisms

Acute health effects of chloroform exposure include dizziness, fatigue, headaches, liver damage, and, at extreme concentrations, death [266,267]. Chronic exposure to chloroform has been associated with renal and hepatic system damage, in addition to adverse reproductive outcomes. Animal studies demonstrating similar adverse effects have also contributed to the understanding of the health effects associated with long-term exposure to chloroform [266,267].

Additionally, chloroform is classified as “reasonably anticipated to be a human carcinogen” by the NTP, as Group 2B human carcinogens by the IARC, and as “likely to be carcinogenic to humans by all routes of exposure,” but only “under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues,” by the USEPA [19,267,268]. Evidence establishing the carcinogenicity of chloroform in humans is limited. The available studies most strongly support an association between chloroform exposure and urinary bladder cancer [269–272]. However, kidney and liver cancer rates have consistently been found to be elevated in mice and rats chronically exposed to chloroform [266,267].

The mechanism of action of chloroform toxicity begins with its metabolism by the cytochrome P450 isoform, CYP2E1, found in the kidney and liver [273]. Its major metabolite, phosgene, is a very reactive cytotoxicant and induces cell damage and death of the surrounding hepatocytes and renal cells. Cellular repair and proliferation in response to phosgene toxicity increases the likelihood of mutations of protooncogenes to oncogenes, contributing to unregulated cell growth [273]. Chloroform is only one of many drinking water disinfection byproducts, and this broad class of environmental contaminants recently has been emphasized as pollutants of growing public health concern [274–277].

ENVIRONMENTAL CONTAMINANTS OF EMERGING CONCERN

One of the great challenges in the field of environmental public health is identifying which contaminants to prioritize for regulation and research. Reviews of water contaminants have identified multiple new contaminants of concern [277–279]. Descriptions of three of these emerging contaminants as contaminants of concern at Superfund hazardous waste sites are included.

However, other environmental toxicants have been identified in multiple reviews as emerging environmental contaminants of concern. These are bisphenol A, drinking water disinfection byproducts, ionic liquids, and nanomaterials [277,280,281]. These contaminants and their exposure sources and health effects have been summarized in Table 2.

Flame Retardants: Background

Flame retardants refer to a broad class of chemicals used in the production of a variety of commercial goods [282,283]. Flame retardants can be composed of many different materials, but brominated compounds, including polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls, hexabromocyclododecanes, and tetrabromobisphenol A are the compounds of greatest concern [282–284]. Compounds with fewer bromines are expected to be more toxic [285]. Brominated flame retardants (BFRs) are semivolatile organic compounds and are lipophilic [286,287].

BFRs are either additive or reactive [288]. Of great concern in the context of environmental health, additive BFRs do not form chemical bonds with the parent material and are therefore much more likely to leach out of the product [288]. In the controversy surrounding the endocrine-disrupting nature of BFRs, alternative “novel” BFRs and halogen-free flame retardants have been produced [284,286]. There are insufficient data to provide an accurate risk assessment of these new products, although some may be promising alternatives to the BFRs currently used [284,289].

Exposure Sources of Flame Retardants

BFRs are not naturally occurring and have only been manufactured in the United States since the mid-1900s [290]. BFRs are incorporated into many different items used daily, including textiles, toys, cars, plastics, wiring, and electronics [286,287]. Humans can be exposed to BFRs through inhalation, ingestion, and dermal contact [287]. Due to their lipophilic nature, BFRs bioaccumulate up the food chain and therefore dairy products, fish, meat, eggs, and poultry contain the highest concentrations of BFRs. BFRs also persist within the human body for a long period of time after ingestion, as they are stored in lipid deposits [287]. Being fat soluble, BFRs can cross most biological membranes, including the placental and lactational membranes,

increasing the risk for prenatal and infant exposure [283,287]. Children are also at increased risk of exposure to BFRs due to higher hand-to-mouth behavior and closer proximity to the ground [285,287]. Fetuses, infants, and children are also at a greater risk of BFR-induced health effects, as their metabolic detoxification mechanisms are not fully developed and their immature biological systems are more susceptible to toxicity [287,288].

BFRs are typically found at higher concentrations in inside air than outside, as most products containing BFRs are used indoors, and there is less air flow by which BFRs could be dispersed from the air [288]. Some of the highest indoor exposures to BFRs are occupational exposures in the electronic waste recycling industry, although offices and production sites of BFR-containing goods also present opportunities for exposure [285,288].

Health Effects of Flame Retardant Exposure and Potential Biological Mechanisms

Acute exposures to BFRs can result in vomiting, nausea, dizziness, and difficulty breathing, though such concentrated exposures are rare in humans [291]. Chronic BFR exposure has been associated with increased risks for cancer, adverse reproductive and neurobehavioral health effects, diabetes, metabolic syndrome, and thyroid function dysregulation [282,285,287,292]. Cancer target sites associated with BFR exposure are the digestive and lymphatic systems, and the liver [285,287]. Polybrominated biphenyls are classified as Group 2A carcinogens by the IARC [140]. The only BFR included in the NTP's 12th Report on Carcinogens is tris(2,3-dibromopropyl) phosphate, which is categorized as "reasonably anticipated to be a human carcinogen" [19]. The USEPA has only released information concerning brominated dibenzofurans, and they classify these compounds as "not classifiable as to human carcinogenicity" [293].

As demonstrated by their wide range of adverse health effects, BFRs are systemic toxicants and influence human health by a variety of mechanisms [282,292]. BFRs are suspected to induce many of their toxic effects by interrupting the homeostasis of the endocrine system, though most mechanistic studies have focused on PBDEs [282,292]. There is evidence of PBDEs affecting numerous nuclear hormone-mediated pathways, including the thyroid hormone receptor, estrogen receptor, androgen receptor, progesterone receptor, and AhR pathways [292]. However, the manner in which PBDEs interact with the pathway, whether as an antagonist, agonist, cofactor recruiter, or transcriptional modifier, has been demonstrated to vary and to affect the biological outcome [292]. For example, it has been shown PBDEs that cause antiestrogenic activity bind to a different area of the human estrogen receptor alpha than those that induce estrogenic activity [294]. Additionally, there is some evidence from animal studies that PBDEs may affect thyroxine hormone levels, glucose oxidation by insulin, and lipolysis [282]. Kamstra et al. found that tetrabrominated diphenyl ether induced adipocyte differentiation by various mechanisms, including increased gene

expression and DNA hypomethylation [295]. Gassmann et al. reported that PBDEs may induce neurodevelopmental toxicity by disrupting calcium homeostasis [296]. The evidence of PBDEs epigenetic, genetic, proteomic, and metabolic effects underscores the importance of a systems biology approach to studying BFRs.

Perfluorinated Chemicals: Background

Perfluorinated chemicals are a broad class of hydrocarbon compounds in which all the hydrogens have been replaced with fluorine molecules [297]. Two of the most well-known perfluorinated chemicals are perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) [277,297]. Perfluorinated chemicals are both hydrophobic and lipophobic due to the unique chemical properties of fluorine. These properties, in addition to the stability of the covalent carbon–fluorine bonds, make perfluorinated chemicals very persistent in the environment [277,297]. Multiple reviews have identified perfluorinated chemicals of emerging environmental contaminants of concern [277,280,281], including a review by Ela et al. on next-generation Superfund and hazardous waste site contaminants [7].

Exposure Sources of Perfluorinated Chemicals

Perfluorinated chemicals do not occur naturally and were first produced in the 1940s [297]. Presently, they are considered ubiquitous environmental contaminants, being found at high levels in water and human blood serum and tissues [298–300]. Due to their lipophobic and hydrophobic nature, perfluorinated chemicals are used in a wide range of commercial products, including stain repellents on fabrics and carpets, paints, waxes, electronics, and food packaging material [277]. Food and drinking water also present potential exposure sources to perfluorinated chemicals [301,302].

Perfluorinated chemicals can cross the placental barrier, placing pregnant women at increased risk of adverse reproductive health effects from perfluorinated chemical exposure [303]. In addition, perfluorinated chemicals are excreted through human breast milk, placing breastfeeding infants at increased risk of exposure as well [304]. Workers in plants where perfluorinated chemicals are used, processed, or produced have been reported to have higher body burdens of perfluorinated chemicals than the average population [305].

Health Effects of Perfluorinated Chemical Exposure and Potential Biological Mechanisms

The categorization of perfluorinated chemicals as emerging environmental contaminants stems from the numerous adverse health effects resulting from long-term, low-dose exposure, and acute health effects of concentrated exposure to perfluorinated chemicals have not been documented in humans [277,305,306]. Perfluorinated chemicals have long half-lives in humans, with PFOS and PFOA persisting an estimated 5.4 and 3.8 years in the human body, respectively [307]. Perfluorinated chemicals are

reproductive, immune, and endocrine system toxicants [301,303,305]. Specifically, perfluorinated chemicals cause thyroid hormone imbalance and increases in hepatic enzyme and serum cholesterol levels [301]. Increased mortality from diabetes and prostate, kidney, liver, and bladder cancer has also been observed in exposed populations [301,305]. Interestingly, both the half-lives of perfluorinated chemicals and the associated toxic effects of exposure have been reported to vary by gender [305–307].

While perfluorinated chemicals probably have numerous mechanisms of toxic action [308], activation of the nuclear transcription factor peroxisome proliferator-activated receptor α has consistently been linked with biological responses to perfluorinated chemicals in rodent studies, including changes in gene expression [305,309,310]. However, rodent studies have reported that the expression nuclear receptors such as constitutive activated/androstane receptor (CAR) and pregnane X receptor also increase in response to perfluorinated chemical exposure [309,311,312]. An in vitro systems toxicology study of PFOA revealed changes in gene expression related to many metabolic pathways, corresponding to lipid homeostasis disturbance [313]. This publication is an excellent example of the value of systems biology/toxicology. Not only did the researchers identify new biomarkers of PFOA exposure, but they also were able to identify biological pathways by which PFOA causes toxicity [313]. There is a substantive body of literature about the occurrence and toxicity of perfluorinated chemicals underscoring their role as an emerging environmental contaminant of concern [297,314].

Siloxanes: Background

Siloxanes, also known as silicones, are manmade saturated silicone-oxygen hydrides [315]. They occur in both cyclic and linear forms [277]. Siloxanes are used in many commercial and industrial applications due to the compounds' hydrophobicity, low thermal conductivity, and high flexibility [316]. Some of the most common siloxanes include octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), dodecamethylcyclohexasiloxane (D6), and polydimethylsiloxanes [278]. Siloxanes have been included in multiple reviews concerning emerging pollutants [280,281], including Richardson and Ternes 2009 review, *Water Analysis: Emerging Contaminants and Current Issues*, and were highlighted in a review by Ela et al. in 2011 on potential future contaminants of concern at superfund and hazardous waste sites [7,277–279].

Exposure Sources of Siloxanes

Beginning in the 1940s, and continuing today, siloxanes are used in many cosmetic, electronic, household, and medical device products [315]. In addition, siloxanes are used in the automobile industry, both as car waxes and fuel additives [277]. Humans are, therefore, frequently exposed to siloxanes through personal product use and food ingestion, though wastewater, industrial processes, and sewage sludge also present potential routes of exposure [277].

Siloxane waste has been shown to be concentrated in sewage sludge and downstream sediments from wastewater treatment plants [317]. Potential at-risk populations of siloxane exposure could include those living near wastewater treatment plants or near landfills. People receiving silicone breast implants constitute another population that is at-risk for exposure to siloxanes. Breast augmentation remains the most popular cosmetic surgery in the United States, and silicone continues to be used in over half of the surgeries performed annually [318]. Following the introduction of silicone breast implants in 1964, reports of an increased occurrence of connective tissue disorders and autoimmune diseases in patients with silicone implants led to the Food and Drug Administration issuing a moratorium on silicone implants in 1992 [319–321]. Due to a lack of conclusive evidence of a causal relationship between silicone implants and these adverse health effects, the moratorium was revoked in 2006, though contentious reports of the risks of silicone implants continue to be produced [322–325]. For instance, Hajdu et al. concluded that a fibroproliferative inflammation definitely occurred in response to silicone implants, while others claimed that there is no association between silicone breast implants and connective tissue disease [322,326].

Health Effects of Siloxane Exposure and Potential Biological Mechanisms

Safety reviews of both cyclic and linear siloxanes concluded that these compounds, as they are currently used in consumer products, are safe [327,328]. Acute toxicity studies of siloxanes have been conducted in rats and have found no toxic effects in response to acute dermal or oral doses comparable to those of human exposure [327,328]. Short-term inhalation exposure to cyclic siloxanes has demonstrated to be associated with an increase in liver weight [327].

Chronic exposure to siloxanes has become a high-priority public health concern, as siloxanes have begun to appear in measurable concentrations in wastewater, river water, and landfill gases [277]. Little is known about the toxic effects of long-term exposure to low concentrations of siloxanes, as they first emerged as a priority environmental pollutant in 2010 [280,281]. However, limited data indicate that the cyclic siloxane compounds induced hyperplasia in multiple tissues and are potential genotoxicants, cytotoxicants, and immune system disruptors [327].

The broad range of biological targets of siloxanes suggest that these compounds elicit effects through several mechanisms. An increase in antisilicone antibodies has been detected in the plasma and capsular tissue of patients with silicone implants, though it remains unclear how and if this increase contributes to immune disorders [324,329,330]. D4 and D5 are known to induce liver cytochrome P450 (CYP) enzymes and CAR expression in rodents, indicating that both compounds are potentially regulators of important xenobiotic metabolic pathways [327]. In addition, it has been reported that D4 induces weak estrogenic effects [331]. A review by Hajdu et al. [322] focusing on the association of autoimmunity and silicone exposure through breast implants underscores that there are multiple reasonable pathways of siloxane toxicity.

CONCLUSIONS

Environmental contaminants threaten human health around the globe and continue to be of significant public health concern. Their presence in the environment occurs through a variety of anthropogenic and natural sources (Figure 1). This chapter details the basic properties, sources of exposure, susceptible populations, health effects, and biological mechanisms of action of some of the highest prioritized pollutants and emerging contaminants of concern in the environment today. A summary of these environmental contaminants, exposure sources, and health effects is provided in Tables 1 and 2.

This chapter has detailed the wide variety of the health outcomes that can result from exposure to environmental contaminants (Figure 2). Current research suggests the role of multiple factors in environmental exposure-induced disease, including the timing of exposure and the role of inter-individual differences in genetics and epigenetics. An increased understanding of the biological mechanisms underlying exposure-induced health effects and disease could lead to the identification of biological targets for disease treatment and prevention. As environmental factors continue to account for a large portion of the global disease burden [1], greater understanding and awareness of the health threats of environmental exposures presents an opportunity to improve the length and quality of human life.

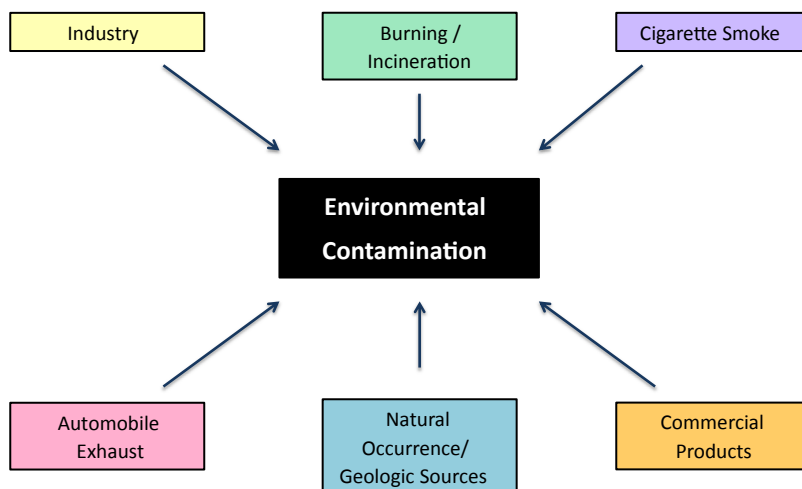


Figure 1 There are many sources of environmental contamination. Both biogenic and anthropogenic processes contribute to this contamination.

Table 1 Summary of Priority Environmental Contaminants, Common Sources of Exposure, and Health Effects of Exposure

Prioritization Resource and Ranking	Substance Name	Sources of Exposure	Health Effects	
			Acute	Chronic
ATSDR #1	Arsenic	Food, drinking water [8–10]	Nausea, vomiting, diarrhea, fatigue, heart arrhythmias, dark spots on skin [8–10]	Cancers of the skin, lung, bladder, liver, kidney, lymphatic and hematopoietic systems, birth defects [8–10]
ATSDR #2	Lead	Lead dust, food, drinking water, cigarette smoke, mining, battery operations; historically: gasoline [31,32]	Nausea, vomiting, constipation, encephalopathy [31,32]	Neurotoxicity, birth defects, cancers of the lung, stomach, and bladder [31,32]
ATSDR #3	Mercury	Seafood, dental amalgams [85]	Nausea, diarrhea, ulcers, brain damage, kidney damage, kidney failure [85]	Behavioral and personality changes, fatigue, headaches, paraesthesia, diminished cognitive function [85]
ATSDR #4	Vinyl chloride	Plastic industries, drinking water, air, cigarette smoke [109,110]	Dizziness, fainting [109,110]	Liver damage, nerve damage, immune disruption, cancers of the liver, lung, and connective tissues [109,110]
ATSDR #5	Polychlorinated biphenyls	Electric industry, seafood [126,332]	Chloracne, nose, lung, and gastrointestinal tract irritation, fatigue [126]	Cancers of the kidney, liver, pancreas, brain, and skin; immune and endocrine dysregulation [126,332]
ATSDR #6	Benzene	Chemical, pharmaceutical, textile, and oil industries, automobile exhaust, cigarette smoke, forest fires, oil seeps [146,147]	Eye irritation, confusion, Tachycardia, headaches, drowsiness, dizziness, fainting [146]	Leukemia, cancers of the lymphatic systems [146]
ATSDR #7	Cadmium	Batteries, electroplates and coatings, plastics, food, cigarette smoke [19,164,165]	Lung and nasal cavity damage, stomach irritation, vomiting, diarrhea [164]	Kidney disease [164], osteoporosis and low bone mineral density [174,179], neurotoxicity [171], dysregulation of the reproductive system [172,180,181], cancers of the lung, bladder, breast, prostate, pancreas, and kidney [IARC, 2012 #910]

Continued

Table 1 Summary of Priority Environmental Contaminants, Common Sources of Exposure, and Health Effects of Exposure—cont'd

Resource and Ranking	Substance Name	Sources of Exposure	Health Effects	
			Acute	Chronic
ATSDR #8–10	Polycyclic aromatic hydrocarbons [9] (Benzo[a] pyrene [8] & Benzo[b] fluoranthene [10])	Incomplete combustion of fossil fuels, construction and paving operations, cigarette smoke, food, drinking water [192]	Lung, skin, and eye irritation, difficulty breathing, nausea, vomiting, diarrhea [192]	Immunosuppression, birth defects, cancers of the skin, lung, bladder, and gastrointestinal tract [192]
Lo et al. 2007#1	1,3-Butadiene	Chemical, pharmaceutical, textile and oil industries, automobile exhaust, cigarette smoke, gasoline, forest fires [202]	Respiratory irritation and inflammation [19,202–204]	Cancers of the lymphatic and hematopoietic systems [19,202–204]
Lo et al. 2007#2	Formaldehyde	Industrial combustion, automobile exhaust, cigarette smoke, cosmetics, furniture, wood and paper products [214,215]	Respiratory irritation and inflammation, eye and skin irritation [214]	Immune system dysregulation [220], upper respiratory tract inflammation [222], nasopharyngeal cancer [223]
Lo et al. 2007#3	Dioxin	Paper, chemical, and agricultural industries, combustion operations, incineration processes [234,235]	Chloracne, skin irritation and discoloration, excess growth of body hair [234]	Cancers of the rectum, lung, prostate, soft tissue sarcomas, nonHodgkin lymphoma, birth defects [251,257]

Lo et al. 2007#4	Chloroform	Chlorinated water, air [266,267]	Dizziness, fatigue, headaches, liver damage [266,267]	Cancers of the urinary bladder, kidney, and liver [266,267, 269–272]
Ela et al. 2011	Flame retardants	Food, especially dairy products, eggs, meat, and poultry [285], various commercial goods (textiles, plastics, electronics, etc.) [283,286,287]	Vomiting, nausea, dizziness, difficult breathing [291]	Diabetes [287], thyroid homeostasis disruption [292], reproductive, metabolic, neurobehavioral, and developmental disorders [287], cancers of the liver and digestive and lymphatic systems [285,287]
Ela et al. 2011	Perfluorinated chemicals	Drinking water, food, various commercial goods (textiles, electronics, paints, etc.) [277]	Not documented	Reproductive, immune, and endocrine system dysregulation, diabetes, cancers of the liver, bladder, and kidney [301]
Ela et al. 2011	Siloxanes	Wastewater [317], sewage sludge [317], cosmetics [317], car wax [277], car fuel [277], silicone implants [322,323], common electronic and household items [315]	Increase in liver weight [327]	Autoimmune disorders [322], hyper- plasia [327], endocrine disruption [331]

Table 2 Summary of Other Environmental Contaminants of Emerging Concern, Common Sources of Exposure, and Health Effects of Exposure

Substance Name	Classification	Sources of Exposure	Health Effects	
			Acute	Chronic
Bisphenol A	Chemical monomer predominantly used in plastics [333]	Plastics, food, paper, medical devices, dust, epoxy resins, dental materials [334]	Eye and skin sensitivity [335]	Adverse reproductive health effects, metabolic disease, cardiovascular disease, liver function, obesity, immune and endocrine system dysregulation [336]
Drinking water disinfection by-products	Chemical products formed from reactions of drinking-water disinfectants with natural materials or other contaminants [277]	Drinking water, swimming pools [274]	Liver and kidney damage [337]	Cancers of the bladder and colon, adverse birth outcomes [274–276]
Ionic liquids	Organic salt solvents made of ions; often used as a “green” alternative to existing organic solvents [338]	Wastewater, contaminated soil [338]	Dermal irritation in rats, enzyme inhibition in vitro [339]	Tertaogenic in zebrafish, cytotoxic in vitro [339]
Nanomaterials	Anthropogenic materials ranging from 1 to 100 nm in size [277]	Air, food, drinking water pharmaceuticals, clothing, toothpaste, sunscreen, shampoo, detergent [277]	Myocardial infarction, lung inflammation [340]	Increase in heart rate, blood pressure, increased risk of cardiovascular and respiratory disease [340], genotoxicity

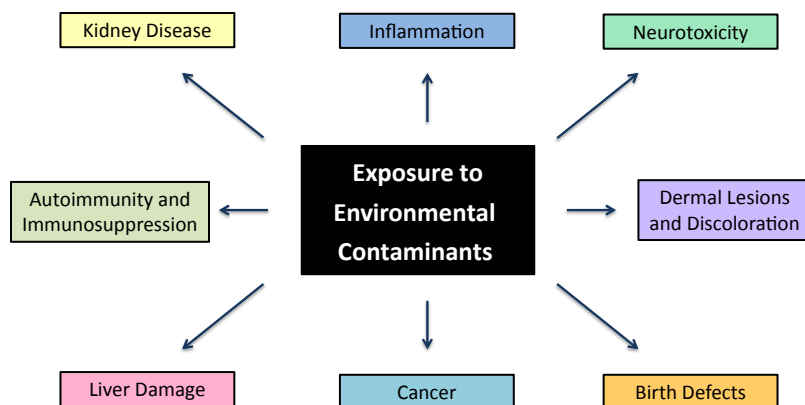


Figure 2 The health effects associated with exposure to environmental contaminants are numerous and vary depending on the contaminant, dose, duration of exposure, and host susceptibility factors. Thus, better understanding of the sources of exposure to environmental contaminants and their biological modes of action is crucial to protecting human health.

REFERENCES

- [1] Prüss-Ustün A, Corvalán C. Preventing disease through health Environments: towards an estimate of the environmental burden of disease. Geneva: World Health Organization; 2006.
- [2] Prüss-Ustün A, Vickers C, Haefliger P, Bertollini R. Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environ Health* 2011;10:9.
- [3] ATSDR. Support document to the 2013 priority list of hazardous substances that will be the subject of toxicological profiles. Atlanta: Division of Toxicology and Environmental Medicine; 2014.
- [4] ATSDR. The ATSDR 2013 substance priority list. Atlanta: Center for Disease Control; 2013.
- [5] Sigman R, Hilderink H, Delrue N, Braathen NA, Leflaive X. Health and Environment. In *OECD Environmental Outlook to 2050: The Consequences of Inaction*. OECD Publishing; 2012.
- [6] Loh MM, Levy JI, Spengler JD, Houseman EA, Bennett DH. Ranking cancer risks of organic hazardous air pollutants in the United States. *Environ Health Perspect* 2007;115(8):1160–8.
- [7] Ela WP, Sedlak DL, Barlaz MA, Henry HF, Muir DC, Swackhamer DL, et al. Toward identifying the next generation of superfund and hazardous waste site contaminants. *Environ Health Perspect* 2011;119(1):6–10.
- [8] ATSDR. Toxicological profile for arsenic. Atlanta: Center for Disease Control; 2007. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=22&tid=3>.
- [9] IARC. Arsenic in drinking water. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Geneva: World Health Organization Press; 2012.
- [10] IARC. Arsenic and arsenic compounds. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Geneva: World Health Organization Press; 2012.
- [11] Watanabe T, Hirano S. Metabolism of arsenic and its toxicological relevance. *Arch Toxicol* 2013;87(6):969–79.
- [12] Cohen SM, Arnold LL, Beck BD, Lewis AS, Eldan M. Evaluation of the carcinogenicity of inorganic arsenic. *Crit Rev Toxicol* 2013;43(9):711–52.
- [13] Kitchin KT, Wallace K. The role of protein binding of trivalent arsenicals in arsenic carcinogenesis and toxicity. *J Inorg Biochem* 2008;102(3):532–9.
- [14] Suzuki N, Naranmandura H, Hirano S, Suzuki KT. Theoretical calculations and reaction analysis on the interaction of pentavalent thioarsenicals with biorelevant thiol compounds. *Chem Res Toxicol* 2008;21(2):550–3.

- [15] Bhattacharjee P, Chatterjee D, Singh KK, Giri AK. Systems biology approaches to evaluate arsenic toxicity and carcinogenicity: an overview. *Int J Hyg Environ Health* 2013;216(5):574–86.
- [16] Uddin R, Huda NH. Arsenic poisoning in Bangladesh. *Oman Med J* 2011;26(3):207.
- [17] Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bull World Health Organ* 2000;78(9):1093–103.
- [18] UNICEF. In: Arsenic mitigation in Bangladesh. (New York): UNICEF; 2008.
- [19] NTP. 12th Report on Carcinogens. Research Triangle Park (NC): U.S. Department of Health and Human Services; 2011.
- [20] Araujo J. Use Terminations and Existing Stocks Provisions; Amendments: Organic Arsenicals. Virginia: Environmental Protection Agency, Office of Pesticide Programs, Pesticide Re-evaluation Division; 2013. p. 18590–91 <http://www.regulations.gov/-/documentDetail;D=EPA-HQ-OPP-2009-0191-0026>.
- [21] FDA. In: FDA, editor. FDA response to citizen petition on arsenic-based animal drugs. Silver Spring: U.S. Department of Health and Human Services; 2013. <http://www.fda.gov/libproxy.lib.unc.edu/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm370568.htm>.
- [22] WHO. Guidelines for drinking water quality. Geneva (Switzerland): World Health Organization Press; 2006.
- [23] Maharjan M, Watanabe C, Ahmad SA, Ohtsuka R. Arsenic contamination in drinking water and skin manifestations in lowland Nepal: the first community-based survey. *Am J Trop Med Hyg* 2005;73(2):477–9.
- [24] Berg M, Stengel C, Pham PT, Viet PH, Sampson ML, Leng M, et al. Magnitude of arsenic pollution in the Mekong and Red River Deltas—Cambodia and Vietnam. *Sci Total Environ* 2007;372(2–3):413–25.
- [25] Rager JE, Bailey KA, Smeester L, Miller SK, Parker JS, Laine JE, et al. Prenatal arsenic exposure and the epigenome: altered microRNAs associated with innate and adaptive immune signaling in newborn cord blood. *Environ Mol Mutagen* 2014;55(3):196–208.
- [26] Sanders AP, Messier KP, Shehee M, Rudo K, Serre ML, Fry RC. Arsenic in North Carolina: public health implications. *Environ Int* 2012;38(1):10–6.
- [27] Peters SC, Blum JD, Karagas MR, Chamberlain CP, Sjostrom DJ. Sources and exposure of the New Hampshire population to arsenic in public and private drinking water supplies. *Chem Geol* 2006;228(1–3):72–84.
- [28] Vahter M. Effects of arsenic on maternal and fetal health. *Annu Rev Nutr* 2009;29:381–99.
- [29] Zheng X, Pang L, Wu J, Pei L, Tan L, Yang C, et al. Contents of heavy metals in arable soils and birth defect risks in Shanxi, China: a small area level geographic study. *Popul Environ* 2012;33(2–3):259–68.
- [30] Wu J, Zhang C, Pei L, Chen G, Zheng X. Association between risk of birth defects occurring level and arsenic concentrations in soils of Lvliang, Shanxi province of China. *Environ Pollut* 2014;191:1–7.
- [31] Li D, Lu C, Wang J, Hu W, Cao Z, Sun D, et al. Developmental mechanisms of arsenite toxicity in zebrafish (*Danio rerio*) embryos. *Aquat Toxicol* 2009;91(3):229–37.
- [32] Ahir BK, Sanders AP, Fry RC. Inhibition of the Glucocorticoid receptor Protects against arsenic-induced birth defects. *Birth Defects Res A Clin Mol Teratol* 2012;94(5):330.
- [33] Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. *PLoS Genet* 2007;3(11):e207.
- [34] Broberg K, Ahmed S, Engstrom K, Hossain MB, Jurkovic Mlakar S, et al. Arsenic exposure in early pregnancy alters genome-wide DNA methylation in cord blood, particularly in boys. *J Dev Orig Health Dis* 2014;5(4):288–98.
- [35] NRC. Pesticides in the diets of infants and children. Washington (DC): National Academy Press; 1993.
- [36] Saha KK, Engstrom A, Hamadani JD, Tofail F, Rasmussen KM, Vahter M. Pre- and postnatal arsenic exposure and body size to 2 years of age: a cohort study in rural Bangladesh. *Environ Health Perspect* 2012;120(8):1208–14.
- [37] USEPA. Arsenic, inorganic. Washington (DC): U.S. Environmental Protection Agency; 1998. <http://www.epa.gov/iris/subst/0278.htm>.
- [38] Dangleben NL, Skibola CF, Smith MT. Arsenic immunotoxicity: a review. *Environ Health* 2013;12(1):73.
- [39] Stea F, Bianchi F, Cori L, Sicari R. Cardiovascular effects of arsenic: clinical and epidemiological findings. *Environ Sci Pollut Res Int* 2014;21(1):244–51.

- [40] Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. *Curr Environ Health Rep* 2014;1:132–47.
- [41] Moore LE, Karami S, Steinmaus C, Cantor KP. Use of OMIC technologies to study arsenic exposure in human populations. *Environ Mol Mutagen* 2013;54(7):589–95.
- [42] Smeester L, Rager JE, Bailey KA, Guan X, Smith N, García-Vargas G, et al. Epigenetic changes in individuals with arsenicosis. *Chem Res Toxicol* 2011;24(2):165–7.
- [43] van Breda SG, Claessen SM, Lo K, van Herwijnen M, Brauers KJ, Lisanti S, et al. Epigenetic mechanisms underlying arsenic-associated lung carcinogenesis. *Arch Toxicol* 2014;1–11.
- [44] Kile ML, Baccarelli A, Hoffman E, Tarantini L, Quamruzzaman Q, Rahman M, et al. Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes. *Environ Health Perspect* 2012;120(7):1061–6.
- [45] Majumdar S, Chanda S, Ganguli B, Mazumder DN, Lahiri S, Dasgupta UB. Arsenic exposure induces genomic hypermethylation. *Environ Toxicol* 2010;25(3):315–8.
- [46] Bailey KA, Wu MC, Ward WO, Smeester L, Rager JE, García-Vargas G, et al. Arsenic and the epigenome: interindividual differences in arsenic metabolism related to distinct patterns of DNA methylation. *J Biochem Mol Toxicol* 2013;27(2):106–15.
- [47] Chervona Y, Hall MN, Arita A, Wu F, Sun H, Tseng HC, et al. Associations between arsenic exposure and global posttranslational histone modifications among adults in Bangladesh. *Cancer Epidemiol Biomarkers Prev* 2012;21(12):2252–60.
- [48] Suzuki T, Nohara K. Long-term arsenic exposure induces histone H3 Lys9 dimethylation without altering DNA methylation in the promoter region of p16(INK4a) and down-regulates its expression in the liver of mice. *J Appl Toxicol* 2013;33(9):951–8.
- [49] Nesnow S, Roop BC, Lambert G, Kadiiska M, Mason RP, Cullen WR, et al. DNA damage induced by methylated trivalent arsenicals is mediated by reactive oxygen species. *Chem Res Toxicol* 2002;15(12):1627–34.
- [50] Bailey KA, Laine J, Rager JE, Sebastian E, Olshan A, Smeester L, et al. Prenatal arsenic exposure and shifts in the newborn proteome: interindividual differences in tumor necrosis factor (TNF)-responsive signaling. *Toxicol Sci* 2014;139(2):328–37.
- [51] Pierce BL, Kibriya MG, Tong L, Jasmine F, Argos M, Roy S, et al. Genome-wide association study identifies chromosome 10q24.32 variants associated with arsenic metabolism and toxicity phenotypes in Bangladesh. *PLoS Genet* 2012;8(2):e1002522.
- [52] Wu MM, Chiou HY, Ho IC, Chen CJ, Lee TC. Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects. *Environ Health Perspect* 2003;111(11):1429–38.
- [53] Zhao L, Gao Y, Yang Y, Wei Y, Li Y, Feng H, et al. Serum proteomic profiling analysis of chronic arsenic exposure by using SELDI-TOF-MS technology. *Toxicol Lett* 2010;195(2–3):155–60.
- [54] Bhattacharjee P, Banerjee M, Giri AK. Role of genomic instability in arsenic-induced carcinogenicity. A review. *Environ Int* 2013;53:29–40.
- [55] Lopez-Carrillo L, Hernandez-Ramirez RU, Gandolfi AJ, Ornelas-Aguirre JM, Torres-Sanchez L, Cebrian ME. Arsenic methylation capacity is associated with breast cancer in northern Mexico. *Toxicol Appl Pharmacol* 2014;280(1):53–9.
- [56] Currier JM, Ishida MC, Gonzalez-Horta C, Sanchez-Ramirez B, Ballinas-Casarrubias L, Gutierrez-Torres DS, et al. Associations between arsenic species in exfoliated urothelial cells and prevalence of diabetes among residents of Chihuahua, Mexico. *Environ Health Perspect* 2014;122(10):1088–94.
- [57] Steinmaus C, Yuan Y, Kalman D, Rey OA, Skibola CF, Dauphine D, et al. Individual differences in arsenic metabolism and lung cancer in a case-control study in Cordoba, Argentina. *Toxicol Appl Pharmacol* 2010;247(2):138–45.
- [58] ATSDR. Toxicological profile for Lead. Atlanta: Center for Disease Control; 2007. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=96&tid=22>.
- [59] IARC. Inorganic and organic lead compounds. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2006.
- [60] Heskell DL. A model for the adoption of metallurgy in the ancient Middle East. *Curr Anthropol* 1984;24(3):362–6.

- [61] Hong S, Candelone JP, Patterson CC, Boutron CF. Greenland ice evidence of hemispheric lead pollution two millennia ago by greek and roman civilizations. *Science* 1994;265(5180):1841–3.
- [62] Willies L, Craddock PT, Gurjar LJ, Hegde TM. Ancient lead and zinc mining in Rajasthan, India. *World Archaeol* 1984;16(2):222–33.
- [63] Newell RG, Rogers K. The U.S. Experience with the Phasedown of Lead in Gasoline. Resources for the Future; 2003.
- [64] Staudinger KC, Roth VS. Occupational lead poisoning. *Am Fam Physician* 1998;57(4):719–26. 31–32.
- [65] Gottesfeld P, Pokhrel AK. Review: lead exposure in battery manufacturing and recycling in developing countries and among children in nearby communities. *J Occup Environ Hyg* 2011;8(9):520–32.
- [66] Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ Health Perspect* 2002;110(7):721–8.
- [67] Helmfrid I, Berglund M, Lofman O, Wingren G. Health effects and exposure to polychlorinated biphenyls (PCBs) and metals in a contaminated community. *Environ Int* 2012;44:53–8.
- [68] Malcoe LH, Lynch RA, Keger MC, Skaggs VJ. Lead sources, behaviors, and socioeconomic factors in relation to blood lead of native american and white children: a community-based assessment of a former mining area. *Environ Health Perspect* 2002;110(Suppl. 2):221–31.
- [69] Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. Absorption and retention of lead by infants. *Pediatr Res* 1978;12(1):29–34.
- [70] Wigle DT, Arbuckle TE, Turner MC, Bérubé A, Yang Q, Liu S, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 2008;11(5–6):373–517.
- [71] CDC. In: Health NCfE, editor. Blood lead levels in children: what do parents need to know to protect their children. Atlanta (GA): Center for Disease Control and Prevention; 2012. http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm.
- [72] Mason LH, Harp JP, Han DY. Pb neurotoxicity: neuropsychological effects of lead toxicity. *Biomed Res Int* 2014;2014:840547.
- [73] Sanders T, Liu Y, Buchner V, Tchounwou PB. Neurotoxic effects and biomarkers of lead exposure: a review. *Rev Environ Health* 2009;24(1):15–45.
- [74] Lanphear BP, Dietrich K, Auinger P, Cox C. Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents. *Public Health Rep* 2000;115(6):521–9.
- [75] Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect* 2005;113(7):894–9.
- [76] Hu H, Tellez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. *Environ Health Perspect* 2006;114(11):1730–5.
- [77] Wasserman GA, Liu X, Popovac D, Factor-Litvak P, Kline J, Waternaux C, et al. The Yugoslavia Prospective Lead Study: contributions of prenatal and postnatal lead exposure to early intelligence. *Neurotoxicol Teratol* 2000;22(6):811–8.
- [78] Grosse SD, Matte TD, Schwartz J, Jackson RJ. Economic gains resulting from the reduction in children's exposure to lead in the United States. *Environ Health Perspect* 2002;110(6):563–9.
- [79] USEPA. Lead and compounds (inorganic). Washington (DC): U.S. Environmental Protection Agency; 1993. <http://www.epa.gov/iris/subst/0277.htm>.
- [80] Patrick L. Lead toxicity part II: the role of free radical damage and the use of antioxidants in the pathology and treatment of lead toxicity. *Altern Med Rev* 2006;11(2):114–27.
- [81] Kasten-Jolly J, Heo Y, Lawrence DA. Central nervous system cytokine gene expression: modulation by lead. *J Biochem Mol Toxicol* 2011;25(1):41–54.
- [82] Kumawat KL, Kaushik DK, Goswami P, Basu A. Acute exposure to lead acetate activates microglia and induces subsequent bystander neuronal death via caspase-3 activation. *Neurotoxicology* 2014;41:143–53.
- [83] Liu MC, Liu XQ, Wang W, Shen XF, Che HL, Guo YY, et al. Involvement of microglia activation in the lead induced long-term potentiation impairment. *PLoS One* 2012;7(8):e43924.

- [84] WHO. Guidance for identifying populations at risk from mercury exposure. Geneva: United Nations Environmental Program, Division of Technology, Industry, and Economics: Chemicals; 2008.
- [85] ATSDR. Toxicological profile for mercury. Atlanta: Center for Disease Control; 1999. <http://www.atsdr.cdc.gov/toxfaqs/TFaqs?id=113&tid=24>.
- [86] Waldron HA. Did the Mad Hatter have mercury poisoning? *Br Med J* 1983;287:24–31.
- [87] Visnjevec AM, Kocman D, Horvat M. Human mercury exposure and effects in Europe. *Environ Toxicol Chem* 2014;33(6):1259–70.
- [88] Al-Saleh I, Al-Sedairi A. Mercury (Hg) burden in children: the impact of dental amalgam. *Sci Total Environ* 2011;409(16):3003–15.
- [89] Choi BH. The effects of methylmercury on the developing brain. *Prog Neurobiol* 1989;32:447–70.
- [90] Bertossi M, Girolamo F, Errede M, Virgintino D, Elia G, Ambrosi L, et al. Effects of methylmercury on the microvasculature of the developing brain. *Neurotoxicology* 2004;25(5):849–57.
- [91] Null DH, Gartside PS, Wei E. Methylmercury accumulation in brains of pregnant, non-pregnant and fetal rats. *Life Sci* 1973;12(2):65–72.
- [92] Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol* 1995;25(1):1–24.
- [93] Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, al-Rawi NY, et al. Methylmercury poisoning in Iraq. *Science* 1973;181(4096):230–41.
- [94] Amin-zaki L, Majeed MA, Clarkson TW, Greenwood MR. Methylmercury poisoning in Iraqi children: clinical observations over two years. *Br Med J* 1978;1(6113):613–6.
- [95] Amin-Zaki L, Elhassani S, Majeed MA, Clarkson TW, Doherty RA, Greenwood M. Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 1974;54(5):587–95.
- [96] IARC. Methylmercury compounds. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Geneva: World Health Organization Press; 1993.
- [97] Carocci A, Rovito N, Sinicropi MS, Genchi G. Mercury toxicity and neurodegenerative effects. *Rev Environ Contam Toxicol* 2014;229:1–18.
- [98] Yoshimasu K, Kiyohara C, Takemura S, Nakai K. A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/hyperactivity disorder in the childhood. *Neurotoxicology* 2014;44C:121–31.
- [99] Mutter J, Yeter D. Kawasaki's disease, acrodynia, and mercury. *Curr Med Chem* 2008;15(28):3000–10.
- [100] Tan SW, Meiller JC, Mahaffey KR. The endocrine effects of mercury in humans and wildlife. *Crit Rev Toxicol* 2009;39(3):228–69.
- [101] Bhowmik N, Patra M. Assessment of genotoxicity of inorganic mercury in rats in vivo using both chromosomal aberration and comet assays. *Toxicol Ind Health* 2013;1–7.
- [102] Schurz F, Sabater-Vilar M, Fink-Gremmels J. Mutagenicity of mercury chloride and mechanisms of cellular defence: the role of metal-binding proteins. *Mutagenesis* 2000;15(6):525–30.
- [103] USEPA. Methylmercury (MeHg). Washington (DC): U.S. Environmental Protection Agency; 1995. <http://www.epa.gov/iris/subst/0073.htm>.
- [104] Mitsumori K, Maita K, Shirasu Y. Chronic toxicity of methylmercury chloride in rats: pathological study. *Nihon Juigaku Zasshi* 1984;46(4):549–57.
- [105] Hirano M, Mitsumori K, Maita K, Shirasu Y. Further carcinogenicity study on methylmercury chloride in ICR mice. *Nihon Juigaku Zasshi* 1986;48(1):127–35.
- [106] Ceccatelli S, Dare E, Moors M. Methylmercury-induced neurotoxicity and apoptosis. *Chem Biol Interact* 2010;188(2):301–8.
- [107] Farina M, Rocha JB, Aschner M. Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. *Life Sci* 2011;89(15–16):555–63.
- [108] Koedrich P, Kim H, Weon JI, Seo YR. Toxicogenomic approaches for understanding molecular mechanisms of heavy metal mutagenicity and carcinogenicity. *Int J Hyg Environ Health* 2013;216(5):587–98.
- [109] IARC. Vinyl chloride. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Geneva: World Health Organization Press; 2012.
- [110] ATSDR. Toxicological profile for vinyl chloride; 2006. Atlanta (GA). <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=282&tid=51>.

- [111] USEPA. In: Agency EP, editor. National primary drinking water regulations. 2009.
- [112] USEPA. Vinyl chloride. Washington (DC): U.S. Environmental Protection Agency; 2000. <http://www.epa.gov/iris/subst/1001.htm>.
- [113] Feron VJ, Hendriksen CFM, Speek AJ, Til HP, Spit BJ. Lifespan oral toxicity study of vinyl-chloride in rats. *Food Cosmet Toxicol* 1981;19(3):317–33.
- [114] Til HP, Feron VJ, Immel HR. Lifetime (149-Week) oral carcinogenicity study of vinyl-chloride in rats. *Food Chem Toxicol* 1991;29(10):713–8.
- [115] Maltoni C, Cotti G. Carcinogenicity of vinyl-chloride in Sprague-Dawley rats after prenatal and postnatal exposure. *Ann NY Acad Sci* 1988;534:145–59.
- [116] Krishnan K, Johanson G. Physiologically-based pharmacokinetic and toxicokinetic models in cancer risk assessment. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2005;23(1):31–53.
- [117] Bolt HM. Vinyl chloride—a classical industrial toxicant of new interest. *Crit Rev Toxicol* 2005;35(4):307–23.
- [118] Sherman M. Vinyl chloride and the liver. *J Hepatol* 2009;51(6):1074–81.
- [119] Frullanti E, La Vecchia C, Boffetta P, Zocchetti C. Authors' reply: comment to "Vinyl chloride exposure and cirrhosis: a systematic review and meta-analysis". *Dig Liver Dis* 2013;45(8):702.
- [120] Mastrangelo G, Cegolon L, Fadda E, Fedeli U. Comment to "Vinyl chloride exposure and cirrhosis: a systematic review and meta-analysis". *Dig Liver Dis* 2013;45(8):701–2.
- [121] Frullanti E, La Vecchia C, Boffetta P, Zocchetti C. Vinyl chloride exposure and cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis* 2012;44(9):775–9.
- [122] Dogliotti E. Molecular mechanisms of carcinogenesis by vinyl chloride. *Ann Ist Super Sanita* 2006;42(2):163–9.
- [123] Li YL, Marion MJ, Zipprich J, Santella RM, Freyer G, Brandt-Rauf PW. Gene-environment interactions between DNA repair polymorphisms and exposure to the carcinogen vinyl chloride. *Biomarkers* 2009;14(3):148–55.
- [124] Wang Q, Ji F, Sun YA, Qiu YL, Wang W, Wu F, et al. Genetic polymorphisms of XRCC1, HOGG1 and MGMT and micronucleus occurrence in Chinese vinyl chloride-exposed workers. *Carcinogenesis* 2010;31(6):1068–73.
- [125] Wang Q, Tan HS, Zhang F, Sun Y, Feng NN, Zhou LF, et al. Polymorphisms in BER and NER pathway genes: effects on micronucleus frequencies among vinyl chloride-exposed workers in northern China. *Mutat Research-Genetic Toxicol Environ Mutagen* 2013;754(1–2):7–14.
- [126] ATSDR. Polychlorinated biphenyls; 2000. Atlanta (GA). <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=142&tid=26>.
- [127] Rosner D, Markowitz G. Persistent pollutants: a brief history of the discovery of the widespread toxicity of chlorinated hydrocarbons. *Environ Res* 2013;120:126–33.
- [128] Ashworth W. The late, Great Lakes: an environmental history. (New York): Wayne State University Press; 1986.
- [129] USEPA. Hudson river PCBs superfund site; 2014. Available from: <http://www.epa.gov/hudson/>.
- [130] USEPA. Calumet and Hecla (C & H) power plant. 2013. Available from: <http://www.epa.gov/region5/cleanup/chpowerplant/index.html-latest>.
- [131] Dyke PH, Foan C, Fiedler H. PCB and PAH releases from power stations and waste incineration processes in the UK. *Chemosphere* 2003;50(4):469–80.
- [132] Forns J, Lertxundi N, Aranbarri A, Murcia M, Gascon M, Martinez D, et al. Prenatal exposure to organochlorine compounds and neuropsychological development up to two years of life. *Environ Int* 2012;45:72–7.
- [133] Gascon M, Verner MA, Guxens M, Grimalt JO, Forns J, Ibarluzea J, et al. Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children. *Neurotoxicology* 2013;34:9–15.
- [134] El Majidi N, Bouchard M, Gosselin NH, Carrier G. Relationship between prenatal exposure to polychlorinated biphenyls and birth weight: a systematic analysis of published epidemiological studies through a standardization of biomonitoring data. *Regul Toxicol Pharmacol* 2012;64(1):161–76.
- [135] Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, et al. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European birth cohorts. *Environ Health Perspect* 2012;120(2):162–70.

- [136] Kramer S, Hikel SM, Adams K, Hinds D, Moon K. Current status of the epidemiologic evidence linking polychlorinated biphenyls and non-hodgkin lymphoma, and the role of immune dysregulation. *Environ Health Perspect* 2012;120(8):1067–75.
- [137] Passarini B, Infusino SD, Kasapi E. Chloracne: still cause for concern. *Dermatology* 2010;221(1):63–70.
- [138] Brouwer A, Longnecker MP, Birnbaum LS, Coglianò J, Kostyniak P, Moore J, et al. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. *Environ Health Perspect* 1999;107(Suppl. 4):639–49.
- [139] Parent AS, Naveau E, Gerard A, Bourguignon JP, Westbrook GL. Early developmental actions of endocrine disruptors on the hypothalamus, hippocampus, and cerebral cortex. *J Toxicol Environ Health B Crit Rev* 2011;14(5–7):328–45.
- [140] Lauby-Secretan B, Loomis D, Grosse Y, El Ghissass F, Bouvard V, Benbrahim-Tallaa L, et al. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. *Lancet Oncol* 2013;14(4):287–8.
- [141] USEPA. Polychlorinated biphenyls (PCBs). Washington (DC): U.S. Environmental Protection Agency; 1997. <http://www.epa.gov/iris/subst/0294.htm>.
- [142] Ruder AM, Hein MJ, Nilsen N, Waters MA, Laber P, Davis-King K, et al. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. *Environ Health Perspect* 2006;114(1):18–23.
- [143] Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med* 1997;54(10):720–8.
- [144] Shalat SL, True LD, Fleming LE, Pace PE. Kidney Cancer in utility workers exposed to polychlorinated-biphenyls (Pcbs). *Br J Ind Med* 1989;46(11):823–4.
- [145] Robertson LW, Ludewig G. Polychlorinated biphenyl (PCB) carcinogenicity with special emphasis on airborne PCBs. *Gefährst Reinhalt Luft* 2011;71(1–2):25–32.
- [146] ATSDR. Toxicological profile for benzene. Atlanta: Center for Disease Control; 2007. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14>.
- [147] IARC. Benzene. Lyon: World Health Organization Press; 2012.
- [148] NIOSH. National occupational exposure survey (1981–83). Atlanta: National Institute for Occupational Safety and Health; 1990. <http://www.cdc.gov/noes/noes2/18500occ.html>.
- [149] van Wijngaarden E, Stewart PA. Critical literature review of determinants and levels of occupational benzene exposure for United States community-based case-control studies. *Appl Occup Environ Hyg* 2003;18(9):678–93.
- [150] Murray FJ, John JA, Rampy LW, Kuna RA, Schwetz BA. Embryotoxicity of inhaled benzene in mice and rabbits. *Am Ind Hyg Assoc J* 1979;40(11):993–8.
- [151] Kuna RA, Kapp Jr RW. The embryotoxic/teratogenic potential of benzene vapor in rats. *Toxicol Appl Pharmacol* 1981;57(1):1–7.
- [152] Ungvary G, Tatrai E. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. *Arch Toxicol Suppl* 1985;8:425–30.
- [153] Keller KA, Snyder CA. Mice exposed in utero to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. *Fundam Appl Toxicol* 1988;10(2):224–32.
- [154] Kirkeleit J, Riise T, Bratveit M, Moen BE. Increased risk of acute myelogenous leukemia and multiple myeloma in a historical cohort of upstream petroleum workers exposed to crude oil. *Cancer Causes Control* 2008;19(1):13–23.
- [155] Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, et al. Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med* 1987;316(17):1044–50.
- [156] USEPA. Benzene. Washington (DC): U.S. Environmental Protection Agency; 2003. <http://www.epa.gov/iris/subst/0276.htm>.
- [157] Infante PF. Benzene exposure and multiple myeloma: a detailed meta-analysis of benzene cohort studies. *Ann NY Acad Sci* 2006;1076:90–109.
- [158] Miligi L, Costantini AS, Benvenuti A, Kriebel D, Bolejack V, Tumino R, et al. Occupational exposure to solvents and the risk of lymphomas. *Epidemiology* 2006;17(5):552–61.
- [159] Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol* 2001;153(5):433–43.

- [160] Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. *Am J Ind Med* 1997;31(3):287–95.
- [161] Kolachana P, Subrahmanyam VV, Meyer KB, Zhang L, Smith MT. Benzene and its phenolic metabolites produce oxidative DNA damage in HL60 cells in vitro and in the bone marrow in vivo. *Cancer Res* 1993;53(5):1023–6.
- [162] McHale CM, Zhang L, Smith MT. Current understanding of the mechanism of benzene-induced leukemia in humans: implications for risk assessment. *Carcinogenesis* 2012;33(2):240–52.
- [163] Aksoy M, Dincol K, Akgun T, Erdem S, Dincol G. Haematological effects of chronic benzene poisoning in 217 workers. *Br J Ind Med* 1971;28(3):296–302.
- [164] ATSDR. Toxicological profile for cadmium. Atlanta: Center for Disease Control; 2012. <http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=15>.
- [165] IARC. Cadmium and cadmium compounds. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2012.
- [166] Aoshima K. Itai-itai disease: cadmium-induced renal tubular osteomalacia. *Nihon Eiseigaku Zasshi* 2012;67(4):455–63.
- [167] Kasuya M. Recent epidemiological studies on itai-itai disease as a chronic cadmium poisoning in Japan. *Water Sci Technol* 2000;42(7–8):147–55.
- [168] Uetani M, Kobayashi E, Suwazono Y, Okubo Y, Kido T, Nogawa K. Investigation of renal damage among residents in the cadmium-polluted Jinzu River basin, based on health examinations in 1967 and 1968. *Int J Environ Health Res* 2007;17(3):231–42.
- [169] Ishihara T, Kobayashi E, Okubo Y, Suwazono Y, Kido T, Nishijyo M, et al. Association between cadmium concentration in rice and mortality in the Jinzu River basin. *Jpn Toxicol* 2001;163(1):23–8.
- [170] Kobayashi E, Suwazono Y, Dochi M, Honda R, Kido T. Association of lifetime cadmium intake or drinking Jinzu River water with the occurrence of renal tubular dysfunction. *Environ Toxicol* 2009;24(5):421–8.
- [171] Wang B, Du Y. Cadmium and its neurotoxic effects. *Oxid Med Cell Longev* 2013;2013:898034.
- [172] Thompson J, Bannigan J. Cadmium: toxic effects on the reproductive system and the embryo. *Reprod Toxicol* 2008;25(3):304–15.
- [173] Rani A, Kumar A, Lal A, Pant M. Cellular mechanisms of cadmium-induced toxicity: a review. *Int J Environ Health Res* 2014;24(4):378–99.
- [174] Akesson A, Barregard L, Bergdahl IA, Nordberg GF, Nordberg M, Skerfving S. Non-renal effects and the risk assessment of environmental cadmium exposure. *Environ Health Perspect* 2014;122(5):431–8.
- [175] Prozialeck WC, Edwards JR. Mechanisms of cadmium-induced proximal tubule injury: new insights with implications for biomonitoring and therapeutic interventions. *J Pharmacol Exp Ther* 2012;343(1):2–12.
- [176] Fujiwara Y, Lee JY, Tokumoto M, Satoh M. Cadmium renal toxicity via apoptotic pathways. *Biol Pharm Bull* 2012;35(11):1892–7.
- [177] Bernhoft RA. Cadmium toxicity and treatment. *ScientificWorldJournal* 2013;2013:394652.
- [178] Tellez-Plaza M, Jones MR, Dominguez-Lucas A, Guallar E, Navas-Acien A. Cadmium exposure and clinical cardiovascular disease: a systematic review. *Curr Atheroscler Rep* 2013;15(10):356.
- [179] James KA, Meliker JR. Environmental cadmium exposure and osteoporosis: a review. *Int J Public Health* 2013;58(5):737–45.
- [180] Kolusari A, Kurdoglu M, Yildizhan R, Adali E, Edirne T, Cebi A, et al. Catalase activity, serum trace element and heavy metal concentrations, and vitamin A, D and E levels in pre-eclampsia. *J Int Med Res* 2008;36(6):1335–41.
- [181] Semczuk M, Semczuk-Sikora A. New data on toxic metal intoxication (Cd, Pb, and Hg in particular) and Mg status during pregnancy. *Med Sci Monit* 2001;7(2):332–40.
- [182] USEPA. Cadmium. Washington (DC): U.S. Environmental Protection Agency; 1992. <http://www.epa.gov/iris/subst/0141.htm>.
- [183] Thevenod F, Lee WK. Cadmium and cellular signaling cascades: interactions between cell death and survival pathways. *Arch Toxicol* 2013;87(10):1743–86.
- [184] Feki-Tounsi M, Hamza-Chaffai A. Cadmium as a possible cause of bladder cancer: a review of accumulated evidence. *Environ Sci Pollut Res Int* 2014;21(18):10561–73.

- [185] Hartwig A. Mechanisms in cadmium-induced carcinogenicity: recent insights. *Biometals* 2010;23(5):951–60.
- [186] Miura N. Individual susceptibility to cadmium toxicity and metallothionein gene polymorphisms: with references to current status of occupational cadmium exposure. *Ind Health* 2009;47(5):487–94.
- [187] Wang B, Li Y, Shao C, Tan Y, Cai L. Cadmium and its epigenetic effects. *Curr Med Chem* 2012;19(16):2611–20.
- [188] Ballatori N. Transport of toxic metals by molecular mimicry. *Environ Health Perspect* 2002;110(Suppl. 5):689–94.
- [189] Bridges CC, Zalups RK. Molecular and ionic mimicry and the transport of toxic metals. *Toxicol Appl Pharmacol* 2005;204(3):274–308.
- [190] Chmielewska-Bak J, Izbianska K, Deckert J. The toxic Doppelgänger: on the ionic and molecular mimicry of cadmium. *Acta Biochim Pol* 2013;60(3):369–74.
- [191] Crisponi G, Nurchi VM, Crespo-Alonso M, Toso L. Chelating agents for metal intoxication. *Curr Med Chem* 2012;19(17):2794–815.
- [192] Kim KH, Jahan SA, Kabir E, Brown RJ. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. *Environ Int* 2013;60:71–80.
- [193] IARC. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2010.
- [194] IPCS. Environmental health criteria No. 202. Selected non-heterocyclic polycyclic aromatic hydrocarbons. Geneva: International Programme on Chemical Safety; 1998. <http://www.inchem.org/documents/ehc/ehc/ehc202.htm>.
- [195] NIOSH. NIOSH Pocket Guide to Chemical Hazards: Appendix C – Supplementary Exposure Limits. Available from: <http://www.cdc.gov/niosh/npg/nengapdxc.html> [accessed 05.09.14].
- [196] ATSDR. Toxicological profile for polycyclic aromatic hydrocarbons. Atlanta: Center for Disease Control; 1995. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=122&tid=25>.
- [197] USEPA. Benzo[a]pyrene (BaP). Washington (DC): U.S. Environmental Protection Agency; 1994. <http://www.epa.gov/iris/subst/0136.htm>.
- [198] USEPA. Benzo[b]fluoranthene. Washington (DC): U.S. Environmental Protection Agency; 1994. <http://www.epa.gov/iris/subst/0453.htm>.
- [199] Jarvis IW, Dreij K, Mattsson A, Jernstrom B, Stenius U. Interactions between polycyclic aromatic hydrocarbons in complex mixtures and implications for cancer risk assessment. *Toxicology* 2014;321:27–39.
- [200] Harris KL, Banks LD, Mantey JA, Huderson AC, Ramesh A. Bioaccessibility of polycyclic aromatic hydrocarbons: relevance to toxicity and carcinogenesis. *Expert Opin Drug Metab Toxicol* 2013;9(11):1465–80.
- [201] Verma N, Pink M, Rettenmeier AW, Schmitz-Spanke S. Review on proteomic analyses of benzo[a]pyrene toxicity. *Proteomics* 2012;12(11):1731–55.
- [202] ATSDR. Toxicological profile for 1,3-Butadiene. Atlanta: Center for Disease Control; 2012. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=459&tid=81>.
- [203] IARC. 1,3-Butadiene. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2012.
- [204] USEPA. 1,3-Butadiene. Washington (DC): U.S. Environmental Protection Agency; 2002. <http://www.epa.gov/iris/subst/0139.htm>.
- [205] Dollard GJ, D P, Telling S, Dixon J, Derwent RG. Observed trends in ambient concentrations of C2–C8 hydrocarbons in the United Kingdom over the period from 1993 to 2004. *Atmos Environ* 2007;41(12):2559–69.
- [206] Christian MS. Review of reproductive and developmental toxicity of 1,3-butadiene. *Toxicology* 1996;113(1–3):137–43.
- [207] Macaluso M, Larson R, Delzell E, Sathiakumar N, Hovinga M, Julian J, et al. Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. *Toxicology* 1996;113(1–3):190–202.

- [208] Cheng H, Sathiakumar N, Graff J, Matthews R, Delzell E. 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. *Chem Biol Interact* 2007;166(1-3): 15-24.
- [209] Sathiakumar N, Delzell E, Cheng H, Lynch J, Sparks W, Macaluso M. Validation of 1,3-butadiene exposure estimates for workers at a synthetic rubber plant. *Chem Biol Interact* 2007;166(1-3):29-43.
- [210] Sielken Jr RL, Valdez-Flores C, Gargas ML, Kirman CR, Teta MJ, Delzell E. Cancer risk assessment for 1,3-butadiene: dose-response modeling from an epidemiological perspective. *Chem Biol Interact* 2007;166(1-3):140-9.
- [211] Albertini RJ, Carson ML, Kirman CR, Gargas ML. 1,3-Butadiene: II. Genotoxicity profile. *Crit Rev Toxicol* 2010;40(Suppl. 1):12-73.
- [212] Hong HH, Devereux TR, Melnick RL, Moomaw CR, Boorman GA, Sills RC. Mutations of ras protooncogenes and p53 tumor suppressor gene in cardiac hemangiosarcomas from B6C3F1 mice exposed to 1,3-butadiene for 2 years. *Toxicol Pathol* 2000;28(4):529-34.
- [213] Zhuang SM, Wiseman RW, Soderkvist P. Frequent mutations of the Trp53, Hras1 and beta-catenin (Catnb) genes in 1,3-butadiene-induced mammary adenocarcinomas in B6C3F1 mice. *Oncogene* 2002;21(36):5643-8.
- [214] ATSDR. Toxicological profile for formaldehyde. Atlanta: Center for Disease Control; 1999. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=220&tid=39>.
- [215] IARC. Formaldehyde. Lyon: World Health Organization Press; 2012.
- [216] USEPA. In: Programs OoP, editor. Reregistration eligibility decision for formaldehyde and paraformaldehyde. Washington (DC): United States Environmental Protection Program; 2008.
- [217] McGwin G, Lienert J, Kennedy JI. Formaldehyde exposure and asthma in children: a systematic review. *Environ Health Perspect* 2010;118(3):313-7.
- [218] Kleinnijenhuis AJ, Staal YC, Duistermaat E, Engel R, Woutersen RA. The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure. *Food Chem Toxicol* 2013;52:105-12.
- [219] Lu K, Collins LB, Ru H, Bermudez E, Swenberg JA. Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. *Toxicol Sci* 2010;116(2):441-51.
- [220] Rager JE, Moeller BC, Miller SK, Kracko D, Doyle-Eisele M, Swenberg JA, et al. Formaldehyde-associated changes in microRNAs: tissue and temporal specificity in the rat nose, white blood cells, and bone marrow. *Toxicol Sci* 2014;138(1):36-46.
- [221] USEPA. Formaldehyde. Washington (DC): U.S. Environmental Protection Agency; 2012. <http://www.epa.gov/iris/subst/0419.htm>.
- [222] Lyapina M, Zhelezova G, Petrova E, Boev M. Flow cytometric determination of neutrophil respiratory burst activity in workers exposed to formaldehyde. *Int Arch Occup Environ Health* 2004;77(5):335-40.
- [223] Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, et al. Mortality from solid tumors among workers in formaldehyde industries: an update of the NCI cohort. *Am J Ind Med* 2013;56(9):1015-26.
- [224] Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst* 2009;101(10):751-61.
- [225] Casanova M, Heck HD, Everitt JI, Harrington Jr WW, Popp JA. Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food Chem Toxicol* 1988;26(8):715-6.
- [226] Heck HD, Casanova-Schmitz M, Dodd PB, Schachter EN, Witek TJ, Tosun T. Formaldehyde (CH₂O) concentrations in the blood of humans and Fischer-344 rats exposed to CH₂O under controlled conditions. *Am Ind Hyg Assoc J* 1985;46(1):1-3.
- [227] Lu K, Moeller B, Doyle-Eisele M, McDonald J, Swenberg JA. Molecular dosimetry of N₂-hydroxymethyl-dG DNA adducts in rats exposed to formaldehyde. *Chem Res Toxicol* 2011;24(2):159-61.
- [228] Edrissi B, Taghizadeh K, Moeller BC, Kracko D, Doyle-Eisele M, Swenberg JA, et al. Dosimetry of N(6)-formyllysine adducts following [(1)(3)C(2)H(2)]-formaldehyde exposures in rats. *Chem Res Toxicol* 2013;26(10):1421-3.

- [229] Gentry PR, Rodricks JV, Turnbull D, Bachand A, Van Landingham C, Shipp AM, et al. Formaldehyde exposure and leukemia: critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. *Crit Rev Toxicol* 2013;43(8):661–70.
- [230] Chang JC, Gross EA, Swenberg JA, Barrow CS. Nasal cavity deposition, histopathology, and cell proliferation after single or repeated formaldehyde exposures in B6C3F1 mice and F-344 rats. *Toxicol Appl Pharmacol* 1983;68(2):161–76.
- [231] Monticello TM, Miller FJ, Morgan KT. Regional increases in rat nasal epithelial cell proliferation following acute and subchronic inhalation of formaldehyde. *Toxicol Appl Pharmacol* 1991;111(3):409–21.
- [232] Andersen ME, Clewell 3rd HJ, Bermudez E, Dodd DE, Willson GA, Campbell JL, et al. Formaldehyde: integrating dosimetry, cytotoxicity, and genomics to understand dose-dependent transitions for an endogenous compound. *Toxicol Sci* 2010;118(2):716–31.
- [233] USEPA. Persistent bioaccumulative and toxic chemical program: dioxins and furans. Available from: <http://www.epa.gov/pbt/pubs/dioxins.htm> [accessed 10.10.14].
- [234] ATSDR. Toxicological profile for chlorinated dibenzo-p-dioxins. Atlanta: Center for Disease Control; 1998. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=459&tid=81>.
- [235] IARC. 2,3,7,8-tetrachlorodibenzo-para-dioxin and 2,3,4,7,8-pentachlorodibenzofuran, and 3,3',4,4',5-pentachlorobiphenyl. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2012.
- [236] Buckingham WJ. In: History of USAF, editor. Operation ranch hand: the air force and herbicides in Southeast Asia 1961–1971. Washington (DC): Office of United States Air Force History; 1982.
- [237] Schecter A, Ryan J, Lizotte R, Sun WF, Miller L, Gitlitz G, et al. Chlorinated dibenzodioxin and dibenzofuran levels in human adipose tissues in exposed and control New York state patients. *Chemosphere* 1985;14(6/7):933–7.
- [238] Schecter A, Constable J, Arghestani S, Tong H, Gross M. Elevated levels of 2,3,7,8-tetrachlorodibenzodioxin in adipose tissue of certain U.S. Veterans of the Vietnam war. *Chemosphere* 1987;16(8/9):1997–2002.
- [239] Schecter A, Ryan J, Constable J. Chlorinated dibenzo-p-dioxin and dibenzofuran levels in human adipose tissue and milk samples from the north and south of Vietnam. *Chemosphere* 1986;15(9–12):1613–20.
- [240] USEPA. In: Superfund, editor. Love canal. Washington (DC): U.S. Environmental Protection Agency; 2012. <http://www.epa.gov/region2/superfund/npl/lovecanal/>.
- [241] USEPA. In: Superfund, editor. NPL site narrative for Times Beach. Washington (DC): U.S. Environmental Protection Agency; 1983. <http://www.epa.gov/superfund/sites/npl/nar833.htm>.
- [242] USEPA. Environmental monitoring at the Love Canal. Washington (DC): U.S. Environmental Protection Agency; 1982. p. 156–61.
- [243] USEPA. In: Systems SI, editor. Times beach: record of decision. Washington (DC): U.S. Environmental Protection Agency; 1988. <http://cumulis.epa.gov/superrods/index.cfm?section=data.rodinfol&id=0701237&mRod=07012371988ROD015>.
- [244] Baccarelli A, Mocarelli P, Patterson Jr DG, Bonzini M, Pesatori AC, Caporaso N, et al. Immunologic effects of dioxin: new results from Seveso and comparison with other studies. *Environ Health Perspect* 2002;110(12):1169–73.
- [245] Cerlesi S, Di Domenico A, Ratti S. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) persistence in the Seveso (Milan, Italy) soil. *Ecotoxicol Environ Saf* 1989;18(2):149–64.
- [246] di Domenico A, Silano V, Viviano G, Zapponi G. Accidental release of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. II. TCDD distribution in the soil surface layer. *Ecotoxicol Environ Saf* 1980;4(3):298–320.
- [247] Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, et al. Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol* 2001;153(11):1031–44.
- [248] Stehr-Green PA, Andrews Jr JS, Hoffman RE, Webb KB, Schramm WF. An overview of the Missouri dioxin studies. *Archives Environ Health* 1988;43(2):174–7.
- [249] Austin AA, Fitzgerald EF, Pantea CI, Gensburg LJ, Kim NK, Stark AD, et al. Reproductive outcomes among former Love Canal residents, Niagara Falls, New York. *Environ Res* 2011;111(5):693–701.
- [250] Gensburg LJ, Pantea C, Kielbaso C, Fitzgerald E, Stark A, Kim N. Cancer incidence among former Love Canal residents. *Environ Health Perspect* 2009;117(8):1265–71.

- [251] White SS, Birnbaum LS. An overview of the effects of dioxins and dioxin-like compounds on vertebrates, as documented in human and ecological epidemiology. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2009;27(4):197–211.
- [252] Le TN, Johansson A. Impact of chemical warfare with agent orange on women's reproductive lives in Vietnam: a pilot study. *Reprod Health Matters* 2001;9(18):156–64.
- [253] Kang HK, Dalager NA, Needham LL, Patterson DG Jr, Lees PS, Yates K, et al. Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. *Am J Ind Med* 2006;49(11):875–84.
- [254] Milbrath MO, Wenger Y, Chang CW, Emond C, Garabrant D, Gillespie BW, et al. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. *Environ Health Perspect* 2009;117(3):417–25.
- [255] Flesch-Janys D, Becher H, Gurn P, Jung D, Konietzko J, Manz A, et al. Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans in occupationally exposed persons. *J Toxicol Environ Health* 1996;47(4):363–78.
- [256] Chopra M, Schrenk D. Dioxin toxicity, aryl hydrocarbon receptor signaling, and apoptosis—persistent pollutants affect programmed cell death. *Crit Rev Toxicol* 2011;41(4):292–320.
- [257] Frumkin H. Agent Orange and cancer: an overview for clinicians. *CA Cancer J Clin* 2003;53(4):245–55.
- [258] Mocarelli P, Gerthoux PM, Patterson Jr DG, Milani S, Limonta G, Bertona M, et al. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. *Environ Health Perspect* 2008;116(1):70–7.
- [259] Ngo AD, Taylor R, Roberts CL. Paternal exposure to Agent Orange and spina bifida: a meta-analysis. *Eur J Epidemiol* 2010;25(1):37–44.
- [260] USEPA. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD). Washington (DC): U.S. Environmental Protection Agency; 2012. <http://www.epa.gov/iris/subst/1024.htm>.
- [261] Leng L, Chen X, Li CP, Luo XY, Tang NJ. 2,3,7,8-Tetrachlorodibenzo-p-dioxin exposure and prostate cancer: a meta-analysis of cohort studies. *Public Health* 2014;128(3):207–13.
- [262] Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect* 1998;106(Suppl. 2):655–62.
- [263] Kogevinas M, Kauppinen T, Winkelmann R, Becher H, Bertazzi PA, Bueno-de-Mesquita HB, et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. *Epidemiology* 1995;6(4):396–402.
- [264] Denison MS, Soshilov AA, He G, DeGroot DE, Zhao B. Exactly the same but different: promiscuity and diversity in the molecular mechanisms of action of the aryl hydrocarbon (dioxin) receptor. *Toxicol Sci* 2011;124(1):1–22.
- [265] Sorg O. AhR signalling and dioxin toxicity. *Toxicol Lett* 2014;230(2):225–33.
- [266] ATSDR. Toxicological profile for chloroform. Atlanta: Center for Disease Control; 1997. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=53&tid=16>.
- [267] IARC. Chloroform. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Geneva: World Health Organization Press; 1999.
- [268] USEPA. In: Chloroform. Washington (DC): U.S. Environmental Protection Agency; 2001. <http://www.epa.gov/iris/subst/0025.htm>.
- [269] Hogan MD, Chi PY, Hoel DG, Mitchell TJ. Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. *J Environ Pathol Toxicol* 1979;2(3):873–87.
- [270] Cantor KP, Hoover R, Mason TJ, McCabe LJ. Associations of cancer mortality with halomethanes in drinking water. *J Natl Cancer Inst* 1978;61(4):979–85.
- [271] Villanueva CM, Cantor KP, Cordier S, Jaakkola JJ, King WD, Lynch CF, et al. Disinfection byproducts and bladder cancer: a pooled analysis. *Epidemiology* 2004;15(3):357–67.
- [272] Villanueva CM, Cantor KP, Grimalt JO, Malats N, Silverman D, Tardon A, et al. Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. *Am J Epidemiol* 2007;165(2):148–56.
- [273] Boobis AR. Mode of action considerations in the quantitative assessment of tumour responses in the liver. *Basic Clin Pharmacol Toxicol* 2010;106(3):173–9.

- [274] Richardson SD, Plewa MJ, Wagner ED, Schoeny R, Demarini DM. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. *Mutat Res* 2007;636(1–3):178–242.
- [275] Hamidin N, Yu QJ, Connell DW. Human health risk assessment of chlorinated disinfection by-products in drinking water using a probabilistic approach. *Water Res* 2008;42(13):3263–74.
- [276] Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res* 2009;43(8):2057–92.
- [277] Richardson SD, Ternes TA. Water analysis: emerging contaminants and current issues. *Anal Chem* 2014;86(6):2813–48.
- [278] Richardson SD. Water analysis: emerging contaminants and current issues. *Anal Chem* 2009;81(12):4645–77.
- [279] Richardson SD, Ternes TA. Water analysis: emerging contaminants and current issues. *Anal Chem* 2011;83(12):4614–48.
- [280] Clarke BO, Smith SR. Review of ‘emerging’ organic contaminants in biosolids and assessment of international research priorities for the agricultural use of biosolids. *Environ Int* 2011;37(1):226–47.
- [281] Howard PH, Muir DC. Identifying new persistent and bioaccumulative organics among chemicals in commerce. *Environ Sci Technol* 2010;44(7):2277–85.
- [282] De Coster S, van Larebeke N. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. *J Environ Public Health* 2012;2012:713696.
- [283] Faniband M, Lindh CH, Jonsson BA. Human biological monitoring of suspected endocrine-disrupting compounds. *Asian J Androl* 2014;16(1):5–16.
- [284] Waaijers SL, Kong D, Hendriks HS, de Wit CA, Cousins IT, Westerink RH, et al. Persistence, bioaccumulation, and toxicity of halogen-free flame retardants. *Rev Environ Contam Toxicol* 2013;222:1–71.
- [285] ATSDR. Toxicological profile for polybrominated biphenyls and polybrominated diphenyl ethers. Atlanta: Center for Disease Control; 2006. <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=529&tid=94>.
- [286] Liagkouridis I, Cousins IT, Cousins AP. Emissions and fate of brominated flame retardants in the indoor environment: a critical review of modelling approaches. *Sci Total Environ* 2014;491–492:87–99.
- [287] Kim YR, Harden FA, Toms LM, Norman RE. Health consequences of exposure to brominated flame retardants: a systematic review. *Chemosphere* 2014;106:1–19.
- [288] Basis A, Samara C. Polybrominated diphenyl ethers (PBDEs) in the indoor and outdoor environments—a review on occurrence and human exposure. *Environ Pollut* 2012;169:217–29.
- [289] Stieger G, Scheringer M, Ng CA, Hungerbühler K. Assessing the persistence, bioaccumulation potential and toxicity of brominated flame retardants: data availability and quality for 36 alternative brominated flame retardants. *Chemosphere* 2014;116:118–23.
- [290] van der Veen I, de Boer J. Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere* 2012;88(10):1119–53.
- [291] Bulathsinghala AT, Shaw IC. The toxic chemistry of methyl bromide. *Hum Exp Toxicol* 2014;33(1):81–91.
- [292] Ren XM, Guo LH. Molecular toxicology of polybrominated diphenyl ethers: nuclear hormone receptor mediated pathways. *Environ Sci Process Impacts* 2013;15(4):702–8.
- [293] USEPA. Brominated dibenzofurans. Washington (DC): U.S. Environmental Protection Agency; 1990. <http://www.epa.gov/iris/subst/0514.htm>.
- [294] Yang WH, Wang ZY, Liu HL, Yu HX. Exploring the binding features of polybrominated diphenyl ethers as estrogen receptor antagonists: docking studies. *SAR QSAR Environ Res* 2010;21(3–4):351–67.
- [295] Kamstra JH, Hruba E, Blumberg B, Janesick A, Mandrup S, Hamers T, et al. Transcriptional and epigenetic mechanisms underlying enhanced in vitro adipocyte differentiation by the brominated flame retardant BDE-47. *Environ Sci Technol* 2014;48(7):4110–9.
- [296] Gassmann K, Schreiber T, Dingemans MM, Krause G, Roderigo C, Giersiefer S, et al. BDE-47 and 6-OH-BDE-47 modulate calcium homeostasis in primary fetal human neural progenitor cells via ryanodine receptor-independent mechanisms. *Arch Toxicol* 2014;88(8):1537–48.

- [297] Lindstrom AB, Strynar MJ, Libelo EL. Polyfluorinated compounds: past, present, and future. *Environ Sci Technol* 2011;45(19):7954–61.
- [298] Kannan K, Corsolini S, Falandysz J, Fillmann G, Kumar KS, Loganathan BG, et al. Perfluorooctane-sulfonate and related fluorochemicals in human blood from several countries. *Environ Sci Technol* 2004;38(17):4489–95.
- [299] Llorca M, Farre M, Pico Y, Muller J, Knepper TP, Barcelo D. Analysis of perfluoroalkyl substances in waters from Germany and Spain. *Sci Total Environ* 2012;431:139–50.
- [300] Perez F, Nadal M, Navarro-Ortega A, Fábrega F, Domingo JL, Barceló D, et al. Accumulation of perfluoroalkyl substances in human tissues. *Environ Int* 2013;59:354–62.
- [301] Post GB, Cohn PD, Cooper KR. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. *Environ Res* 2012;116:93–117.
- [302] Domingo JL. Health risks of dietary exposure to perfluorinated compounds. *Environ Int* 2012;40:187–95.
- [303] White SS, Fenton SE, Hines EP. Endocrine disrupting properties of perfluorooctanoic acid. *J Steroid Biochem Mol Biol* 2011;127(1–2):16–26.
- [304] Llorca M, Farre M, Pico Y, Teijon ML, Alvarez JG, Barcelo D. Infant exposure of perfluorinated compounds: levels in breast milk and commercial baby food. *Environ Int* 2010;36(6):584–92.
- [305] Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. Perfluoroalkyl acids: a review of monitoring and toxicological findings. *Toxicol Sci* 2007;99(2):366–94.
- [306] Lin CY, Wen LL, Lin LY, Wen TW, Lien GW, Hsu SH, et al. The associations between serum perfluorinated chemicals and thyroid function in adolescents and young adults. *J Hazard Mater* 2013;244–245:637–44.
- [307] Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* 2007;115(9):1298–305.
- [308] Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, et al. PPARalpha agonist-induced rodent tumors: modes of action and human relevance. *Crit Rev Toxicol* 2003;33(6):655–780.
- [309] Bjork JA, Butenhoff JL, Wallace KB. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. *Toxicology* 2011;288(1–3):8–17.
- [310] Rosen MB, Abbott BD, Wolf DC, Corton JC, Wood CR, Schmid JE, et al. Gene profiling in the livers of wild-type and PPARalpha-null mice exposed to perfluorooctanoic acid. *Toxicol Pathol* 2008;36(4):592–607.
- [311] Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, et al. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. *Toxicol Sci* 2011;123(1):290–303.
- [312] Elcombe CR, Elcombe BM, Foster JR, Farrar DG, Jung R, Chang SC, et al. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPARalpha and CAR/PXR. *Arch Toxicol* 2010;84(10):787–98.
- [313] Peng S, Yan L, Zhang J, Wang Z, Tian M, Shen H. An integrated metabolomics and transcriptomics approach to understanding metabolic pathway disturbance induced by perfluorooctanoic acid. *J Pharm Biomed Anal* 2013;86:56–64.
- [314] Fisher M, Arbuckle TE, Wade M, Haines DA. Do perfluoroalkyl substances affect metabolic function and plasma lipids?—Analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) Cycle 1. *Environ Res* 2013;121:95–103.
- [315] Colas A, Curtis J. Silicone biomaterials: history and chemistry & medical applications of silicones. In: Ratner B, Hoffman A, Schoen F, Lemons J, editors. *Biomaterials science: an introduction to materials in medicine*. (USA): Elsevier Academic Press; 2005.
- [316] Surita SC, Tansel B. A multiphase analysis of partitioning and hazard index characteristics of siloxanes in biosolids. *Ecotoxicol Environ Saf* 2014;102:79–83.
- [317] Zhang Z, Qi H, Ren N, Li Y, Gao D, Kannan K. Survey of cyclic and linear siloxanes in sediment from the Songhua River and in sewage sludge from wastewater treatment plants, Northeastern China. *Arch Environ Contam Toxicol* 2011;60(2):204–11.

- [318] ASPS. 2010 quick facts: cosmetic and reconstructive plastic surgery trends. Arlington Heights: American Society of Plastic Surgeons; 2010.
- [319] Sergott TJ, Limoli JP, Baldwin Jr CM, Laub DR. Human adjuvant disease, possible autoimmune disease after silicone implantation: a review of the literature, case studies, and speculation for the future. *Plast Reconstr Surg* 1986;78(1):104–14.
- [320] Kessler DA. The basis of the FDA's decision on breast implants. *N Engl J Med* 1992;326(25):1713–5.
- [321] Marshall WR. Re: augmentation mammoplasty associated with a severe systemic illness. *Ann Plast Surg* 1997;39(6):668.
- [322] Hajdu SD, Agmon-Levin N, Shoenfeld Y. Silicone and autoimmunity. *Eur J Clin Invest* 2011;41(2):203–11.
- [323] Herink C, Zwaka PA, Schon MP, Mempel M, Seitz CS. Serious complications following gluteal injection of silicone. *Hautarzt* 2013;64(8):599–602.
- [324] Bekerecioglu M, Onat AM, Tercan M, Buyukhatipoglu H, Karakok M, Isik D, et al. The association between silicone implants and both antibodies and autoimmune diseases. *Clin Rheumatol* 2008;27(2):147–50.
- [325] Lipworth L, Holmich LR, McLaughlin JK. Silicone breast implants and connective tissue disease: no association. *Semin Immunopathol* 2011;33(3):287–94.
- [326] Lipworth L, Tarone RE, McLaughlin JK. Silicone breast implants and connective tissue disease: an updated review of the epidemiologic evidence. *Ann Plast Surg* 2004;52(6):598–601.
- [327] Johnson Jr W, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, et al. Safety assessment of cyclomethicone, cyclotetrasiloxane, cyclopentasiloxane, cyclohexasiloxane, and cycloheptasiloxane. *Int J Toxicol* 2011;30(6 Suppl.):149S–227S.
- [328] Becker LC, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, et al. Safety assessment of silylates and surface-modified siloxysilicates. *Int J Toxicol* 2013;32(3 Suppl.):5S–24S.
- [329] Pastor JC, Puente B, Telleria J, Carrasco B, Sanchez H, Nocito M. Antisilicone antibodies in patients with silicone implants for retinal detachment surgery. *Ophthalmic Res* 2001;33(2):87–90.
- [330] Evans GR, Slezak S, Rieters M, Bercow GM. Silicon tissue assays in nonaugmented cadaveric patients: is there a baseline level? *Plast Reconstr Surg* 1994;93(6):1117–22.
- [331] Quinn AL, Regan JM, Tobin JM, Marinik BJ, McMahon JM, McNett DA, et al. In vitro and in vivo evaluation of the estrogenic, androgenic, and progestagenic potential of two cyclic siloxanes. *Toxicol Sci* 2007;96(1):145–53.
- [332] IARC. Polychlorinated biphenyls. In: WHO, editor. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: World Health Organization Press; 2013.
- [333] Teeguarden JG, Hanson-Drury S. A systematic review of Bisphenol A “low dose” studies in the context of human exposure: a case for establishing standards for reporting “low-dose” effects of chemicals. *Food Chem Toxicol* 2013;62:935–48.
- [334] Geens T, Aerts D, Berthot C, Bourguignon JP, Goeyens L, Lecomte P, et al. A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem Toxicol* 2012;50(10):3725–40.
- [335] CDC. Bisphenol a. Atlanta: Center for Disease Control and Prevention; 2013. http://www.cdc.gov/biomonitoring/BisphenolA_BiomonitoringSummary.html.
- [336] Rochester JR. Bisphenol A and human health: a review of the literature. *Reprod Toxicol* 2013;42:132–55.
- [337] IARC. Trihalomethanes in drinking water. In: WHO, editor. WHO guidelines for drinking-water quality. Geneva: World Health Organization Press; 2004.
- [338] Bubalo MC, Radosevic K, Redovnikovic IR, Halambek J, Srcek VG. A brief overview of the potential environmental hazards of ionic liquids. *Ecotoxicol Environ Saf* 2014;99:1–12.
- [339] Pham TP, Cho CW, Yun YS. Environmental fate and toxicity of ionic liquids: a review. *Water Res* 2010;44(2):352–72.
- [340] Gwinn MR, Vallyathan V. Nanoparticles: health effects—pros and cons. *Environ Health Perspect* 2006;114(12):1818–25.