Emerging Contaminants and Associated Treatment Technologies

Muhammad Sajid Hamid Akash
Kanwal Rehman *Editors*

Environmental Contaminants and Neurological Disorders

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This book is dedicated
To
Our Beloved and Adorable Little Twinkles Muhammad Aqdas Akash and Zainab Akash*, and without their love and prayers, the compilation of this book would not have been possible.*

Preface

We decided to write this book as, thus far, no such extensive writing has been offered in a single volume that can essentially deliver a comprehensive concept of environmental contaminants (ECs)-induced neurological disorders (NDs) under unique single point. This book entitled *Environmental Contaminants and Neurological Disorders* is envisioned to primarily offer an overview of neurological disorders and their associated ailments followed by a reflective and detailed discussion on the role of various ECs, their sources, determinants, prevalence, and progression to NDs. Moreover, we have also provided an account of various prevention and therapeutic interventions by elaborating the treatment strategies of ECs-induced neurological disorders.

The prevalence of NDs is rapidly increasing with the growing population. This greatly affects the social and financial status of individuals all over the world. Unfortunately, specific environmental contaminants and habitual impurities that can be considered as foremost keystones are not only accountable for the onset of NDs but also lead to the progression of NDs. Human exposure to ECs can occur via ingestion of food, dust, and water, via inhalation of gases and particles present in the air, and through the skin. This emphasizes the desire to better understand the principal disease mechanisms, which will not only help to eradicate these sustaining causative factors but may also help to propose targeted therapy for ECs-associated neurological diseases. An added value to this book is a section on the occurrence and exposure of ECs to human beings.

We promise that the contents of this book will motivate and encourage research to promote and broaden the information concerning the determinants that can critically affect the human well-being, with the definitive aim of understanding the factual data provided in this book into valuable novelties.

Faisalabad, Pakistan

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We would like to offer our sincere thanks to the authors for being essential contributors to each chapter of this volume who supported us and collaborated, which really helped us achieve this goal. Without any doubt, it can be said that the expertise of each author demonstrated is significant in the accomplishment of our objective.

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Lastly, we, editors, would like to acknowledge Springer for giving us the support to complete this book and for providing essential information regarding the exposure of environmental contaminants and their association with the development of neurological disorders.

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Chapter 1
Pathogenesis of Neurodegeneration and Associated Neurological Disorders

Tauqeer Hussain Mallhi, Amna Saifullah, Yusra Habib Khan, Amjad Khan, Nasser Hadal Alotaibi, and Abdulaziz Ibrahim Alzarea

Abstract The term neurodegeneration refers to the progressive neuronal damage. Since neurons are the cells present in the brain and spinal cord and do not replicate, any damage to these cells results in brain dysfunction and incurable neurological diseases. Neurodegenerative disorders are classifiable according to primary clinical characteristics (predominantly motor or cognitive function decline) or principal molecular abnormalities due to protein aggregation. The most prevalent proteinopathies of neurodegenerative origin are amyloidosis, tauopathies, alpha-synucleinopathies, and transactivation response DNA-binding protein 43 proteinopathies. These neurodegenerative disorders share some common histopathological, clinical, and molecular features. The underlying mechanisms involved in neurodegenerative disorders are the specific protein accumulation, genetic mutations, neuronal vulnerability, aberrant RNA metabolism, oxidative stress, mitochondrial dysfunction, microglial activation, neuro-inflammation, and disrupted axonal transport. The biomarkers which may assist in the detection of these debilitating and globally prevalent disorders are desperately pursued and required. The spectrum of biofluid biomarkers of neurodegenerative disorders is explained in this chapter.

Keywords Neurodegeneration · Neurodegenerative disorders · Pathogenesis · Proteinopathies

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Introduction

The term neurodegeneration is a combination of two words: ‘neuro’ referring to neurons and ‘degeneration’ pointing towards progressive damage. Neurons are the cells present in the brain and spinal cord and do not replicate. Any damage to these cells results in brain dysfunction and incurable neurological disorders. More than six million individuals in the US, and perhaps more than 50 million globally, have a neurodegenerative disorder [1]. The most prevalent neurodegenerative disorders include Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), amyotrophic lateral sclerosis [2], frontotemporal dementia (FTD), and prions disease. The invariably disruptive, devastatingly crippling and inevitably fatal nature of these disorders mark them among the hardest challenge to address in biomedicine. With the progression of disease, the victim, family, and friends may undergo an overwhelming physical, mental, and financial strain. The healthcare expenses are growing exorbitant, and as age is typically the main risk factor for developing a neurodegenerative disease, population trends indicate that populations may be overburdened over the coming decades [1]. At most, all approved treatments function at the symptomatic level; none delay or reverse the inexorable depletion of neurons and neuronal linkages. Additionally, these disorders share some common molecular, histopathological, and clinical features. Although considerable progress has been made in understanding the molecular and cellular origin of neurodegenerative disorders, this progress is yet to be converted into efficacious treatment strategies. The aim of this chapter is to explain the general trends underlying the major neurodegenerative diseases and draw biochemical, histopathological, and molecule-genetic similarities as well as divergence throughout the numerous categories of diseases.

Common Pathological and Clinical Manifestations of Neurodegenerative Disorders

Neurodegenerative disorders are illnesses that involve the death of certain parts of the brain. They are, by far, some of the toughest diseases to cure with debilitating outcomes. Parkinson’s and Huntington’s disease are among the most severe and common movement disorders. Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons normally do not reproduce or replace themselves, so when they become damaged or died, they cannot be replaced by the body. Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. This causes problems with movement (called ataxias) or mental functioning (called dementias). The spectrum of neurodegenerative disorders varies from mild to lethal. The important facts regarding these neurodegenerative disorders are given below:

- The neurodegenerative disorders affect a unique subset of neurons, without any explicit reason and could be either hereditary or acquired.
- The onset of familial forms of disease occurs at early age than sporadic forms. These diseases tend to develop "relentlessly" until death and are often accompanied with an advancing age.
- Microscopic signs ranging from neuronal dysfunction, cell death, neuronal loss, and proliferation of glial cells are commonly associated with neurodegeneration.
- No proven treatment reverses the condition but the therapies can offer minimal and transient change.
- Phenotypic heterogeneity is normally observed.
- Cognitive disability and dementia are typical in neurodegenerative diseases which do not appear in all cases.
- In one case, symptoms of multiple neurodegenerative disorder may seem to coexist. For instance, both ALS and FTD have clinical similarities; however, some assume that the two disorders reflect a continuum rather than distinct diseases.

Classification of Neurodegenerative Disorders

Neurodegenerative disorders can be classified as following:

Molecular Pathological Classification

Neurological disorders caused by the aberrant or accumulated proteins in certain regions of brain are broadly classified under the term proteinopathies [3, 4]. After a size change in their three-dimensional form, these proteins become pathologically active and culminate in self-association, elongation, and accumulation in various brain regions. The possibility of such transitions, whether or not linked with genetic disorder, is significantly enhanced by the inherent capability of proteins, experiencing drastic changes in their conformation [3, 4]. An overview of selective proteinopathies is given in Table 1.1. The following proteins are thought to be associated with the pathogenesis of proteinopathies [5, 6].

1. MAPT, the microtubule-associated protein tau with monogene encoding on the chromosome 17q21.
2. Aβ (Beta-amyloid) protein, cleaved by a large transmembrane amyloid-precursor protein (APP). The gene encoding APP is mapped on 21 chromosomal centromeres at position 21.

Table 1.1 Overview of selective proteinopathies

Disease	Main neuropathology	Protein aggregates	Main anatomic vulnerability
Amyloidosis			
Creutzfeldt–Jakob disease (genetic, variant, sporadic, iatrogenic)	Spongiform changes Prion protein (PrP) accumulation	PrP	Cerebral cortex Neostriatum Thalamus Cerebellum
Gerstmann–Sträussler–Scheinker disease	Spongiform changes Multicentric PrP plaques	PrP	Cerebral cortex Cerebellum
Familial British dementia	Amyloid angiopathy Parenchymal amyloid plaques	ABR1	Cerebral cortex Cerebellum
Alzheimer's disease	Neurofibrillary tangles (NFTs) Neuropil threads Neuritic and amyloid plaques Amyloid angiopathy	Aβ 3R + 4R tau	Basal forebrain Frontal and temporal lobes Limbic structure Locus coeruleus Olfactory bulb
Taupathies			
Chronic traumatic encephalopathy	Astrocytic tau tangles Neuropil threads NFTs	3R + 4R tau	Frontal, temporal, and parietal lobes Depth of sulci and surrounding vasculature
Primary age-related tauopathy	NFTs	3R + 4R tau	Basal forebrain Brainstem Medial temporal lobe Olfactory bulb
Pick's disease	Pick bodies, Pick cells/ballooned neurons	3R tau	Basal forebrain Frontal and temporal lobes Limbic structures Striatum
Progressive supranuclear palsy	Globose NFTs tufted astrocytes Oligodendroglial coiled bodies Neuropil threads	4R tau	Subthalamic nucleus Substantia nigra Superior colliculus Cerebellar dentate
Corticobasal degeneration	Pretangles Astrocytic plaques Neuropil threads Ballooned neurons	4R tau	Frontoparietal association cortices Neostriatum Substantia nigra
Argyrophilic grain disease	Argyrophilic grains Ballooned neurons Coiled bodies Ramified astrocytes	4R tau	Limbic structures

(continued)

Table 1.1 (continued)

Disease	Main neuropathology	Protein aggregates	Main anatomic vulnerability
Ageing-related tau astrogliopathy	Thorn-shaped astrocytes Granular astrocytes	4R tau	Subpial and perivascular spaces Mediobasal forebrain Amygdala
Synucleinopathies			
Lewy body disorders	Lewy bodies Lewy neurites	α-synuclein	Amygdala Cerebral cortex Dorsal motor nucleus Hippocampus (CA2) Locus coeruleus Olfactory bulb Substantia nigra
Multiple system atrophy	Glial cytoplasmic inclusions	α-synuclein	Putamen Substantia nigra Pontine nuclei Medulla (inferior olivary nucleus) Cerebellum
TDP-43 proteinopathies			
Frontotemporal lobar degeneration	Neuronal cytoplasmic inclusions Neuronal nuclear inclusions Dystrophic neurites	TDP-43	Frontal and temporal cortices Basal ganglia Substantia nigra
Amyotrophic lateral sclerosis	Upper and lower motor neuron loss Bunina bodies Neuronal inclusions Astrocytic hyaline inclusions	TDP-43	Motor cortex Brainstem motor neurons Spinal cord motor neurons
Primary lateral sclerosis	Upper motor neuron loss Corticospinal tract degeneration	TDP-43	Motor cortex Corticospinal tracts
Progressive muscular atrophy	Lower motor neuron loss Swollen motor neurons	TDP-43	Brainstem motor neurons Spinal cord motor neurons

This table is adopted from source [4] which is open access and does not require permission

3. A transactive response [7] DNA-binding protein-43 (TDP-43) is a highly conserved nuclear protein. It is encoded by the gene of TARDBP located on chromosome 1.
4. A single gene encoded protein, α-synuclein (SNCA) on chromosome 4.
5. Fused-in sarcoma (FUS) included FET proteins, TATA-binding protein-associated factor 15 (TAF15), and the Ewing sarcoma RNA-binding protein 1 (EWSR1). The most observed FUS is a long protein with a total of 526 amino acids, coded by the gene positioned on chromosome 16.

6. A 253 amino acids protein named as prion protein (PrP). The gene involved in the coding of PrP (PRNP) is positioned to chromosome 20. These proteins are produced by genes connected to repeat defects of the neuronal trinucleotide, neuroserpin, neurodegenerative conditions related to ferritin, and cerebral amyloidosis of familial origin. These proteins are mostly correlated with inherited neurodegenerative disorders.

Types of Proteinopathies

Amyloidosis

The proteinopathies caused by the aggregation of fibrous insoluble amyloid proteins are termed as amyloidosis. A proteolytic form of APP, β-amyloid, or Aβ aggregation in AD is the most common type of amyloidosis. While β-amyloid is a defining characteristic of AD, such deposits are also known to be comorbid features of multiple other neurodegenerative disorders especially among elders present with apolipoprotein E4 (ApoE4), the AD's main genetic risk factor. In addition to β-amyloid, the aggregation of PrP and two peptides such as British Amyloid (ABri) and Danish Amyloid (ADan) results in other less common types of amyloidosis. Prions are infectious protein agents which trigger neurological diseases that are inheritable, sporadic, and infectious. The genetic mutations in BR12 genes result in the production of ABri and ADan. Examples include the prion protein deposited familial and sporadic Creutzfeldt—Jakob disease (CJD) and Gerstmann–Sträussler–Scheinker disease (GSS), ABri deposited inherited British and ADan deposited Danish dementias [3, 4].

Synucleinopathies

This group of proteinopathies is distinguished by the deposition of, a presynaptic protein named as, α-synuclein, within neuronal or glial cells (predominantly oligodendrocytes). Pathological aggregation of α-synuclein has been observed in disorders of Lewy bodies and multiple system atrophy (MSA). The disorders of Lewy bodies include range of syndromes such as PD as well as dementias with Lewy bodies (DLB) and PD. The α-synucleinic deposits of oligodendritic origin are observed in MSA while Lewy body disorders are presented with neuronal aggregates of α-synuclein [3, 4, 8].

Taupathies

The neuropathies caused by pathological deposition of tau proteins in neuronal and neuroglial cells are grouped under the term taupathies [9]. The microtubule-associated proteins, tau (MAPT), are phospho proteins promoting the polymeriza-

tion and stabilization of microtubules. Alternative mRNA splicing of two, three, and ten exons of the MAPT produces six isoforms. Repetition of 31 or 32 amino acids of exons 10 produces three isoforms of both 3R (three repeats) and 4R (four repeats) tau proteins [4, 9]. The abnormal aggregation of tau proteins in neurodegenerative diseases include phosphorylation and posttranslational modification processes such as ubiquitination, acetylation, nitration, and glycation. The taupathies are distinguished on the basis of relative accumulation of 3R and 4R proteins [4, 9]. The 3R taupathies are observed in picks diseases (PID) and some forms of frontotemporal dementia and PD associated with chromosome number 17 (FTID-17); however, progressive supranuclear palsy (PSD), argyrophilic brain disease (AGD), corticobasal degeneration (CBD), and some forms of FTID-17 are observed with the accumulation of 4R tau proteins [4]. Mixed 3R + 4R taupathies include primary age-related taupathy/neurofibrillary tangle (PART/NFT) dementia, AD, chronic traumatic encephalopathy (CTE), and some forms of FTID-17 [3, 4, 9].

TDP-43 Proteinopathies

The transactive response [7] DNA-binding protein of 43 KDa (TDP-43) is a versatile protein involving in RNA metabolism, gene splicing modulation, transcriptional repression processes, and stress granules. Although TDP-43 is of nuclear origin, it forms inclusions in nucleus, cytoplasm, and other cell processes in neurodegenerative diseases. The deposition of hyperphosphorylated and ubiquitinated inclusion bodies in certain parts of brain and spinal cord results in proteinopathies such as frontotemporal lobar degeneration (FTLD) and ALS. Among the ALS cases, almost 90–95% cases show sporadic disease. Inherited mutations of TDP-43 result in 5–10% of familial ALS cases while mutations in other genes such as NEK1, C9ORF72, FUS, and SOD1 result in remaining cases of familial ALS [3, 4].

Clinicopathological Classification

This classification is based on clinical presentation of neurological disorders as a result of anatomic involvement and corresponding neuronal dysfunction (Fig. 1.1). Clinical manifestations of neurodegenerative disorders are classified among the following groups [5, 6]:

Disorders Involving Predominantly Cognitive Symptoms

It involves altered high-order brain functionality, dementia, and cognitive decline. Related anatomical brain areas include the hippocampal, entorhinal cortical, limbic, and neocortical regions. The FTLD is consistent with frontal and temporal lobes of the brain.

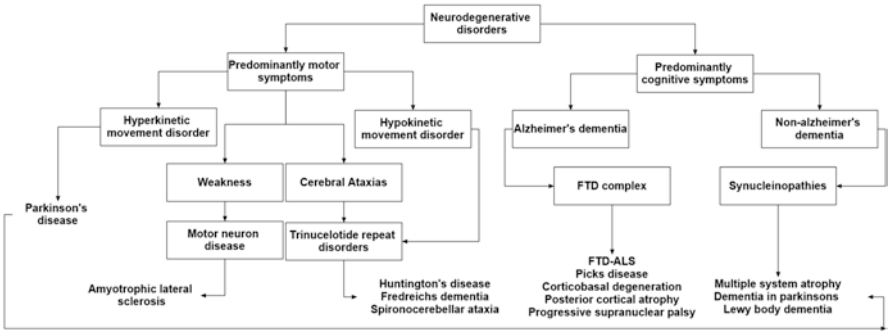

Fig. 1.1 Clinicopathological classification of neurodegenerative disorders. (This figure is self-constructed by taking the information from source [2])

Disorders Involving Predominantly Motor Symptoms

It involves the symptoms related to hypo- and hyper-kinetic movement disorders, cerebellar dysfunction, and disturbances of upper and lower motor neuronal activity. The basal ganglion, thalamic region, nuclei of brain stem, cerebellar cortex and nuclei, areas of motor cortex, and lower motor neurons of the spinal cord are the main anatomical areas implicated with motor movement disorders.

Molecular and Cellular Mechanisms of Neurodegeneration

In the pathogenesis of multiple neurodegenerative disorders, a variety of popular trends have arisen. Whether such commonalities are merely secondary systems, representing the fact that neurons have a small range to die by or whether they expose essential initiation mechanisms remains uncertain. Any putative specific pathogenic molecular and cellular pathways will be addressed in the following section, although it is worth noting that at present it is impossible to differentiate between underlying mechanisms involved in disease occurrence and progression. Both can generate appropriate therapeutic options, but only the former may provide information to prevent disease.

Neuronal Vulnerabilities

Among certain different types of regenerating cells, neurons could be more susceptible to cellular toxicity because of their post-mitotic existence. Furthermore, neuronal cells are comparatively over-reliant on ATP making them more vulnerable to energy crisis triggered by shifts in membrane potential and mitochondrial distress.

Although, selective neuronal vulnerabilities have been observed among both sporadic and familial cases of neurodegenerative disorders (Fig. 1.2), nonetheless two important queries need to be answered. Firstly, what does selective neuronal toxicity compensate for? And secondly why does such toxicity remain latent during growth phases which becomes dangerous with age? Such selective neuronal vulnerabilities share some distinctive features from disease to disease while may remain indistinguishable between patients with familial and sporadic diseases. Therefore, we can speculate the link between genetic and environmental predisposing factor and of selective neuronal vulnerabilities. For example, PD is often correlated with genetic mutations as well as environmental toxins leading to mitochondrial dysfunction. Irrespective of the causative agents, the dopaminergic neurons in substantia nigra pars compacta (SNpc) are found to be more susceptible to damage caused by reactive oxygen species (ROS) in PD. This selective vulnerability may stem from the fact that higher amounts of iron and copper in these neurons catalyses the ROS production. Additionally, the low levels of antioxidants in substantia nigra are evidenced to be the cause of damages secondary to ROS generation [10].

As in the case of PD, upper and lower motor neurons (MN) are more susceptible to neurodegeneration in cases with ALS. Since MN are highly oxidative, they rely on high ATP demands. In addition, deficiency of antioxidants and presence of calcium-binding proteins make MN more prone to neuronal stress. Any one or many

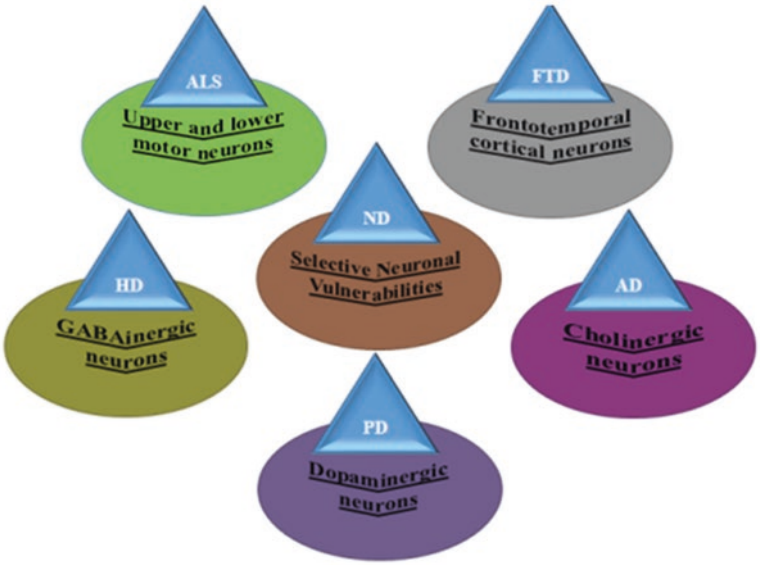

Fig. 1.2 Selective neuronal vulnerabilities and neurodegenerative disorders. *ND* neurodegenerative disease, *ALS* amyotrophic lateral sclerosis, *FTD* frontotemporal dementia, *AD* Alzheimer's disease, *PD* Parkinson's disease, *HD* Huntington's disease. (This figure is self-constructed by taking the information from source [10])

of these contributing factors render MN more selectively susceptible to neurodegeneration [6, 10].

Protein Misfolding and Accumulation

Under normal circumstances, the protein homeostasis is maintained by cells through the utilization of protein quality control system (PQC). The misfolded proteins are identified, refolded, and repaired with the help of molecular chaperons such as heat shock proteins (hsp) of PQC system. These molecular chaperons also help in degradation of misfolded proteins by interacting with ubiquitin–proteasome system (UPS) and autophagosome–lysosome pathways (ALP) [11]. The dearth of these PQC systems leads to the aberrant aggregation of proteins in neurodegenerative disorders. Moreover, the PQC and other protein clearance systems can be overwhelmed by the excessive deposition of proteins which may lead to further exaggerated accumulation, cellular stress, and ultimate neurodegeneration [6].

In AD, the main clinical features of different cortical brain regions comprise extracellular amyloid plaques containing Aβ peptides and aggregated and hyperphosphorylated tau protein comprising intracellular neurofibrillary tangles (NFTs). Seeding polymerization is a critical mechanism in pathogenesis of AD. The APP is cleaved by the complexes of β and γ secretases and forms Aβ monomers. In cytoplasm, these monomers may undergo polymerization to oligomers. After secretion into interstitial fluid of brain, the Aβ oligomers polymerize to form insoluble amyloid fibrils. The aggregation of these fibrils results in the production of spherical plaques and ultimate neuronal dysfunction. The activation of cytoplasmic kinases causes the hyperphosphorylation of protein tau. Polymerization of this protein results in production of insoluble neurofibrillary tangles, causing further neurotoxicity. The mechanism of Aβ aggregation is shown in Fig. 1.3.

The tau- or TDP-43-positive inclusions are also detected among some patient populations observed with FTD [12]. In PD, the pathological hallmark includes the aggregated α-synuclein comprising intracellular Lewy bodies (Fig. 1.4). The aggregation of α-synuclein takes place in the cell membrane or cytoplasm. Phosphorylation of this protein results in the formation of oligomeric fibrils in cytosol. Often during the aggregation phase, intermediates are formed which affect certain processes such as mitochondrial function, protein degradation, synaptic transmission, and Golgi trafficking resulting in neurodegeneration. High concentrations of these fibrils result in the production of polymerized aggregates. These accumulated β sheets cause neuronal cell death through the formation of inclusions known as Lewy bodies (LBs).

While in HD, the polyglutamine Q (polyQ) expansion containing nuclear inclusions of aggregated huntingtin protein is observed. The motor neurons with deposited superoxide dismutase (SOD) are detected in ALS [2, 4, 12].

Genetic defects, environmental factors, or multiple stress conditions have been proposed to cause protein misfolding and aggregation in neurodegenerative disor-

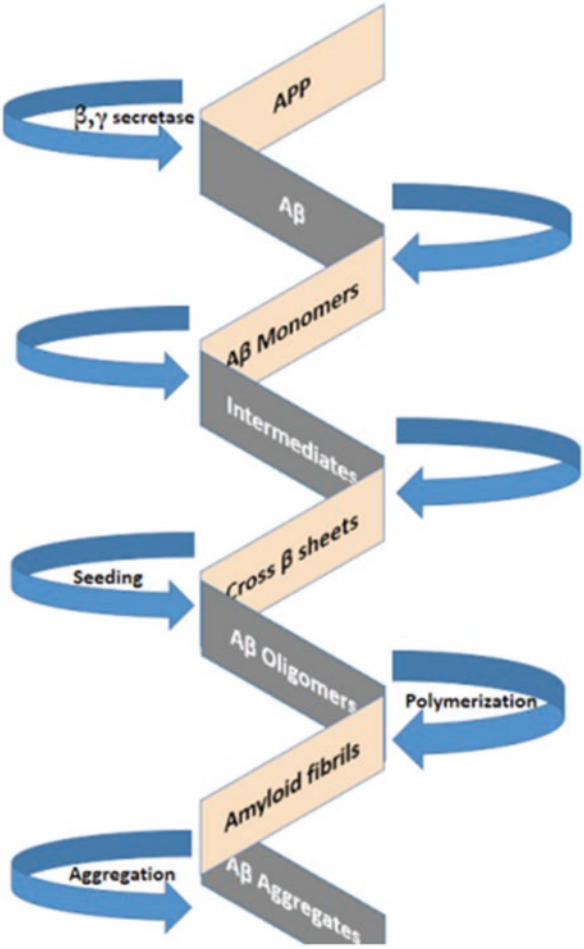

Fig. 1.3 Mechanism of β-amyloid aggregation. (This figure is self-constructed by taking the information from source [25])

ders, suggesting that same pathways may contribute towards their pathogenesis. These include genetic mutations, polymorphic conformational changes, ineffective biogenesis of proteins, excessive dispersed complexes of protein oligomers, debilitating transport of mitochondrial or precursors of secretory protein, metabolic or environmental stress, and ageing (Fig. 1.5).

Recent evidence also suggests the spread of aggregated proteins from one brain cell or region to another, its action as seedlings to trigger protein misfolding and deposition in these healthy and formerly naive cells or regions. This may clarify the progressive brain development of defects over time, in certain neurodegenerative disorders [11].

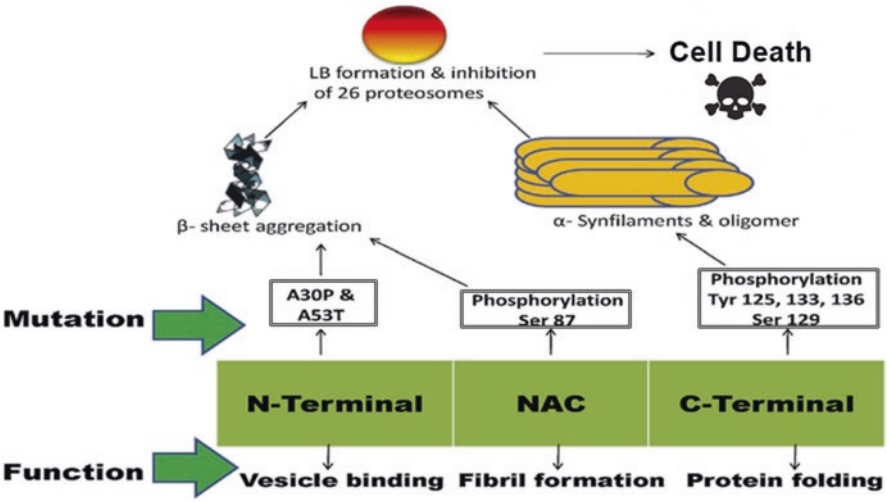

Fig. 1.4 Mechanism of α-synuclein aggregation. (Figure is adopted from [25] after modifications)

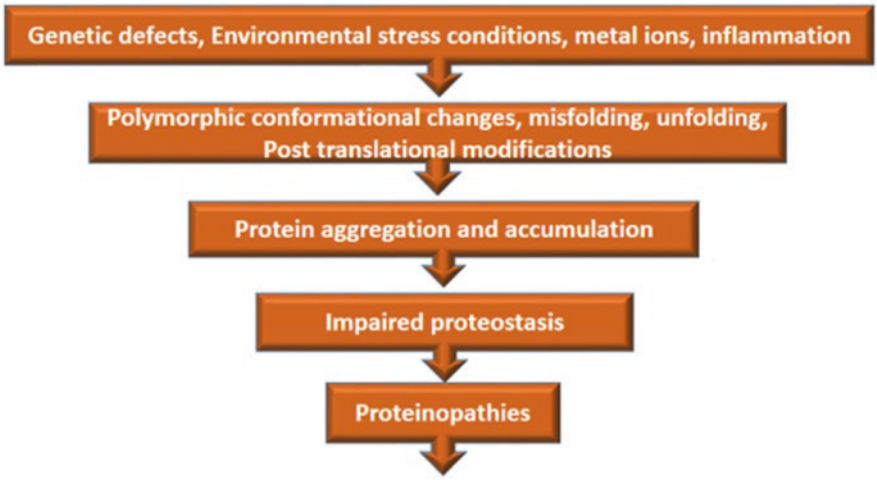

Fig. 1.5 Pathways of protein aggregation. (This figure is self-constructed by using the information provided in source [2])

Genetic Mutations

Majority of the neurodegenerative disorders are sporadic in nature. However, a few diseases are familial and involve the pathogenic mutations of certain genes. Phenotypic and histologic patterns of sporadic and familial neurodegenerative diseases are almost indistinguishable; however, the onset of familial diseases occurs

earlier in age than sporadic diseases, while the mutative genes-derived molecular processes may result in late onset of sporadic diseases [2].

The mutative triplication of APP resulting from the trisomy of chromosome 21 and mutations in presinilin (PSEN) I & II cause increased biogenesis of APP proteins and augmented aggregation of β-amyloid proteins in AD [2, 11, 13]. The genetic mutations in other neurodegenerative disorders are outlined in Table 1.2 [2, 13]. In addition to gene mutations, polymorphism of promoter regions of specified genes may contribute to enhanced transcription and alternate gene splicing leading to a rise in levels of proteins and aggregation-prone transcription factors [11].

Aberrant RNA Metabolism

During its life cylce, mRNA undergoes various processes ranging from pre-mRNA splicing, polyadenylation, editing, translocation, maintenance, translation, and breakdown. These co- and posttranscriptional processes are controlled through certain RNA-binding proteins (RBP) complexes. Following the gene transcription, spliceosomes convert the pre-mRNA to mRNA to continue the process of proteinogenesis and RNA metabolism. The translationally inert mRNA molecules are transported through RNA granules towards the neuronal sites of protein synthesis. The unbundling of transport RNA granules causes the release of translationally active polysomes to synthesize proteins. The mature neurons also contain two other forms of granulated RNA named as stress granules and cytosolic processing bodies. Being named as degradation granules or p-bodies, the cytosolic processing bodies are involved in degradation of RNA while the stress granules banish the mRNA to translationally quiescent state in response to neuronal injury [14–16].

In mammalian cells, the degradation of RNA is carried out in certain processes. It involves the deadenylation and decapping followed by the exonucleolytic cleavage at 3′-5′ and 5′-3′ positions in exosomes (the multiprotein complexes), respec-

Table 1.2 Genetic mutations in certain neurological disorders

Disease	Mutant genes
Alzheimer's disease (AD)	APP PSEN1 PSEN2
Parkinson's disease (PD)	PARK2 PARK7 PARK6
Frontotemporal dementia (FTD)	MAPT C90RF72 GRN
Familial amyotrophic lateral sclerosis (fALS)	SOD1 TARDBP FUS

This table is self-constructed by taking information from the source [13]

tively. Unwinding of RNA is processed by helicases to reach the internalized catalytic domains of exosomes. The presence of decapping enzymes and associated proteins, GW182 RBP, and 5′-3′ exonuclease XRN1 also catalyses the degradation of RNA in p-bodies [14, 16].

The endogenous genes-derived microRNA (micRNA) is a single-stranded RNA proved to control the growth of dendritic synaptic spines and neurons and is also involved in metabolism of mRNA (Fig. 1.6). It is increasingly evident that the microRNA often takes a larger part in neurodegeneration such as Alzheimer and prion-like disorders. It modulates the expression of β-amyloid-precursor protein cleaving enzyme (BACE) in neurodegenerative diseases [14].

These mechanisms are crucial for neurodegeneration, neuroplasticity, and neuronal health. However, any disturbances in these processes may lead to neurodegenerative diseases [14, 17].

The RNA metabolism is altered by altering the gene transcription, pre-mRNA interlacing, ribonucleoprotein complex (RNPC), translocation, translation, or metabolism [14]. Most genetic mutations are found in the genes such as FUS/TLS, TDP-43, SOD1 and have been identified to alter RNA metabolism in patients with ALS and FTD [2, 14, 15, 18].

Both in sporadic and familial cases of ALS, the mRNA present in motor neurons or spinal cord undergoes oxidation (Fig. 1.6). The oxidation of mRNA causes retarded rate of translation, production of defective proteins, ribosomal stallation, or trigger of translational error. The mRNAs involved in mitochondrial functioning, ribosomal composition, and in cytosol are thought to be vulnerable for pathogenic alterations [2, 14, 15].

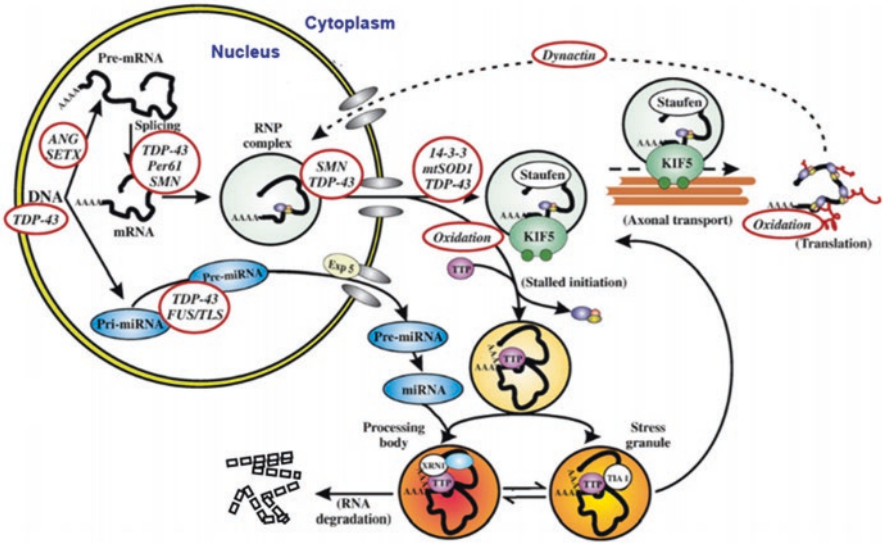

Fig. 1.6 Schematic illustrations of ALS-associated disrupted RNA metabolism, mutations, and disease process. (Figure is adopted from source [14] after few modifications)

In Alzheimer's disease, spliceosomal components aberrantly accumulate and mislocalize to the tau-mediated neurofibrillary tangles, affecting the normal RNA splicing. Moreover, the transgenic expression of tau proteins results in the reduced expression of spliceosomal components and loss of the main spliceosome protein (SmB) functionality. It results in neuronal dysfunction and toxicity independent of tau pathology [18].

Mitochondrial Dysfunction

Mitochondria play a pivotal part in cellular power supply, biosynthesis of key elements, and management of oxidative stress in body. The energy produced in the form of ATP is crucial for cellular functions, signalling pathways, and overall molecular and cellular activities. Since the brain tissues have higher energy needs, the normal functioning of CNS depends upon mitochondrial efficiency.

Accumulated mitochondrial dysfunctions such as genomic mutations, production and presence of reactive oxygen species (ROS), functional defects, defects secondary to protein aggregation, and environmental factors are implicated in altered energy metabolism and subsequent neurodegeneration [19]. The underlying pathological mechanisms involved have failed to fulfil cellular energy demands, misregulation of calcium levels, cytochrome c-induced apoptosis, and cellular death [2, 19] as shown in Fig. 1.7.

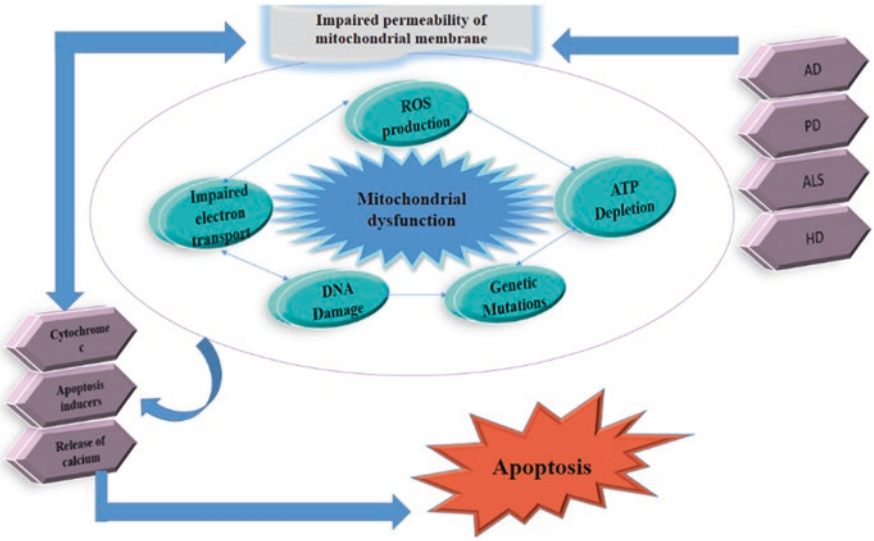

Fig. 1.7 Mitochondrial dysfunction and neurodegeneration. (Figure is self-constructed by taking the information from the source [19])

Several studies have looked up into the involvement of mitochondrial malfunction in neurodegenerative pathogenesis; it is, however, uncertain if mitochondrial and oxidative distress directly lead to the onset and development of neurodegenerative disorders such as PD, AD, ALS, and HD.

Mitochondrial Dysfunction and Parkinson's Disease

Various studies have suggested that the substantia nigra shows a compromised function of mitochondrial complex I (respiratory electron transport chain NADPH dehydrogenase) among patients with PD. Certain neurotoxins and pesticides have also shown to cause neurodegeneration. One such example is methyl phenyl tetrahydropyridine (MPTP), a contaminant present in synthetic heroin derivative named as methyl phenyl propionoxy piperidine (MPPP). The neurotoxin MPTP traverses the blood–brain barrier (BBB) and is transformed to MPDP+ and then to MPP+ after an uptake by glial cells and serotonergic neurons. After its release, the MPP+ is taken up by dopaminergic neurons, strongly inhibits the mitochondrial complex I, and produces irreversible Parkinsonism [2, 19].

Recent studies have revealed that α-synuclein also interacts with mitochondrial inner membranes and complex I, through its amino-terminal targeting series [19]. The aggregation and mutations of α-synuclein cause the mitochondrial dysfunction, oxidative stress, and apoptosis [19].

The protein parkin and a mitochondrial kinase, named as phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1), act as protective agents by preventing mitochondrial swelling, cytochrome *c* release, actuation of caspases, and apoptosis. The deficiency of both agents results in impaired action of mitochondrial complex I and neurodegeneration. While the negative regulator of PTEN-tumour suppressor proteins, DJ-1, activates the Akt pathway by phosphorylating the phosphatidyl inositol triphosphate (IP3) and serves as a potent sensor/predator of ROS. Any mutations in DJ-I may lead to oxidative stress, apoptosis, and neurodegeneration. Moreover, mutations in a mitochondrial quality control agent HTRA2 result in mitochondrial swelling and membrane dysfunction [19].

Mitochondrial Dysfunction and Alzheimer's Disease

Several evidences indicate that mitochondrial malfunction and oxidative damage play a vital part in AD pathogenesis. Overexpression of amyloid protein precursors (APP) blocks the importation of mitochondrial proteins, impairs the energy metabolism secondary to mitochondrial dysfunction. B-amyloid protein diminishes the activity of mitochondrial respiratory complexes, causes mitochondrial damage and

oxidative stress. It interacts with a mitochondrial matrix protein named as amyloid-binding alcohol dehydrogenase (ABAD), a pro-apoptotic serine protease HtrA2/Omi (high temperature requirement protein A2/Omi). It also causes the inhibition of ketoglutarate dehydrogenase complex and cytochrome *c* oxidase (COX) activity which results in tau phosphorylation and ultimate neurodegeneration [19–21].

It has recently been proposed that Aß crucially modulates the proteins taking part in mitochondrial fission/fusion reactions. Decreased amounts of Drp1, OPA1, Mfn1, Mfn2 and elevated levels of Fis1 have been shown in hippocampal tissues of patients with AD, suggesting mitochondrial dysfunction to promote fission [20]. In addition, overexpression of APP in hippocampal neurons causes the mitochondrial accumulation in perinuclear region suggesting that Aß may impede mitochondrial transportation process, and thus leads to synaptic dysfunction [19, 20].

Deficits of mtDNA base excision repair (BER) and primary nuclear and mtDNA repair mechanism for minor underlying moderations may also be involved in AD pathology [19].

Mitochondrial Dysfunction and Huntington's Disease

The Huntington's genes HTT modulate the mitochondrial activity by influencing the transcription process of nuclear-encoded proteins and by regulating their fission/fusion composites. Mutations in HTT can induce mitochondrial dysfunction through direct interaction with organelles, respiratory regulation, membrane potential, and calcium buffering. Nuclear translocation and binding of mutant HTT to p53 sites triggers the production of pro-apoptotic polymers of bcl-2 genre, BAX, and PUMA. In addition, the activity of respiratory transport chain complex II has been shown to reduce in patients with HD. Similarly, 3-nitropropionic acid, a neurotoxin, causes the sudden onset of Huntington-type syndrome through inhibition of mitochondrial complex II [2, 7, 19, 22].

Mitochondrial Dysfunction and Amyotrophic Lateral Sclerosis

Mutations in copper–zinc superoxide dismutase type 1 (SOD1) gene cause mitochondrial dysfunction by altering the activity of electron transport chain and by impeding the importation of mitochondrial membrane, impairment of calcium buffering, and production of ROS [23]. They cause the apoptotic cellular death via the release of cyt *c* and suppression of anti-apoptotic protein bcl-2 in patients with ALS [19, 23].

Excitotoxicity and Neurodegeneration

Hyperstimulation of glutamate receptors by excitatory amino acids results in neuronal destruction or excitotoxicity. Being the big thrilling neurotransmitter, the glutamate involves in synaptic transmission, plasticity, conception, cognition, and sensory and motor functions [2, 24].

Glutamate performs its functions through the activation of three major receptors: kainate receptor [25], *N*-methyl-D-aspartate receptors (NMDA), and a-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptors [2, 24]. The overactivation of these receptors results in an increased cytoplasmic concentration of Ca^{2+}, which in turn leads to increased metabolic rate and ROS production. The released NO produces peroxynitrite ($ONOO^-$), which damages the DNA, lipids, and proteins via a range of oxidation reactions. It also causes the expansion of mitochondrial permeability transition pore (mPTP) in membrane. The mPTP gives rise to an augmented release of calcium by disrupting metabolic gradient between cytosol and mitochondria, resulting in discharge of cyt *c*. In the cytosol, the cyt *c* turns up the caspases by interplaying with apoptosis protease activating factor 1 (Apaf 1) to produce apoptosomes. The active caspases cause the poly ADP-ribose polymerase-I (PARP-I) cleavage and ultimate DNA damage, energy failure, and cell death. Moreover, the polymers of caspases and PAR (poly ADP-ribose) lead to caspase-independent cell death by triggering the calpain activation, structural protein cleavage and inactivation, and release of apoptosis-inducing factor (AIF) [24] as shown in Fig. 1.8.

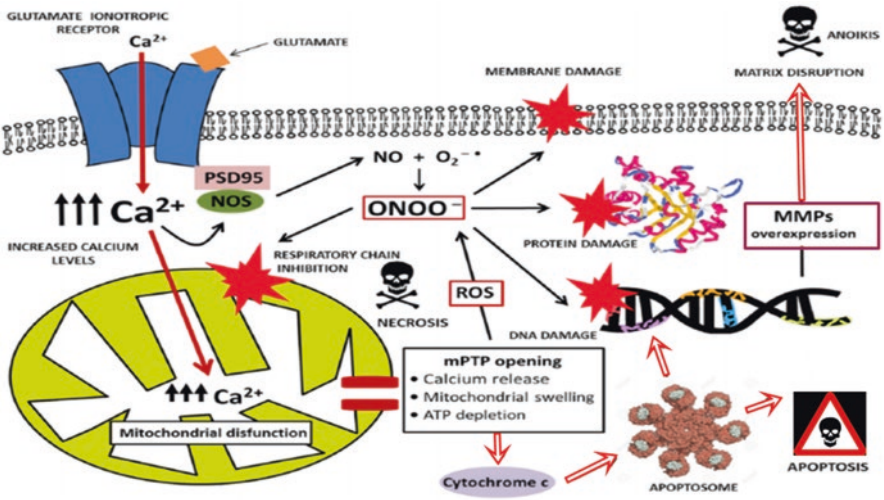

Fig. 1.8 An overview of excitotoxicity and neurodegeneration. (Figure is adopted from [24])

Excitotoxicity and Alzheimer's Disease

The AD-related excitotoxicity is observed to be caused by the Aβ and tau deposits. The Aβ plaques have been shown to cause extracellular aggregation of glutamate and the subsequent intracellular rise of the Ca^{2+} concentrations. The increased cytoplasmic concentration of Ca^{2+} results in hyperactivation of calcineurin (CaN), a calcium-dependent protein phosphatase. This CaN causes neurodegeneration through the dephosphorylation of nuclear factor of activated T cell (NFAT). The over trigger of NFAT results in certain morphological abnormalities such as loss of dendritic spines, dendritic simplification, and neuronal dystrophy [26]. Additionally, the AB plaques are also found to increase the vulnerability of neurons towards excitotoxicity and loss of synaptic proteins [24]. The underlying mechanism to excitotoxicity induced by tau protein includes the generation of ROS and by the modulation of tyrosine kinase FYN [24].

Excitotoxicity and Parkinson's Disease

The degeneration of dopaminergic neurons secondary to α-synuclein aggregation and Lewy bodies production results in over activation of glutaminergic neurons in certain regions of basal ganglia. This leads to hyperstimulation of NMDA receptors and subsequent excitotoxicity. It has also been evidenced that an increase in cytosolic levels of calcium results in alteration of mitochondrial bioenergetics and generation of free radicals triggering neuronal death [24].

Parkin, a PARK2's gene product, has regulatory effects on exciting the glutaminergic synapses. Parkin production abnormalities result in increased number of glutamate receptors and augmented synaptic activity [2].

Excitotoxicity and Amyotrophic Lateral Sclerosis

The transport of cerebral glutamate is mediated through the excitatory amino acid transporter 2 (EAAT2) in order to prevent the neural toxicity. Patients with ALS were postulated to have a reduced expression of this protein. Moreover, an AMPA glutamate sub receptor, GLUR2, is shown to have a reduced expression owing to deficits in coding processes of mRNA in patients with ALS. The functional loss of GLUR2 results in over influx of postsynaptic calcium and subsequent cellular damage [2, 24].

Neuroinflammation and Microglial Activation

Microglia, being the inhabitant immune cells of CNS, assumes a significant role in keeping up tissue regulation and confers brain development under ordinary circumstances. Nonetheless, when a nervous or other distress happens, depending upon the nature and severity of stimulus, microglia may be actuated [27, 28]. This activation causes the discharge of either pro-inflammatory components that improve cytotoxicity or anti-inflammatory neuroprotective agents that aid in healing of wounds and tissue repair [28]. Excessive microglial activity destroys the underlying neuronal tissues, and the elements discharged by the deceased or dying neurons intensify the persistent activation of microglia, contributing to dynamic loss of neurons [27, 28]. It is the situation seen in numerous neurodegenerative disorders, for example, AD, PD, HD, and ALS.

Neuroinflammation and Alzheimer's Disease

The Aβ peptides form the microglia-activating aggregates, partially by signalling through Toll-like receptors (TLRs) and receptors for advanced glycoxidation end products (RAGE) [29]. Such receptors activate the NF-kB and AP-1 transcription factors, which thus prompt the ROS generation and elucidation of inflammatory regulators (e.g., IL-1b, TNF-a, IL-6) [29, 30]. These inflammatory mediators directly affect cholinergic neurons and amplify pro-inflammatory signals through the stimulation of astrocytes and cause neuronal damage. Additionally, the pro-inflammatory cytokines also regulate the expression of presenilin (a component of γ-secretase), APP, and BACE1 (β-secretase) by acting on NF-kB regions [29, 30]. It further activates the microglial-associated inflammation and neuronal damage. The ATP released by the apoptotic and necrotic neurons results in the P2X7 receptor-mediated microglial activation. Cholinergic neurons are thought to be significant victims of inflammation triggered toxicity in basal forebrain of patients with AD, but other neurons such as GABAergic and glutaminergic can also be affected [29] as shown in Fig. 1.9.

Neuroinflammation and Parkinson's Disease

Different lines of research suggest that neuronal death in PD is modulated by microglial-derived inflammatory amplifiers such as TNF-α, ROS, NO, and IL-1β [29]. The intermediate state oligomers formed by α-synuclein aggregates cause microglial actuation via TLRs independent mechanisms (Fig. 1.10). It influences activation of NF-kB and generation of NO, ROS, and inflammatory intermediates. The actuation of NF-kB and oxidative distress–associated nitration of α-synuclein

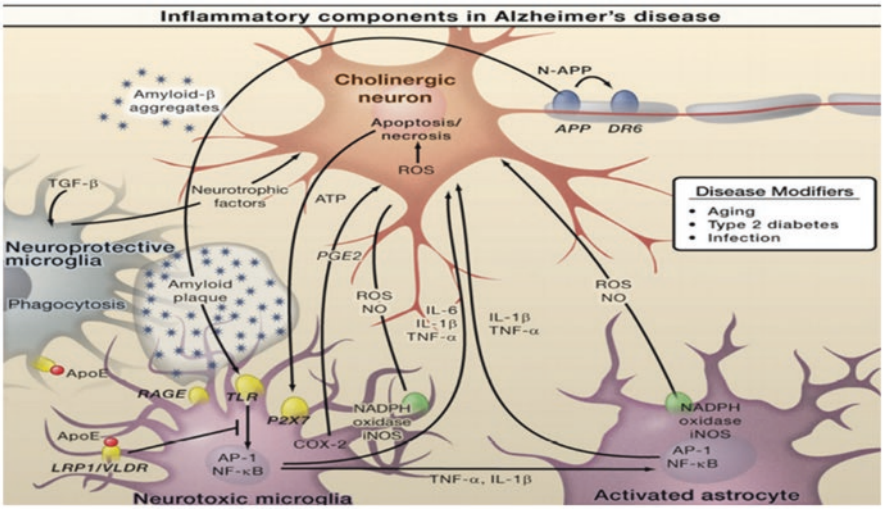

Fig. 1.9 Neuroinflammation in Alzheimer's disease. (Figure is adopted from [29] which is an open access source)

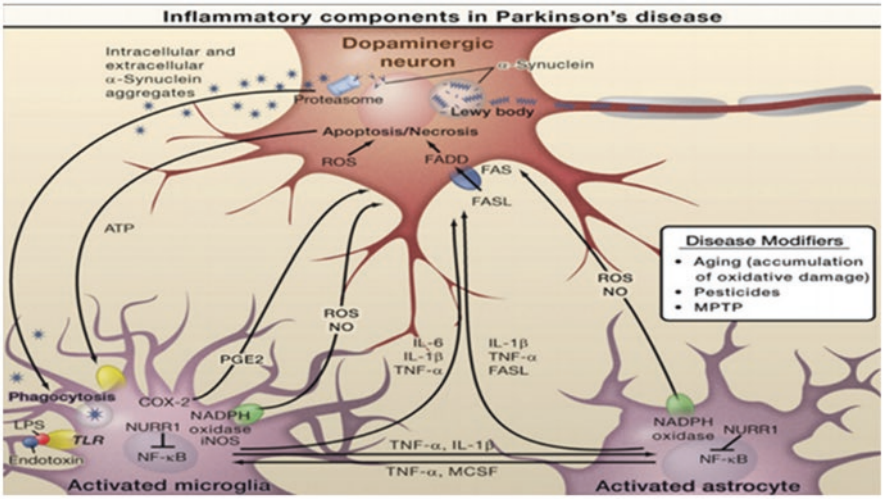

Fig. 1.10 Neuroinflammation in Parkinson's disease. (Figure is adopted from [29] which is an open access source)

leads to the overexpression of certain neurotrophins such as NFKB1, BDNF, GDNF TNF-α, and TNFRSF1A [29, 31]. A recent study has also suggested that dopaminergic toxicity in PD is also mediated by the infiltration of $CD4^+$ T lymphocytes through FasL expression [29, 32].

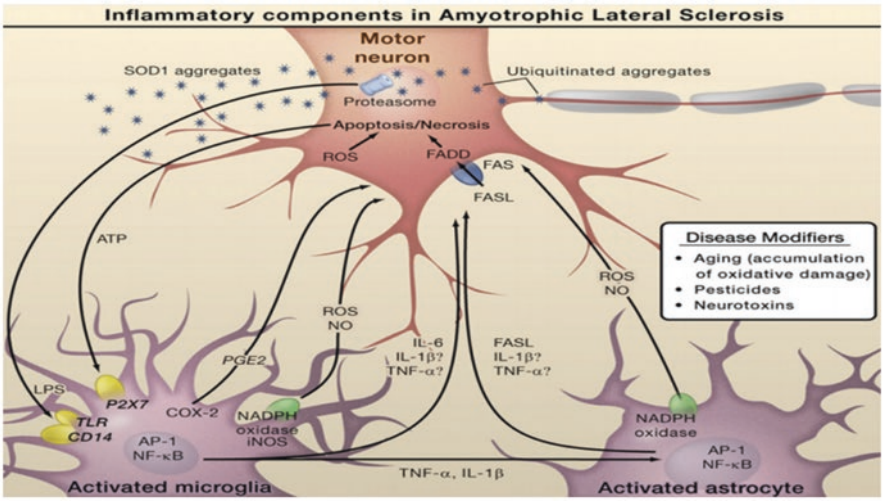

Fig. 1.11 Neuroinflammation in amyotrophic lateral sclerosis. (Figure is adopted from [29] which is an open access source)

Neuroinflammation and Amyotrophic Lateral Sclerosis

Toxic aggregates in patients with ALS can initiate inflammatory responses through the activation of microglial TLR2 and CD14. The microglial-released cytokines cause the activation of astrocytes, which in turn activates pro-inflammatory cytokines and apoptosis inducers such as FasL and TNF-a. These agents cause the activation of NF-KB and AP-I resulting in amplification of neuronal damage. The microglial cells are further activated by the action of ATP released from damaged neurocytes on P2X7 and result in augmented neuronal damage [29] as shown in Fig. 1.11.

Disrupted Axonal Transport and Neurodegeneration

Neurons utilize a bidirectional, ATP-dependent mechanism known as axonal transport to transfer complex substances through axon microtubules. The substances such as proteins, RNAs, and organelles are transported towards the axonal tip via kinesin-derived anterograde transport mechanism. In the other way, retrograde transport relies on cytoplasmic dynein and is important for processes including signalling neurotrophic factors, degradation, and response to stress insult. Axonal transport therefore involves numerous intracellular long-distance transmissions that require excellent control to maintain cellular function and viability [12]. The transport machinery of axons is composed of microtubules, motor as well as motor

adapter proteins. Moreover, the efficient transmission of neuronal substances is regulated by kinases and posttranslational modification of microtubules [12].

The kinesin superfamily of proteins consists of 15 subfamilies, among which the axonal transport is most importantly derived by kinesin 1, 2, and 3. Kinesin-1 comprises of dimers of two light (KLC) and two heavy chains (KHC) encoded by KLC1, KLC2, KLC3, and KLC4, as well as, KIF5A, KIF5B, and KIF5C genes, respectively [12]. In contrast to kinesin, dynein is involved in retrograde transport and consist of two heavy, medium, light medium and three lighter chains. The core motor is composed of heavy chain (encoded by DYNC1H1) and forms a complex by binding different other dynein subunits. This complex hydrolyses the ATP by binding to microtubules and involves in transportation process with the aid of adapter proteins [12].

Several microscopic studies have suggested that defective axonal transport is also associated with the development of neurodegenerative disorders (Table 1.3). It results in the accumulation of certain cargoes such as mitochondrial or cytoskeletol components in cell body, proximal or distal segments of axons [33].

Table 1.3 An overview of disrupted axonal transport in neurodegenerative diseases

Diseases	Mutant genes	Underlying mechanism
Alzheimer's disease (AD) and related dementias	APP	• Unknown effects • Retrograde transport of nerve growth factors (NGF)
	PSEN1	• Activation of GSK3β • Phosphorylation of KLCs • Kinesin-release
	MAPT	• Activation of GSK3β • Phosphorylation of KLCs • Kinesin-release
Huntington's disease (HD)	HTT	• Deacetylation of tubulin • JNK-3 activation, phosphorylation of kinesin-1, and impaired microtubular binding • Disruption of HTP1 and dynein-derived axonal transport of lysosomes, endosomes, and BDNF
Amyotrophic lateral sclerosis [2]	SOD 1	• Phosphorylation of KHCs and neurofilaments • Impaired binding of kinesin to microtubules
	DCTN 1	• Disruptions in proper functioning of dynein complex
Parkinson's disease (PD)	SNCA	• Unknown mechanism
	PARK 2	• Disruption of mitochondrial function
	PINK 1	• Disruption of mitochondrial function
	PARK 7	• Disruption of mitochondrial function
	DCTN 1	• Improper functioning of dynein complex

This table is self-constructed by taking information from the source [33]

Disrupted Axonal Transport and Alzheimer's Disease

The pathological transformation of β-amyloid, APP, PS1, and tau has been shown to affect the axonal transportation in patients with AD. Gene mutations in APP, tau, and PS1 may result in transportation deficits and axonal swelling proceeding to the deposition of β-amyloid and tau aggregates. It suggests that early abnormalities in AD could be such defects [33].

The APP is transported across anterograde axonal path and can interact directly with KLCs to connect PS1 and BACE 1 with kinesin motors. The APP-driven Aβ aggregates are generated amid its axonal transportation and may be triggered by axonal impedance. The depletion of KLC1 results in impaired anterograde transport and provokes retrograde transport of APP, leading to overproduction of Aβ in swollen axons [33].

Aβ has also been evidenced to directly impair axonal transport through certain mechanisms. It involves the polymerization and accumulation of actin microtubules, resulting in irreversible and progressive damage to vesicular transport. The Aβ can also retard the mitochondrial transport via NMDA-glutamate receptors and activation of GSK3β [33]. Moreover, the axoplasmic perfusion of soluble Aβ oligomers activates the casein kinase 2 and phosphorylates the KLCs. It further hinders the bidirectional vesicular transport. Mutations in PS1 can provoke the release of kinesin 1 through the activation of GSK3β and phosphorylation of KLCs [33] as shown in Fig. 1.12a.

The pathological effects of tau deposits on axonal transport are a matter of great controversy. Certain evidences suggest that tau monomers may impair the anterograde transportation by impeding the earlier connection and motility of kinesin motors along the microtubules. In contrast to this, other studies have proved that the wild-type filamentous tau activates the PP1, which undergoes dephosphorylation to activate GSK3β. The activated GSK3β causes the phosphorylation of KLCs and ultimate liberation of kinesin motors. The main trigger behind this process is N-terminal phosphatase-activating region of monomeric tau proteins [33]. Since the monomeric tau proteins are involved in stabilization processes of microtubules, hyperphosphorylated neurofibrillary tangles in patients with AD can irreversibly damage the cytoskeleton. It involves the retarded acetylation of tubulin and impaired stabilization of microtubules [33] as shown in Fig. 1.12b.

Disrupted Axonal Transport and Huntington's Disease

HTT, HTP1 (HTT-associated protein 1), and dynactin are involved in the dynein-associated transport of lysosomes and endosomes as well as transport of brain-derived neurotrophic factors (BDNF). Poly Q HTT affects the axonal transport by deacetylation of tubulin, by the actuation of C-Jun-N-terminal kinase 3 (JNK-3), and by the disruption of HTP 1–derived axonal transport (Fig. 1.12c). The deacety-

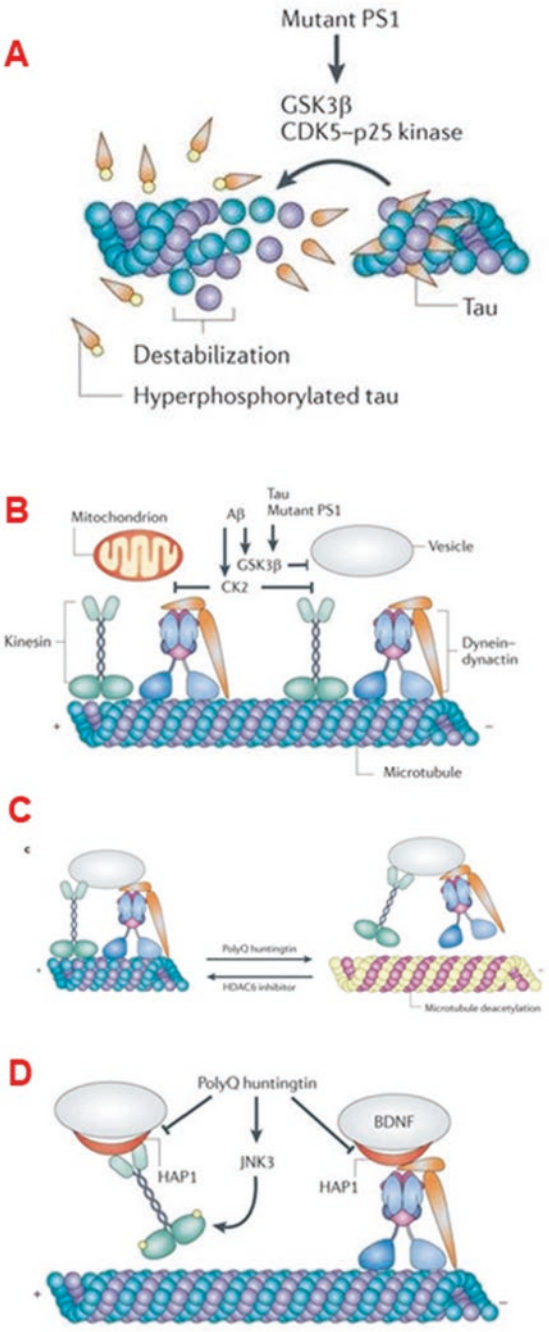

Fig. 1.12 Disrupted axonal transport in Alzheimer's and Huntington's disease. (Figure is adopted from source [33] after some modifications)

lated tubulin results in disrupted mobility of vesicles along the microtubules. In addition, the activation of JNK-3 phosphorylates the kinesin 1 and impairs its binding to microtubules. These disrupted processes are the key factors behind the neurotoxicity in patients with HD [33] as shown in Fig. 1.12d.

Disrupted Axonal Transport and Amyotrophic Lateral Sclerosis

In patients with ALS, microscopic examinations have revealed that swellings containing lysosomes, intermediate filaments, vesicles, and mitochondria appear in the first part of axons. Glutamate-triggered excitotoxicity in ALS leads to activation of JNK, CDK5-p25 kinase, and adopter molecule crk (also known as p38). It also debilitates the axonal transit of neurofilaments through phosphorylation. The kinesin binding to microtubules and cargoes is disrupted by the phosphorylation of KHC (activated JNK driven) and KLC (P-38 driven), respectively [33]. Additionally, mutations in SOD1 also result in activation of p38 and CDK5-p25 leading to phosphorylation of KHCs and neurofilaments. It causes the impaired binding of kinesin to microtubules and disrupts the axonal transport preceding to neurotoxicity. Moreover, the ALS-associated disruptions in microtubular-based axonal transport are also shown to be associated with mutations in dynactin subunit 1 (DCTN1) [33] as shown in Fig. 1.13.

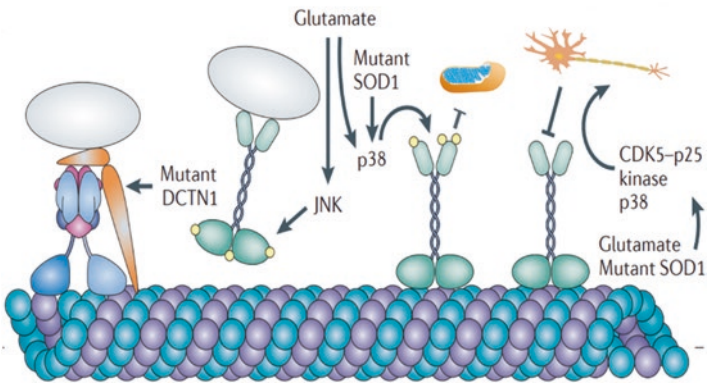

Fig. 1.13 Impaired axonal transport in amyotrophic lateral sclerosis. (Figure is adopted from source [33] after few modifications)

Impaired Axonal Transport and Parkinson's Disease

Missense or point anomalies in genes coding for α-synuclein retard its axonal transport through mimicking the permanent phosphorylation of protein. Mutations in genes such as PARK 2, PARK 7, and PINK 1 affect the axonal transport by disruption of mitochondrial function, which provides energy for transport. In addition to this, impaired axonal transport in Parkinsonism is also associated with mutation in DCTN1 [33].

Biomarkers of Neurodegenerative Disorders

Biomarkers are objective laboratory measurements, representing the alterations in different biological pathways during development and progression of a disease. Biomarkers can aid in a quicker and potentially more precise diagnosis of a disease, stratify the patient groups to recognize those who will better respond to the given treatment, provide prognosis of disease progression, show that a medication "hits its target" inside the nervous system, or anticipate response towards specific treatment. Due to the sporadic and many different genetic forms as well as inherent heterogeneity of neurodegenerative diseases, the biomarker-based stratification of diseased patient populations will considerably help the design and will potentially decrease the number of required patients for clinical trials. Biological markers are assessed using a variety of specific methods and expressed as diverse forms such as biochemical, genetic, and imaging based.

We cannot identify biomarkers in detail through all neurodegenerative processes. We should concentrate our attention on a handful of neurodegenerative disorders that have seen the biggest improvements in biomarkers. Such diseases include AD, PD, and ALS. The mutant genes previously discussed in this chapter (Table 1.4) serve the purpose of genetic biomarkers. The details of biofluid biomarkers used in diagnosis of neurodegenerative disorders are provided in Table 1.5.

Table 1.4 Neurotoxins involved in disrupted axonal transport

Neurotoxins	Neurodegenerative disease	Underlying mechanism
MPTP	PD	A reduction in anterograde transport mechanism and increase in retrograde transport
Rotenone	PD	An increase in retrograde transport
Glutamate	ALS	Phosphorylation and coupling of neurofilaments to motor proteins kinesin linkage to mitochondria Binding of kinesin to microtubular assembly

This table is self-constructed by taking information from the source [33]

Table 1.5 Biofluid biomarkers of neurodegenerative disorders

Biofluid biomarkers	Change	Reflects	Diagnosis
Alzheimer's disease (AD)			
CSF: β-amyloid 42	Decreased	Amyloid plaque pathology	Diagnostic factors for AD
CSF: NFL	Increased	Degeneration of myelinated axons	Rapid progression of AD and cognitive impairment
CSF: Total of tau proteins	Increased	Degradation of cortical axons	Progression of MCI to AD
Parkinson's disease (PD)			
CSF: oligomer/ total α-synuclein ratio		α-synuclein aggregation and Lewy bodies	Diagnostic factor for PD
Serum levels of uric acid	Increased	Oxidative stress	Risk and prognostic factor of PD
Serum BDNF	Decreased	Loss of dopaminergic neurons Severity of PD symptoms and cognitive decline	Diagnostic and prognostic factor for PD
Serum levels of IGF-1	Increased	Motor neuronal function decline	Progression of PD
CSF: p-tau and p-tau/AB 42 ratio	Increased	Subsequent cognitive decline in PD	Progression of cognitive decline and neuronal dysfunction in treatment cases of levodopa
Amyotrophic lateral sclerosis [2]			
CSF: NFL	Increased	Degradation of myelinated axons	Diagnosis of ALS prognosis of survival
CSF: pNFH	Increased	Degradation of myelinated axons	Diagnosis of ALS prognosis of survival
CSF: SOD1	Increased	Genetic mutations in SOD1	Pharmacodynamic biomarker
Serum uric acid	Increased	Survival	Prognostic indication of survival

This table is self-constructed by taking information from the source [34]

Conclusion

Notable advancements in elucidating the causes of several neurodegenerative disorders have been made. Determining the nature of pathological plaques along with developments in the genetic makeup of these diseases offered valuable cue. It has helped researchers to establish and test comprehensive hypothesis, concerning the molecular and cellular processes of neurodegeneration. Misfolding and aggregation of proteins, impaired protein processing, defective mitochondria and energy metabolism, impaired axonal transmission, glial cell activation, proliferation and neuroinflammation, RNA-mediated toxicity, excitotoxicity are popular concepts that are thought to be involved in neurodegeneration. The spread of prion-like protein

pathology is also evolved as a popular trend and could create new avenues for therapeutic advancement. Because of their peculiar anatomy, neurons are often postmitotic in nature and are selectively vulnerable to damage caused by genetic or environmental stress. Moreover, with the advancing age, the neurons are less capable of preventing the aggregation of misfolded proteins and retaining overall homeostasis. Although hypotheses can be made for pathophysiological mechanisms that render neurons prone to degeneration, it is not entirely known that why certain individuals are physiologically more sensitive to particular neurodegenerative diseases, and why certain neurodegenerative diseases are clustering within certain parentage. The popular neurodegenerative disorders are apparently sharing related mechanisms. Increased knowledge of pathophysiological pathways for neurodegenerative disorders is expected to result in disease-modifying therapeutic strategies that may be useful in a number of specific clinical phenotypes.

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Chapter 2
Air Pollutants and Neurological Disorders: From Exposure to Preventive Interventions

Tauqeer Hussain Mallhi, Muhammad Hammad Butt, Abrar Ahmad, Shahzadi Misbah, Suleman Atique, and Yusra Habib Khan

Abstract Air pollutants are referred to as chemicals, particles, or biological materials in the air. They primarily affect the heart and lungs resulting in various cardiovascular and respiratory complications. However, the association of air pollutants with neurological disorders such as Alzheimer's, Epilepsy, Parkinson's disease, and Stroke has been established. The air pollutants causing neurological disorders include nitrogen oxide, ozone, sulfur dioxide, carbon monoxide, lead, and particulate matter. The majority of the air pollutants are anthropogenic, originating from human activities such as industrial processes, power generation, fossil fuel combustion, and use of vehicle engines. Natural sources of pollutants include volcanic eruptions and forest fires. These pollutants enter the body through inhalation and reach to the central nervous system (CNS) where they cause tissue damage in the brain and affect molecular, inflammatory, and cellular pathways. Several animal, human, and cell culture studies have demonstrated the relationship of air pollutants with neuroinflammation, CNS oxidative stress, neuron damage, blood–brain barrier changes, and cerebrovascular damage. Prevention from detrimental effects of air pollutants can be limited by maintaining air safety levels, making policies, developing surveillance system, and collaborating with organizations involved environmental sciences. Moreover, production of energy from natural sources such as wind and solar power is another effective measure to control to the air pollutants–induced neurological disorders.

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Introduction

Air pollutants refer to the substances such as chemicals, particles, or biological material in the air. Pollution is defined as the presence of air pollutants in the environment in concentrations that are detrimental to the human health and other forms of life. Pollutants are present in various physical forms including solids, liquids, or gases [1]. Sources of air pollutants can be either natural such as volcanoes or anthropogenic (manmade) such as industries. With the rapid expansion of industries, air pollution has become a substantial danger to human health. A large population around the globe is chronically exposed to such pollutants in levels higher than what is considered safe [2]. Research in the last three decades evidences that air pollutants affect cardiovascular and respiratory health among humans and contribute to substantial mortality consequential of myocardial ischemia, arrhythmia, heart failure, and respiratory diseases such as lung cancer and asthma [3–6]. Pollutants in the air have also been extensively correlated with the increased risks of adverse outcomes during pregnancy such as preterm delivery [7, 8], low birth weight [9], intrauterine growth retardation [10], and other birth defects [11].

Recently, more attention has been paid to the relationship between air pollutants and neurological disorders. Evidences from clinical, epidemiological, observational, and experimental studies have strongly associated with air pollution with certain neurological diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and stroke [2, 12–14].

This chapter aims to describe the air pollutants, their types, sources, neurological effects consequential of their exposure, pathways, mechanisms by which air pollutants lead to neurological disorders, preventive interventions, and experimental linking of exposure to neurological disorders.

Types of Air Pollutants

Air pollutants are of a wide and diverse variety including particulate matter (PM), organic compounds (polycyclic aromatic hydrocarbons, bacterial endotoxins, etc.), gases (ozone, carbon monoxide, sulfur oxides, nitrogen oxides, etc.), and toxic metals (vanadium, lead, nickel, copper, manganese, etc.). Of these, PM and ground-level ozone, which form mainly from nitrogen oxides and volatile organic compounds, are usually the most prevalent and detrimental. PM is a mixture of solid particles and liquid droplets that can have effects on the nervous system. The com-

ponents of PM individually are not usually hazardous such as sodium chloride which is innocuous [15–17].

Carbon Monoxide

Carbon monoxide (CO) is formed with incomplete combustion of fossil fuel. In unsafe levels, their inhalation leads to poisoning with symptoms such as headache, dizziness, weakness, nausea, vomiting, and loss of consciousness. Poisoning and the symptoms occur because of the greater affinity of CO towards binding with hemoglobin as compared to oxygen. As a consequence of CO binding, oxygen is lost which results in hypoxia and ischemia. Its prolonged exposure may lead to cardiovascular diseases. CO is also believed to affect greenhouse gases and is linked with global warming and climate change. However, studies have also linked CO with increased plant growth [1, 18].

Lead

Lead is one of the heavy metals that are used in industries and is discharged into the air from automobiles, batteries, radiators, waste incinerators, and wastewaters. Furthermore, the main contributors to lead in the air are metals, ore, and piston-engine aircraft. Lead poisoning is especially a threat to public health in developing countries. Lead can enter the body through inhalation, ingestion, and dermal absorption. Lead can also cross the placental barrier and may cause teratogenicity. The toxic effects of lead are more harmful in the early stages of fetal development. Lead toxicity in the fetus leads to edema or swelling of the brain. Inhalation of Lead results in its accumulation in blood, liver, lungs, bones, and cardiovascular, nervous and reproductive systems. Lead toxicity causes loss of memory in adults in addition to pain in muscles and joints. Infants, neonates, and children are extremely prone to lead toxicity even at minimal levels. Moreover, neurotoxic intricacies such as learning disabilities, impairment of memory, hyperactivity, and mental retardation have also been observed in children following the lead toxicity. Elevated levels of lead in the atmosphere are also detrimental to plants (crops) and animals [19–22].

Particulate Matter

Particulate Matter (PM) in the air is generally the result of chemical reactions among the various pollutants. PM consists of PM10 (particles with 10 μm or smaller diameters) and PM2.5 (extremely fine particles with 2.5 μm or smaller diameters). PM can be inhaled and has deleterious health effects. PM10 can reach the lungs and

Table 2.1 Types and size of particulate matter

Types of air pollutants		PM diameter in μm
Biological contaminants	Bacteria	0.7–10
	Viruses	0.01–1
	Fungi and molds	2–12
	Allergens	0.1–100
Gases	Gaseous contaminants	0.0001–0.01
Types of dust	Atmospheric dust	0.01–1
	Heavy dust	100–1000
	Settling dust	1–100
	Cement dust	8–100
Particulate contaminants	Smog	0.01–1
	Soot	0.01–0.8
	Tobacco smoke	0.01–1
	Ash	1–100

Adopted from an open access article (Heal, M.R. et al.) and reconstructed [26]. Major types of particulate matters consist of gas, particulate and biological contaminants and types of dust. All were categorized according to PM size

even blood following the inhalation. PM2.5 is linked with a greater risk to health amid its very small size. Numerous studies have shown that short-term and long-term exposures of PM2.5 are associated with acute nasopharyngitis. Long-term exposure to PM is also associated with cardiovascular diseases and infant mortality [23–25]. Table 2.1 demonstrates the information regarding various types of PM along with their sizes.

Nitrogen Oxide

Nitrogen oxides (NO_x) are primarily discharged from the automobiles. They are respiratory irritants and can penetrate deep into the lungs causing respiratory diseases, coughing, wheezing, dyspnea, bronchospasm, and even pulmonary edema (when inhaled at higher levels). NO_x at concentrations of ≥0.2 ppm cause these harmful effects in humans, whereas NO_x in concentrations higher than that of 2.0 ppm affect T lymphocytes, especially the CD8+ cells and natural killer (NK) cells that are responsible for immune response. The long-term exposure of increased levels of nitrogen dioxide (NO_2) is reported to be associated with chronic lung disease and impairment in smell sensation. Other than respiratory effects, symptoms such as eye, nose, and throat irritation have also been observed following the contact of these pollutants. In addition, NO_2 in high levels are reported to be associated with a reduction in plant growth and crop yield [27–29].

Ozone

Ozone (O_3) gas is generated from oxygen when exposed to high-voltage electric discharge. It is an oxidant with oxidation activity 52% stronger than that of chlorine. It generally occurs in the stratosphere. However, chain reactions of photochemical smog in the troposphere can also lead to its production. It moves with air and can be present in areas distant from its source. It has deleterious effects on plants such as reduced growth and yield and disturbs the plant microflora because of its antimicrobial ability. It can cause increased damage to DNA in keratinocyte cells of the epidermis leading to impaired cellular function. Ozone at the ground level is known as ground-level ozone (GLO). A chemical reaction of NO_x and volatile organic carbons (from natural sources or human activity) generates GLO. O_3 usually enters the body through the inhalation route and affects the epidermis and tear ducts. A short-term high-level exposure study on mice showed malondialdehyde formation in the epidermis and depletion of vitamin C and E. Due to the relatively lipophilic nature of O_3, it can reach deep into the lungs upon inhalation. Toxic effects of O_3 such as morphologic, biochemical, functional, and immunological disorders have been reported in urban areas around the globe. Air Pollution on Health: a European Approach (APHEA2) is a European project to monitor the short-term effects of O_3 on mortality. The daily mortalities and GLO concentrations were recorded for 3 years in different European cities and compared. It was seen that the GLO concentration increased around summer resulting in daily mortalities (0.33%). Increase in mortalities related to respiratory and cardiovascular issues have been recorded as 1.13% and 0.45%, respectively [30–34].

Sulphur Dioxide

Sulfur dioxide (SO_2) is one of the harmful and toxic gases that are produced upon combustion of fossil fuel. Primary sources include industrial activities, fossil fuel, and volcanic eruptions. The United States Environmental Protection Agency (U.S. EPA) has set the standard annual average to be 0.03 ppm for SO_2. Sulphur dioxide can affect humans, animals, and plants. Major effects on human health include respiratory irritation, overproduction of mucus, bronchitis, and bronchospasm. Other effects also include redness of the skin, irritation of the eye, lacrimation, corneal opacity, mucous membrane damage, and cardiovascular disease worsening. The old, children, and those with respiratory diseases are more susceptible to the toxic effects. Furthermore, it also has impact on the environment such as acid rain and soil acidification [1, 29].

Source of Air Pollutants

The majority of the pollutants in the environment are anthropogenic, originating from human activities such as industrial processes, power generation, fossil fuel combustion, and the use of vehicle engines. It is estimated that automobiles are responsible for about 80% of the current pollution. Natural sources of pollutants include volcanic eruptions and forest fires. Air pollutants are usually classified based on their sources [1, 35].

- Major sources of air pollutants come from industries (chemical, petrochemicals, fertilizer, metallurgical), power stations, and refineries.
- Indoor areas from which air pollutants cause neurological disorders include gas stations, print shops, dry cleaners, and indoor cleaning activities.
- Mobile sources of air pollutants include automobiles, railways, airplanes, and other vehicles.
- Natural sources of air pollutants include natural disasters such as volcanic eruption, forest fires, and dust storms.

Neurological Disorders associated with Air Pollution

The relationship of air pollution and neurological disorders is well established. Ischemic stroke can be caused by chronic exposure to air pollution, multiple sclerosis can be caused by exposure to secondhand smoking, and PD can result through exposure to manganese content in the ambient air. It is also very likely that other disorders of the brain are also attributable to air pollution [36, 37].

Stroke

Stroke occurs when the blood supply is obstructed or reduced to a certain region of the brain due to a clot or hemorrhage preventing oxygen and nutrient supply. The toxic effects of air pollutants on the respiratory and cardiovascular systems are well known. However, recent studies are showing the additional deleterious effects on the nervous system. Initial reports of the toxic effects on the human brain showed an increased incidence of stroke in individuals exposed to coal fumes [15].

Stroke is considered as the leading cause of disability in adults and the third leading cause of death (after cancer and cardiovascular disease) in the United States. Even though the data on the cerebrovascular effects of air pollution is limited, epidemiological studies of exposure to air pollutants show association with increased risk of ischemic cerebrovascular events [38]. Air pollution is associated with an increased risk of ischemic stroke even in regions having pollutant concentrations lower than the U.S. EPA standards. Even though the mechanisms behind these

cerebrovascular effects are not defined, O_3 and PM have demonstrated the ability to modulate the gene expressions that are involved in key vasoregulatory pathways in the cerebrovascular system, corroborating the idea that inhalation of pollutants can have cerebrovascular effects [34, 39, 40]. In vitro exposure of cultures of neurons, astrocytes, and microglia to PM of air pollution demonstrated increased susceptibility to glucose and oxygen deprivation [41], variation in synaptic function [42], and increase in inflammatory cytokines [43].

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease that manifests as dementia, beginning with memory loss, progressing to severe decline in cognitive function, and disability [44]. The neuropathological marks of AD are neurofibrillary tangles and senile plaques [45]. Exposure of PM2.5 specifically has been associated with AD [46].

The PM exposure can be linked with AD through two mechanisms. First, it can cause production pro-inflammatory cytokines that induces chronic respiratory and systemic inflammation, which can affect the blood–brain barrier (BBB), triggering neural–immune interactions leading to chronic oxidative stress [47]. Second, it can directly produce reactive oxygen species (ROS) which damage the BBB and increase the amyloid-beta (Aβ) peptides production. Both mechanisms cause brain inflammation and accelerate the accumulation of Aβ peptide, which are linked with neuronal dysfunction and later senile plaques and formation of neurofibrillary tangles [45, 48].

Epilepsy

Epilepsy is a complex neurological disorder which involves excessive, abnormal, and synchronous electrical discharges from neurons in the brain. Air pollutants such as PM, NO_2, and SO_2 are known to cause epilepsy [49, 50]. The PM2.5 and ultrafine PM can be inhaled and cause activation of cerebral innate immune response through cytokines which activates receptors on endothelial cells in brain. This induces inflammation and oxidative stress which damages cells in the brain [51]. PM can also reach the brain directly via the olfactory tract, activating microglia (the resident innate immune cell), which then release cytokines including interleukin1B (IL-1b), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) through a nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb) mediated pathway [52]. Cytokines cause brain swelling and pro-inflammatory factors release, which leads to widespread neuroinflammation [53, 54].

Parkinson's Disease

Parkinson's disease (PD) is progressive neurological disorder affecting movements. It leads to stiffness, shaking, and difficulty with balance, coordination, and walking. Its symptoms typically begin gradually and become worse over the time. Significant association between PD and ambient manganese exposure in Hamilton has been observed [55]. NO_2, CO, PM, and O_3 have been in some ways associated with PD in several studies [50, 56–59].

Being a mixture of various components, air pollutants might be responsible for development of PD through multiple synergistic mechanisms. Pollutants might cause inflammation in peripheral organs leading to systemic inflammation which could cause of respiratory, olfactory, and BBB. These pathways allow the pollutants and inflammatory mediators to access the central nervous system (CNS) consequentially causing neurotoxicity and neuroinflammation [15, 60, 61]. PM exposure over long term has been known to cause neuroinflammation, α-synuclein aggregation, and oxidative stress, which are the hallmarks of PD [50]. Animal studies related to PM and traffic pollution exposure have displayed neuropathology of PD (substantial decrease of dopaminergic neurons in the substantia nigra, raised α-synuclein in the midbrain, and stimulation of unfolded protein response in the striatum) [62–64].

Prevalence of Neurological Disorders

According to the World Health Organization (WHO), the global prevalence of neurological disorders is 6.3% of the total disease burden along with 12% of mortality. The WHO has listed the prevalence of noncommunicable neurological disorders as 55% cerebrovascular disease followed by AD (12%), migraine (8.3%), PD (1.8%), and epilepsy (7.9%) [65]. The prevalence of PD per 100,000 individuals ranges from 100 to 200 [66]. Globally, stroke prevalence per 100,000 population ranges from 500 to 1000 and around 24.3 million suffers from dementia. For epilepsy, the global prevalence per 1000 population ranges from 2.7 to 41 [65].

Air Pollution and Global Burden of Neurological Disease

As air pollutants are a mixture of various components, several approaches can be used to measure them. Of these components, PM2.5 is most important and harmful. It is widely used as a key indicator for air pollution. Levels of PM2.5 above 35.40 μg/m^3 air are considered unsafe for human health. The World Health Organization (WHO) recommends that the PM2.5 levels should be kept below 10 μg/m^3 air. The most and least polluted countries according to the data of International Energy Agency and the WHO are listed in Table 2.2 [67].

Table 2.2 Worst and best countries according to air pollution with corresponding prevalence rate of neurological disorders

Country	APL[a]	PR of ND[b]	PR of EP[b]	PR of AZ[b]	Country	APL[a]	PR of ND[b]	PR of EP[b]	PR of AZ[b]
Saudi Arabia	108	42,687.0	354.0	159.4	New Zealand	5	45,084.7	264.3	1056.0
Qatar	103	44,990.2	317.9	79.6	Brunei	5	39,612.1	280.7	272.6
Egypt	93	40,220.9	343.4	239.6	Sweden	6	48,042.0	274.1	1280.2
Bangladesh	84	46,336.0	285.4	285.4	Australia	6	44,178.8	262.2	1014.4
Kuwait	75	43,596.6	319.7	280.8	Canada	7	47,959.6	280.9	1051.5
Cameroon	65	38,791.1	536.6	124.0	Finland	7	47,537.1	380.3	1225.2
UAE	64	46,311.9	320.8	62.9	USA	8	48,714.4	435.5	887.8
Nepal	64	47,756.6	456.0	245.9	Iceland	8	46,952.7	355.1	997.2
India	62	45,193.1	293.8	237.4	Estonia	8	48,398.8	383.4	1533.6
Libya	61	41,520.9	248.8	323.0	Spain	9	50,255.8	285.2	1630.8

Data from WHO, International Energy Agency and Institute for Health Metrics and Evaluation [67, 68]

AP air pollution, *ND* neurological disorder, *AZ* Alzheimer's disease, *EP* epilepsy, *UAE* United Arab Emirates, *USA* United States of America, *PR* prevalence rate

[a]Units are in PM 2.5 μg/m^3 air

[b]Per 100,000

Routes of Exposure

The primary route for air pollutants exposure is inhalation. Larger particles (PM10) get filtered out through upper airways, whereas PM2.5 remains mostly unfiltered [69]. The PM2.5 enters the epithelium and moves into the olfactory bulb, followed by traveling into the cortex and at the end into the brain [70]. Ultrafine PM enters into the brain by olfactory nerves and disperses to the cerebral cortex and cerebellum [71, 72]. Likewise, pollutant particles could be swallowed if too large to enter lungs or followed by clearance from lung by mucociliary escalator. The afferent dorsal vagus nerve in gut is believed to be an alternative entry route as it communicates directly with neurons in brain stem [60]. Table 2.3 describes the penetration of particulate into the human body according to their size.

Mechanisms of Air Pollutants

Mechanistically, air pollutants affect the CNS through molecular, inflammatory, and cellular pathways and damage brain tissues directly which leads to neurological diseases. Figure 2.1 illustrates the pathways and mechanisms of air pollutants. Air pollutants may not enter directly in the CNS but can exert adverse effects by activating the release of inflammatory mediators. This release leads to the vulnerability of neurodegeneration and neuroinflammation in the CNS. The nanoparticles (NPs) due

Table 2.3 Penetration of particles according to the size

Particle size (μm)	Penetration in the human body
0.43–0.65	Penetrate in alveolis
0.65–1.1	Penetrate in bronchioles
1.1–2.1	Penetrate in terminal bronchial area
2.1–3.3	Penetrate in secondary bronchial area
3.3–4.7	Penetrate in bronchial-trachea area
4.7–7	Penetrate in larynx
7–11	Penetrate in the nasal cavity
>11	Penetrate in the upper respiratory tract

Adopted and modified from Manisalidis et al. [1] which is open access source

to their specific physicochemical properties can effectively cross the alveolar barrier and rapidly invade the blood circulation and affect the vascular system.

Experimental Studies

There have been several exposure studies involving humans, animals, and cell cultures. These studies show that pollutants can cause neuroinflammation, CNS oxidative stress, neuron damage, BBB changes, development of abnormal filamentous proteins (Aβ and α-synuclein), and cerebrovascular damage. Even though the evidence of neurological effects of short-term exposure is compelling, human exposure to air pollution is generally chronic (spanning the entire lifetime including the crucial developmental period) and is not well studied. Nevertheless, in vitro methods and short-term animal exposure studies provide the groundwork essential for identifying the air pollutants having neurological toxicities and detailed experimental studies to understand their role in neurological diseases (Table 2.4).

Preventive Interventions

Air pollution is responsible for considerable burden on human health because of the unsafe levels of air pollutants in the majority of the countries. The primary measure to decrease the detrimental effects of air pollution such as neurological disorders incidence is to maintain the safety levels of air pollutants This warrants policy changes and collaboration on national, regional, and international levels. One of the major contributors in air pollution–induced neurological disorders is the use of fossil fuels. Fossil fuels are not only deleterious for human health but also responsible for the climate change through greenhouse gases. The most effective way to mitigate such effects is to move towards renewable energy sources including wind and

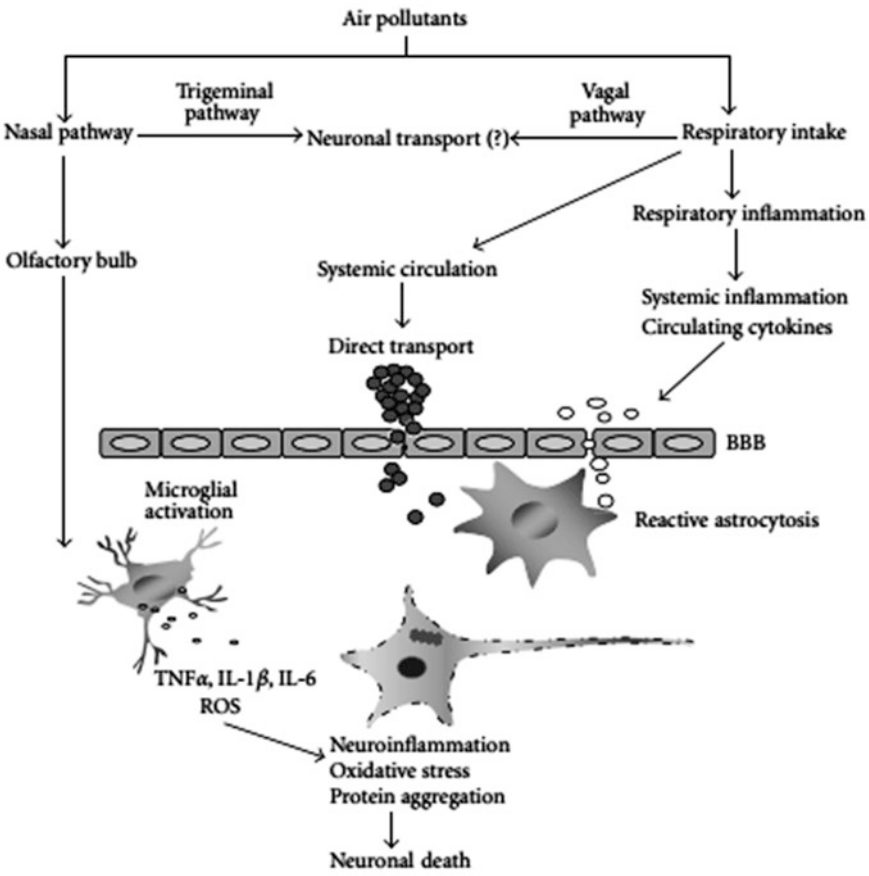

Fig. 2.1 Mechanism and pathway of air pollutant. (This figure is available freely and adopted from Genc et al. [2])

solar power. Innovation in transportation industry technology with focus on electric power and reduced emission and the promotion of integrated public transport systems have the potential to most significant contribution in the efforts. Rapidly developing countries can play an important role by considering these measures. Industries should be restricted to regions distant from the population and cities. City planning must take air pollution into account and keep the industries and heavily congested roads away from residential areas. There should be an established reporting system for PM2.5 levels throughout the country, and they should be reported in the weather reports so that the population, especially those at risk (e.g., children, elderly, and those with relevant morbidities) can take precautionary measures and could take necessary measures to avoid outdoor exposure.

Individuals should also adapt practices that reduce their exposure to air pollutants. Avoiding the use of personal motor vehicles and using public transport,

Table 2.4 Experimental studies and air pollutants

Air pollutant	Experimental model	Marker	Changes	Reference
Ozone	Rat	Astrocyte IL-6	Increase in brainstem expression	[73]
	Rat	N/T	Lipid peroxidation and impaired memory	[74]
	Rat	N/T	Lipid peroxidation, motor deficits, death in substantia nigra, and neuron damage	[75]
	Rat	Astrocyte	Increased lipid peroxidation Decreased cell viability	[76]
	Cell culture	N/T	Astrocyte death	[76]
Nanoparticles	Mouse	N/T	Oxidative stress	[77]
	Cell culture	N/T	HBMEC toxicity, lower junction expression	[78]
	Cell culture	Microglial activation superoxide production	DA neuron damage	[79]
Particlate matter	Rat	N/T	Lipid peroxidation, decrease in exploratory behavior	[80]
	Rat	Neuroglia	DA neurotoxicity	[81]
	Cell culture	Microglial activation TNFα and IL6 production	N/T	[82]
	Cell culture	Microglial activation superoxide production	DA neuron damage	[81]
	Brain capillary tissue	TNFα and ROS production	PGP and MRP2 increase tight junction protein decrease	[83]
	Mouse	IL1-β, TNFα, and INFγ	Changes in neurotranmitter	[84]
	Mouse	N/T	Changes in neurotranmitter	[85]
	Mouse	N/T	DA neuron damage in the substantia nigra	[62]
Air pollution	Human	COX2, IL1-b, iNOS, and CD14 increase	White matter lesions, diffuse Ab plaques, α-synuclein aggregation, BBB damage, cognitive deficits, and DNA damage	[86]
Air pollution	Human	COX2, IL1-b	White matter lesions, diffuse Ab plaques	[87]

N/T not tested, *DA* dopamine, *INFγ* innterferony, *IL-6* interleukin 6, *IL1-β* interleukin 1 β, *TNFα* tumor necrosis factor α, *ROS* reactive oxygen species, *PGP p*-glycoprotein, *MRP2* multidrug resistance-associated protein, *HBMEC* human brain microvascular endothelial cells

cycling, or walking will be an effective approach at community level. Moreover, public should avoid exposure during rush hour traffic, reduce the domestic use of fossil and biomass fuels, and improve the ventilation systems. Individuals, especially those at risk, should be educated and made aware to keep eye on the air pollution level reports so they could take necessary precautions.

Conclusion

Air pollution is an intricate mixture of potentially toxic components that can have their effects on the cerebrovascular system by various cellular and molecular pathways, causing diseases. Air pollution specifically causes neuroinflammation, oxidative stress, cerebrovascular damage, and neurodegenerative diseases. Because of the complicated nature of air pollutants, neurological effects involve a synergy of multiple mechanisms and pathways, making air pollutants a significant toxic environmental exposure. Some of the preventive interventions by which harmful effects of air pollutants can be restricted are maintaining air safety levels, making policies, developing surveillance system, collaborating with environmental organizations, and making energy from natural sources such as wind and solar power.

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Chapter 3
Bacterial Endotoxins and Neurological Disorders: From Exposure to Therapeutic Interventions

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Abstract Endotoxins are the lipopolysaccharide components of the outer membrane of gram-negative bacteria. Existing data illustrate the potential of endotoxins to induce neurodegenerative disorders. Plasma levels of endotoxins are comparatively higher in various bacterial infections, gut and gum inflammation, liver disease, and neurodegeneration as compared to normal physiological state. Increased levels of endotoxin in plasma lead to systemic inflammation which in turn activates the microglia cells that release pro-inflammatory cytokines. Endotoxin also synergizes with different aggregable proteins causing their abnormal accumulation in certain areas of the brain leading to various neurodegenerative diseases. In Alzheimer's disease, endotoxin levels are markedly increased in both the blood and brain, due to gum disease and/or altered gut microbiota, leading to accelerated systemic infection. Altered gut microbiome has been observed in many patients with neurodegenerative disorders. Changing the endotoxin-producing bacterial species can affect the disease pathology. Peripheral diseases associated with elevation of blood endotoxin such as sepsis, liver failure, and autoimmune skin disease also result in neurodegeneration. Neurodegeneration might be reduced to a maximum extent by limiting the exposure to particular endotoxin or by decreasing the endotoxin levels and endotoxin-induced neuroinflammation.

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Introduction

Bacterial endotoxins are complex lipopolysaccharides (LPSs) which are major components of cell wall of gram-negative bacteria. Endotoxins are usually released during the cell lysis and active cell growth. Moreover, they are also released physiologically as outer membrane vesicles [1]. LPS consists of two regions: lipid A and polysaccharides. Lipid A typically is six acyl chains attached to a phosphorylated disaccharide that is linked to the "core" attached to the O-antigen comprising of long linear chain of sugar molecules of variable length [1]. Lipid A constitutes middle portion of gram-negative bacteria's cell wall while O-antigen is found in the outer-facing surface of the bacterium [1]. Endotoxin can disrupt the both humoral and cellular immune response as it is not an infectious particle but can be recognized as an antigen by human body [2]. Endotoxin can lead to endotoxemia (entering blood stream) either through the local or systemic infection by extrinsic gram-negative bacteria or through intrusion of intrinsic bacteria into the blood stream via inflamed gums or leaky gut due any stress, tissue insult, or trauma [3]. If the integrity of the gut becomes compromised as in leaky gut syndrome (LGS), it can lead to systemic- and neuroinflammation causing the disruption in normal functioning of the cerebellum and hippocampus [3]. The bidirectional link between immune response and gut microbiota drives the event in the pathophysiology of brain ischemia, trauma, infection, and neurodegenerative diseases, respectively [4–7]. In response to any event effecting motility, secretions, permeability, and immune reactivity of gut, CNS regulates gut functioning, whereas any modification or alteration in gut microbiota may cause behavioral and neurochemical changes [3, 5]. Elevation in blood plasma endotoxin levels during infections, gum diseases, or neurodegenerative diseases can result in systemic inflammation and brain microglia activation [1]. Microglia are brain immune cells which are regulated by interactions with neurons under normal conditions. In case of any tissue injury or inflammation, microglia activate and worsen the brain diseases through the discharge of such molecules that can affect neuronal functioning such as release of inflammatory cytokines and reactive oxygen species (ROS) [4]. Systemic endotoxins cause neurodegeneration in animal models of Alzheimer's and Parkinson's diseases [1]. Mild systemic infection, in case of urinary tract infection (UTI), has been linked with mild cognitive impairment whereas repeated strong systemic inflammation has been associated with worsen course of Alzheimer's disease [4, 8]. Likewise, concurrent cerebrovascular accident and systemic inflammation can increase the ischemic lesion [4]. According to recent studies, the importance of microbiome (community of microbes residing in human body) has been highlighted in pathogenesis of

multiple sclerosis [9]. Therefore, systemic inflammation is linked with faster progression, and this has been postulated to implicate activation of microglia [4]. In this chapter, our main focus is on neurodegenerative disorders that are caused by exposure to different bacterial endotoxins along with their mechanism of induction. This chapter will also elaborate protective mechanisms and therapeutic interventions that play vital role in prevention of such exposures.

Basic Biology of Endotoxin

LPSs are present in the cell wall of gram-negative bacteria and are primarily involved in the protection of cells from the external environment [4]. Moreover, LPSs help the cells in hiding from onslaught of host immune system [10]. LPS molecules are arranged in outer side of the cell wall whereas glycerophospholipids are confined to the inner leaflet. As compared to many other cell wall components, LPS is produced in cytoplasm of the inner membrane of the cell and transported across the two bilayers and periplasm to be incorporated in the outer membrane [10]. LPS, also known as endotoxin, is released into the blood during cell lysis and/or active growth of gram-negative bacteria [2]. Toll-like receptors present in innate immune cells including macrophages, neutrophils, and monocytes recognize the released endotoxin and initiate phagocytosis leading to secretion of cytokines including IL-6, IL-12, IL-1β, and TNF-α. The released cytokines lead to a cascade of inflammatory reactions and exacerbation of asthma symptoms [2, 4]. According to the recent studies, inhalation is the main route of endotoxin exposure that results in respiratory distress [2].

Endotoxin Structure and Function

Endotoxins are produced following the lysis of gram-negative bacteria. It is not an infectious particle but a biologically derived active material. However, it can interrupt the host humoral and cellular mediation systems [2]. The toxicity and immunogenicity of LPS is related to its components [11]. LPS usually consists of three components including lipid A, core oligosaccharide, and O-antigen. Lipid A is hydrophobic in nature having six acyl chains attached to a phosphorylated disaccharide constituting the inner leaflet of membrane. It is attached to the core which is a short chain of sugar molecules with multiple modifications. This core is further attached to O-antigen which is a long linear chain of sugars with variable length constituting the outer leaflet of membrane [1, 12]. Soluble endotoxin is not only released after cell lysis but also released physiologically as outer membrane vesicles [1].

LPS is solely responsible for biological activity of endotoxin. Toxicity of LPS is attributed to Lipid A component while immunogenicity is attributed to the

polysaccharide components. These polysaccharide molecules are basically the key virulence factor in a gram-negative bacteria [12]. These bacterial cell wall components elicit a host inflammatory response from immune cells by activating complement through alternative (properdin) pathway leading to inflammation [11, 12]. Lipid A component of LPS is responsible for host recognition of gram-negative infection [10] while O-antigen determines its antigenicity [1]. The O-antigens contribute to the virulence and play a significant role in bacterial pathogenesis. These antigens protect the bacteria from immune cells (neutrophils) mediated phagocytosis and inhibit the killing of bacteria mediated by complement [13, 14].

Types of Bacterial Endotoxin

Extraordinary LPS modification systems have led to a better knowledge of bacterial pathogenic mechanisms and their contribution towards human diseases and immunity [10]. Based on the diversity of LPS modification system, various serotypes of gram-negative bacteria have been identified [10, 13]. LPS usually consists of highly preserved core of Lipid A and repeating subunits of O-antigens which vary among various strains on the basis of different sugar linkages with repeating subunits [13]. Modification in lipid A component of endotoxin can result in altered membrane permeability, increased resistance to antimicrobial peptides, and disrupting ability of host to recognize LPS as a conserved microorganism-associated molecular pattern (MAMP), resulting in altered pathogenesis [10].

As previously described, bacterial endotoxin is primarily composed of three portions:

- Lipid A.
- Core.
- Antigen.

Some organisms (for example, *Neisseria* spp.) contain lipooligosaccharide (LOS), in which the extended core region replaces the repeating O-antigen domain. Similarly, *Escherichia coli* contain extracellular polysaccharides consisting of two cell surface–associated polysaccharides including capsular and O-antigen. These antigens protect *E. coli* against phagocytosis by immune cells and impede the complement-mediated killing [13].

In contrast to old view of conserved static nature of lipid A, it has been observed that lipid A structure becomes modified after synthesis that leads to various endotoxin types and altered bacterial pathogenesis. Therefore, gram-negative organisms have developed numerous LPS modification schemes that permit these organisms to adjust in their surroundings [10, 15]. For instance, in response to cystic fibrosis, a little change in lipid A structure of *Pseudomonas aeruginosa* from 5 to 6 acyl results in augmented activation of MD2/TLR4 receptors [16]. It is pertinent to mention that *E. coli* contains six acyl chains in lipid A, whereas *Bacteroides dorei* has four or five

acyl chains. In this context, LPSs of *E. coli* produces a robust inflammatory response as compared to the LPS of *B. dorei* [1].

Source of Exposure

Endotoxins are primarily located in the mammalian gut as microbial flora. However, they are also present in saliva, skin, lungs, dental plaques, and urinary tract in variable quantities. Approximately 1 g of endotoxin is normally present in mammalian gut. These endotoxins are mostly concentrated in the lower section of intestine. The small concentration of endotoxin, even as low as 100 ng, in the blood and CNS can induce inflammatory reaction. Moreover, several studies have described that human beings are found to be more sensitive to endotoxins than other mammals [1]. The exposure of endotoxin is categorized into two main types. These types include occupational and environmental exposure [4]. Airborne endotoxin exposure or exposure through inhalation route is considered as most direct route of exposure [2, 4]. The endotoxin molecules can easily reach immune cells via alveolar spaces through inhalation and induce inflammatory response [17]. Dusty occupational facilities including industrial environments, cotton processing factories, and agricultural settings can increase airborne endotoxin exposure. Whereas indoors, having pets (dog), moisture or humidified mechanical air conditioning systems can also increase the likelihood of endotoxin exposure [2]. The concentration of endotoxin is quite high in occupational settings as compared to environmental settings. Nevertheless, the key difference between these exposures is their variable impact on human health. Many studies have reported the prevalence of adverse health effects including fever, cough, shortness of breath, and asthmatic symptoms following these exposures [18]. In addition, severity of these adverse effects varies from mild to severe in environmental settings [4].

Routes of Exposure

Endotoxins can enter into the blood stream and ultimately reach CNS through various pathways. They can release into the blood stream through leaky gut as in leaky gut syndrome or via inflamed gums or tooth brushing. Moreover, during active bacterial infections, endotoxins may enter the blood circulation resulting in inflammation and thereby neurodegenerative disorder (Fig. 3.1). For instance, urinary tract infections are linked with dementia, delirium, and other neuropsychiatric disorders [19]. Moreover, endotoxins can also enter into the blood in the absence of any infection through altered intestinal permeability [1]. As previously described, exposure of endotoxin via inhalation elicits an immune response leading to inflammation [1, 2]. Very high levels of endotoxins in the blood can be fatal due to septic shock.

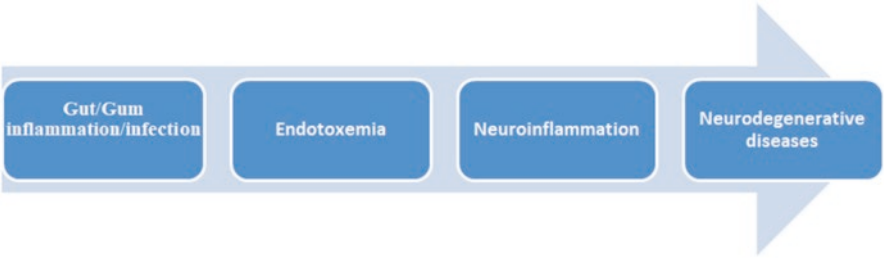

Fig. 3.1 Routes of endotoxin entry in blood leading to neurodegeneration

Moreover, high concentration promotes a chronic inflammatory state, which may lead to multiple chronic diseases [1].

Endotoxin–Host Interaction

Endotoxin can interact in host with a panoply of naturally occurring cellular and humoral components and can cause variety of diseases including neurodegeneration [1]. These components normally mediate the normal host defense reaction against infectious insults. Endotoxin may give rise to different neurodegenerative diseases by pairing with different aggregable proteins to induce neurodegeneration [1].

Activation of Cellular Mediators

Endotoxin usually interacts with all elements of cellular immune response of the host. Lipid A component of LPS is recognized by main LPS receptors including MD2/TLR4 (a composite of myeloid differentiation factor 2 and Toll-like receptor 4), which ultimately determines inflammation and toxicity [1]. Various components of bacterial endotoxins including LPS, peptidoglycan, cell wall remains, and lipoteichoic acid are cumulatively known as pathogen-associated molecular patterns (PAMPs). Since these PAMPs are highly immunogenic in nature, they elicit a strong inflammatory host response [11, 12]. Antigen presenting cells (APCs) recognize the specific components present in endotoxin and bind through pattern recognition receptors (PRRs), including the Toll-like receptors (TLRs). Existing data confirms the presence of 11 members of the TLR family in humans till date. TLRs are both present at the cell surface for extracellular ligand recognition and localized inside the endosomal sections for recognition of pathogen-related nucleic acids. Nineteen TLRs are present in all innate immune cells including macrophages, neutrophils,

and monocytes which recognize the released endotoxin causing initiation of phagocytosis and secretion of cytokines including IL6, IL12, IL1β, and TNF-α. This ultimately leads to a cascade of inflammatory reactions and exacerbation of asthma symptoms [4].

Microglial cells that involve in pathogenesis of neurodegenerative diseases also express all TLRs. Astrocytes that contain TLR 2, 3, and 9, TLR 3, 7, 8, and 9 are expressed by neurons, while TLR 2 and 3 reside in oligodendrocytes [19]. Many TLRs transduce their signal by interacting with intracellular adapter protein known as myeloid differentiation factor 88 (MyD-88). MyD-88 is linked with Interleukin-1 (IL-1) and receptor-associated kinase-4 (IRAK-4), which performs an essential part in signal transduction by Toll/IL-1 receptors (TIRs). Consequently, IRAK interacts with the tumor necrosis factor alpha (TNF-α) receptor-associated factor (TRAF) family, resulting in the nuclear translocation of necrosis factor (NF-κB). NF-κB is responsible for transcriptional activation of various genes involved in neuronal pathogenesis and in the production of cytokines and chemokines. These inflammatory mediators are highly immunogenic and provoke a robust inflammatory responses in the host [12].

Activation of Humoral Mediators

Inflammatory mediators produced as a result of cellular host response elicit an inflammatory reaction. Pro-inflammatory cytokines including TNF-α, IL-6, and pro-IL-1β, if released in limited quantity and in confined area, can actually help in stimulating the host defense system thus eliminating the invading bacteria. However, in case of endotoxemia, it can lead to progressive inflammation. TNF-α, IL-1, and IL-6 intensify the host defense response towards LPS. Lipopolysaccharide-binding protein (LBP) is a soluble plasma protein which facilitates the transfer of LPS to membrane-bound CD14. Subsequently, CD14 transfers LPS to TLR4 [12]. Moreover, lipoteichoic acids present in the cell wall of *L. monocytogenes* c are recognized by TLR2 with the help of CD14 [12]. Moreover, intracellular LPS can also directly activate human caspase-4 or caspase-5. These proteins may split and activate caspase-1. Caspase-1 has ability to cleave pro-IL-1β into IL-1β [20]. These pattern recognition receptors may serve to remove LPS and bacteria-expressing LPS from blood and tissues but at the same time they may also initiate inflammation and LPS toxicity [21]. The production of microglial reactive oxygen species (ROS) by CD11b/CD18 results in neurotoxicity and phagocytosis of neurons. These oxidative reactions cause significant neurodegeneration [1, 20]. Findings from recent study demonstrate that level of CD11b is markedly increased in rabbits as compared to low CD45 level resulting in microglial activation after intrauterine endotoxin exposure in the first postnatal week [21].

Pathogenesis of Endotoxin-Induced Neurological Disorders

Systemic inflammation caused by endotoxemia can activate the brain immune cells known as microglia which are generally regulated by interaction with neurons [4, 22]. Activation of microglia is the key event in pathophysiology of various brain diseases. Major function of microglia under normal physiology is to repair the damage, but in case of systemic infection, they can aggravate the brain diseases by releasing neuro-damaging molecules such as inflammatory cytokines and ROS. Microglial activation by systemic inflammation is bidirectional controlled signaling between the immune system and brain. It has been reported that acute and long-term cognitive impairment was observed among patients of mild cognitive impairment with concomitant sepsis. Similarly, repeated mild systemic infection like urinary tract infection in patients of mild cognitive impairment was linked with the worsening of Alzheimer's disease [8]. In a study conducted on rodents, the authors reported the acute microglial activation in the brain which persisted for at least 12 months resulted in dopaminergic neurons loss in substantia nigra after 10 months [23]. Therefore, systemic inflammation has a well-known effect on the course and severity of variety of brain diseases, and this effect can be speculated by the activation of microglia [4].

Microglia activation hypothesizing the role of gut–brain axis has also been established in mediating various behavioral and neurochemical changes [5, 6, 24]. There is a two-way interaction between CNS and gut microbiota. Any physical or psychological stressor causes CNS to induce changes in the gut motility, secretion, and immune response system. While on the other hand, gut microbiota may cause behavioral or neurochemical changes. This term is usually referred as microbiota–gut–brain (MGB) axis [24, 25]. The MGB controls the gastrointestinal tract (GIT) and CNS through vagus nerve, hypothalamic–pituitary–adrenal (HPA) axis, and various inflammatory mediators including cytokines. In case of compromised intestinal barrier, the bacterial endotoxins can enter into blood stream causing systemic inflammation which may further lead to release of harmful metabolites resulting in neuroinflammation. The resulting systemic- and neuroinflammation can cause dysfunction in the cerebellum and hippocampus [24]. Various studies have indicated that patients with neurodegenerative diseases found to have increased intestinal permeability [24, 26]. Other studies have also highlighted the prominent role of dysbiosis (a functional gastrointestinal disorders (FGID) in mood disorders [5].

Another proposed pathogenesis of endotoxin-induced neurological disorders is by synergizing with various aggregable proteins [1]. According to the conventional amyloid cascade hypothesis of Alzheimer's disease (AD), the aggregation of soluble amyloid-β (Aβ) monomers into fibrillar plaques consecutively leads to tangles in neurofibrils, hyperphosphorylation of tau protein filaments, gliosis, neuronal loss, and resultantly dementia. These aggregable proteins in presence of endotoxin cause neurodegeneration, depending on their distribution in the brain. However, the sole presence of an aggregable protein, such as Aβ, Tau, or α-synuclein, in brain is not usually enough to induce neurodegeneration [1, 27]. In a recent study, a single intraperitoneal injection of 10 mg/kg of LPS endotoxin induces amyloid-β and p-tau formation in the rat brain resulting in neuroinflammation [27].

Bacterial Endotoxin-Induced Neurological Disorders

Normally the concentration of endotoxin is very low in blood. However, levels of endotoxins markedly increased during infections, gum diseases, leaky gut, or neurodegenerative disorders. Increased levels of endotoxins in the blood lead to endotoxemia which ultimately causes systemic inflammation, brain microglial activation, priming and/or tolerance, memory defects, and loss of brain neurons/synapses. Endotoxin encourages amyloid-β and tau accumulation and neuropathology, proposing the possibility that endotoxin synergizes with different aggregable proteins to produce various neurodegenerative illnesses [1, 4, 27].

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder commonly characterized by loss of dopaminergic neurons in substantia nigra [17, 28, 29]. The clinical manifestations of PD include tremor, stiffness, slow movement, and unstable posture. Currently available literature suggests aging as major risk factor for the progression of disease [30]. The prevalence of PD in general population is 0.3%. The pathogenesis of PD remains unclear and is considered to be multifactorial [28]. The proposed pathological mechanism of PD is the presence of neuronal network named as Lewy bodies comprising α-synuclein protein as a main element. Recent findings have suggested the correlation of these Lewy bodies with intestinal enteric nerves [17]. Thus, suggesting the intestine as primary site for PD progression as compared to other etiological agents including environmental toxins and pathogens [17, 28]. The gut microbiota has been proposed to play an important role in effecting brain activity, therefore, suggesting the role of compromised intestinal barrier in progression of PD [17].

Recent studies have confirmed the role of brain inflammation in the pathogenesis of PD. Bacterial endotoxin after entering in blood causes systemic inflammation, macrophage activation, and sepsis [31]. Sepsis interfere with the integrity of blood–brain barrier (BBB) which ultimately allows endotoxin entry in cerebrospinal fluid [29]. Major characteristic of PD is abnormal production of α-synuclein protein which poses changes in all levels of brain–gut axis. These levels include various types of nervous systems such as central, autonomic, and enteric nervous systems. Later, the role of gut microbiota in modulating the brain–gut axis via immunological, neuroendocrine, and direct neural processes has been documented [32]. Dysregulation of the MGB axis in PD may be linked with motor symptoms right after the gastrointestinal signs, along with the pathogenesis of PD itself. This particular progression of symptoms actively suggests the supporting hypothesis of progression of neurodegenerative disease from the gut to the brain. Meanwhile, stimulation of intrinsic immune system from any gut abnormality including gut dysbiosis, small intestinal bacterial overgrowth, or leaky gut syndrome may induce systemic inflammation [6, 30]. On the other hand, the activation of enteric neurons

and enteric glial cells may add to the misfolding of α-synuclein protein in brain. Moreover, bacterial proteins cross-react with human antigens, thereby resulting in disturbance of adaptive immune system [6, 30].

Role of microglial immune cells has been highlighted extensively. According to numerous postmortem and experimental studies, the loss of dopaminergic neurons is linked with neuroinflammation initiated by activated microglial cells. Infiltrated marginal immune cells and their neurotoxic products include pro-inflammatory cytokines, reactive oxygen species, and nitric oxide [30]. Similarly, the role of systemic inflammation caused by endotoxin exposure has been proved, and many researchers are using a purely inflammation-driven animal model for the initiation of nigrostriatal dopaminergic neurodegeneration. Other genetic and toxin-based models are also being employed solely or in combination with inflammation-driven animal models. This provides an essential tool to demarcate the accurate mechanisms of neuroinflammation-mediated dopaminergic neuron loss [30].

Primary progression of PD is thought to be via Lewy bodies which are aggregates of α-synuclein proteins. As a result of endotoxin exposure, the innate immune response of host causes deposition of these proteins in neurons or glial cells in form of clumps. α-Synuclein, which is chiefly present in the form of fibrils as well as exists in monomeric and oligomeric forms within the CNS, can elicit a central immune response orchestrated by microglia. Likewise, any mutation in α-synuclein can drive PD risk [33]. In a recent research, the authors documented a robust cytokine response in both PD and control patients, by α-synuclein fibrils monomers which are comparable to that induced by bacterial LPS. These findings effectively suggest the role of α-synuclein in inflammasome-related cytokine production in PD [34].

Alzheimer's Disease

Alzheimer's disease (AD) is characterized by progressive neurodegeneration and most commonly occurs in elder people. AD is clinically manifested as short- and long-term memory deficits, compromised decision-making, absentmindedness, and mood swings [35]. It is fifth most leading cause of death in patients over 65 of age. Approximately, 60–80% of dementia cases account for Alzheimer's disease [24]. The pattern of AD progression varies among population. Familial AD accounts for early onset (before 56 years of age) of the disease and is characterized by gene mutations in the amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes. Various predictors that are involved in pathogenesis of AD include genetic, environmental, and lifestyle factors [3, 35]. Following pathologies are distinctive features of AD: neuronal cell loss, certain brain regions atrophy including the hippocampus and cortex, due to development of amyloid-β (A) plaques and tangles of neuro fibrils. The manifestation of these pathologies hinders the normal signaling properties and eventually leads to learning and memory deficits [36].

Major mechanism responsible for pathogenesis of AD is characterized by the development of amyloid plaques and neurofibrillary tangles (NFTs) which further consist of aggregated b-amyloid (Ab) and tau proteins, respectively. The amyloid hypothesis of AD progression has provided the basic framework for research for over two decades. The hypothesis states that the accumulation of Ab in the form of misfolded amyloid peptides in the form of senile plaques in the brain initiates the pathogenesis of AD [3]. Exposure to LPS or endotoxin results in inflammation which actively adds to the augmented fibrillogenesis of Ab by stimulating fibril elongation [35] and diminished amyloid clearance by downregulating triggering receptors expressed on myeloid cells TREM2 [37]. At the same time, hyper phosphorylation of tau protein results in formation of neurofibrillary tangles and loss of cholinergic neurons. Increased production of Aβ fibrils prompted by endotoxemia induces the production of NF-κB, known to be engaged in neuroinflammation in the AD brain. Meanwhile microglia contain Toll-like receptor (TLR) 4 with LPS as its ligand that activates other inflammatory mediators [3]. Also, the triggered inflammatory reaction caused by microbiome species and their secretions intensifies the amyloids aggregation into senile plaque lesions [37].

Along with amyloid hypothesis, the role of gut microbiome has also been established in the pathogenesis of AD. Endotoxin released in blood stream through leaky gut can contribute to CNS amyloid burden and ultimately result in neuroinflammation. The major risk factor of AD such as aging accounts for the LPS/amyloid hypothesis. As with advance age, GI tract barrier and blood–brain barrier become compromised resulting in LPS/amyloid leakage into the blood. This eventually triggers many other pro-inflammatory cytokines causing neuroinflammation [15]. Therefore, by eliminating gut bacteria, a reduced plaque load and decreased microglial activation were observed in an amyloid model of AD mice [38]. In the mice model of AD, peripherally administered LPSs causes decrease in both memory consolidation and reconsolidation [39]. Also, LPSs endotoxemia causes increased p-tau in the brain of treated mice, suggesting the Aβ plaque formation [27].

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated age-related progressive neurodegenerative disease. The characteristic features of MS are demyelination, myelin sheet, and axonal damage as well as neurodegeneration. The clinical display of MS includes light-headedness, vision loss, dizziness, pain, motor function discoordination, gliosis, fatigue, unresponsiveness, diminished coordination control, bladder and bowel dysfunction, depression, and focal lesion of inflammation [3, 9]. Microglia cells play an important role in remyelination and demyelination of neurons in MS. Endotoxin exposure either by leaky gut or infection leads to endotoxemia which causes microglia activation in CNS thus resulting in secretion of many pro-inflammatory molecules [40]. Demyelination in MS attracts many macrophages and microglia which are involved in disease pathogenesis. Normally microglia repair any damage caused to myelin sheet and promote remyelination by

secreting anti-inflammatory cytokines. In presence of high endotoxin levels, microglia release pro-inflammatory cytokines and mediators that damage the myelin sheath and/or oligodendrocytes. Microglia are involved in interacting with other immune cells thus leading to the activation of T cells during the process of demyelination and remyelination in MS [4, 40].

MS is chiefly classified into following types:

- Progressive-relapsing MS (PRMS)
- Primary progressive MS (PPMS)
- Secondary progressive MS (SPMS)
- Relapsing-remitting MS (RRMS)

Along with microglia activation, the pathogenesis of MS also depends upon various other factors including genetic and environmental factors. Gut dysbiosis is considered to be a significant environmental factor accountable for the neuropathogenesis of MS [3]. Endotoxin exposure in MS does not only account for microglial activation but also promote the presentation of myelin antigens [1]. Microglia display major histocompatibility (MHC) antigens I and II. Moreover, microglia also cause the discharge of many pro-inflammatory and anti-inflammatory cytokines including IL-1, TNF-α, and IL-10. Microglia also express Fc receptors (I–III) and complement receptors (CR1, CR2, and CR4) resulting in myelin sheet damage leading to MS [40].

Ghareghani et al. [41] indicated a new pathway for production of pro-inflammatory cytokines that leads to neurodegeneration. According to this new mechanism, various factors are concomitantly involved in initiation of MS. These factors include latitude, vitamin D, melatonin, and gut microbiota [41]. Whereas, in another study, organ-particular dysbiosis was concluded to be underlying disease mechanism of MS [42]. Similarly, elevated levels of pro-inflammatory cytokines might cause subjective fatigue in MS patients. It is suggested that endotoxin-induced systemic inflammation amplifies serum levels of TNF-α and IL-6 as well as subjective fatigue in healthy individuals [43]. α-synuclein (clumps of neuronal protein) involved in pathogenesis of Parkinson's disease is also thought to be involved in progression of MS [33]. MS–oxidative stress–microbiota relationship was also reported to be an intrinsic mechanism for MS progression [9].

Endotoxin and Other Brain Pathologies

Disorders that include neurodegeneration of motor neuron are classified as motor neuron disorders. Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disorder which shares genetic and neurological mechanisms with frontotemporal dementia (FTD) [1].

ALS is an advanced neurodegenerative disorder involving death of motor neurons, brain and spinal cord. The classic symptoms contain muscle weakness, cramping, coordination difficulties, muscles rigidity/spasms, and muscle twitching. This

progressively causes speaking, swallowing, and breathing difficulties. There are two sorts of ALS: (a) Sporadic ALS, with unknown etiology and (b) Familial ALS, which is caused by genetic mutation [3]. The role of gut microbiota in progression of ALS has been well elaborated. Leaky gut or altered gut microbiome can release endotoxins in blood which activate the innate immune response leading to progression in pathogenesis of ALS. A hypothesis that gut-derived neurotoxins cause ALS has also been suggested [28]. Due to inflamed/leaky gut and/or altered gut microbiome, the level of endotoxins rises in blood. Additionally, astrocytes lead to motor neuroinflammation [1]. Butyrate has been suggested as a prospective therapeutic agent for repairing ALS-related dysbiosis [44].

Another neurodegenerative syndrome caused by endotoxin exposure is dementia which is characterized by memory loss and cognitive impairment to such an extent that it interferes with normal life functioning. According to recent studies, dementia is also linked with altered gut microbiota, releasing LPS into blood stream that triggers metabolic diseases and low-grade inflammation [45, 46]. MGB axis has also been involved in pathogenesis of dementia. Pathogenic gut microbiota can cause increase in LPS, pro-inflammatory cytokines, and barrier dysfunction which will lead to systemic inflammation [7]. The resultant endotoxemia may trigger neuroinflammation enhancing abnormal functioning of certain brain regions (hippocampus and cerebellum). Neuroinflammation along with dysfunctional MGB axis may stimulate cognitive impairment. Certainly, inflammation is a characteristic of broad-spectrum neurodegenerative diseases that manifest dementia. Therefore, suitable therapeutic measures may prevent cognitive impairment and minimize susceptibility to dementia [47]. Moreover, since LPS is one of the key factors involved in the progression of dementia, therefore it is also an important clinical target for therapeutic intervention [8].

Prevention and Management Endotoxin Exposure

Endotoxin exposure from any source and route can be prevented by eliminating or evading the particular source. The uptake and exposure route of endotoxin from environmental source can be avoided by limiting such exposure as much as possible. For instance, the exposure through inhalation route can be minimized by taking appropriate measures of limiting inhalation time. In occupational setting, duty hours or mode of exposure can be managed accordingly by implementing the job rotations. The most sensitive group includes infants and elderly that are exposed to endotoxins via environmental sources. The main source of inhaled endotoxin exposure is settled dust particles present in homes and mattresses. Endotoxin exposure could elicit an inflammation response but immune response only occurs after repeated exposures. Therefore, it is crucial to avoid or minimize such preventable environmental exposures by regular cleaning [4].

The most important route of endotoxin exposure which leads to neurodegeneration is through MBG axis, leaky gut, or altered gut microbiome. All the mechanisms

lead to the increased endotoxin levels in blood causing neuropathologies. In such cases, the beneficial effects of prebiotics, probiotics, and synbiotics on human microbiome have been well elaborated. Gut dysbiosis may offered to be a significant therapeutic target for the prevention/treatment of irritable bowel syndrome (IBS-related disorders), including cognitive impairment. Most importantly, special consideration should be given to control of gut inflammation, and models should be analyzed to develop new therapeutic regimens to relieve and prevent the progression of gut inflammation. Moreover, the composition of innate microbial flora can be regularized by taking appropriate probiotics and prebiotics. This preventive approach offers the possibility of mediating the mucosal and systemic immunity dysfunction and balancing GI homeostasis [47]. Similarly, the role of nutrition and diet intake on gut microbiome can prove to be a beneficial tool in preventing endotoxin exposure from GI tract. Changes in the composition of *Firmicutes* and *Bacteroides* due to unnecessary fat intake have been reported to cause metabolic endotoxemia, but many human epidemiological studies have not found a relationship between fat intake and blood LPS levels. In conclusion, there is dire need to search and reduce intake of dietary factors that cause metabolic endotoxemia and increase intake of nutrients that maintain a healthy gut [48].

Therapeutic Intervention to Control Neurodegenerative Damage by Endotoxin

Various treatment approaches have been reported to lower the blood endotoxin levels. These approaches include: lipopolysaccharide binding protein (LBP), apolipoprotein E (APOE2), polymyxin B, or other antibodies against LPS that could be injected into the blood to reduce the endotoxin levels. However, these interventions are impractical for the long-term management [1]. The beneficial role of polymyxin B-immobilized fiber column hemoperfusion in removing endotoxins is also suggested [49]. On the other hand, albumin dialysis is already used to lower LPS levels in patients with liver failure and therefore can be utilized to assess beneficial effect of low endotoxin levels for treatment of neurodegeneration. The use of albumin dialysis for several years would be perplexing and might reduce patient compliance. Vaccines against LPS are suggestive as long-term solution for endotoxin-associated neurodegeneration [1].

Similarly, as inflammation plays a key role in the progression of neurodegeneration, anti-inflammatory agents can be used as potential therapeutic alternatives in ameliorating the neurodegenerative disease symptoms. Beneficial role of following anti-inflammatory agents has been pointed out by several studies: betulinic acid, luteolin, imatinib IM, fluoxetine, and anthocyanins. In a recent study, betulinic acid, a lupane-type triterpene, has been used to treat mouse model of lethal endotoxemia by modulating TNF-α production by macrophages [50, 51]. Besides inflammation,

microglia activation acts as a fundamental agent in driving neuropathology caused by high endotoxin levels.

Microglial cells modulate the immune response by releasing pro-inflammatory cytokines and nitric oxide. Therefore, luteolin, a naturally found polyphenolic flavonoid antioxidant, with strong anti-inflammatory and neuroprotective activities has been used in rat model of endotoxemia both in vivo and in vitro. Luteolin exerted an inhibitory effect on NF-κB, STAT1, and IRF-1 signaling, thus tempering the inflammatory response of brain microglial cells [51]. Moreover, a recent research has shown that peripheral treatment with imatinib methane sulfonate salt (IM) decreases Aβ protein accumulation in the hippocampus, thus relieving LPS-induced peripheral inflammation and cognitive impairment [52]. Likewise, anthocyanins also protect against endotoxin-induced neuroinflammation in adult mouse cortex [53]. Besides that anti-inflammatory effects of fluoxetine in LPS-stimulated microglial cells have also been reported [54].

As endotoxins are gram-negative bacteria outer wall, a subunit vaccine can be developed to prevent neurodegenerative diseases caused by endotoxins. In previous studies, beneficial effect of antibodies targeted against LPS was outlined. Both O and core-antigen–specific vaccines had been developed and can be utilized, given the fact of increasing antibiotic resistance these days [55].

Various studies have suggested the important role of MBG axis, gut dysbiosis, and leaky gut in neurodegeneration and therefore they should be targeted to relieve endotoxin-induced neuropathology. A recent study found the valuable effects of vagus nerve stimulation (VNS) and its mechanisms that attenuated the LPS-induced (intraperitoneally injected) acute lung injury (ALI). Therefore it can be proved as potential therapeutic agent in reducing endotoxin levels [47]. Similarly, it is quite possible that dysbiosis, immunologically mediated adjustments, increased GIT penetrability of LPS/pro-inflammatory cytokines, and other metabolic disorders can be controlled and reversed by therapeutic use of "prebiotics, probiotics and synbiotics, and VNS" [47].

Impact of Endotoxins on Patients with Preexisting Neurodegenerative Diseases

Roles of microglia activation, gut dysbiosis, and MBG axis are well established to increase endotoxin levels leading to systemic inflammation but the effect of systemic inflammation on diseased brain is quite pronounced as compared to healthy brain [8]. Similarly, systemic inflammation effects only behavior and brain metabolism in healthy subjects [56]. In many patients with depression, there is a state of mild systemic inflammation, which may contribute to marked depressive symptoms through effects on microglia [4]. Likewise, in patients with mild cognitive impairment, systemic inflammation in form of sepsis causes severe systemic inflammation, resulting in acute and long-term cognitive defects [57] mediated by activation

of microglia. Milder forms of systemic inflammation (e.g., urinary tract infections) can lead to delirium in patients with mild cognitive defects while it is assumed that repeated systemic inflammation deteriorates the course of Alzheimer's disease [8]. Likewise, when systemic inflammation ensues alongside a cerebrovascular accident, the ischemic lesion becomes larger [58]. Another study showed faster progression of multiple sclerosis with subsequent systemic inflammation [4].

Conclusion

Bacterial endotoxins are lipopolysaccharide (LPS), a major constituent of cell wall of gram-negative bacteria. Endotoxins are usually released during cell lysis or active cell growth and disrupt both humoral and cellular immune response in host. Endotoxin can lead to endotoxemia by entering into the blood stream either by inflamed gums or by leaky gut following any stress, tissue insult, or trauma. MBG axis drives the event in the pathophysiology of brain ischemia, trauma, infection, and in neurodegenerative diseases. Increased blood plasma endotoxin results in systemic inflammation and brain microglia activation, which eventually worsen the brain diseases through the discharge of pro-inflammatory molecules [4]. Many studies have highlighted the importance of microbiome in the pathogenesis of neurodegenerative diseases including multiple sclerosis, Parkinson's, or Alzheimer's disease. Therefore, various treatment approaches aiming to reduce endotoxin level in blood can be considered in future. These approaches include: lipopolysaccharide binding protein (LBP), APOE2, polymyxin B, or other antibodies. Keeping in view the high microbial resistance against antibiotics, vaccine against specific part of endotoxin should be prepared. Moreover, anti-inflammatory agents can also be considered to reduce endotoxin-induced neuroinflammation in neurodegenerative diseases. Maintaining a healthy gut by use of probiotics, prebiotics, and symbiotics is also a possibility to avoid endotoxin exposure through GI tract. Though substantial investigations on endotoxin-induced neurological disorders have been carried out but still there are numerous areas yet to be explored in terms of pathogenesis, prevention, and treatment.

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Chapter 4
Heavy Metals and Neurological Disorders: From Exposure to Preventive Interventions

Qudsia Rehman, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Heavy metals are available abundantly in nature, especially in the soil, mines, drinking water, some in vapor form in the air, and also constitute the Earth's crust. These are widely used in pesticides, herbicides, paints, gasoline, etc., and their main route of exposure encompasses anthropogenic sources. Among several heavy metals, lead, cadmium, mercury, and arsenic cover the most part. One of the most important contributing factors are industrial pollutants that have an important role in contaminating the plant and marine life, which indirectly affect the human health. The brain is the functional unit of body which is sensitive to such heavy metals, and suffers a lot through their contamination in comparison to the other parts of the body. If the exposure of heavy metals becomes prolonged, they will have deleterious effects on the nervous system. Heavy metals toxicity is responsible for many neurodegenerative diseases particularly Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and attention-deficit hypertensive disorders. There are number of epidemiological, experimental, *in vivo* and *in vitro* data which represent the significant association or correlation between the exposure of heavy metals and neurotoxicity. The probable reason behind this correlation is mostly due to oxidative stress, the participation of certain proteins/enzymes as well as an interruption in the normal secretion of neurotransmitters on account of heavy metal exposure. The resultant effects and intensity of diseases can be prevented by taking the adequate preventive measures with possible therapeutic interventions.

Keywords Lead exposure · Mercury exposure · Cadmium exposure · Arsenic exposure · Neurotoxicity

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Introduction

Heavy metals can be termed as the metals that weigh more than 5 g cm^{-3}, such as arsenic, cadmium (Cd), lead (Pb), and mercury (Hg). Almost there exist 40 elements that are included in the category of heavy metals out of which the abovementioned heavy metals play an important contribution in the toxicity and neurological disorders. Naturally, they are found in the Earth's crust in the form of dispersed rocks and ores. The anthropogenic contribution of heavy metals in the biosphere has been associated with industrialization and urbanization; due to this fact, they are widely available in the soil and aquatic environment. These metals become the cause of adverse reactions occurring in plants, animals, and human and affect the entire ecosystem [1]. In human, they are inhaled, ingested, and got in contact with skin, resulting in the inhibition of growth during the developmental stage, mental retardation, death of either particular cells of organism or whole of it, abnormalities in the immune system, endocrine system, and overall metabolism.

There are two ways of destructing metabolic functions; firstly, in the brain, heart, liver, kidneys, and some other parts, the heavy metals get accumulated and affect the proper functioning of them. Secondly, the displacement of necessary minerals from their origin, with heavy metals, occurs, which ultimately disrupts the biological functioning [2]. Therefore, considering these types of abnormal alterations in the body of human, there should be some safety standard levels of interactions with heavy metals for the protection of health and those interactions must be within the safest limits [3].

This chapter mainly focuses on the effects of Pb, Cd, Hg, and arsenic on neurological health and their underlying mechanisms. These metals when present in the body in excess amount cause toxicity in the form that they disrupt the mitochondrial function and disable the activity of enzymes. Most importantly, they induce the oxidative stress and increase the production of reactive oxygen species (ROS). Many epidemiological and clinical studies have been conducted that show the correlation between the exposure of heavy metals and neurological disorders, such as Alzheimer's disease, autism spectrum disorders (ASD), amyotrophic lateral sclerosis (ALS), Gulf War syndrome, Guillain–Barré disease, Huntington's disease, multiple sclerosis, Parkinson's disease, and Wilson's disease [4]. For instance, considering the exposure of Hg, it is involved in the lipid peroxidation and becomes the source of cell damage that is a similar process incriminated in case of Parkinson's disease pathogenesis [5]. This chapter also explains the ways of prevention as well as the protection against the exposure of heavy metals and possible therapeutic interventions being applied to relieve the symptoms of neurological disorders. There are also certain antidotes that are used in case of life-threatening exposure.

Sources of Exposure to Toxic Metals

Lead

Lead (Pb) is one of the highly toxic metals that has a bright silvery, moderately bluish appearance. Industrial processes, food, drinking water, and smoking are the main sources of exposure to it. The other origins include gasoline and house paints that emerge from storage batteries, toys, lead bullets, faucets, etc. The particles of soil, sediment, and sewage sludge get strongly bind to Pb in the environment. Human beings are exposed to Pb through vehicle exhaust, industrial fumes, and contaminated food and water. Fixation of Pb to the soil particles and flow into the water generally cause the exposure to human beings. The occupational exposure of Pb gives rise to many neurological and non-neurological signs and symptoms such as headaches, encephalopathy, loss of memory, hallucination, dullness, irritability, poor attention span anemia, nausea, muscular tremor, and saturnism. The cross-sectional (descriptive and analytical) survey conducted on 40 female solderers who were working in 2 electrical parts manufacturing factories in Neyshabur city in 2017–2018. Their blood test showed increased Pb concentration, as they were highly exposed to Pb during work [6]. Another cross-sectional study held in Duhok City, Kurdistan Region, Iraq, found that the main exposure of Pb was occupational that the workers were being employed as gasoline power generators, traffic policemen, and working in petrol filling stations and batteries repairing workshops [7]. A survey-based study was performed among Australian workers to estimate the prevalence of work-related exposure of organic and inorganic Pb compounds. The conclusion described that this occupational exposure could be the leading cause of life-threatening diseases [8]. In an experimental study, the influence of occupational exposure of Pb was evaluated on hematological indices among petrol station attendants and automobile mechanics in Nnewi, South-East Nigeria. The results indicated that Pb exposure leads to the adverse effects on the hematopoietic system; as a fact, they were highly exposed to Pb and alcohol was exacerbating the hepatotoxic signs and symptoms due to this Pb subjection [9]. The possible sources of Pb pollution in the environment have been shown in Fig. 4.1.

Cadmium

The seventh most toxic heavy metal is Cd that is the by-product of zinc production, through which human can get exposed. It was first used during the World War I, in place of tin and as a pigment in paint industries. It is relatively water-soluble than other heavy metals; so, the accumulation occurs in the soil and ultimately in fruits and vegetables. Nowadays, it is being used in rechargeable batteries, alloys, and also in tobacco smoke. There are several epidemiological studies including cohort and cross-sectional studies that bring attention to nonoccupational and occupational

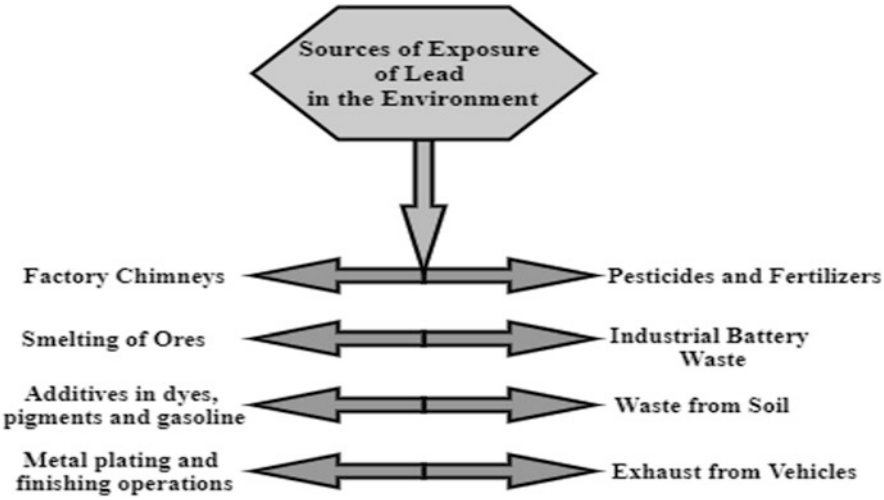

Fig. 4.1 Schematic representation of possible sources of the exposure of lead

exposure of Cd. Human beings are exposed to Cd by inhaling and ingesting it, via tobacco smoke and agriculture crops. After inhalation, Cd enters into the brain via olfactory bulb and even it enters into the brain via cerebrospinal fluid (CSF) barrier [10]. The sources of exposure of Cd in an adult urban population in southern Brazil and its level in the blood were investigated. It was concluded that levels of Cd in the blood were associated with smoking and alcohol drinking; these parameters were the main causative factors to the increased concentration of Cd in the blood [11]. A study carried out among Canadian adults aged from 20 to 79 years showed that smoking has a major contribution to Cd exposure; while, the diet has not contributed a lot [12]. Another study describes that occupational exposure of Cd could be associated with neurological signs and symptoms of myalgic encephalomyelitis/chronic fatigue syndrome [13]. These are the neurological diseases characterized by widespread inflammation and multisystemic neuropathology [14]. The occupational exposure of Cd encompasses those people working as technicians in jewelry industries. Such industries usually make jewelry that is not of pure precious metals rather it contains some heavy metals like Cd, to make them cheaper. The occupational exposure of a few heavy metals was studied, among the workers in jewelry manufacturing. The results manifested that workers were significantly exposed to Cd as it was released during the jewelry processing, as compared to the control group. The mean concentration of Cd in their urine samples was 12.65 (+ SD 11.12) μg/L and among the controls it was 4.66 ± 2.27 μg/L [15].

Mercury

Mercury (Hg) is found naturally, possessing shiny silver-white liquid appearance without any odor and exists in three forms, i.e., as a metallic element, inorganic salts, and organic compound. Such forms have different bioavailability and toxicity. Hg is transformed into methylmercury and dimethylmercury either biologically or chemically, where methylmercury is bioaccumulative and causes toxicity. It is inhaled and ingested by human through the vapors of Hg in elemental form and food containing methylmercury, respectively. Anthropogenic activities of human in agriculture, mining, municipal wastewater discharges, incineration, and discharges of industrial wastewater are the main sources of exposure on humans. The most direct exposure to human involved is through amalgams which are used as a tooth filler to prevent it from decaying. A study was conducted to assess the levels of aluminum, Pb, and Hg in the hair of 100 autistic Egyptian children; their ages ranged from 2.5 to 15 years so that the environmental and genetic risk factors associated with them could be estimated. The result of this study exhibited the significant levels of aluminum, Pb, and Hg in the hair of autistic children than patients which were kept as controls. There was a positive correlation between the maternal fish consumptions and level of Hg metal and in this study; it was also found that the level of Hg in children with ASD was increased as the usage of maternal dental amalgam increased, albeit not significantly increased, in terms of stats [16]. A 2014 meta-analysis of the evidence of the impact of prenatal and early infancy Hg exposures on autism risk found a significant correlation between the increased exposures of environmental Hg and an increased risk in ASD [17].

Arsenic

Arsenic is found in organic and inorganic form. Fertilizers, phosphates, paints, dyes, semiconductors, drugs are the sources of exposure. The encounter with human may occur by drinking water, contaminated with arsenical compounds; present in pesticides, disposals, and natural mineral deposits/ores. This type of exposure is particularly more associated with toxicity caused by arsenic compounds which is usually termed as arsenicosis [18]. The occupational exposure of arsenic encompasses the herbicides and pesticide production, mining, smelting, manufacturing of glass, semiconductors, and some professions like carpentry that incriminate the removal or exposure to structures/materials treated with arsenate wood preservatives [19]. According to US Agency for Toxic Substances and Disease Registry publication, inhalation and the dermal layer is contemplated as a minor way of exposure in the general population, but a major way of exposure of arsenic is the occupational worker [20]. Arsenic exposure through water and consumption of rice was investigated in epidemiological studies that manifested the association with this type of exposure and increased urine concentration of arsenic in 229 pregnant

women [21]. There are many metal mines that contain arsenic in South Korea. These mines contribute to the contamination of the environment [22]. Thus, the accumulation of arsenic during the childhood in the body could lead to the neurobehavioral abnormalities during puberty [23]. The association of exposure of arsenic with neuronal development and behavioral disorder was found through meta-analysis, which showed that arsenic exposure affected memory, verbal, and performance domains in children, although to a lesser extent [24].

Mechanism of Induction of Neurotoxicity

The general mechanism of heavy metal–induced neurotoxicity is almost the same. Nearly, all heavy metals particularly Pb, Cd, mercury, and arsenic induce the cellular damage by the production of free radicals or ROS like $O_2^{\bullet}$, OH, $NO^{\bullet}$, $RO^{\bullet}$, and $ONOO^{\bullet}$, H_2O_2. This production is accelerated when the availability of antioxidants is reduced or the overall balance of activity of antioxidant enzymes (SOD, GSH, GST, catalase) is disturbed as shown in Fig. 4.2. Few of them also produce reactive nitrogen species (RNS). In addition to this, the release of synaptic neurotransmitters is also drastically affected, resulting in neurotoxicity mainly, impairment in the

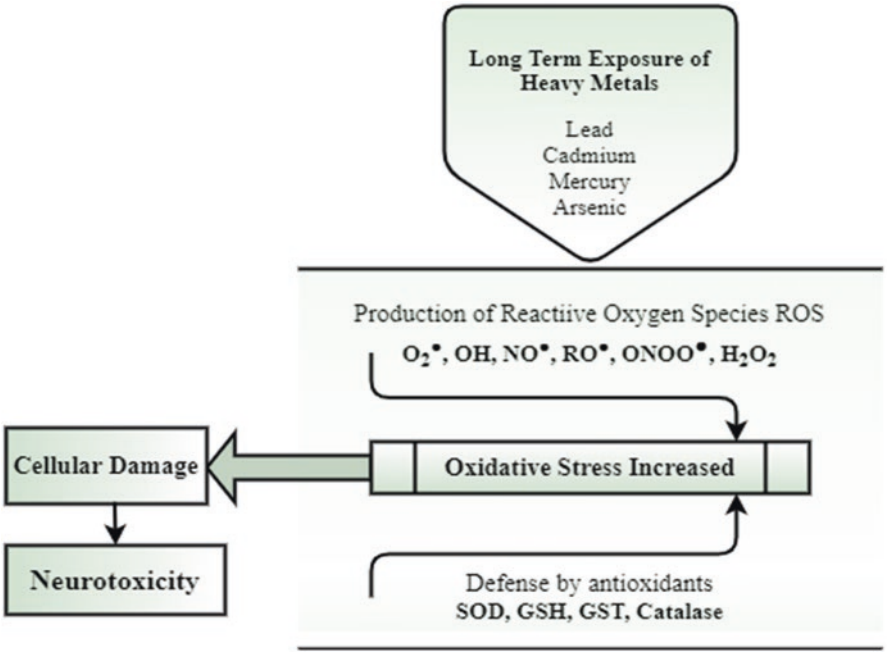

Fig. 4.2 General mechanism of oxidative stress induced by the exposure of heavy metals

body balance, tremors, hearing and vision problems, loss in memory, low IQ level, learning disabilities, and several others.

Lead-Induced Neurotoxicity

There are some mechanisms involved through which Pb induces the neurotoxicity, and Fig. 4.3 shows the possible mechanisms involved in the induction of neurotoxicity that can be associated with the morphological and pharmacological effects.

Some in vitro studies reveal that Pb can inhibit the Na^+/K^+-ATPase in the cell membrane and activate the protein tyrosine kinase in the capillary, which hinders the energy metabolism [25]. Two mechanisms are associated with the production of ROS by which deterioration in living systems occurred. The first one is the direct generation of free radicals like O_2 and H_2O_2 due to the overload of heavy metals. The second one is the indirect mechanism that is executed by the depletion of antioxidants and inhibition of enzymes. The enzymes with antioxidant activity that Pb inhibits are delta-aminolevulinic acid dehydratase (ALAD) and glutathione reductase (GSR). The inhibition of ALAD and GSR causes the imbalance, and the resultant effect will be oxidative damage to DNA and lipids. The inhibition of ALAD gives rise to the circulating ALA, which is also termed as a weak gamma-aminobutyric acid (GABA) agonist, this causes in the reduction of releasing of GABA through presynaptic inhibition leading to the onset of excitatory activity as seen in some neurodegenerative diseases. Pb not only participates in the production of ROS but also in the production of RNS, which has a detrimental effect on vascular endothelial [3, 26]. A meta-analysis following epidemiological studies illustrated that occupational exposure of Pb attributes in endangering the development

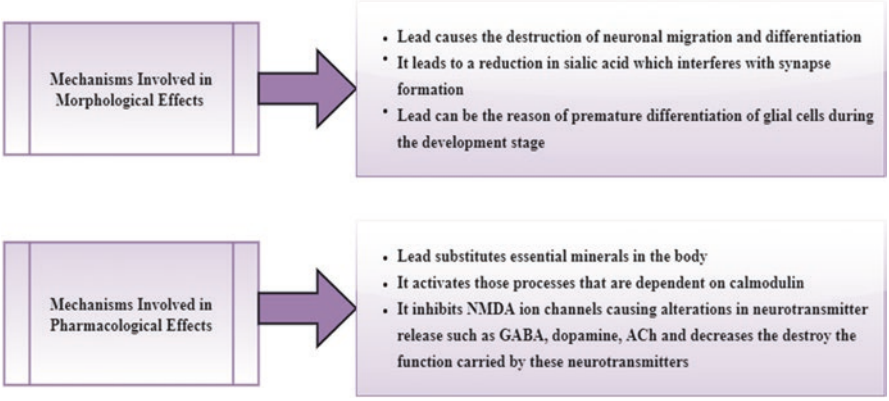

Fig. 4.3 Possible mechanisms involved in the morphological and pharmacological effects of lead. *NMDA N*-methyl-D-aspartic acid, *GABA* gamma-aminobutyric acid, *ACh* acetylcholine, *calmodulin* calcium-binding messenger protein

of motor neuron disease, amyotrophic lateral sclerosis. Pb affects the normal functioning of the body and causes high blood pressure, renal system damage, reduced fertility, anorexia, damage to neurons, chronic nephropathy, hyperactivity, insomnia, and learning deficits, and it is also a risk factor for Alzheimer's disease [27]. Multiple sclerosis, an inflammatory demyelinating disease in which the protective myelin sheath covering the nerve fibers gets degenerated, in consequence of immune system attack either by environmental or pathological cause. The study conducted in Taiwan detailed the association between the concentrations of heavy metals and multiple sclerosis incidence, using spatial regression. This epidemiological study ended up by finding that soil containing Pb had a positive relation with multiple sclerosis incidence in Taiwan. Among the affected people, the ratio of males was higher as compared to the females.

Cadmium-Induced Neurotoxicity

Some evidences illustrate morphological changes and biochemical changes due to Cd toxicity, and it might be the contributing factor in neurodegenerative diseases, mainly Alzheimer's disease and Parkinson's disease. Figure 4.4 displays the general

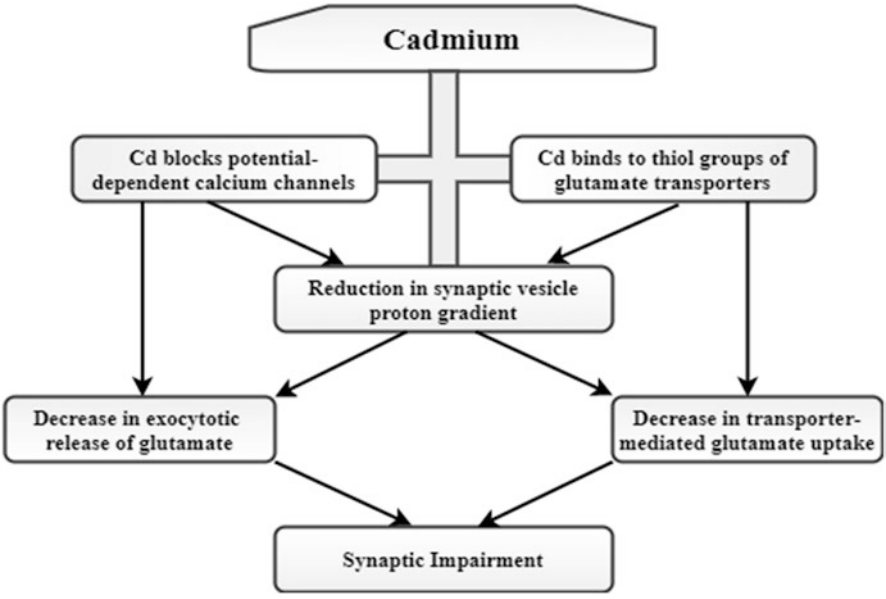

Fig. 4.4 Mechanism of action of cadmium in disruption of synaptic transmission. The blockage of Ca^{++} channels leads to decrease in synaptic vesicle proton gradient and exocytotic release of glutamate. The binding of Cd to thiol groups of Glu transporters induces reduction in synaptic vesicles proton gradient and also decreases in transporter-mediated Glu uptake. These alterations ultimately cause synaptic impairment

mechanism of action of Cd that disrupts the synaptic transmission. The neurons in the cerebral cortex are considered to be the targets that are involved in Cd-induced toxicity and apoptosis as well. The biochemical changes mediated by Cd are associated with an imbalance between the excitatory and inhibitory neurotransmitters and levels of antioxidants in the brain. Studies have shown that the release of acetylcholine is inhibited by the interference in the metabolism of calcium, whereas the sensibility of serotonin increases on account of raised levels of Cd [28].

In animal studies, increase in exposure to Cd causes a significant increase in Cd concentration in the brain that ultimately results in the biochemical changes which are related to the changes in the synthesis and release of neurotransmitters, disturbances in memory/behavior also the alteration in the function of receptors and ion channels occurs [29]. These neuronal and CNS disturbances happen because of the morphological damage in choroid plexus (a plexus of cells responsible for the production of cerebrospinal fluid), induced by a high concentration of Cd. The mechanism behind the biochemical changes related to Cd exposure entails the interference in the cholinergic system. Acetylcholine being a vital neurotransmitter in this system controls various cognitive functions, the levels of acetylcholine are maintained by the balance of enzymatic activities of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Cd hinders this balance of synaptic neurotransmitters. Experimental studies detected the alterations in AChE and Na^+/K^+-ATPase enzymes in the cerebellum, cerebral cortex, hypothalamus, and hippocampus of adult Wistar rats that were exposed with Cd for several days [28]. Cd induces the neurotoxicity by altering the permeability of BBB, resulting in amyloid-β (Aβ) aggregation; a protein linked with Alzheimer's disease and by the production of tau neurofibrillary tangles. Several human aging studies are associating Alzheimer's disease with Cd exposure, as it is thought that Cd impairs the cognitive function [10]. *In vitro* study was conducted to analyze the neurotoxic effect of cadmium selenide (CdSe) and its potential uptake in neural cell lines by using PC-12 cells of rats, and the results showed that neurodegeneration occurs at higher level of CdSe exposure [30].

Amyotrophic lateral sclerosis (ALS) is a disease in which the motor neurons are affected that cause the disablement of movement and control of muscles. It involves the gene mutation such as superoxide dismutase 1 (SOD1) [31]. Cd, through the induction of metallothionein (MT) expression, alters SOD1 which might influence the zinc (Zn) homeostasis. The activity of SOD1 enzyme could be decreased as the availability of Zn decreased because there might be a binding between the Zn and increased levels of MT. Contradictorily, the overload of Cd and deficiency of Zn may hinder the functions of SOD1 by the impedance of the secondary structure which induces misfolding and part aggregation of SOD1. This could ultimately bring about the risk of developing ALS [32]. Cd has the capacity of interaction with micronutrients such as Zn, copper, iron, and calcium. It replaces the Zn at MTs and replaces iron and calcium from prosthetic groups. These replacements contribute to alter the enzymatic reactions, by depleting the thiol groups present in enzymes and antioxidants. There are some physiological functions of micronutrients such as copper or Zn while Cd has no any participation in physiological functions rather it leads to the cellular damage [33].

Mercury-Induced Neurotoxicity

As aforementioned, Hg exists in three forms that are inorganic (divalent and monovalent cationic forms; Hg^{2+} and Hg^{+}), organic methylmercury (MeHg), and elemental Hg vapor. These different forms induce the toxicity, distribution, and metabolism of Hg. Majorly, studies explained the neurotoxic effects of MeHg, an organic form of mercury, as this form has a relatively greater ability to enter into the CNS. The resultant effects are the hearing and speech impairment, visual disturbance, paresthesia, cerebellar ataxia, and psychiatric effects [34]. The elemental form of Hg oxidizes into an inorganic form of Hg and gets excreted through urine while the former is well distributed in the kidney and also has the capacity to accumulate in the brain [35]. The distribution of MeHg to the different regions of the brain takes place by crossing the BBB. Previous studies illustrated that the BBB is relatively more sensitive to the organic Hg rather than inorganic form, but the inorganic Hg has a direct toxic effect on BBB [36]. It is suspected that neutral amino acid carrier systems are responsible for the transportation of MeHg–cysteine complexes. In the brain, demethylation of MeHg appears to occur and the resultant inorganic form has long half-life in the thalamus and pituitary. A family of cysteine-sufficient protein, i.e., MT, has high affinity towards metals, so these proteins bind within organic form of Hg or its demethylated form [37].

One study described the effect of Hg on human neuronal-glial (HNG) cells, by the utilization of pro-inflammatory transcription factor NF-kB (p50/p65) complex as an indicator for the onset of inflammatory neurodegeneration. The results showed that mercuric sulfate significantly induced the NF-kB (p65) activator complex in HNG cells. Such activation depicts that there is a possibility of the onset of Alzheimer's disease by heavy metals like Hg. Along with this, the mechanism involved in the production of ROS is also suspected to be activated [38]. Hg is an etiological factor for Alzheimer's disease because of the involvement of neurofibrillary tangles consisting of hyperphosphorylated tau protein, as this phosphorylation is induced by mercury; also Hg stimulates the secretion of Aβ protein. These functional and structural changes are the major attributes in Alzheimer's disease. Furthermore, the disturbances in neurotransmitters seen in Alzheimer's disease are the same as seen in Hg-induced Alzheimer's disease, particularly the reduction of acetylcholine, inhibition of serotonin binding with its receptors, and glutamate uptake [39]. Experimental studies have revealed that at sub-cytotoxic concentrations of Hg, there is no direct breakdown of DNA strands, but ROS like H_2O_2 caused the breakage of DNA strands. Astrocytes and microglia are affected due to the Hg exposure. Both of these cells are responsible to protect the brain activity [40].

Figure 4.5 represents the neurotoxicity induced by MeHg mediated by ROS. In step 1, MeHg inhibits the astrocytic glutamate (GLU) uptake, which results in an increased level of GLU. In step 2, release of GLU from presynaptic is stimulated. In step 3, the uptake of vesicular GLU also inhibits. In step 4, *N*-methyl D-aspartate (NMDA)-type GLU receptors are hyperactivated due to increased extracellular GLU levels, also the influx of calcium into neurons is raised. In step 5, the raised

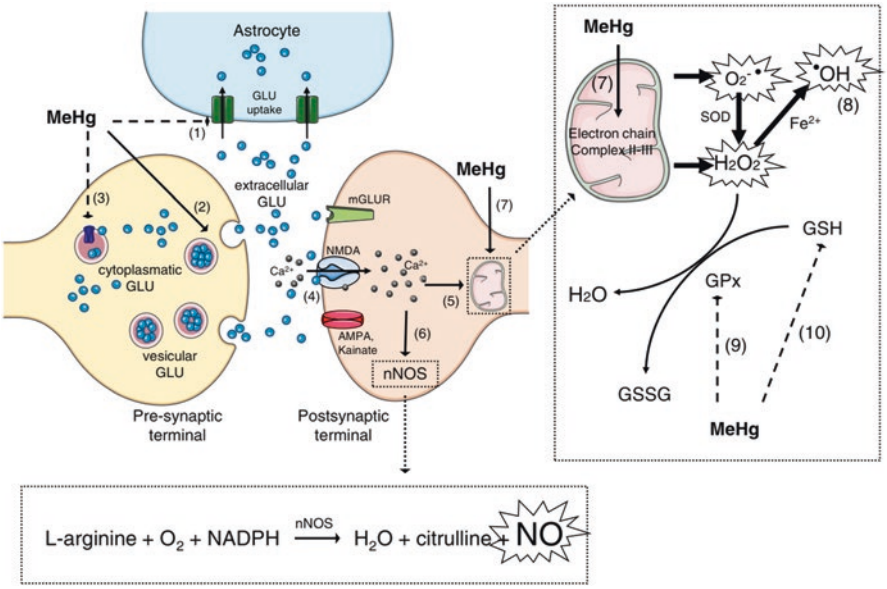

Fig. 4.5 Role of methyl mercury in the alteration of synaptic signaling and production of ROS [42]

intracellular level of calcium causes the mitochondrial collapse. In step 6, neuronal nitric oxide synthase (nNOS) is activated. In step 7, due to nNOS activation, nitric oxide (NO) formation is increased. MeHg affects the mitochondrial electron transfer chain (mainly at the level of complexes II–III). In step 8, the formation of H_2O_2 and superoxide anions ($O_2^{\bullet -}$) is increased. H_2O_2 can produce hydroxyl radical anion ($^{\bullet}OH$) through Fenton's reaction. In step 9, MeHg-induced H_2O_2 levels can be a consequence of a reduction in glutathione peroxidase (GPx) activity. Lastly, the glutathione (GSH) is depleted [41, 42]. MeHg is also known to induce neurotoxicity by depositing in astrocytes and microglia, where it generates ROS. The rapid increase in ROS reduces the GSH which is supposed to detoxify the MeHg at an earlier stage [43].Epidemiological studies explain the correlation between the brain biomarkers with Hg levels in children with autism spectrum disorder (ASD), and the increase in blood mercury levels is shown to associate with the worsening of symptoms of ASD [44].

Arsenic-Induced Neurotoxicity

The two forms of organic and inorganic arsenic metabolites exist in trivalent or pentavalent oxidation states. These different states have various biological effects. The metabolic pathway of arsenic is shown in the Fig. 4.6. The primary pathways of

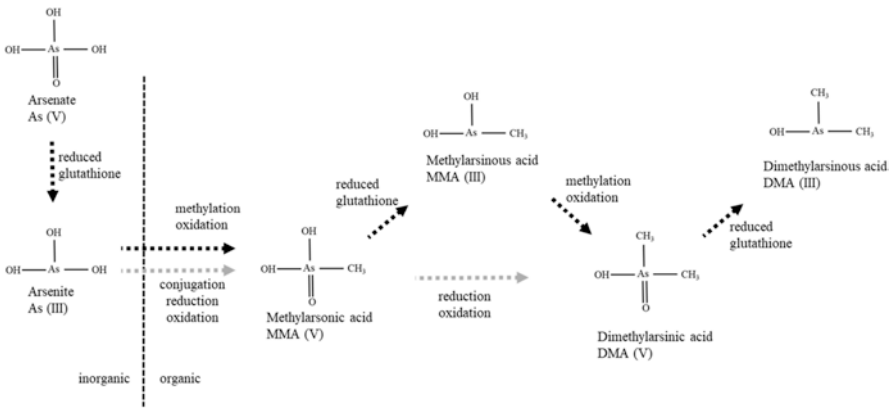

Fig. 4.6 Metabolic pathway of arsenic. (Adopted from [45])

arsenic metabolism are oxidative methylation and GSH conjugation. Inorganic arsenic (V) is reduced to arsenic (III), which is important for methylation in mammals. Inorganic arsenic (III) is methylated to methylarsonic acid (MMA) and dimethylarsinic acid (DMA) by alternating the reduction of pentavalent arsenic to trivalent arsenic [45] as shown in Fig. 4.6.

Arsenic can cross BBB, which comprises three cellular components that are endothelial cells, astrocytes, and pericytes (PCs). The diffusion of gases, water, and nonpolar molecules occurs via the diffusion barrier or tight junctions (TJs) that are present between the endothelial cells. The destruction in this barrier due to increased arsenic exposure could lead to the development of neurodegenerative disease [46]. In controlled experimental study in Swiss albino mice, there was a significant reduction in GSH level in the brain of arsenic-treated mice. This explains that arsenic also causes a reduction in antioxidative enzymes, due to oxidative stress. It was found that neurobehavioral changes along with the reduction in cholinesterase enzymes also occurred [47]. Another study described that postnatal low concentration of arsenic exposure in rats induces autism-like behavior which includes problems linked with learning abilities and social skills. Moreover, abnormal frontal cortex neurogenesis was seen and this effect was produced by arsenic exposure [48]. The possibility of this unusual neurological behavior could be because of increased oxidative stress and decreased ATP production with the disturbances and mutations in structural and functional maturity of nerve cells, owing arsenic exposure [49]. There are high levels of inorganic arsenic in drinking water due to industrial pollution, the major source of exposure to arsenic. For the investigation of inorganic arsenic-induced apoptosis in the cerebral cortex and in vivo analysis was carried out in mice. There were some underlying mechanisms connected to this apoptosis. Figure 4.7 indicates the reduced GSH levels in cerebral cortex in inorganic arsenic-

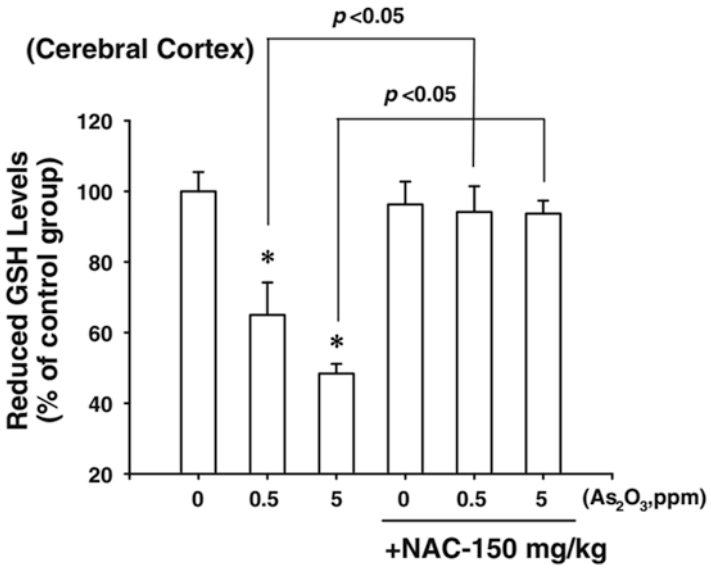

Fig. 4.7 Effect of different doses of arsenic exposure on glutathione (GSH) level in cerebral cortex in inorganic arsenic-exposed mice. (Adopted from [50] after some modifications)

exposed mice. These mice were exposed to 0, 0.5, and 5 ppm inorganic arsenic via the drinking water for almost 6 consecutive weeks in the presence or absence of *N*-acetylcysteine (150 mg/kg/day). This apoptotic effect could be the cause of Alzheimer's disease [50].

In Japan, people who had survived with the probable exposure of arsenic, neurological and electrophysiological sign and symptoms showed that these residential people complained about the hearing problem. On examination, it was discovered that sensory dysfunction worsened gradually [51]. Figure 4.8 shows the pathways by which arsenic induces neurotoxicity. The first pathway illustrates that exposure of arsenic accelerates the activity of ROS and lipid peroxidase enzymes but decreases the activity of SOD, this gives rise in oxidative stress. The second one explains the apoptosis in cerebral neurons by the upregulation and activation of p38 MAPK, JUNK3. The third pathway depicts the effect of arsenic exposure which contributes to the destabilization and disruption of the cytoskeletal framework by the alteration of protein composition or protein hyperphosphorylation [52].

The mechanism in Fig. 4.9 shows how neurodegenerative prototypic proteinopathy diseases like Alzheimer's disease are occurred due to the involvement of inorganic arsenic exposure. The *in vivo* study using transgenic animals described that the presence of amyloid plaques and neurofibrillary tangles containing hyperphosphorylated tau protein along with oxidative stress can be the contributing factors in the development of Alzheimer's disease [53].

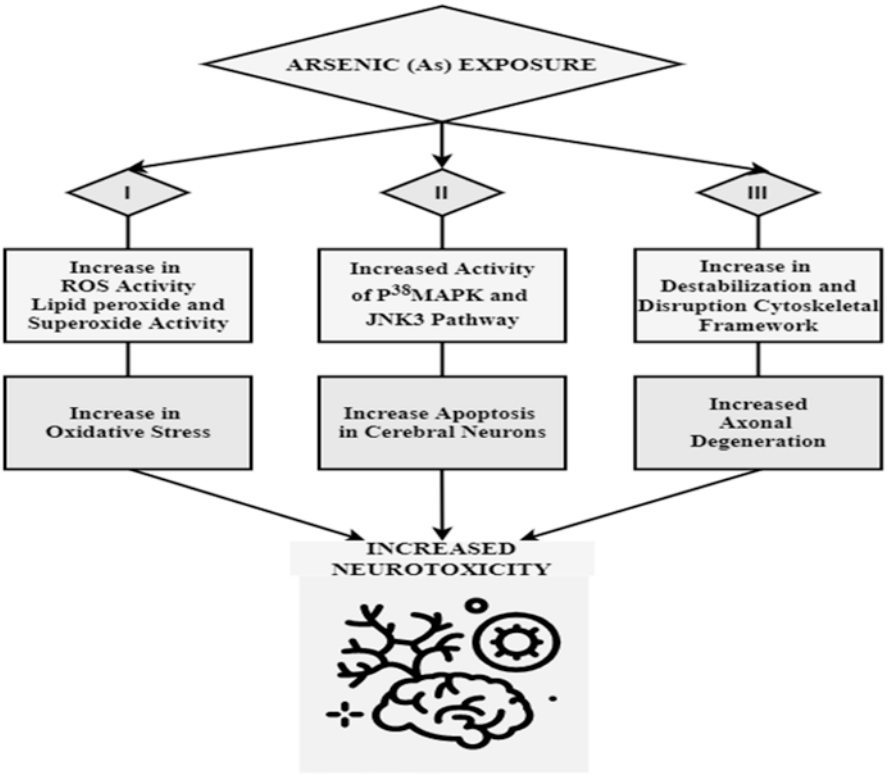

Fig. 4.8 Schematic representation of arsenic-induced neurotoxicity. *ROS* reactive oxygen species, *P38MAPK* P38 mitogen-activated protein kinase, *JNK3* c-jun N-terminal kinase 3

Preventive Interventions

The overall preventive measures for heavy metals include cessation of smoking, more intake of iron-containing diet and filtered drinking water, maintenance of adequate occupational hygiene, and avoid further exposure if once affected. Some specific preventive and therapeutic interventions have been discussed ahead. Environmental poisoning of Pb cannot always be handled by the chelation using dimercaptopropane sulfonate (DMPS), dimercaptosuccinic acid (DMSA), dimercaprol (British Anti-Lewisite, BAL), and $CaNa_2EDTA$, as there are the chances of redistribution of Pb even after the chelation therapy. So, the levels of Pb in the blood must be monitored and screened at appropriate intervals to avoid and prevent the neurotoxic effects in case of presence of toxic level of Pb in the blood. Most importantly, Pb exposure can be reduced and prevented through the awareness of its possible hazards [54]. Likewise, in Pb chelators, clinical studies have shown that usage of EDTA, DMPS, DMSA, and British Anti-Lewisite (BAL) could help out in Cd-induced toxicity. Selenium (Se) is thought to act as a protective agent in

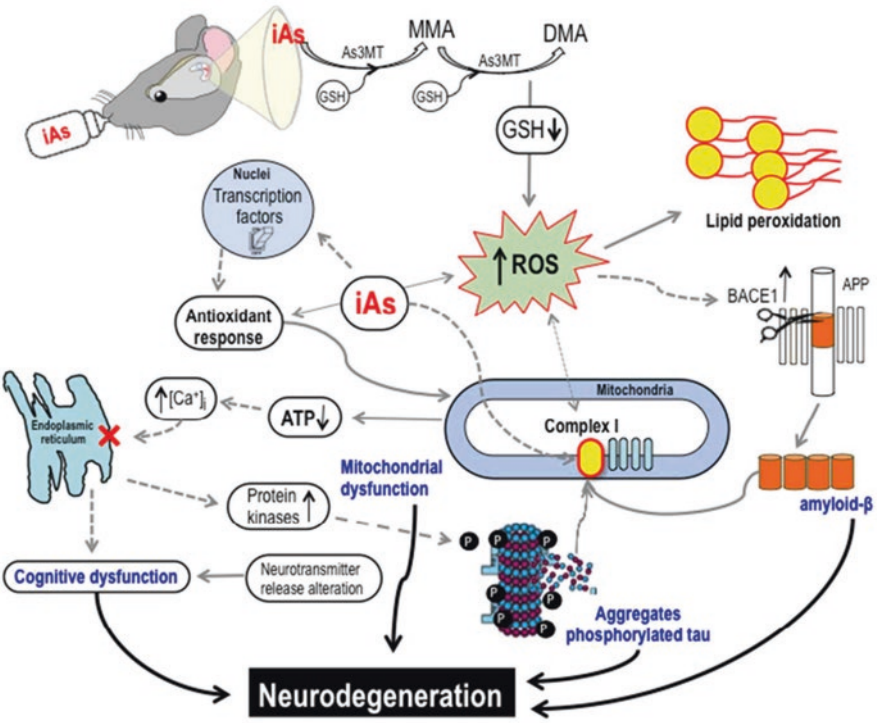

Fig. 4.9 Schematic representation of mechanism of arsenic-induced neurodegeneration. (Adopted from [53] after some modifications)

Hg-induced neurotoxicity. Experimental studies indicate the association between Hg and Se, generally in nervous tissue and particularly in the whole brain [55]. The in vivo study indicated the shielding effect of Vitamin C in metal-induced toxicity [56]. In rodent studies, loss of neurogenesis in adults can be reduced by almost complete eradication of exposure to arsenic in water or drinking water containing arsenic [57]. The use of arsenic chelators, Se, and Zn can lessen the damage that occurred due to arsenic exposure. The antioxidant and antidotal property of Se is highly investigated through experimental studies. Se induces antioxidant activity by the expression of selenoproteins which include thioredoxin reductases and glutathione peroxidases. These proteins help in the reduction of ROS production. Moreover, the Se accelerates the capacity of conjugation reaction of arsenic, i.e., methylation of arsenic aids in the excretion of methylarsinous acid (MMA) into the bile. The methylation process takes place in the liver as it has relatively higher concentration of GSH. So, overall Se promotes the detoxification process [58, 59]. Studies have also found that the arsenic-induced deficiencies in mice can be recovered by the treatment of Zn as it elevates GSH level and ameliorates lipid peroxidation, consequently assisting in the reduction of oxidative stress [60].

Conclusion

The vulnerability of heavy metals primarily Pb, Cd, Hg, and arsenic is strongly linked with the sufferings of neurotoxicity or neurodegenerative diseases. The clinical signs and symptoms in Alzheimer's disease, multiple sclerosis, and Parkinson's disease are almost the same as that of indications or manifestations observed with the subjection of these heavy metals. A firm need of awareness regarding the risk of hazardous metals, yet useful in certain means and along with this the preventive measures during the handling of these metals must be practiced as a means for sound and safe health.

Conflict of Interest Nothing to declare.

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Chapter 5
Pesticides and Neurological Disorders: From Exposure to Preventive Interventions

Sumera Qasim, Yusra Habib Khan, and Tauqeer Hussain Mallhi

Abstract Pesticides are described as environmental contaminants that are intentionally introduced into the environment for controlling pests. Despite the fact that pesticides play a beneficial role in augmentation of crop production by protecting crops from vector-borne disorders, there is considerable concern regarding potential toxic attributes of these pesticides. The major reason of their toxicity might be due to presence of similar targets in both pest and nontarget species including human beings. This lack of selectivity results in unwanted effects of pesticides in nontarget organisms. Majority of the pesticides, especially insecticides, have well-documented neurotoxic effects. In this chapter, we will highlight the neurotoxic effects of most commonly employed pesticides along with their possible mechanism of neurotoxicity and available treatment options. Special emphasis has been given to establish correlation between exposure of pesticides with subsequent alterations in neurological manifestations observed in humans and also mechanistic outcomes revealed by different studies conducted on animals and humans.

Keywords Pesticides · Neurological disorders · Herbicides · Insecticides · Fungicides · Neuroinflammation · Neurodegeneration

Introduction

According to an estimate, the global population is expected to be around nine billion till 2050 and will need more food production to meet the basic needs of human beings. On the contrary, due to rapid commercialization and industrialization, agri-

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cultural land is meagering. The only solution to combat the future possible food insecurity would be to increase the productivity of available limited agricultural land [1]. Food being produced per capita currently can be augmented by inflating crop production which is achievable if soil and water related issues are properly managed and also by employing agrochemicals. Agrochemicals include two types of chemical moieties namely fertilizers and pesticides. However, this augmentation of food production with extensive use of fertilizers not only resulted in contamination of aqua life but also imposed serious consumption problems observed in humans [2].

Pesticides are widely employed commercially for augmentation of crop production and pests control including garden as well as household pests. About 50% of the vegetables, fruits, and cereals grown worldwide contains pesticides remain [3]. Along with the beneficial effects, pesticides have associated shortcomings as well. Great attention has been diverted towards widespread use of pesticides owing to their lethal attributes being observed among persons exposed to these pesticides either directly or indirectly. Pesticides in comparison to other chemical entities are different as these toxic chemical moieties are deliberately introduced into environment with an intention to control undesirable living organisms for the purpose of providing benefits to crops, food preservation, and protection from vector-borne diseases [4]. Pesticides are aimed mainly to kill the pests but their toxicity is not only limited to pest but also it poses a major threat to human health. Pesticides provoked toxicity remained to be a serious problem worldwide. According to an estimation, more than five billion pounds of pesticides are consumed annually. Toxic exposure to pesticides can occur during their introduction to kill pests, by their drainage into water supplies, and also through consumption of food provided with these pesticides [5]. According to World Health Organization (WHO), more than three million cases of pesticides induced poisoning are reported annually leading to approximately 25,000 deaths per year. Pesticide poisoning is relatively common in countries such as Sri Lanka, Venezuela, Indonesia, South Africa, and Brazil. Among numerous pesticides, organophosphate insecticides are the most common mortality causing agents due to their high toxicity [4].

Major concern regarding the use of pesticide is similarity in molecular targets among both target (pests) and nontarget organisms. Commonly employed pesticides instigate their toxic effects on undesirable living species by acting on nervous system, for instance, organophosphorus entities endeavor its neurotoxic manifestations via inhibition of cholinesterase in central nervous system, pyrethroids exert their toxic effect by prolonging neuronal sodium channels opening, organochlorinated agents act as stimulant of central nervous system (CNS), morpholine derivatives induce an imbalance between inhibitory and excitatory control in neurons, and formamidines have alpha 2-catecholamine receptor agonistic attribute [6]. Likewise, mitochondrial I inhibitors are also employed extensively as miticides (mites) as well as acaricides (mites and ticks). Despite the fact that herbicides and fungicides have their targets not found in mammals but still several studies have documented toxic attributes of these pesticides on mammalian brain [5].This chapter will highlight the impact of commonly employed pesticides on neurological functioning of mammals on the basis of data obtained through experimental, clinical, and epidemiological studies.

Classification of Pesticides

The classification of pesticides can be made by using various criteria based on toxicity, type of organism killed, chemical composition, mode of entry, mechanism of action, duration of action, formulations, and sources of origin [7] as shown in Fig. 5.1. The most widely adopted criterion is based on toxicity and chemical structure. In this context, same classification will be used throughout the chapter.

Pesticides Classification Based on Their Toxicity Profile

The toxicity of pesticides largely relies on their dose as well as duration of exposure. Pesticides induced toxicity can be acute or chronic. Acute toxicity can be evident even after single, short-term exposure to causative agent. Thus, a highly acute toxic pesticide can prove to be deadly even with the small dose. Acute toxicity can be estimated as oral acute toxicity, dermal acute toxicity, and inhalation acute toxicity. Chronic toxicity can be described as delayed deleterious effects after repeated exposure to large amount of pesticides. Pesticides induced chronic toxicity is of great

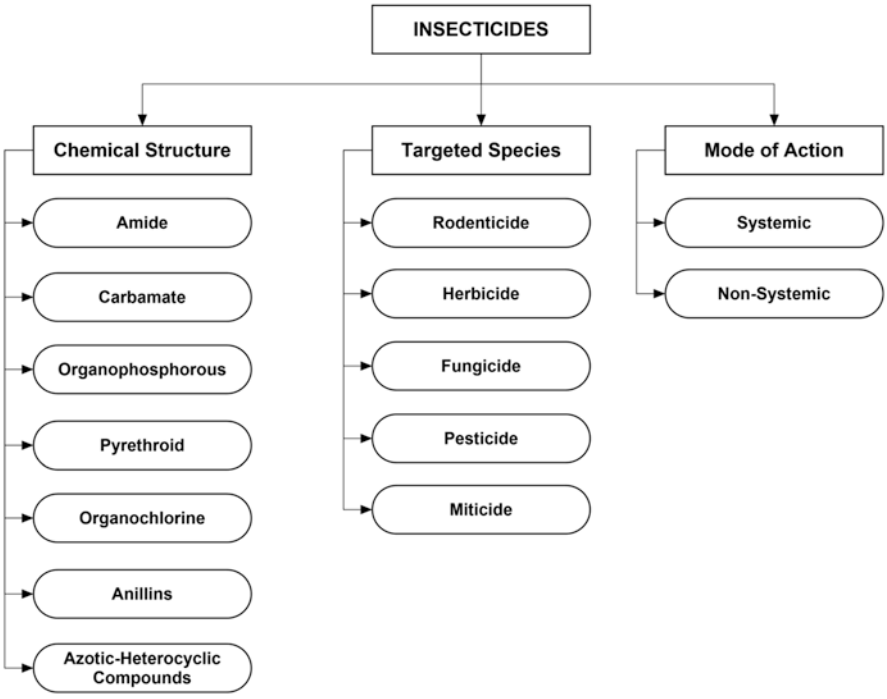

Fig. 5.1 Classification of pesticides

concern for general public and for workers directly engaged with pesticides use because of remains of these pesticides on or in food products, water, and the air [8].

World Health Organization (WHO) has classified pesticides on the basis of acute toxicity. According to WHO, pesticides are classified as acute oral and acute dermal pesticides using the estimated respective lethal dose LD50 as presented in Fig. 5.2.

Pesticides Classification Based on Their Chemical Nature

The classification of pesticides according to their chemical composition has been considered as the most widely used classification. According to this criterion, pesticides can be broadly divided into four main categories comprising of insecticides, fungicides, herbicides, and rodenticides. Each of these classes is further classified into subclasses based on their chemical formulae.

Insecticides

Insecticides according to their chemical nature are classified into carbamates (carbofuran), organophosphorus (parathion), organochlorine (dieldrin), neonicotinoids (imidacloprid), pyrethroids (allethrin), and miscellaneous pesticides including benzoylureas (diflubenzuron), spinosyns (spinosad), and antibiotics (abamectin).

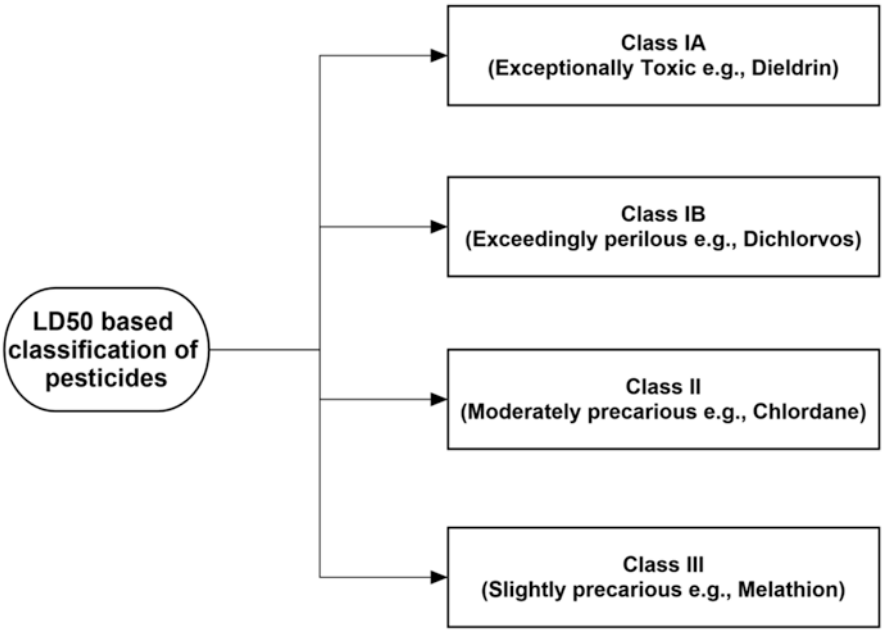

Fig. 5.2 Toxicity-based classification of pesticides

Fungicides

This class includes aliphatic fungicides (dodine), aromatic fungicides (chlorothalonil), amide fungicides (carpropamid), dicarboximide fungicides (famoxadone), and dinitrophenol fungicides (dinocap).

Herbicides

The herbicides can be categorized as phenoxyacetic herbicides (2,4-D), quaternary ammonium herbicides (paraquat), anilide herbicides (flufenacet), sulfonylurea herbicides (chlorimuron), and chlorotriazine herbicides (atrazine).

Rodenticides

They include inorganic rodenticides such as aluminum phosphide, zinc phosphide, and coumarin rodenticides, e.g., bromadiolone, coumatetralyl.

Biotransformation of Pesticides

Phase I– and phase II–mediated biotransformation of pesticides convert them into hydrophilic intermediates [9] (Fig. 5.3). Enzymes involved in phase I metabolism comprise of cytochrome P450 members such as heme-thiolate. Other enzymes like amine oxidases, flavin monooxygenases, xanthine oxidases, and peroxidase are involved in functional group oxidation while epoxide hydrolase and carboxylases cause hydrolytic reactions.

The resultant products of phase I metabolic reactions do not eradicate quickly and enter other successive reactions: conjugation with *glucuronic acid, acetic acid, sulfuric acid,* or an addition of *amino acid* for synthesis of more polar compounds for ease of excretion [11]. Enzymes involved in biotransformation of pesticides are categorized according to their function as phase I oxidative enzymes, phase II conjugative enzymes, or phase III transporters enzymes. Phase I enzymes are responsible for producing functional groups having exposed sites for conjugation reaction with enzymes of phase II comprising of *UDP-glucuronosyltransferases (UGT), glutathione S-transferase* [9]*, sulfotransferases (SULT), and N-acetyltransferase (NAT).* Metabolism of pesticides by enzymes is an essential phase for transforming lipophilic moieties into water-soluble compounds for their easy elimination through urine. *P-glycoprotein (Pgp)*, *organic anion transporting polypeptide 2 (OATP2),* and *multidrug resistance-associated proteins (MRPs)* expression can be found in intestine, kidney, liver, and brain where they have evident role in absorption, distribution, and excretion of pesticides. Aside from these phases of biotransformation, inhibition, induction, or pretreatment with many inhibitors or inducers results in

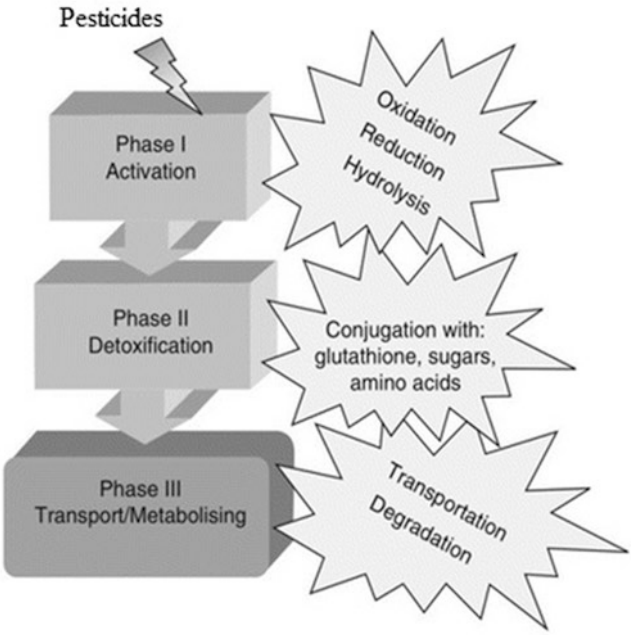

Fig. 5.3 Biotransformation of pesticides. (This picture is self-constructed and adopted from [10] with some modifications)

altered expression of phase III transporters promoting final elimination of pesticides from body. Pesticides exposed to phase I, II, and III inducers might instigate cellular stress activation that amplifies gene expression with ultimate removal of pesticides [12].

Neurotoxicity: A General Concept

Neurotoxicity can be described as any deleterious effects observed on peripheral or central nervous system by any chemical compound, biological agent, or physical moiety. A wide array of chemical compounds have documented neurotoxic attributes such as metals (lead), pharmaceutical agents (doxorubicin), industrial chemicals (acrylamide), natural toxins (domoic acid), and pesticides [13]. On the basis of mode of neurotoxicity, neurotoxicants can be broadly divided into four categories: neuronopathy-causing agents, axonopathy-induced agents, myelinopathy-provoking agents, and neurotransmission-altering agents.

Neuronopathy is the loss of neurons induced by neurotoxicants via multiple pathways including oxidative stress, cytoskeleton disruption, mitochondrial damage, and/or calcium overload. This neuronal loss is mostly irreversible and can lead to loss of specific function. For instance, MPTP administration resulted in dopami-

Table 5.1 Neurotoxic mechanism and examples of commonly employed pesticides

Pesticide class	Mechanism of neurotoxicity	Examples
Organophosphorus compounds	Inhibition of acetylcholinesterase (AChE)	Malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos
Carbamates	Inhibition of acetylcholinesterase (AChE)	Carbofuran, aldicarb, and carbaryl
Pyrethroids	Inhibition of voltage-gated sodium channels	Allethrin, resmethrin, permethrin, and cyfluthrin
Neonicotinoids	Overstimulation of nicotinic acetylcholine receptor	Acetamiprid, clothianidin, imidacloprid, nitenpyram, nithiazine, thiacloprid, and thiamethoxam
Fungicides	Oxidative stress, decline in level of antioxidant enzymes, inhibiting mitochondria	Dimethomorph, dodine, chlorothalonil, and famoxadone
Herbicides	Oxidative damage to neural cells leading to cell death	Diclofop, dinoseb, diquat, and paraquat
Rodenticides	Inhibition of Na/K ATPase by decline in ATP synthesis	Warfarin, bromadiolone, and difenacoum

nergic neurons degeneration leading to Parkinson's disease (PD) [14]. Similarly, some of the neurotoxicants exert their effect by targeting primarily axon resulting in axonopathies. In majority of cases, degeneration occurs in axon only while cell body remains intact. Mostly axonopathies can be manifested by peripheral neuropathy affecting the feet and hand and if the insult is not severe, there are chances of regeneration and recovery [15]. Other chemicals can target myelin resulting in demyelination while neurons remained unaffected structurally but some functional alterations are observed [16]. Hexachlorophene is a chemical that can induce demyelination, thus causing brain spongiosis. Finally, some neurotoxicants exert their effect by interfering with neurotransmission and ultimately inhibit release of neurotransmitter, for instance, botulinum toxin and atropine [17]. Table 5.1 describes the neurotoxic mechanisms of commonly used pesticides.

Insecticide-Induced Neurotoxicity

Insecticides have a pivotal role in the controlling insect pests. Majority of widely employed chemical insecticides are termed as neurotoxicants as they attack the target organism's nervous systems. As such, target sites are also present in mammals, therefore increasing the toxic potential of such insecticides in all mammals. Along with this nonselectivity, the concomitantly observed more pronounced neurotoxic effects in nontarget species, as compared to target species, make them even more vulnerable. Insecticides fall into different categories; however, widely employed are cholinesterase inhibitors including carbamates and organophosphorus compounds followed by pyrethroids and some recently developed entities, such as neonicoti-

noids. Organochlorine compounds such as DDT were also widely employed before the start of 1980s when the use of these compounds was banned. However, some of these compounds are still used in certain countries as mosquito killer leading to increased exposure of human population to these toxic agents.

Neurotoxic Attributes Associated with Organophosphorus Compounds

Organophosphorus (OP) insecticides were employed as pesticides from 1930 to 1940s; however, the very first OP moiety was synthesized in early 1800s. Gerhard Schrader proposed that OP compounds bear the potential of acting as insecticides. He continued his work on OPs and discovered several insecticides including parathion and tabun from these OP compounds. Subsequent work carried on by his coworkers resulted in synthesis of newer nerve agents comprising of sarin, cyclosarin, and soman. The formula of these nerve agents was later taken by German government for large-scale production of these agents [18].

General chemical formulae for OP insecticides comprise of phosphorus atom that can bound with different groups most often with two alkoxy molecules and with another molecule termed as "leaving group." Majority of OPs with insecticidal tendency have phosphorus atom conjugated with sulfur atom. This conjugation makes such OPs metabolically active by desulfuration phenomenon resulting oxon formation. Desulfuration reaction occurs by members of cytochrome P450 family in liver. However, such reactions are also evident in target organs such as lungs, brain, and others. During desulfuration reaction, an intermediate specie (phosphooxythiran) is formed that defines the ratio of oxon formation [19].

OPs instigate neurotoxic attributes primarily by inhibiting acetylcholinesterase (AChE). Oxon moiety produced via desulfuration reaction phosphorylates a serine hydroxyl group present in AChE active site [20]. This binding of oxon with AChE results in phosphorylated serine generation via spontaneous hydrolysis. Rate of this hydrolysis reaction depends largely upon characteristics of leaving group as compounds having less alkylated attributes (i.e., dimethyl) are hydrolyzed rapidly as compared to more alkylated compounds (i.e., diethyl). AChE, in some instances, becomes "aged," leading to a state of permanent deactivation of the enzyme might be because of losing alkyl groups. AChE inhibition results in acetylcholine built up in synapse leading to cholinergic receptor hyperstimulation in both central and peripheral nervous system. Classic symptoms of OP-induced toxicity become evident after this hyperstimulation and abbreviated as SLUD syndrome (salivation, lacrimation, urination, and diarrhea), or sometimes DUMBBELS (diarrhea, urination, miosis/muscle weakness, bronchorrhea, bradycardia, emesis, lacrimation, salivation/sweating). These symptoms are noticed after acute poisoning resulting in more than 70% AChE inhibition [21]. Respiratory center depression and diaphragm paralysis have been observed in case of prolong and severe inhibition of

AChE. Countermeasures to combat this OP intoxication involve administration of muscarinic receptor antagonist atropine, AChE reactivator such as oximes and benzodiazepines particularly midazolam or diazepam for controlling seizures.

Additionally, two more syndromes were noticed in less than 20% human population with these OP compounds. The first syndrome "intermediate syndrome" was first discovered in 1980s and became evident after many days of poisoning event [22]. Manifestations of this syndrome involve respiratory muscles' weakness especially intercostals, diaphragm, and neck muscles with weakness of proximal limbs muscles. Up till now, there is no established relationship between this syndrome and specific pesticides. Clinical management primarily relies on maintenance of respiratory function, and majority of the patients who suffered have shown full recovery. Second syndrome of OP intoxication has been termed as organophosphate-induced delayed polyneuropathy(OPIDN) is relatively rare and appears after days of OP intoxication [23]. OPIDN was encountered during Unites State's Prohibition Era where about 10,000 of men presented OPIDN manifestations comprising of weakness of arms and legs after consuming "Ginger Jake," a medicine containing large concentration of alcohol. Further studies carried out on this aspect revealed that the medicine was adulterated with an OP moiety namely tri-*ortho*-cresyl phosphate (TOCP). TOCP exposure resulted in axonal damage, especially in spinal cord leading to characteristic "jake leg" symptom manifested by rapid contact of toes to the ground before the foot due to loss of toe muscle motor control [24]. Studies suggest that molecular target for OPIDN is a protein named neuropathy target esterase (NTE) rather than AChE [25]. Just like AChE, NTE also becomes aged and this aging has been considered necessary for appearance of OPIDN syndrome. However, inhibition of NTE does not always result in OPIDN and structure activity relationships analysis revealed that only some phosphates, phosphoramidates, and phosphonates can exhibit this syndrome [25]. Thus, these findings support detailed screening of all OPs for development of delayed neuropathy as a part of regulatory approval, and pesticides producing OPIDN should not be approved.

Occupational exposures to a moderate level of OP insecticides that will not result in any overt toxicity have gained much attention due to increased chances of delayed neurological implications with such insecticides. A study conducted by Munoz-Quezada and coworkers highlighted the impact of chronic OP exposure on neuropsychological attributes among farm workers dealing with OP insecticides [26]. The study revealed a significant attenuation of neuropsychological functioning with chronic occupational OP exposure. Likewise, Ross and coworkers conducted a meta-analysis of 14 studies related to low-level occupational exposure of OP insecticides [27]. A significant correlation has been observed between impaired neurobehavioral implications and OP exposure. Sanchez-Santed and coworkers also reviewed potential association between overt neurodegeneration and OP exposure and revealed a significant correlation between AD risk and OP exposure, moderate evidence for relationship of OPs with PD and weak evidence for amyotrophic lateral sclerosis (ALS) [28]. Due to limited research, tentative links have been established between OP exposure, particularly occupational exposures, and risk of AD [29, 30]. Similarly, link between OP exposure and ALS has been established but not

as much consistent and significant as of AD [29, 30]. Thereby, occupational OP exposure can lead to impairment in neurological functioning; however, detailed mechanistic work is still missing for establishing the exact relationship between OP exposure and neurological impairment.

Additional targets for OP insecticides include axonal outgrowth, axonal transport, disruption of neurotrophin levels, acetylcholine receptor binding, and inhibition of other serine hydrolases [31]. Axonal transport disruption has been linked to direct OP binding with kinesin and tubulin leading to alterations in neurite outgrowth [32]. It has also been suggested that chlorpyrifos can impair STAT1 signaling pathway leading to induction of dopaminergic neurotoxicity, advocating non-cholinergic mechanisms for OP instigated neurotoxicity [33].

Neurotoxic Attributes Associated with Organochlorine Pesticides

Organochlorine insecticides are composed of DDT and its analogues including cycloidians moieties comprising of aldrin, chlordane, or dieldrin; the hexachlorocyclohexanes including lindane; and finally some cage-structured entities, e.g., chlordecone. Organochlorine compounds were widely employed from 1940s to 1980s for controlling insects and malaria. Although, acute toxicity of organochlorine compounds is moderate compared to that of OPs, chronic exposure has deleterious health impacts especially on reproductive system and liver also. Owing to ecological considerations, almost all of these mentioned compounds have been banned in majority of countries. However, mammals especially humans are still exposed to these banned compounds through diet due to their long persistence in environment and lipophilic nature. Moreover, some compounds like DDT are still in use for controlling malaria. Slow degradation of these compounds makes them the most persistent chemical entity found in mammalian tissues. The exposure of human beings to this notorious pesticide occurs via contaminated vegetables, fruits, meat, dairy products as well as via agricultural settings [34].

DDT [1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane] insecticidal activity was first discovered in 1939. DDT comprises of a mixture of several isomers, with *p*,*p*′-DDT being responsible for the insecticidal activity. Moderate toxicity has been observed with DDT, having LD50 of about 250 mg/kg in rats. Rats exposed to high dose of DDT develop hypersensitivity to external stimuli, motor unrest, and increased frequency of spontaneous movements followed by tremors and tonic–clonic convulsions. Toxicity manifestations are observed after several exposures and sometimes death have been observed as a result of respiratory failure [34]. Earliest clinical manifestation of DDT intoxication includes hyperesthesia of lower face parts and mouth with subsequent paresthesia of tongue and mouth. Confusion, dizziness, vomiting, and extremities tremor are common symptoms while convulsions are evident in case of severe intoxication. DDT exerts its neurotoxic effect by altering sodium channels in axonal membrane [35]. This blockage will lead to enhanced neuronal excitation due to prolonged depolarization of sodium channel.

In animals, DDT-induced neurotoxicity can be managed by administration of calcium gluconate and phenytoin. In humans, aside from supportive treatment, phenobarbital or diazepam are used against associated seizures [36].

Lindane has been known to be the only benzene hexachloride (BHC) isomer possessing insecticidal attribute [37]. Cyclodiene moieties including dieldrin, aldrin, chlordane, and heptachlor were introduced as insecticides in early 1950s and were widely employed class of insecticides. However, their use, except for lindane, has been now banned in majority of countries due to their long-term prevalence in environment and associated toxic effects to human health [38]. Lindane and cyclodienes possess moderate to high acute oral toxicity, targeting primarily CNS, with convulsions being the prominent feature of intoxication. These compounds exert their neurotoxic effects by interfering with GABAergic neurotransmission [39]. Cyclodienes and lindane bind with specific site on chloride channel leading to blockage of channel opening and ultimately antagonizing GABA inhibitory attributes. Symptomatic treatment is usually employed in case of intoxication where diazepam or phenobarbital can be used as an anticonvulsant. The association of dieldrin exposure with Parkinson's disease has been well established in the literature [40]. The repeated exposure of dieldrin leads to oxidative damage of nigrostriatal system in mice [41].

Endosulfan, another organochlorine insecticide, has been widely employed in agriculture and forestry. The US Environmental Protection Agency (EPA) included endosulfan in "extremely hazardous substances" list in 1987. Though US imposed ban on endosulfan but still it is used globally for numerous purposes [42]. Neurotoxic effects associated with endosulfan are primarily due to its long persistence and high accumulation in animals and human tissues [43]. Endosulfan has been linked with both developmental neurotoxicity and neurodegeneration in rodents [44]. Moreover, occupational exposure to endosulfan has been associated with neurological dysfunctioning including memory impairment, hyperactivity disorders, and epilepsy [44]. Endosulfan exposure also leads to inflammatory implications along with glial activation in cell culture and animal models [45]. Endosulfan provoked neurotoxicity also alters dopaminergic neurotransmission leading to PD-related neuropathological alteration [46]. The available evidence from animal studies have underscored the association of endosulfan in mediating PD-related neuropathological changes and neurochemical deficits, comprising dopamine deficiency and increased levels of both normal and aggregated α-synuclein in mice [47]. One of the study revealed that rats provided with endosulfan (2 mg/kg) for 6 days manifested damaged brain mitochondria marked with significantly attenuated catalase, glutathione [48], and superoxide dismutase levels [49], with increased lipid peroxidation [50].

Neurotoxic Attributes Associated with Pyrethroids

The first natural pyrethroid insecticide was discovered from crude chrysanthemum extracts in the eighteenth century. First synthetic pyrethroid was derived from structure of pyrethrin, a natural compound from chrysanthemum, about 30 years ago.

Nowadays, pyrethroid insecticides are employed commonly as household and agricultural insecticides [51]. Pyrethroids are also being widely used for commercial concerns and public health measures such as mosquito control for prevention of malaria, dengue fever, and for prevention of bedbug infestation [52]. Because of these beneficial uses, the use of these insecticides is increasing [53].

Neurotoxicity instigated by pyrethroids occurs via some modifications observed in voltage-gated sodium channels (Nav), leading to prolonged deactivation of sodium channels [54]. Studies regarding pyrethroid provoked neurotoxicity focused initially on acute intoxication associated different syndromes. Two major types of pyrethroid neurotoxicity were reported by these studies [49]. First syndrome, being termed as T syndrome, manifests prominent symptoms of intoxication including twitching, tremor, coma, and in some cases, it might proceed to death. Introduction of deltamethrin, a pyrethroid with cyano group, led to second neurotoxic syndrome presented by jerking leg movements, salivation, and choreoathetosis. This syndrome was termed as CS syndrome. Subsequently, alternative nomenclature to describe pyrethroid-induced neurotoxicity was proposed by the researchers from Casida's laboratory. This classification was based on clinical manifestations following intoxication, chemical structure, and electrophysiological actions in insects. These researchers classified pyrethroids as type I and type II. The toxic manifestations of type I and type II were similar to those described for T syndrome and CS syndrome, respectively [55]. Mechanistically, type I pyrethroids exert their neurotoxic impact via short-term prolongation of action potential while type II compounds cause repetitive firing of the action potential and a depolarizing block, respectively [49].

Occupational exposures to tolerable amount of pyrethroids that lack any overt toxicity have gained much attention as there are chances of delayed neurological implications. Since enzyme carboxylesterase required for pyrethroid detoxication is absent in human beings, humans have reduced capacity of metabolizing pyrethroids. Data from a recent physiologically based pharmacokinetic (PBPK) study revealed that exposure of type II pyrethroid resulted in twofold greater peak brain concentration of pyrethroid in humans compared to rats [56]. Neurological effects such as cognitive impairment have been observed following pyrethroid exposure of pesticide applicators and their families [57]. Neurotoxic effects of pyrethroid insecticides have also been observed in children [58]. The association of age with pyrethroid-induced toxicities has been intensively investigated. Initial findings indicate the substantial sensitivity of higher levels of pyrethroids among younger animals as compared to those with advance age [59]. Pregnant women and children exposed to these pesticides might develop neurotoxic effects due to lack of carboxylesterase enzyme [60]. In order to elucidate the age-related differences of pyrethroid metabolism, several PBPK modeling techniques have been implicated into the research [61]. These models corroborate the previously established differences in toxic susceptibility. In addition, incomplete development of the blood–brain barrier (BBB) during early years of the life may lead to accumulation of toxicants in the brain [62].

Based on neurobehavioral toxicity of different pyrethroids in adults after acute exposure, it has been observed that type I pyrethroids can enhance the amplitude of

acoustic-evoked startle response [63]. On the contrary, type II pyrethroids considerably reduce this response. Pyrethroids, especially deltamethrin, have been also found to induce apoptosis by activating endoplasmic reticulum stress pathway in animals [64, 65]. Repeated exposure to pyrethroids, particularly type II, can provoke dopaminergic degeneration along with alteration of mitochondrial functioning [66]. Also, repeated exposure to pyrethroid exposure is associated with direct impact on glial cells leading to neuroinflammation, and this neurodegeneration can be significantly reduced with anti-inflammatory treatment [67]. These findings can be correlated to neurotoxicity in human beings as postmortem analysis of Parkinson's disease brain indicated enhanced microglial expression of Nav1.6, which is among primary targets of pyrethroids [68]. The exposure of pyrethroid, particularly permethrin, either alone or in combination with other neurotoxicants or prophylactic treatments (such as pyridostigmine bromide) has also been associated to Gulf War illness. This illness might be attributed to pro-inflammatory mechanism [69].

Neurotoxicity of Herbicides

Research regarding the neurotoxic effects of herbicides in nontarget species has been very limited. The primary reason behind absence of this nontarget effect is that these agents alter plant pathways which are obviously absent in other nontarget species including humans and other mammals. Most widely employed glyphosate-containing herbicide produce its herbicidal action via inhibiting shikimic acid pathway, which is responsible for aromatic amino acid synthesis in the plants. As this pathway is not found in mammals, toxicity associated with use of glyphosate was ignored till early 2000s [70]. Likewise, atrazine produce its herbicidal effect by blocking photosystem II complex protein D2 [70]. Moreover, commercial formulations for herbicides are made up of more than one active ingredient thereby making it complicated to find out exact nature of particular herbicide. Thereby detailed research is still required to find out the exact mechanism responsible for herbicide-associated neurotoxicity. This would not only explain the mechanism but also helpful in formulation of future herbicides with reduced neurotoxicity in humans and other mammals.

Glyphosate-Containing Herbicides

Herbicides are classified as Roundup and Touchdown classes where former uses the isopropyl amine salt, whereas Touchdown is formulated as either a trimethyl sulfonium or a diammonium salt. The use of these herbicides was over four times higher than that of the second-place pesticide during 2012–2015 [66]. The active ingredient, glyphosate was considered to be a nontoxic agent owing to its higher LD50 in both mice (10 g/kg) and rats (5.6 g/kg) [71]. This assumption is still in consistent

with recent studies which proved that glyphosate alone has less toxic implications as compared to commercial formulations which are made up of mixture of active ingredients [72]. Limited studies are available regarding the neurotoxicity of glyphosate or formulations containing glyphosate. Some studies postulate that the neurotoxicity of glyphosate is due to inhibition of AChE [73]. However, this seems to be an unlikely mechanism of glyphosate-provoked neurotoxicity. It has also been suggested that neuropathology associated with glyphosate might be due to neurodegeneration of GABAergic neurons [74]. Mitochondrial inhibition along with oxidative stress was thought to be the responsible factor for this neurodegeneration [75]. Another study revealed that glyphosate exposure to zebra fish resulted in abnormal brain development [76], possibly due to glutamate excitotoxicity [77]. The use of commercial formulation containing glyphosate in rats has shown the symptoms of depression and anxiety. These symptoms were also correlated with alterations in diversity and frequency of gut microbiota [78]. As many bacteria need shikimic pathway for synthesis of cyclic amino acids, blocking this pathway by glyphosate causes reduced tryptophan catabolism. Tryptophan is the precursor of serotonin which has evident role in depression and anxiety. These studies also support the need of more detailed research in this area regarding neurotoxicity associated with glyphosate-containing herbicides.

Paraquat-Containing Herbicides

Paraquat intoxication has been allied to increased Parkinson's disease development [79], which might be due to dopaminergic neurons loss, increased oxidative stress, and neuroinflammation [80]. Moreover, paraquat exposure is also found to be associated with tyrosine phosphorylation of parkin in SH-SY5Y cells [81]. Since parkin regulates the protein functions, any posttranslational modification in parkin inhibits these functions. These posttranslational inhibitions of protein's function further attribute to the disease progression. The exposure of paraquat has been found to be associated with the induction of hyperacetylation in the cell models of Parkinson's disease. These findings underscore the promotion or increased epigenetic reprograming following the exposure of paraquat [82]. Moreover, increased levels of pro-inflammatory cytokines and interleukin-6 (IL-6) have been observed following the treatment of pluripotent human stem cells with paraquat. These cytokines are also components of the senescence-associated secretory phenotype in both astrocytes and fibroblasts [83]. Furthermore, conditioned media from paraquat-treated astrocytes can induce dopaminergic cell death. Increased production of secretogranin II (SCG2) in astrocytes has been observed after paraquat incubation [84]. SCG2 is associated with large, dense core vesicles that colocalized with IL-6. The available evidence suggest that paraquat exposure along with oxidative stress can also increase the release of IL-6. The increased production of IL-6 promotes neuroinflammation in human beings. Though the mechanism of herbicide-induced neurotoxicity is primarily explained through inflammatory cytokines, further studies are

needed to confirm these findings. A better insight on how herbicides modulate inflammatory pathways and neurodegeneration can be observed with detailed investigations.

Neurotoxicity of Fungicides

During early 1700s, fungus control was attained by adding arsenic to the fields for improving crop production. Later in 1800s, lime, dolomite, and copper sulfate were employed for fungal control. In 1900s, methylmercury was used to prevent plants and seeds from fungal infection outbreaks [70]. However, the use of heavy metals for controlling fungal growth has been associated with deleterious effects on human health. Such hazardous effects associated with methylmercury use were reported in early 1970s in Iraq, resulting in intoxication and death of hundreds of people [85, 86]. Despite the associated harmful effects, heavy metals are still the most widely used active ingredient in many fungicides. Fungicides can cause fungal death by altering multiple pathways in fungus therefore they have multimodal mechanism for controlling fungus growth. More commonly employed pathways include oxidative stress generation by increasing ROS production, declining level of antioxidant enzymes such as catalase, glutathione transferase, and SOD, and inhibiting mitochondria and chelation of some essential metals [87]. Unfortunately, majority of the aforementioned pathways are also found in many species of mammals. Moreover, majority of these targets are also present in brain. Therefore, it is not surprising that exposure to fungicides can provoke neurotoxic effect.

Manganese Ethylene-Bis-Dithiocarbamates (EBDC)-Containing Fungicides

Existing data suggest no systemic neurotoxicity with many EBDC-containing fungicides. However, the association of manganese/zinc–EBDC fungicides has been proposed in the literature. Mn/Zn–EBDC (mancozeb) has not been as well studied as Mn–EBDC (maneb). Mn–EBDC was voluntarily withdrawn from the US market in 2010. Mn/Zn–EBDC has become the second most common commercial fungicide following the removal of Mn-EBDC [88]. Studies on humans [89], human-derived cell culture, [90] and nontarget animals [91] have demonstrated the increased levels of Mn in blood, cells, and tissues, respectively, following the exposure of Mn/Zn–EBDC. EBDC-based fungicides are metabolized to ethylene thiourea. The higher levels of Mn along with quantifiable amount of ethylene thiourea were observed in children raised near banana plantations in Costa Rica. These elevated levels of both Mn and ethylene thiourea were found to be the causative agents for neurological alterations being observed. However, research in this area is still lacking to postulate whether Mn/Zn–EBDC also possess same potential of altering

dopaminergic neurons leading to PD as being revealed by manebor [92]. However, studies conducted on *C. elegans* have demonstrated that exposure to fungicides whether acute or chronic leads to alteration in dopaminergic system [93]. As Mn/Zn–EBDC provoked toxicity has been shown to occur by increasing oxidative stress [94] as well as inhibition of mitochondria [95], it is reasonable to assume that neurons, as like other cells, would be equally vulnerable to exposure of Mn/Zn–EBDC. However, the exact mechanism that how fungicide cross the blood–brain barrier (BBB) remained unclear up till now. Further research in this aspect will not only give deep understanding about Mn/Zn–EBDC intoxication associated neurotoxic manifestations but also give detailed mechanistic perspective about these fungicide-induced neurotoxicity.

Safety Measures While Handling Pesticides

Following precautionary measures should be adopted before handling any pesticide:

- Identification of the target.
- Proper labeling of pesticides in accordance with the WHO instructions. Precautionary measures should be written in both English and local language.
- Pesticides should be stored in original container away from children access and pets.
- Safety measures regarding pesticides use should be followed strictly, and protective clothing including shirts with long sleeves, rubber gloves, mask, and other protective equipment should be employed before handling.
- For mixing of pesticides, the area should be well ventilated and only concerned person should be present there.
- Spray workers should wear long-sleeves clothes with gloves, mask, hat, and long shoes.
- Pesticides should be stored in dry places.
- After use, pesticides should be disposed into dug hole in the ground. It should not be disposed near running water area.
- Hands should be washed after working with pesticides.
- While spraying pesticides on agricultural land, workers should be removed from that area and proper warning signs should be placed and reentry date that is safe for workers should be mentioned.

Conclusions

Pesticides play a pivotal role in augmentation of crop production by protecting crops from various vector-borne disorders but at the same time they pose toxic manifestations on human health. These toxic effects are primarily attributed to nonselec-

tive nature of pesticides for pests and other species including animals and humans. All the commonly employed pesticides are associated with neurotoxicity in human beings. Of these, insecticides are more common resulting in various neurological disorders. These pesticides contribute to neurotoxicity through several mechanisms including inhibition of acetylcholinesterase, voltage-gated sodium channels, mitochondria and Na/K ATPase, overstimulation of nicotinic acetylcholine receptors, oxidative stress, or decline in levels of antioxidant enzymes. Although specific antidotes and pharmacological interventions are available against most of the insecticide-associated neurotoxicity but safety or preventive measures carry utmost value to alleviate the growing burden of neurological disorders.

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Chapter 6
Cigarette Smoking and Neurological Disorders: From Exposure to Therapeutic Interventions

Yusra Habib Khan, Arooj Abid, Aroosa Liaqat, Muhammad Hammad Butt, Abrar Ahmad, Shahzadi Misbah, and Tauqeer Hussain Mallhi

Abstract Tobacco smoking is a major global health problem that kills millions of individuals annually and is responsible for many preventable deaths. Cigarette smoke is accompanied by several harmful effects on human health. Tobacco smoke consists of many toxic and carcinogenic chemicals. Human beings are exposed to tobacco smoke by smoking or using tobacco products or by inhalation of tobacco smoke from the environment. Nicotine is a major component of tobacco which exerts neurotoxic effects and is responsible for morphological and neurobiological changes in brain resulting in various neurological diseases. Smoking is a major risk factor for many non-communicable diseases. These can be prevented by reducing smoking and introducing lifestyle changes. Moreover, smoking cessation programs are of utmost importance to reduce the risks associated with cigarette smoke. Several behavioural and pharmacological interventions can be adapted to mitigate the harmful effects of smoking. Moreover, limiting the exposure to passive smoke is also of paramount importance to minimize its harmful effects.

Keywords Neurological disorders · Cigarette smoking · Nicotine · Burden · Interventions

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Introduction

Tobacco is highly addictive and is smoked all over the world by burning the tobacco products (e.g. cigarette). Tobacco smoking exposes human beings to a variety of toxic compounds. It has harmful effects on human health: reduces life expectancy and increases morbidity and healthcare-related costs. Tobacco smoke does not only have hazardous effects on the smokers but it also affects the people living in surroundings, particularly pregnant women where it can cause the deleterious effects on foetus [1]. Smoking is a risk factor for many negative health outcomes like chronic obstructive pulmonary disease (COPD), cancers, cardiovascular diseases, ischemic stroke, and osteoporosis. Chronic exposure to tobacco smoke leads to respiratory tract infections and asthma in babies. It also diminishes the immune cells' activity and enhances allergic responses [2]. Recently, the role of smoking and its association in vascular and degenerative neurological disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), stroke, and anxiety have also been established [3, 4]. Maternal smoking during pregnancy has been linked to increased neurodevelopmental disorders [5]. Almost, 0.48 million deaths annually are reported in United States of America due to active and passive smoking. The prevalence of smokers declined from 20.9% in 2005 to 15.5% in 2016 but significant change has not been observed yet [6]. According to the estimates by the World Health Organization (WHO), around nine million deaths yearly will be linked to the smoking by 2030 [7]. This chapter aims to describe the components of cigarette smoke, routes of inhalation or intake, mechanisms or roles of smoking in neurological disorders and interventions needed to curb this addictive habit and its hazardous effects.

Components of Cigarette Smoke

Tobacco in cigarette has more than 7000 compounds that are harmful and lethal [8]. The smoke of the cigarette contains a complex mixture of compounds [9]. Cigarette smoke can be divided into two phases, gas-phase smoke and tar, by the use of filter. Both phases have radicals which differ widely. Tar contains approximately 10^{17} free radicals per gram while gas-phase smoke has over 10^{15} radicals per puff. The free radicals in the gas-phase have short lifespan, in seconds, such as nitric oxide, dienes and reactive olefins. However, radicals in tar phase are stable and long-lived with lifespan ranging from hours to months such as catechol and hydroquinone radicals [10, 11]. The primary constituent of tobacco smoke which is responsible for the addiction and many harmful effects is nicotine. Other constituents include heavy metals (lead, arsenic), carbon monoxide, hydrogen cyanide, formaldehyde, nitrosamines, ammonia, polycyclic aromatic hydrocarbons (PAHs) radioactive elements, and many others [12].

Nicotine

In vivo study involving the animals and humans exposed to tobacco smoke or nicotine shows that its chronic exposure causes increase in the number of nicotinic acetylcholine receptors (nAChRs) in the central nervous system CNS [13] as shown in Fig. 6.1. These receptors are ligand-gated ion channels comprising of two subunits including alpha (α) and beta (β). There have been at least 12 nAChRs in CNS where heteromeric α4β2 is the most common subtype while homomeric α7 is the second most common. These receptors are present all over the CNS. The highest density of these receptors is identified in thalamus followed by in basal ganglia, cerebral cortex, hippocampus, and cerebellum in respective order [15].

Acute exposure of nicotine or tobacco smoke causes cerebral responses such as decrease in global brain activity, activation thalamus, prefrontal cortex, and visual cortex systems, increase in concentration of dopamine in the ventral striatum/nucleus accumbens. Chronic exposure of nicotine or tobacco smoke causes decrease in activity of monoamine oxidase (MAO) A and B in the basal ganglia and reduced availability of α4β2 nAChRs in the thalamus and putamen. The ultimate acute effect of smoking is neurotransmission enhancement which results in cognitive effects such as sustained and improved attention, improved reaction times, arousal, and motivation [16].

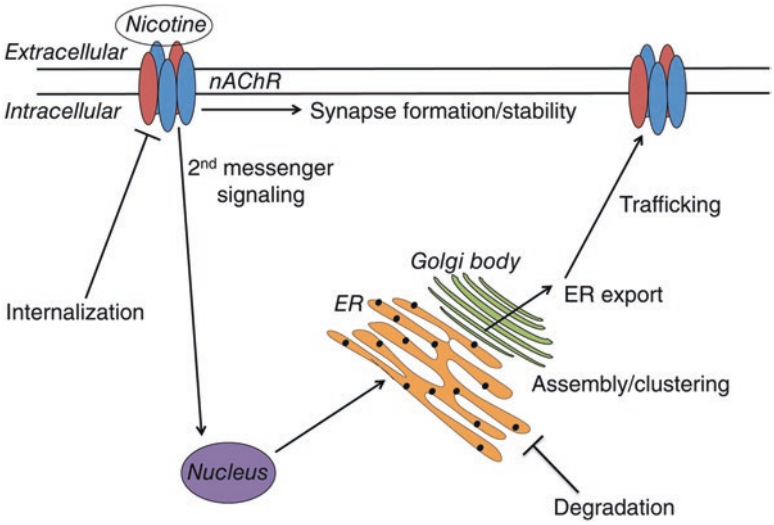

Fig. 6.1 Mechanism of upregulation of NAChRs. (Adopted from Melroy-Greif et al. [14] after some modifications)

Heavy Metals

Strong epidemiologic evidence links heavy metal exposure to increased oxidative stress and AD [17]. Since cigarette smoke comprises of heavy metals such as lead and arsenic, chronic exposure can cause deleterious impact on human health. Elderly people with marked levels of lead in their bones have been observed to have significant decrease in cognitive function with decline in functioning in learning, verbal memory, visual memory, visual construction, processing speed, language, executive functioning, and eye–hand coordination [18, 19]. Moreover, smoking has also been associated with the increase in white matter lesion and decrease in total brain, frontal, total grey matter, and parietal lobe white matter volume [20, 21] (Fig. 6.2).

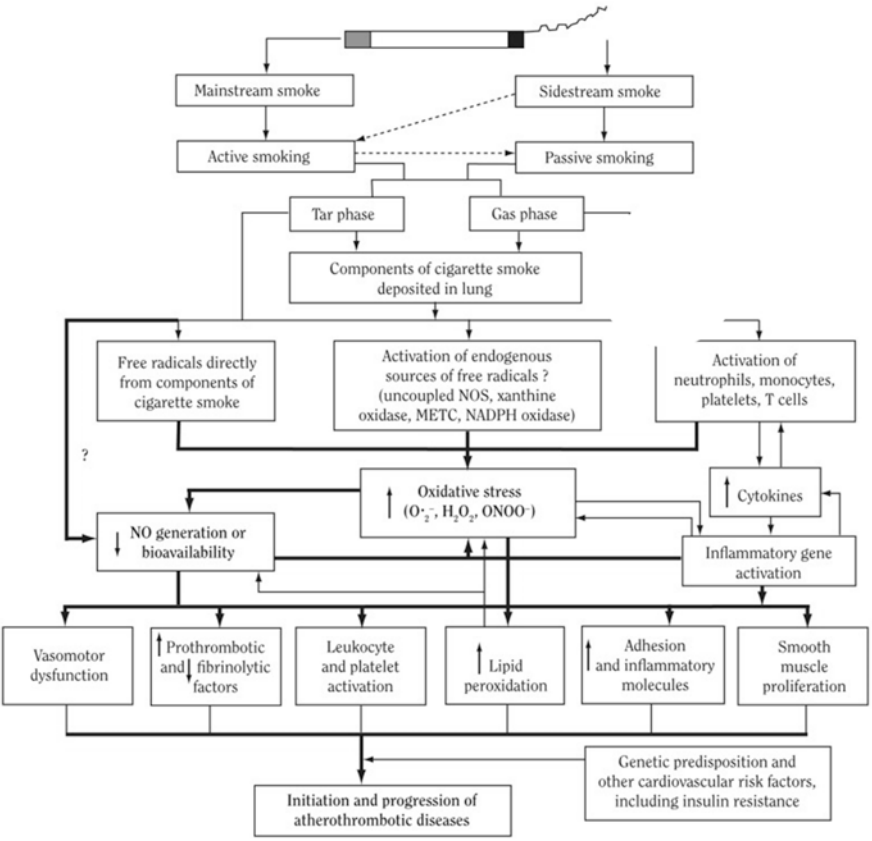

Fig. 6.2 Components of cigarette smoke and their effects. (Adopted from Gary et al. [10] after some modifications)

Carbon Monoxide

Carbon monoxide (CO) in cigarette smoke binds irreversibly with haemoglobin (Hb) in red blood cell to form COHb, which is stable and circulates in the body. This causes the amount of oxygen in the blood to reduce considerably, leading to hypoxia. Tissues that require the most oxygen such as those in brain and the heart are the affected severely by CO exposure [12].

Burden of Smoking

Tobacco is a major concern and leading public health threat, accountable for the death of more than 5.4 million people annually, and is expected to cross eight million by 2030 [22]. In developing countries, tobacco is a major risk factor for non-communicable diseases (NCDs), which are responsible for two-thirds of deaths. As per the Sustainable Development Goal 3, the target is to reduce the premature deaths from NCDs by 2030 [23].

Cigarette smoking reduces the overall health of smokers and exerts harmful effects on every organ of the body. It is believed to affect both the quality and quantity of life. It has many serious adverse effects including inflammation and decreased immunity. It is also known to be a risk factor for rheumatoid arthritis. About 90% deaths in lung cancer are due to cigarette smoking [24]. Similarly, smoking is reported by the Centre for Disease Control and Prevention (CDC) to be a higher cause of death in women than breast cancer. Lung diseases including COPD occur as a result of airway damage ultimately destroying alveolar cells. COPD, a chronic inflammatory disease, causes obstructed airflow from the lungs which results in breathing difficulty. Smoking also affects oral health, stains teeth and can cause gum diseases and loss of tooth. It increases the risks of oropharyngeal cancers. Moreover, it has been found that active smokers are more prone to develop diabetes, almost 30–40% higher, than non-smokers. Smokers who have diabetes (Type 2) find it difficult to control the glucose levels even adhering to the therapy. There is an increased risk for cataracts and age-related macular degeneration (AMD) among smokers [25]. The WHO reported that smoking can be the cause of 10% of all deaths from cardiovascular diseases [26]. Many cardiovascular disorders can be prevented by adapting lifestyle changes such as limited or no tobacco and alcohol consumption and physical activity [27]. The tar in the cigarettes when enters blood circulation, it causes the thickening of blood, formation of clots and ultimately narrowing of arteries, increased risk for blood pressure and heart attack. Smokers are 50% more at risk to have a stroke as compared to non-smokers. Premature ageing of skin is also a result of smoking. The association of brittle bones and smoking is also well established in the literature. Women who smoke should be cautious as they are more likely to develop osteoporosis than non-smokers [28].

Routes of Exposure and Pathophysiologic Mechanism

The route of exposure to tobacco smoke is inhalation, and the exclusive source is the combustion of tobacco products. The exposure to tobacco smoke usually happens in indoor air (homes, vehicles, and workplaces) and public places. The extent of exposure is variable, based upon the number of smokers, amount, and type of tobacco products smoked. It also depends upon the ventilation of indoor space and the duration of exposure. However, by diluting the air in the room, the exposure of smoke can be reduced for non-smokers.

Most of the harmful physiologic effects of cigarette smoke are linked with its pro-inflammatory effects. Smokers have enhanced levels of inflammatory cytokines, interleukin-6 (IL-6), C-reactive protein, and tumour necrosis factor–alpha (TNF-α). This causes oxidative tissue injury and inflammation [29]. The smoke of cigarette contains a variety of carcinogenic compounds which at the cellular level contributes to mutations manifesting as tumours. Other cellular effects include negative mitochondrial changes and impairment in the respiratory chain, leading to increased cellular stress [30]. CO when bound to haemoglobin interferes with mitochondrial electron transport chain (ETC), causing decrease in cytochrome *c* oxidase affecting the tissues with high metabolic rate including CNS and muscles the most [31]. Tobacco smoke exposure also reduces red blood cells proliferation, affecting the oxygen transport [32]. In addition to these effects, smoking also decreases antioxidant vitamins and nutrients such as riboflavin and folate, melatonin, and vitamins C and E [33–35].

Cigarette and Neurological Disorders

Parkinson's Disease

PD is a neurodegenerative movement disorder that occurs in approximately 1% of the population with the age of over 55. It is characterized by dopaminergic nigrostriatal neurons damage which causes motor deficits such as bradykinesia, tremor, rigidity, and postural instability [36, 37]. The association of cigarette smoking with a lower incidence of PD has been observed in various epidemiological studies [38–41]. The constituents of tobacco smoke causing this neuroprotective effect are yet to be identified; however, several experimental animal studies propose that nicotine is responsible for such effects. This can be due to the activation of the striatal or mesolimbic dopaminergic system [42], protection contrary to glutamate-induced neurotoxicity in cortical, mesencephalic, and striatal neurons, with nigrostriatal degeneration [37, 41]. Nicotine can also suppress MAOs resulting in decreased formation of toxin [43]. Moreover, nicotine can also induce cytochrome P450 (CYP) enzyme family [44–46]. Additionally, it is an antioxidant which can also act by inducing mitochondrial complex I activity, preserving mitochondrial function, and resulting in reduced neuronal damage [43, 47–49]. Nicotine is also known to stimulate nAChRs such as α7, α4β2, α6β2, α6α4β2 [50–56], altering various signalling pathways, including presynaptic pathways that are involved in neurotransmitter

release control (ACh, GABA, dopamine, and glutamate) [57], postsynaptic pathways that are involved in apoptosis (reactive oxygen species, phospholipase C, arachidonic acid, neuronal nitric oxide synthase, and cGMP) and necrosis (phospholipase C, protein kinase C, MAPK, ERK, and Bcl2) [58–60], immune modulation (IL-6, IL-1, and TNF-α) [39, 61], and neurotrophic factor production (brain-derived neurotrophic factor, fibroblast growth factor 2) [62, 63]. All these processes may attribute to the neuroprotective effects of the cigarette smoking in PD.

Alzheimer's Disease

AD is a progressive and irreversible neurodegenerative disease that manifests as dementia, beginning with memory loss, progressing to severe decline in cognitive function, and disability [64]. It is the most prevalent neurodegenerative disorder and affects approximately 2% of the industrialized countries' population. The neuropathological marks of AD are neurofibrillary tangles (composed of tau protein), senile plaques (composed of β-amyloid peptide), and cholinergic neurons loss of the basal forebrain [65].

The literature revealed conflicting results between AD and smoking. Available studies indicate both neurotoxic and neuroprotective properties of nicotine [66]. A prospective analysis on elderly population indicated that habitual smokers have a twofold higher risk of developing AD [67]. Lifestyle changes attributed to reduction or cessation of cigarette smoking, treatment of hypertension and diabetes, and the improvement of serum lipid levels decline the incidence of cognitive impairment and other associated diseases [68]. Senescence also accelerates the prevalence of dementia mainly due to environmental hardships [69].

A study investigated the effects of cigarette smoking for 2 years and observed the changes in regional brain volumes of healthy elderly individuals. These individuals were compared with non-smokers. According to this cohort study, the elderly with a history of cigarette smoking was found with decreased structural integrity of multiple brain regions and a greater rate of atrophy was also observed [70]. Moreover, recent cross-sectional studies exhibited in magnetic resonance imaging (MRI) that chronic smokers have abnormalities in brain morphology. When smokers and non-smokers were compared, small grey matter (GM) volumes and lower GM densities in the anterior cingulate cortex, orbitofrontal cortex (OFC), dorsolateral cortex, para hippocampal gyrus, and precuneus and lower GM densities in the right cerebellum and smaller volumes in the left dorsal ACC were observed [15, 71–73]. Likewise, previous studies have shown morphological neurobiological abnormalities in similar brain areas in incipient stages of Alzheimer's disease and that of chronic cigarette smoking [74].

Stroke

A stroke can occur due to obstruction or reduction in the blood supply to a certain region of brain attributed to a clot or haemorrhage, preventing oxygen and nutrient supply to that region [75]. Smoking is believed to be one of the most important risk factors for

ischemic and vascular disorders. There is a strong positive dose-dependent association of ischemic stroke and cigarette smoking. Smoking leads to stoke because of its association with inflammatory factors which are responsible for pathogenesis of stroke [76–78].

The mechanism of stroke caused by smoking can involve atherosclerosis of carotid and elevation of the levels of fibrinogen, homocysteine, and oxidized low-density lipoprotein cholesterol [79, 80].

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the CNS and is characterized by inflammation, axonal damage, and demyelination. It typically occurs at the age between 20 and 40 years. It is estimated that around 0.4 million in the United States of America and two million people globally have MS [37]. It can lead to significant disability because of diminishing motor, sensation, autonomic, and neurocognitive function. The positive association of cigarette smoking with MS is very evident by numerous epidemiological studies [81–84]. Cigarette smoking is also associated with progression and disability in MS. The mechanism behind these outcomes is unclear and warrants more studies involving genetic analysis, potential confounders, and more objective smoking exposure measures. Considering the potential risk and cost, it is strongly recommended to avoid smoking.

Prevention and Intervention

Cigarette smoking causes addiction and dependence because of nicotine, the withdrawal of which makes cessation extremely difficult. Half of the people attempting to quit end up failing at it. There are several ways to reduce prevalence of smoking in overall population and facilitate individual cessation. The WHO Framework Convention on Tobacco Control (WHO FCTC) outlines related guidelines for governments. One of the ways of reducing smoking is control of smoking initiation. It can be done by raised and additional taxes on tobacco products. It will not only disincentivize smoking and stop new smokers but is also a revenue stream that can be utilized for tobacco control policies, programs, and their execution and implementation. Another strategy is to regulate the tobacco industry and their marketing by introducing laws that makes it difficult for them to market their products on mass and social media. They can also be required to add warnings and lucid graphics depicting the dangerous outcomes of tobacco such as oral cancer. There can also be awareness campaigns and smoking cessation interventions in schools and colleges. Minors can be restricted access to tobacco products. Interventional programs usually have two strategies: behavioural and pharmacological. Behavioural interventions can be done on two levels: individual and population. On individual level, smokers can be counselled and educated on cessation and harms of smoking. On population level, several strategies can be adopted such as use of text messaging, mass and social media campaigns, and hotlines for smoking cessation help. Pharmacological intervention employs medications and nicotine replacement therapies [85, 86]. Table 6.1 highlights some strategies for smoking cessation.

Table 6.1 Intervention strategies for cessation of smoking

Behavioural interventions	Population-level approaches	Brief advice	During routine clinical interaction/consultation, a few minutes should be taken to advise the smoker to stop tobacco use
		Quit lines	There should be a toll-free phone line services that provide counselling relating to cigarette smoking cessation Smokers in cessation program should be followed up through telephone calls facilitating and supporting tobacco cessation
		Tobacco cessation	Tobacco cessation and intervention programs should include text messaging on mobile phone which are extremely cost effective and can help in reaching and facilitating large population
	Individual specialist approaches	Intensive behavioural support	Individual or group sessions can be held in intensive behavioural support which can help and assist in tobacco cessation, skills, and strategies helpful for changing behaviour
		Cessation clinics	There can also be cessation clinics that specialize in tobacco cessation services. Such clinics can offer advice, medication intervention, or intensive behavioural support
Pharmacological interventions	Nicotine replacement therapies	One of the wide spread strategies is the use of NRTs which provide low and controlled dose of nicotine without cigarette toxins. They are readily available in different forms such as patches, lozenges, gum, inhalers, and nasal spray. NRTs help in cessation by reducing craving of nicotine and its withdrawal symptoms. The strategy behind this method is that the dose of nicotine is reduced gradually over the time, helping in withdrawal from nicotine addiction	
	Non-nicotine pharmacotherapies	Non-nicotine therapies include the use of drugs such as bupropion, cytosine, and varenicline. These drugs help in cessation by reducing craving of nicotine and its withdrawal symptoms, decreasing the pleasurable effects of smoking	

Adopted from WHO Report on Global Tobacco Epidemic 2019 [87] after some modifications

Conclusion

Cigarette smoking can have detrimental effects on human health, resulting in substantial adverse outcomes, morbidity, and mortality. Components of cigarette smoke have neurological effects which are largely negative but, in some cases, can be neuroprotective such as in PD. To reduce the risks of neurological and other harmful effects associated with cigarette smoking, awareness campaigns, cessation support, and treatment should be provided. To discourage smoking, there is also a need to develop and implement targeted policies. These policies may include increasing the tobacco price and comprehensive smoke-free laws that discourage smoking in public spaces, indoor areas, and transport.

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Chapter 7
Mechanistic Insight of Mycotoxin-Induced Neurological Disorders and Treatment Strategies

Zunera Chauhdary, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Numerous fungal species are fabricated into several paradigms of mycotoxins as secondary metabolites notably *Fusarium, Aspergillus,* and *Penicillium*. These toxic metabolites have significant impact on the brain health of human beings if entered through the food chain or from the direct exposure through the modulation of myriad molecular mechanistic signaling pathways. T-2 toxin, macrocyclic trichothecenes, fumonisin B1, and ochratoxin A are recognized as neurotoxic metabolites among the other mycotoxins. T-2 toxins and macrocyclic trichothecenes induce neuronal apoptosis and neuroinflammation. Fumonisin B1 inhibits ceramide synthesis and neurodegeneration in cerebral cortex. Ochratoxin A persuades the dopaminergic neuronal loss and apoptosis in striatum, substantia nigra, and hippocampus. This chapter reviews the biotransformation and detoxification of these mycotoxins in relation to their degrading enzymes. The therapeutic roles of glutathione, sequestering agents, probiotics, and sweat induction to mitigate mycotoxin-induced neurotoxicity have also been overviewed.

Keywords Fumonisin B1 · Neuronal apoptosis · Neurodegeneration · Neurotoxicity · Ochratoxin A · T-2 toxin

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Introduction

Mycotoxins are the small molecules that are toxic in nature and are synthesized by the filamentous molds as secondary metabolites [1]. These metabolites hold a chemical and toxic heterogenic assortment that induces the lethal diseases and death in human beings. These fungal metabolites induce harmful effects on reproductive, digestive, immune, nervous, and urinary system of human and animals. Various food stuffs like fruits, vegetables, cereals nuts, and spices are contaminated by mycotoxins producing molds under warm and damp conditions [2–4]. Mycotoxins are produced before or after harvesting the crops. They are usually resistant to the most of food processing procedures and techniques [5–7]. It is difficult and challenging to categorize the mycotoxins owing to different chemical structure, biological effects, and multiple biosynthetic fungal incipiencies [8]. Mycotoxins are classified by clinicians on the basis of target organs like neurotoxins, nephrotoxins, and hepatotoxins targeting neurons, kidney, and liver, respectively [9, 10]. Mycotoxins are also categorized as allergens, mutagenic, teratogenic, and carcinogenic depending on the nature of health hazard [11]. Human exposure to mycotoxins is common in that part of the world where food processing and preserving is poor and not hygienic [12, 13]. Mycotoxins enter into the human body directly by inhalation, by ingesting mold contaminated food, or indirectly transferred through animals grazing on contaminated crops, particularly through milk [14–16]. Although, several kinds of mycotoxins have been recognized, but fumonisin B (FB1), slaframine, swainsonine, lolitrems, and paspalitrems are observed as neurotoxic mycotoxins in vertebrates [17, 18]. Mycotoxins like ochratoxin A (OTA), patulin, fumonisins, zearalenone, and nivalenol/deoxynivalenol are also associated with adverse health effects in human being [17, 19]. Assorted in vitro and in vivo studies have been performed to elucidate the mechanistic pathways of these mycotoxins to instigate the toxic sequel. Some studies reported that these mycotoxins have membrane active estates which determine their toxic potential. These toxic metabolites attach to membrane receptors and persuade detrimental execution through modulation of second messenger system signal transduction. Under the duress of mycotoxins toxicity, the metabolic pathways, reproduction, growth, and development pathways are endangered owing to anomalous DNA, RNA, and protein synthesis in conjunction with proapoptotic pathways. This chapter outlined the underlying mechanistic pathways modulated by neurotoxic mycotoxins like T-2 toxin, macrocyclic trichothecenes, FB1, and OTA in experimental animal and in vitro models.

Occupational Exposure to Mycotoxins

Organic dust exposure is borne by the workers working in different sectors related to animals, food, soil, and plant. Numerous types of bacteria, fungi, and their metabolites exist in this organic dust responsible for serious health issues. At workplace, biological risks are monitored by bioaerosols in the air, which usually estimate the

airborne bacteria, fungi, and endotoxins. Although, mycotoxins are associated with lethal health effects, these are not measured in routine at workplace. Mycotoxins are very hard to destroy and exist in the environment even after the complete destruction of fungus [20]. They are resistant to high and very low temperature. The neurotoxic mycotoxins are usually associated with agricultural products, and due to the gaps in the toxicological knowledge, their risk assessment at workplace is difficult [21]. Mycotoxins induce lethal neurotoxic effects after the inhalation of fungal spores and hyphae and through the dermal contact [22]. Dust particles containing mycotoxins have dermal absorption and usually infect the workers when they directly handle the mycotoxin-contaminated materials. The severity of neurotoxic effect induced by mycotoxins is dependent on the route of infection, exposure intensity, duration, and health status of an individual [20]. The adverse effects of mycotoxins after the ingestion of contaminated food are well recognized; however, inhalation and dermal contact related lethal effects are not well reported. Sign and symptoms of the mycotoxin-induced infections include skin rashes, nausea, mucous membrane irritation, lung cancer, liver, kidney, and CNS damage. Inhalation of ochratoxin by workers is associated with renal failure and respiratory distress [23, 24].

Mycotoxin-Induced Neurological Disorders

Central nervous system (CNS) is highly vulnerable to oxidative stress due to high polyunsaturated fatty contents and huge oxygen demand [25]. Mycotoxins like trichothecenes are mainly produced by fungus species like *Fusarium* [26, 27]. Trichothecene mycotoxins are highly lipophilic and readily absorbed through dermal contact and GIT mucosa after ingestion of moldy grains. It is suspected that T-2 mycotoxins were used as chemical warfare agent through low flying air crafts in the form of yellow liquid known as yellow rain from 1970s to 1990s [28, 29]. Mycotoxins damage the brain, heart, liver, and kidney. These toxins induce neurotoxicity in the human and animals as they have the ability to cross the blood–brain barrier [30, 31]. It is reported that single dose of T-2 toxin in mice either through subcutaneous (1.54 mg/kg) or percutaneous (5.94 mg/kg) administration can mediate the neurotoxic effect through vicious cycle of oxidative stress [32]. T-2 toxin also induces the neurotoxic effects in neuroblastoma cell line, i.e., IMR-32 through modulation of mitogen-activated protein kinase (MAPK), p53, and neuronal apoptosis [33]. A leucine zipper transcription factor, nuclear factor erythroid 2-related factor (Nrf2), has neuroprotective effect through the modulation of antioxidative mechanism of signaling [34]. Mycotoxins like OTA can induce neurodegenerative disease by decreasing the expression of Nrf2 and downregulation of Nrf2/HO-1 signaling [35]. Disproportion in reactive oxygen species (ROS) and antioxidant defense mechanism leads to induce the lipid peroxidation, mitochondrial dysfunction, and neuronal apoptosis [36]. It is reported that T-2 toxins at the dose of 5 ng/mL concentration induce lipid peroxidation and raise the level of MDA in N2a cells [37]. T-2 toxin significantly decreases the activity of first-line defense antioxidant enzymes like

SOD, GSH, and catalases [38]. Mycotoxins induce the neurotoxicity by mitochondrial dysfunction and decrease mitochondrial membrane potential [30] through the upregulation of Bax and downregulation of mRNA expression of Bcl-2 family proteins, which sequentially escalate the permeability of mitochondrial membrane [17]. Cytochrome c is liberated from highly permeable outer membrane of mitochondria and stimulates the caspases-3 and -9 dependent neuronal apoptosis [39–42]. T-2 toxins increase the caspases-8 pursuit resulting in the cleavage of Bid and fusion with Bcl-XL and BAK which stimulate the death receptor pathways and mitochondrial dysfunction [31, 43]. Most of the mycotoxins induce neurotoxicity via stimulation of death receptor pathways through the upregulation of mRNA and protein expression of p53 and caspases-8 [44]. In the duress of oxidative stress induced by mycotoxins, apoptosis is eventuated by activated p53 expression which triggers the mitochondrial dysfunction and Bax activation [45–47]. In addition to the participation of p53 and other triggering signaling pathways, further authentic mechanistic elucidations are needful to describe the neurotoxic potential of mycotoxins. Mycotoxins downregulate the mRNA expression of key antioxidant player against the cellular oxidative stress such as Nrf2 and OH-1. Mycotoxins inhibit the translocation of Nrf2 to nucleus and downregulate the expression of antioxidant enzymes genes [31]. In Table 7.1, we have summarized the sources of neurotoxic mycotoxins, mechanistic pathways behind the neurotoxic potential, and their degrading enzymes. T-2 toxin induces oxidative stress, mitochondrial dysfunction, and oxidation of DNA in mouse neuroblastoma 2a cells. The neurotoxic effect of T-2 toxin is associated with the upregulation of mRNA expression of BAX, P53, and caspases-9 and inhibition of Nfr/HO-1 pathway [31]. OTA mostly infects the food stuffs that have well-known hepatotoxic and nephrotoxic potential. OTA at the dose level 0.1–2.5 mol/L in primary neuronal cells and SH-SY5Y neuronal cells induces cytotoxicity through the modulation of caspases-9 and -3. It is reported that OTA contributes in the pathogenesis of neurodegenerative disorders through the induction of mitochondrial dysfunction and neuronal apoptosis [50]. FB1, another food contaminating mycotoxin, induces the neurotoxicity in vertebrates through the disruption of lipid metabolism, induction of oxidative and endoplasmic reticulum stress. These mycotoxins modulate the DNA methylation and MAPKs to provoke the neuronal toxicity [53]. Macrocyclic trichothecene mycotoxins produced by molds growing on damp places, nasal instillation of 50 μL (500 μg/kg body weight), induce the olfactory sensory neurons and olfactory epithelium apoptosis. Macrocyclic trichothecene upregulates the mRNA expression of proapoptotic gene FAS, caspases-9 and -3, Bax, and PKR. Also increased mRNA expression of proinflammatory cytokines also augments the neurotoxic effect of macrocyclic trichothecene through neuroinflammation [45].

Table 7.1 Sources of neurotoxic mycotoxins, mechanistic pathways behind neurotoxic potential and their degrading enzymes

Mycotoxin	Genus/species	Food source	Mechanism of neurotoxicity	Biotransformation
T-2	*Fusarium* *Cephalosporium* *Trichoderma* *Fusarium oxysporum*	Cereals, feeds, silage, legumes, fruits, and vegetables	Upregulated mRNA expression of p53, Bax, caspases-8, -3, and -9, downregulated mRNA expression of Nrf/HO-1, oxidative stress, and neuronal apoptosis [31]	UDP-glycosyltransferase and cytochrome P450 [48, 49]
Ochratoxin A	*Aspergillus* *Penicillium* *A. ochraceus* *P. nordicum* *P. verrucosum*	Cereals, herbs, oil seeds, figs, beef jerky, fruits, and wine	Contributed in pathogenesis of Alzheimer's and Parkinson's disease through cytotoxicity to neuronal cells, caspases-9, -8, and -3 activation and decreasing mitochondrial membrane potential [50]	Carboxypeptidases, lipases, amidases, and commercial proteases [51, 52]
Fumonisin B1	*Fusarium verticillioides* *F. culmorum*	Corn, wheat, and other cereals	DNA fragmentations, oxidative stress, inhibition of ceramide and protein synthesis, impairment of sphingolipids metabolism, and activation of MAPKs [53]	Carboxylesterase, Aminotransferase, and fumonisin esterase [54, 55]
Macrocyclic trichothecenes	*Stachybotrys chartarum*	Wheat, rye, rice, barley, cereals, fruits, and vegetables	P38-mediated mitochondrial dysfunction, inhibition of proteins synthesis, DNA fragmentations, neuronal apoptosis, and neuroinflammation [45]	Eubacteria strain BBSH 797 synthesized, de-epoxidase enzymes, microbial flora of GIT [56]

T-2 Toxin

T-2 toxin is a member of trichothecene family, mainly synthesized naturally by *F. sporotichioides*, *F. poae*, *F. equiseti*, and *F. acuminatum* [57, 58]. Many crops like wheat, rice, barley, and corn are infected during harvesting or storage. It is estimated that T-2 toxin has affinity to attach with peptidyl transferases and inhibits its activity [59]. The mechanisms modulated by T-2 toxin are depicted in Fig. 7.1. This subsequent inhibition leads to the activation of JNK/P38 MAPK pathways which in turn expedited to oxidative stress and neuronal toxicity [60]. So far the limited scientific

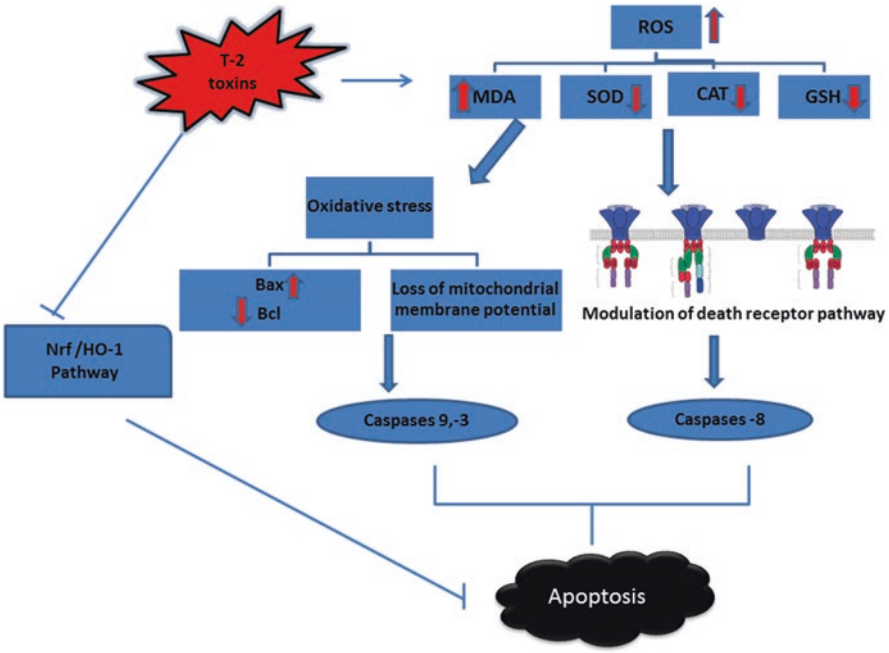

Fig. 7.1 Schematic description of underlying mechanistic pathways modulated by T-2 to induce apoptosis through the stimulation of death receptor pathways. T-2 downregulates Bcl-XL, increases the mRNA expression of BAX, caspases-9, -3, and -8, and inhibits Nrf/HO-1 pathway

literature addressing the effect of T-2 toxins on CNS is available [32]. It is reported that minute concentration of T-2 toxins can alter the metabolism of neurotransmitters in CNS [61]. It was reported that T-2 toxins altered the absorption of amino acids through BBB [62]. This toxic substance is freely penetrated into the fetal brain and induces the fetotoxicity and maternal lethal effects [63]. T-2 toxin induces the fetotoxic effects in pregnant rat. Oral administration of T-2 toxin, at the dose 2 mg/kg body weight at 13th day of gestational period in pregnant rat, increased the number of apoptotic neural progenitor cells in telencephalon after first hour of administration [64]. Findings of microarray analysis expressed that oxidative stress induced the fetal neurotoxicity through the raised expression level of heat shock proteins 70, metallothionein 2,1, and HO-1 along with raised level of SODs after 24 h of T-2 toxin treatment [64]. It is investigated that in fetal brain, T-2 toxin subdues the mRNA expression of enzymes involved in lipid and drug metabolism like stearyl-CoA desaturase, farnesyl diphosphate synthase, and glutathione *S*-transferases [65, 66]. T-2 toxins induce neuronal apoptosis through the downregulation of genes encoded for cytochrome oxidase and NADH-dehydrogenase and trigger mitochondrial dysfunction [64]. In fetal brain, the expression of stress-related genes like MEKK1 is upregulated after 12–24 h of T-2 toxin administration and induced fetal brain apoptosis through the modulation of MAPK-JNK-c-jun signaling pathway

[67, 68]. T-2 toxin induces oxidative stress through the generation of ROS, depletion of GSH by increasing the protein carbonyl contents in adult and fetal brains of mice [32].

Macrocyclic Trichothecenes

Macrocyclic trichothecene, atranones, and simple trichothecenes are produced by mold *Stachybotrys chartarum* that specifically targets the damp building materials like cardboard, ceiling, tiles [69, 70]. These toxins prompt the adverse effects like respiratory and non-respiratory illnesses involved in neurological impairment along with failure of immune system, after persistent indoor subjection [71]. Animal studies have revealed that exposure to this mold can evoke the neurotoxicity, inflammation, and allergic reactions [70]. Macrocyclic trichothecene induce the activation of stress kinases and inhibit the translation and transcription through the formation of covalent protein adduct that is responsible for neurodegeneration and neuroinflammation in the brain of mouse [72]. These macrocyclic toxins activate ERK, JNK, MAPKs, and p38 signaling pathways through the proceedings of ribotoxin stress [73, 74]. The major mechanistic pathway for the induction of neuronal apoptosis by these toxins is inhibition of protein synthesis process through the association with 18S rRNA ribosomal subunit [75]. Satratoxin G (SG) is a kind of trichothecene mycotoxin that provokes the olfactory sensory neuronal apoptosis and bilateral atrophy of olfactory nerve layer of olfactory bulb of brain. SG upregulates the mRNA expression of pro-inflammatory cytokines and chemokines like, macrophages inflammatory proteins-2 (MIP-2), IL-6, IL-1, and TNF-α in mouse brain [76]. It was explored that 24 h exposure of SG remarkably increased the expression of proapoptotic genes Bax, p53, Fas, p75NGFR, FasL, and caspases-3 [45, 76]. It was reported that SG toxins in PC-12 cells significantly elevate the mRNA expression of caspases activated DNase, Bax, and p53 after 6–48 exposure and derived the translocation of apoptosis-inducing factor and mitochondrial flavoproteins to mediate the neuronal apoptosis [77]. Continuous stimulation of apoptotic and inflammatory pathways in response to fungal toxins leads to havoc of neurological tissues through the indirect pathways [78]. Inflammation is a natural process to mend the injured tissues but this mechanism induces the neuronal tissue damage when it is activated through the raised level of inflammatory mediators like iNOS, NF-κB, and TNF-α [79]. These mediators provoke the permanent devastation of nervous tissues through the passage of smaller particles through lung tissues and olfactory epithelium. Inflammation induced by these fungal toxins provokes the access of these mediators to olfactory bulb and frontal cortex, which inspired the deposition of amyloid β plaques, a pathological hallmark of Alzheimer's disease and other neurodegenerative disorders [80].

Fumonisin B1

Fumonisins B1 (FB1) mycotoxins, structurally homologous to sphingolipid, are produced by *Fusarium verticillioides* molds specifically targeting the corn crops and cereals, culpable to cause the various human and animal diseases [81]. These mycotoxins inhibit the biosynthesis of waxy lipid molecules, an integral portion of eukaryotic cell membrane, and ceramide through inhibition of ceramide synthase [82] as shown in Fig. 7.2. The inhibition of sphingolipid biosynthesis and their yield prompts the disruption in lipid metabolism and lipid dependent signaling pathways that are linked to the neurodegenerative disorders [83, 84]. FB1 mycotoxin is associated with a fatal and rare disease of nervous system known as equine leukoencephalomalacia (ELEM) due to the ingestion of mold-infected corn for several days to weeks [85, 86]. Histopathological findings reveal the existence of pathognomonic focal necrotic lesions in subcortical white matter and raised level of free sphingoid bases linkage to FB1-mediated neurotoxicity [81]. The recent neurodevelopmental research on FB1 neurotoxicity described that this mycotoxin is involved in the etiopathogenesis of neural tube defect in infants [87, 88]. This toxin causes the depletion in lipid rafts which in turn induces the folic acid receptor deficiency, neural tube defects in neuralating mouse embryos in ex vivo experimentations [89]. A number of scientific reports described that the neurotoxic potential of FB1 mycotoxin significantly hampered the axonal growth in hippocampal neurons culture system, in brain stem and forebrain of the rats boost the level of sphinganine quantity along

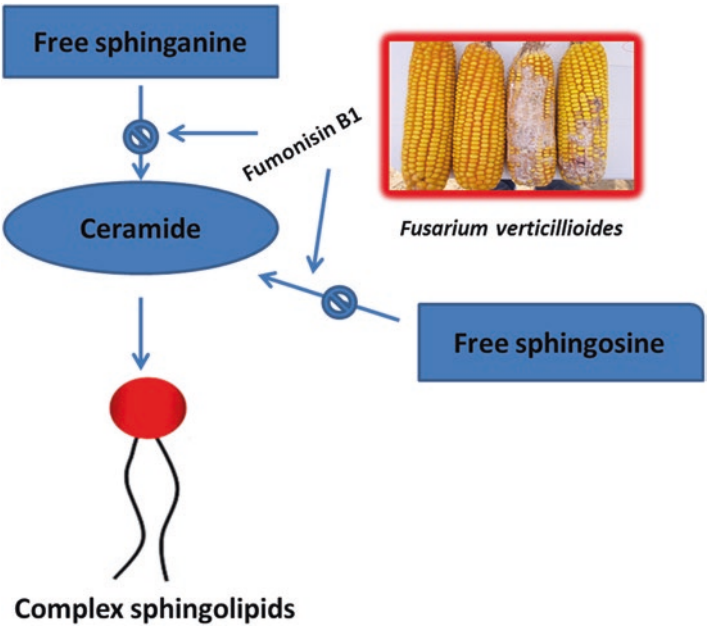

Fig. 7.2 Fumonisin B1 inflection of ceramide synthesis and sphingolipid metabolism

with demyelination and also decomposed the myelination of glial cells [90–92]. These toxins alter the metabolism of neurotransmitters and electrophysiological functions in neocortex of rat [17, 93].

Studies have reported that FB1 mycotoxin has limited access to BBB through the subcutaneous route. When administered through intracerebroventricular route at the dose 10–100 μg/kg, it induces the neurodegeneration in cerebral cortex, inhibits the ceramide biosynthesis, activates the astrocytes, stimulates the pro-inflammatory cytokines, and interferes the brain homeostasis [17, 94, 95]. Elevated expression of mRNA of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α is associated with neuronal injury and brain neutral sphingomyelinase-mediated neurodegeneration in CNS through ceramide arbitrated signaling [96]. The infusion of FB1 toxin in brain provokes the activation of astrocytes and microglial cells that are responsible for neurodegeneration [97]. In recent decades, numerous studies have elucidated the mechanism of oxidative stress and apoptosis signaling as a key pathway of mycotoxin-induced neurotoxicity. FB1 induced oxidative stress in three different types of neural cell lines such as: human SH-SY5Y neuroblastoma, rat C6 glioblastoma, and mouse GT1–7 hypothalamic cells [98]. It is revealed that FB1 mycotoxin dose-dependently increased the ROS in rat C6 and mouse GT1–7 cells with no effect on human SH-SY5Y neuroblastoma cell lines [99]. It is estimated that FB1 increases the level of lipid peroxidation and inhibits the ceramide synthesis in case of oxidative stress induced by the incubation of cell lines of rat, mouse, and human [100]. Contradictory to the above literature, it is reported that FB1 induces neurotoxicity independently to oxidative stress through the modulation of genes responsible for cellular protection like Bcl-2, caspases-3, and internucleosomal DNA fragmentations [101].

Ochratoxin A

Aspergillus ochraceus and *Penicillium verrucosum* molds produce a neurotoxic metabolite, known as ochratoxin A (OTA). This mycotoxin specifically infects the cereals and owned a longer half-life in foods [102]. OTA toxin is detected at nanomolar concentration in human plasma and causes neurotoxic, nephrotoxic, immunotoxic, and genotoxic effects [103]. Even though, due to the availability of insufficient current literature, it is reported that OTA mycotoxin holds the myriad mechanism of neurotoxic potential through evocation of the mitochondrial dysfunctions, impairment in protein synthesis, DNA fragmentation, and oxidative stress via the formation of adduct with DNA as shown in Fig. 7.3 [104]. OTA mycotoxin compromises the bioenergetic pathways and instigates the production of free radicals, nitric oxide, and ROS, resulting in the wide range oxidative damage to DNA, lipids, and proteins [105]. It is also reported that OTA induces mitochondrial toxicity through the inhibition of succinate-dependent electron transfer in electron transport chain and at complex I, proceeds to neurodegeneration [106]. The developing brain is more vulnerable to detrimental neurotoxic effects of OTA by reduc-

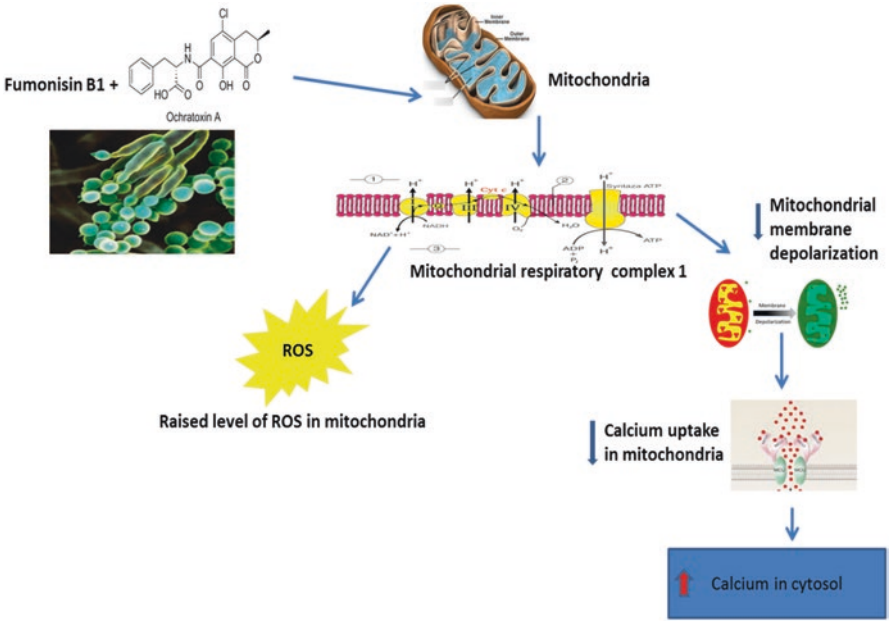

Fig. 7.3 The proffered mechanistic pathways modulated by ochratoxin A and fumonisin B to induce neurological disorder

ing DNA contents and through the modulation of neuronal relocation and propagation [107]. Experimental animal and cell culture studies reveal that OTA subsidizes the systemic and neurodegenerative disorders in animals and humans through provoking the neurotoxicity in striatum, hippocampus, and ventral mesencephalon [108]. It is investigated that OTA toxins induce the acute dopaminergic neuronal apoptosis and depletion of dopamine level and its metabolites in striatum, hippocampus, and cerebellum in the duress of oxidative damage to DNA in male mice [104]. When OTA is subcutaneously administered in rodents with the help of alzet minipump, dopamine turnover is significantly decreases due to the generation of oxidative stress [109]. Previous data suggest that exposure to OTA may induce the early onset of Parkinson's disease and other neurodegenerative disorders [104]. All brain regions exhibit the variable sensitivity to neurotoxic effect of OTA, such as hippocampus, a principal site vulnerable to neurodegeneration in Alzheimer' disease as compared to cerebellum [110]. The level of OTA elevates relatively in hippocampus after the exposure and produces pronounced neurotoxicity. This toxin holds the inhibitory potential to protein synthesis through the competitive inhibition of phenylalanine in aminoacylation reaction of phenylalanine-tRNA, induces the exhaustion of enzymes involved in DNA metabolism, and impairs the synthesis of catecholamines and dopamine [111]. This toxin provokes the deleterious impacts on neurogenic zone in hippocampus to retard neurogenesis in response to injury, irradiation, drugs, or hormones [112]. The cognitive functions are also impaired upon

the sub-chronic exposure to OTA through declined 2A and 2B subunits of NMDA receptors in hippocampus [113]. It was explored that OTA exposure to mouse hippocampal HT22 and human neuroblastoma SH-SY5Y cells decrease the neuronal cell viability through induction of oxidative stress and elevate the phosphorylation of p53 and caspases stimulation [114]. This mycotoxin exposure on HT22 cell lines upregulates the mRNA expression of proteins involved in pathogenesis of neurodegenerative disorders, mitochondrial dysfunction, and neuronal apoptosis [115]. It was also examined that OTA stimulates the expression of caspases-3 and caspases-9. Therefore, caspases inhibitors are suitable choice to inhibit the effect of OTA apoptosis–related neurotoxicity in human neuroblastoma cell lines and rat cortical neuronal cells. It is reported that OTA contributed to pathology of neurodegenerative disorders like Parkinson' disease and Alzheimer's disease due to modulation of apoptosis signaling pathways [116]. Neurotoxic effect of OTA is concomitant to the induction of pro-inflammatory cytokines and neuroinflammation. OTA affects the glial cell reactivity, represses the glial cell neuroprotective potential, and alters the cytoskeletal integrity of astrocytes in serum-free aggregating rat brain cell culture. Furthermore, it was reported that OTA restarted neurite outgrowth, neuronal count, and stimulated activator protein-1 and NF-κB in mid brain cell cultures of embryonic rat. Neurotoxic potential of OTA is inhibited by an agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ) through the modulation of AP-1 and NF-κB signaling pathways [117].

Toxicokinetics of Neurotoxic Mycotoxins

Transformation of mycotoxins to innocuous metabolites through the catalytic action of enzymes/microbes is known as biotransformation of mycotoxins [118]. These toxic metabolites undergo biocatalytic pathways under the action of microorganism, suggesting a valid and cost-effective strategy to destroy mycotoxins [119, 120]. In previous literature, it has been reported that OTA remains unchanged in body and excreted out [121]; however, it is reported that these toxins experience phase 1 and phase II biotransformation pathways and convert to benign metabolites by proteolytic enzymes and bacterial microflora in GIT [122, 123]. Under the alkaline ambience, OTA is converted to open-ring lactone that is a highly toxic metabolite [124]. Under microbial oxidation reaction, OTA is converted to less toxic metabolites like 4 and 10 hydroxy ochratoxin. Phase 1 reactions are experienced by mycotoxins usually by the catalytic action of CYP450 enzyme family [125]. The dechlorination of OTA converts this metabolite to ochratoxin B which is slightly genotoxic [126]. However, in phase II reactions, OTA is conjugated with hexoses, pentoses, sulfates, glucoronides, and glutathiones and converted to less toxic metabolites in urine, blood, and tissues of human and animals [127]. Although, sex difference influences the carcinogenic potential of OTA [128]. The excretion of OTA through glomerular filtration is imperceptible due to robust tie up with albumin and is slowly excreted through tubular secretion [129]. In human, OTA is up taken from blood to tissues

through OTA 1 transporters in kidney and OTA 3 transporters in liver and brain [130]. This toxin is transported through MRP2 transporters from tubules to urine [131]. Regrettably, in vivo studies have reported the reabsorption of OTA at any part of nephron, depending on pH through active transport or passive diffusion mechanisms by the action of microflora [132, 133]. OTA undergoes the enterohepatic circulation and biliary excretion through MRP2 and BCRP receptors [134, 135]. The highest level of OTA was excreted through breast milk after delivery in human [136–138]. T2 toxin is readily absorbed after ingestion and widely distributed in the body with or without accumulation in specific organ and reached highest peak concentration after 30 min [139]. This toxin is swiftly metabolized and excreted without accumulation in animal models like pig, cattle, and dog [140–142]. Intravenous administration of radiolabeled T-2 toxins to pig revealed 15–24% concentration in GIT and 4.7–5.2% in liver and skeletal muscles [142]. FB1 is transformed by the successive catalytic action of carboxylesterase and aminotransferases and is converted into hydrolyzed FB1 with removal of tricarballylic acid moieties after deesterification [143, 144]. Hydrolyzed FB1 is converted to *N*-acetyl HFB1 and 2-oxo-12,16-dimethyl-3,5,10,14,15-icosanepentol hemiketal. fumD and fumI gene clusters were identified by these degrading enzymes [51]. Total deesterification of fumonisin B1 was catalyzed out by fumD 3.34 g/mL in 15 min. Deamination of fumonisin B1 was catalyzed by fumI (8.9 g/mL) in the presence of pyruvate and pyridoxal phosphate [145–147]. Trichothecenes encounter the phases of oxygenation, isomerization, esterification, and cyclization to become bioactive [148]. Macrocyclic trichothecenes are not degraded during food processing and digestion through stomach. 12, 13 epoxytrichothecenes describe the toxicity potential of trichothecenes; while, epimerization, oxidation, acetylation, and deacetylation may decreased the toxicity [149]. However, the principal enzymes responsible for deactivation of trichothecenes are not still identified [150]. Despite that acetylase, deacetylase, or de-epoxidase have significant deactivation role against trichothecenes [151].

Preventive Measures and Treatment Modalities

The best approach to minimize the neurodegenerative effects of mycotoxins is to lemmatize the further exposure as ongoing exposure thwart the detoxification efforts [152]. It is reported that conventional methods to remove such toxins, like ozone and ultraviolet ray, from water damaged surfaces and buildings are expensive and ineffective [153]. Although, boron and ammonium chloride treatments are successful to destroy these mycotoxins. Spores and mycotoxins due to their submicron size and fragmentations inhaled through protective mask induced illness [154]. Exposure to molds and mycotoxins perpetuates the oxidative stress situation which is the ground of neurodegenerative disorders. In case of oxidative stress, the level of GSH is significantly decreased; therefore, GSH and its precursors are reasonable choice to treat mycotoxin-induced neurotoxicity [155]. GSH in reduced state assist the

numerous enzymes systems to detoxify the fat-soluble toxic compounds and act as antioxidant agent [156]. Neurological disorders are associated with subsided level of GSH in brain tissues and treated with GSH precursor *N*-acetyl cysteine [157]. The clinician's examination and genomic testing have revealed that the level of GSH was significantly decreased and associated with global mitochondrial damage in patients exposed to mycotoxins [158]. GSH in reduced state can be administered through various routes but in nebulized state is thought to be the first line of defense in case of oxidative stress [158]. Intranasal administration of GSH significantly mitigates the neurocognitive symptoms in patients exposed to mycotoxins [159]. The toxicity of mycotoxins can be restrained through the administration of sequestering agents; these agents have potentiality to bind with toxins and inhibit their enterohepatic circulation with limited absorption of themselves through GIT [159]. Cholestyramine, chlorella, and activated carbon are the typical sequestering agents to treat OTA and *Fusarium* mycotoxins toxicity [160]. Although, due to food interactions, these agents must be administered with caution along with food. Charcoal and silica are also effective to wipe out the cytokines and TNF-α [161]. The mycotoxins evocate the oxidative stress resulting in DNA fragmentation and lipid peroxidation [162], effectively rehabilitated by the consumption of melatonin, licorice extract, whey proteins, Korean ginseng, coenzyme Q10, vitamin A, C, and E, L-buthionine-(*S*,*R*)-sulfoximine, resveratrol, and curcumin [163–166]. Mycotoxin neurotoxicity is recovered by the administration of bacterial probiotics: like *Lactobacillus rhamnosus* GG, *Lactobacillus casei, Brevibacillus laterosporus,* and eubacterium BSSH797 [167, 168]. The ingestion of apicaceous and cruciferous vegetables containing sulforaphanes is also effective through the modulation of oxidative stress [169]. Broccoli sprout tea, lycopene, and natural phenol in apple leaves "phloretin" have neuroprotective pharmacological activities [170]. Weight management, steam bath, and sweat induction strategies are helpful to reduce the detrimental effects of mycotoxins through excretion via sweating [171].

Conclusion

This chapter overviewed the mechanistic pathways behind the neurotoxicity prompted by T-2 toxin, macrocyclic trichothecenes, FB1, and OTA in animal models and neuronal cell lines. T-2 toxin induces the oxidative stress through the activation of JNK/p38 MAPKs resulting in neuronal apoptosis in fetal brain. T-2 toxin encourages the ribotoxin stress via its binding affinity to the peptidyl transferase and stimulates the caspases-2 in fetal brain. Macrocyclic trichothecenes inhibit the protein synthesis by holding together with 18 s rRNA bigger ribosomal subunit and evocated neuronal apoptosis. Moreover, macrocyclic trichothecenes elevate the expression of mRNA of pro-inflammatory cytokines, proapoptotic genes, and stimulated caspases-3, MAPK, and JNK pathways through depletion of glutathione in PC12 neuronal cell culture system. FB1 induces the lipid peroxidation and disrupts the lipid metabolism and ceramide synthesis. FB1 instigates the neurodegeneration

through the activation of pro-inflammatory cytokines, DNA fragmentation, disruption of protein synthesis, and disturbing sphingolipid metabolism in rat C6 glioma cells and in human glioblastoma cells through modulation of cellular protective genes. OTA evocates the neuronal toxicity through the modulation of bioenergetics, DNA fragmentation, mitochondrial impairment, and inhibition of protein synthesis pathways. OTA induces the depletion of dopamine and its metabolites and dopaminergic neuronal loss during oxidative stress in six brain regions. It urges the cognitive disabilities and depression through modulation of hippocampal neurogenesis appears to be involved in the pathogenesis of Alzheimer's and Parkinson's disease through the modulatory action on neuronal apoptotic pathway. OTA toxin experiences the phase I and II biotransformation by the proteolytic enzymes and microbial flora, however, transformed to toxic metabolite in alkaline conditions. T2 toxin is readily absorbed and widely distributed in the body. FB1 is converted by the catalytic action of carboxylesterase, aminotransferases to hydrolyzed FB1. Macrocyclic trichothecenes toxicity is decreased by epimerization, oxidation, acetylation, and deacetylation. Therapeutic strategies include the use of sequestering agents, antioxidant support, systemic, nebulized and intranasal glutathione, probiotics, nutritional support, and the correction of persistent fungal infections. Sauna and weight management will be thoughtful to mitigate the adverse effects of neurotoxic mycotoxins.

Conflict of Interest Author declared no conflict of interest.

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Chapter 8
Polycarbonate Plastics and Neurological Disorders: From Exposure to Preventive Interventions

Zubair Anwar, Fakhsheena Anjum, and Sana Ghayas

Abstract Plastics are widely used substances that hold a crucial place in today's economy around the world. Despite their low cost and innumerable applications, they are a serious threat to biological systems and the environment. Therefore, industries are forced to look forward to alternatives that are safe for biological systems and environment friendly. Bisphenol A (BPA) is used to create clear and hard polycarbonate plastic (PCP) containers and bottles. It is also used to make epoxy resins, which are the protective lining inside the metal-based food and beverage cans. BPA can leach out from PCP, epoxy resins and other products that are in contact with foods and drinks, leading to various tissue and organ disorders, especially neurological illnesses. Hence, PCPs can pose greater health hazards when containers having food, water and so on are additionally contaminated by mycotoxins (MTs). Human protection from PCPs is essential, for which environmental and biological monitoring can be helpful. MTs are the secondary metabolites of fungi, which may enter into the food chain in the field, during storage, or at later stages. They are the most substantial and chronic dietary risk elements, which can induce acute to severe disease conditions in human and animals. These toxins are more hazardous than pesticide residues or food additives. Various interventional and preventive measures have to be taken to decrease PCP exposure in human beings. Governments and policymakers should set standards for moderate use of PCPs, and funding for pertinent research is also required.

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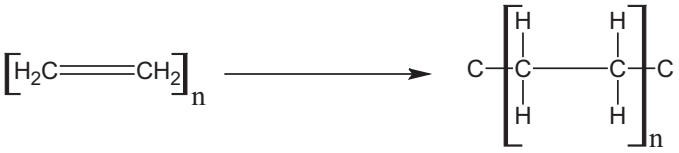
Keywords Polycarbonate plastics · Bisphenol A · Mycotoxins · Neurotoxins · Neurological disorders

Introduction

The word plastic is derived from the Greek word *plastikos*, meaning a material which can be molded into different and/or desirable shapes [1]. Plastics are generally long-chain, polymeric molecules, and several decades have passed since synthetic polymers took over natural materials [2]. The stability and durability of plastics have been considerably improved and they have become irreplaceable substances in human life. They are made up of inorganic and organic raw materials (i.e., carbon, silicon, hydrogen, nitrogen, oxygen, chloride, etc.) which are usually extracted from coal, oil, and natural gas [3]. Chemically, plastics are subdivided into two major types: polymers containing aliphatic (linear) carbon chain and heterochain polymers containing oxygen, nitrogen, sulfur and so on. Different types of plastics are commercially available and their uses are listed in Table 8.1. Plastics are generally prepared by condensation [4, 5], polymerization [6, 7], polyaddition [8, 9] and cross-linking [10, 11].

Plastics are made from different polymers and their chemical properties are based on the nature of polymer used [12]. Their molecular weights sometimes exceed one million, but their properties are based on the basic repeated units which form the polymer chains [13]. Most molecules contain carbon as a basic atom in the structure which has the ability to bond with four different atoms to form different molecules. Double bonds formed in the process of polymerization are highly reactive under favorable conditions (i.e., temperature, catalysts, etc.), polymerized in a chain reaction, which results in the formation of polymers, for example ethylene to polyethylene as shown in Eq. (8.1) [12, 13].



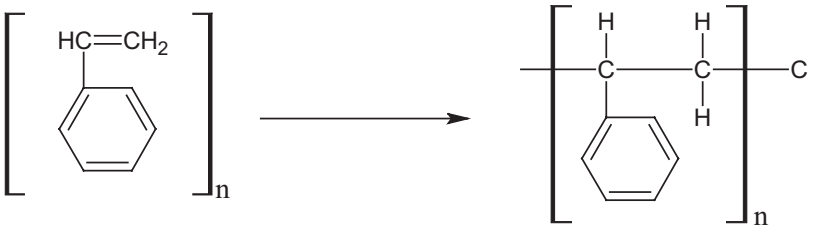
Ethylene Polyethylene (8.1)

Carbon has also the ability to form the ring structure, that is, benzene (C_6H_6) and if one hydrogen is replaced with ethylene, it results in the formation of styrene (Eq. 8.2). This styrene, on polymerization, leads to the formation of polystyrene (Eq. 8.3). Thus, the chemical properties of any plastic material depends on the backbone or monomer used for its preparation [12, 13].

Table 8.1 Types and uses of plastics

Types of plastics	Uses
Polyamide (PA)	Toothbrush bristles, tubing
Polycarbonate (PC)	Eyeglasses, traffic and street lights, car lights, lenses
Polyester (PES)	Fibers, textiles
Nylon	Small bearings, speedometer gears, football helmets, race horse shoes
Polyethylene (PE)	
• High-density polyethylene (HDPE)	Detergent bottles, milk jugs
• Low-density polyethylene (LDPE)	Floor tiles, shower curtains, clamshell packaging
• Polyethylene terephthalate (PET)	Carbonated drinks bottles, peanut butter jars, microwavable packaging
Polypropylene (PP)	Bottle caps, drinking straws, plastic pressure pipe systems
Polystyrene (PS)	Food containers, plastic tableware, disposable cups, plates, cutlery, packaging materials, laboratory ware
Polyurethanes (PU)	Cushioning foams, thermal insulation foams, tires, gaskets, life jackets
Polyvinyl chloride (PVC)	Plumbing pipes, electrical wire/cable insulation, shower curtains, automobile seat covers
Polyvinylidene chloride (PVDC)	Food packaging
Acrylonitrile butadiene styrene (ABS)	Computer monitors, printers, keyboards
Polyepoxide	Adhesive and potting agents
Polymethyl methacrylate (PMMA)	Contact lenses
Polytetrafluoroethylene (PTFE)	Heat resistant and low friction coatings, electronics, bearing, non-stick kitchen utensils, frying pans
Phenolics or phenol formaldehyde (PF)	Heat- and fire-resistant equipment
Melamine formaldehyde (MF)	Cups, plates, bowls
Urea formaldehyde (UF)	Chipboard, hardboard
Polyetheretherketone (PEEK)	Medical implants, aerospace moldings
Maleimide/bismaleimide	Composite materials
Polyetherimide (PEI)	Medical implants
Polyimide (PI)	Kapton tapes
Plastarch	Heat modified thermoplastics
Polylactic acid (PLA)	Heat modified thermoplastics
Furan	Use as binders for casting molds
Silicone	High-temperature cooking utensils
Polysulfone	Filtration media, water heater dip
Polydiketoenamine	Water bottles, syrup bottles

(8.2)



(8.3)

Plastics are widely used in the world; however, their use has some advantages and disadvantages. Some of the advantages and disadvantages of the plastics are listed in Table 8.2. Polycarbonates (PCs) (Fig. 8.1a) are a special group of carbonic acid polyesters and were first prepared in 1898 by Einhorn. He prepared PCs by reacting phosgene (Fig. 8.1b) with hydroquinone (Fig. 8.1c) [14–16].

PCs are thermoplastic resins that are divided according to their molecular structure, that is, aliphatic, alicyclic, aromatic–aliphatic PC. Among all these subdivisions of PCs, aromatic PCs, that is, bisphenol A (BPA), are the most important ones with the molecular weight ranging from 30,000 to 100,000 [14–16]. Generally, PCs are amorphous, odorless, non-toxic and transparent. Mechanically, they have high tensile strength, flexural strength and compression strength. PCs are sensitive to high temperature hydrolysis especially when they are long time exposed to water at 60 °C [14–16]. The applications of PCs are given in Table 8.3.

This chapter aims to highlight the advantages and disadvantages of PC plastics (PCPs) and the mechanisms involved in neurodegeneration in biological systems,

Table 8.2 Advantages and disadvantages of plastics

Advantages	Disadvantages
Light in weight and economical	Non-renewable resources
Easily moulded and excellent finishing	May cause cancer
Good strength and toughness	Deform under pressure
Good shock absorption capacity	Low heat resistance and poor ductility
Corrosion resistant and chemically inert	Toxic fumes evolve when burnt
Low coefficient of thermal expansion	Recycle process is very expensive
Good thermal and electrical insulating property	–
Possess good adhesiveness	–
Can be reused and restored	–
Unbreakable and odorless	–

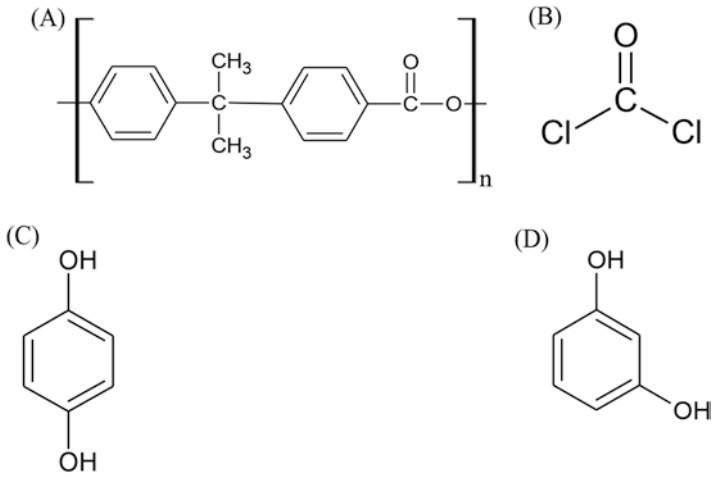


Fig. 8.1 Chemical structures of polycarbonate (**a**), phosgene (**b**), hydroquinone (**c**) and resorcinol (**d**)

Table 8.3 Applications of PCs

Industries	Applications
Electronic Industry	PCs capacitors, switches, connectors, digital products
Automotive Industry	Lightening systems, panel systems, decoration systems, automotive headlamp lenses
Electric Appliances Industry	Hair dryer, coffee maker, refrigerator
Mechanical Industry	Gears, worm gear, bushings, derivative gauges
Medical Industry	Dialysis housings, syringes

when exposed to PCPs. It also provides a brief literature survey of different experimental and epidemiological studies regarding PCPs and also suggests solutions on how to protect humans from the hazardous effects of PCPs [14–16].

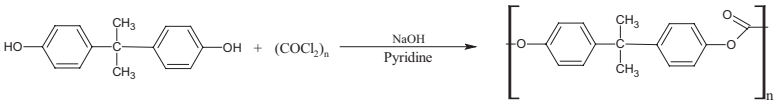
Preparation of Polycarbonates

There are two main methods by which PCs are prepared, which are discussed below.

Phosgene Process

In this method, phosgene (Fig. 8.1b) directly reacts with diphenol (Fig. 8.1c) in the presence of a base, that is, pyridine and NaOH (Eq. 8.4) at 25–35 °C [17, 18]. This reaction occurs in two steps.

General Reaction



(8.4)

First Step

$$\left(C_6H_4OH\right)_2 CMe_2 + 2NaOH \rightarrow Na_2\left(OC_6H_4\right)_2 CMe_2 + H_2O \tag{8.5}$$

In the first step, diphenol reacts with NaOH, which results in deprotonation of hydroxyl groups of diphenol (Eq. 8.5), with formation of diphenoxide.

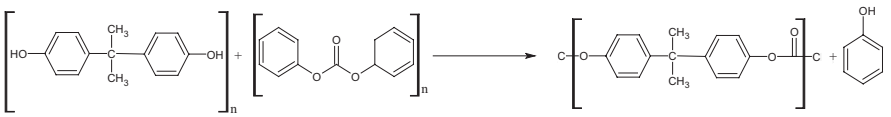
Second Step

$$Na_2\left(OC_6H_4\right)_2 CMe_2 + COCl_2 \rightarrow 1/n\left[OC\left(OC_6H_4\right)_2 CMe_2\right]_n + 2NaCl \tag{8.6}$$

In the second step, diphenoxide reacts with phosgene, leading to the formation of chloroformate, which subsequently reacts with another molecule of diphenoxide, resulting in the formation of PCs (Eq. 8.6). Another route of this reaction, through which PCs are prepared, is via polymerization reaction which occurs at phosgenation stage. The basic solution of diphenol is mixed with an organic chlorinated solvent containing a tertiary amine. By this route, phosgene is bubbled into the reaction mixture at 25 °C and at the end of the reaction, PCs appear in the organic phase. In this process, different alkaline compounds (i.e., NaOH, pyridine, amine) are used which act as scavengers for hydrogen halides. Phenols in small quantities are also used to stop the chain reaction to control the molecular weight.

Transesterification Process

Here, the reaction between diphenol and diphenyl carbonate (DPC) occurs, which leads to the formation of PC and phenol (Eq. 8.7) [19–22].



(8.7)

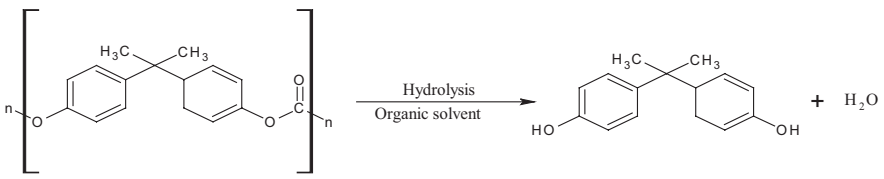
For high molecular weight PCs, this reaction is further carried out with the removal of phenol and the reaction is catalyzed by lithium hydride, zinc oxide or antimony oxide at a temperature of 150 °C [21, 23, 24]. This process has some advantages over phosgene process because of not utilizing phosgene and chlorinated solvents due to their toxicity. The only by-product is phenol, which can be recycled and recovered.

Types of Polycarbonates

PCs are divided into two types based on their structural composition, that is, aliphatic and aromatic PCs. If PCs contain alkyl chain in their structural compositions, they are termed as aliphatic PCs, whereas if alkyl chain is replaced by an aromatic ring, they are aromatic PCs [14–16]. Their general properties are given in Table 8.4.

Human Exposure to Polycarbonate Plastics

PC polymer and plastics are strong enough but when they come in contact with organic solvents (i.e., acetone, methylene chloride), their strength is altered. This alteration in the strength is due to the lowering of glass transition (T_g) which results in hydrolytic degradation of PCs [25]. This hydrolytic degradation leads to the formation of by-products, including BPA and water (Eq. 8.8).



PCs BPA

(8.8)

Table 8.4 General properties of types of PCs

Aliphatic PCs	Aromatic PCs
High elasticity	Stable at high (145–155 °C) and low temperatures (−100 °C)
Low heat resistance	High flame retardancy
Low tensile strength	High impact and weather resistance
High transparency	High insulation property
High gas permeability	High transparency and low water absorbability
High lubricity	Decomposed by alkaline solutions
Excellent adhesion properties	Hydrolyzed when processed at higher temperatures

Chemically, BPA is 2,2-bis(4-hydoxyphenyl) propane and synthetically prepared by the condensation of two molecules of phenol and acetone in acidic and alkaline medium [26, 27]. It is a white crystalline solid with melting and boiling points of 156 and 220 °C, respectively. Structurally, BPA consists of two phenolic rings which are bound together with a methyl bridge and is highly reactive due to the presence of hydroxyl groups [28]. BPA was synthetically prepared by Alexander P. Dianin (a Russian chemist) for the first time in 1891 by the condensation of phenol and acetone molecules in the presence of HCl and an ion exchange resin. The commercial use of BPA was proposed in the USA and Europe for the preparation of PCPs and epoxy in 1957 and 1958, respectively [29]. It possesses high water solubility and due to its physicochemical properties, it is a potential bio-accumulator [29, 30].

Exposure of Bisphenol A

BPA is widely used as a polymeric monomer in the preparation of PCs, epoxy resins, polysulfone, polyvinyl chloride (PVC) plastics and flame retardant (tetrabromobisphenol A) (TBPA) [26, 31]. Nowadays, BPA is widely used in the manufacturing of PCPs for the production of electronic equipment, reusable plastic bottles, bowls, dishes, cups, food containers and microwavable utensils [26, 32]. The wide use of PC and BPA in the manufacturing of a number of products has resulted in BPA being an environmental contaminant [33].

Environmental exposure of BPA results from atmospheric, aquatic and soil contamination which is due to its use in industry and thermal recycling paper [27, 34, 35]. In environment, BPA remains for a short time because it can be biodegraded by *Pseudomonas* sp. and photodecomposition [35, 36]. Food is exposed to BPA widely because most of the cans and plastic containers are made up of PCs and PVC with an inner epoxy resin coating [27]. Therefore, the food containers and cans are the main source of exposure of food to BPA for all age groups [37]. BPA exposure via food to human is worrisome because prolonged exposure with trace amounts cannot be detected [38]. In case of incomplete polymerization, BPA migrates from containers made by PCs and PVC into food material processed at high temperatures [39, 40].

Bisphenol A-Induced Neurodegeneration

BPA is known to act an exogenous endocrine disruptor that is released from the plastic products in food items [41, 42]. It has the ability to cross blood–brain barrier (BBB) which is evident from multiple neuropsychological dysfunctions, neurobehavioral and neurodegenerative disorders [43–45]. The neurodegenerative effect of BPA is still questionable, but studies carried out on stem cells–derived human cortical neurons (hCNs) as a cellular model have been used to investigate the adverse

neurotoxic effects of BPA. hCNs as model cells were treated with BPA (0–10 μM) for 2 weeks and afterwards, the impact of BPA on cell morphology, cell viability, and a neural marker (MAP_2) was evaluated. Intracellular calcium homeostasis, reactive oxygen species (ROS) and functions of organelles were also assessed. It has been found that BPA destroys neural morphology by inducing neuronal apoptosis with a decrease in MAP_2 expression at transcription and translation levels. When hCNs are exposed to BPA, intracellular calcium levels through NMDARs-nNOS-PSD-95 and also oxidative stress by the generation of ROS are increased, which is due to altering the antioxidant defense system in hCNs. BPA also enhances endoplasmic reticulum stress, leading to an increase in the concentration of cytochrome c, by diminishing the mitochondrial function. This results in cell apoptosis by Bcl-2 gene family and caspase-dependent signaling pathway that leads to the neurodegeneration disorders (Fig. 8.2) that is, Alzheimer's and Parkinson diseases [44].

Different studies have been carried out on human beings and animals reporting the exposure to BPA in gestational period, which affects the development of brain and its behavior [46–48]. BPA induces anxiety, high autistic behaviors, impaired memory and learning, and changes in social behavior [49]. In animal studies, it has been found that in anxiety and motor activities dimorphic sexual changes were observed. The behavioral studies (i.e., elevated plus maze and forced swim test) carried out on male and female animals indicate that female animals show less anxiety and depressive behavior. However, further studies indicate that BPA at lower concentration (500,000 ng/kg body weight) eliminates the gender difference in the test conducted previously [46].

Toxicokinetics of Bisphenol A

BPA, after oral administration, is highly absorbed in the biological system [50]. High concentrations of BPA were observed in the blood of primates as compared to that in rats [51]. However, the bioavailability achieved through the subcutaneous route was higher than that of the oral route [51, 52]. BPA, through oral route, is absorbed via gastrointestinal tract (GIT) and leads to the liver where it is metabolized through sulfation (10%) and glucuronidation (90%). This results in the formation of inactive conjugated sulfated and glucuronized BPA. The free forms of BPA were in the concentration of 2.8, 4.3 and 2.4 ng/mL for adolescents, children and adults, respectively [53, 54]. The conjugated forms of BPA were hydrophilic in nature and excreted out by bile and urine [50].

When BPA is excreted in bile to GIT, the separation occurs between unconjugated BPA and glucuronic acid, which results in the reabsorption of unconjugated BPA in the bloodstream and excreted out slowly through enterohepatic circulation [55, 56]. Different studies have been performed to estimate the hepatic first-pass effect [27, 50, 51]. The half-life of BPA is dependent on the presence of glucuronidase in different organs and this enzyme is responsible for deconjugation of BPA and makes it active [57]. The unconjugated form of BPA is lipophilic in nature and

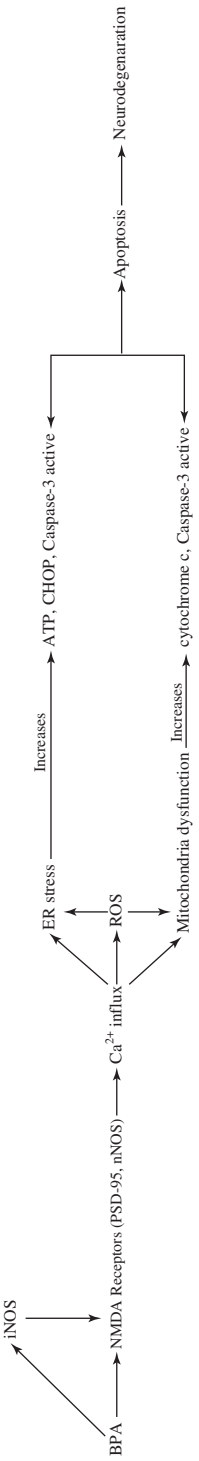


Fig. 8.2 Mechanism of BPA-induced neurodegeneration. BPA exposure leads to apoptosis followed by neurodegeneration in biological system

possesses high affinity towards adipose tissues that afterwards release it in other tissues [58, 59].

The concentration of BPA in human beings depends on its metabolism and it has fast metabolism in males as compared to that in females [60]. The higher concentration of BPA in males is due to the lack of androgen that is responsible for the inhibition of glucuronidase. The concentration of BPA is also dependent on the storage in internal organs and urinary excretion. Therefore, BPA is present in higher concentrations in female internal organs because of greater body fat and males have a high renal clearance rate [61, 62]. The distribution of BPA in humans has been evaluated and it is available in all human tissues. The concentration of BPA is found to be 1.12–12.28, 0.77–3.35 and 2.36 ng/g for adipose tissue, liver and brain, respectively [63]. BPA has also been found in amniotic fluid, umbilical cord, fetal blood and fetal liver tissue [64–67].

Mycotoxins

Mycotoxins (MTs) are secondary metabolites of filamentous fungi that may be formed in food commodities and crops that leads to the mycotoxicosis in human beings [68]. They are low-molecular-weight, natural products. MTs have a chemically and toxigenically heterogeneous congregation that is assembled together only because they may lead to morbidity and mortality in human and other vertebrates. Several MTs exhibit overlapping toxicities to plants, invertebrates and microorganisms [69]. The main fungal genera that are mycotoxigenically involved in the human food chain are Fusarium, Aspergillus, Penicillium and Alternaria [70]. It is quite challenging to define and classify MTs. This is mainly due to their varied biosynthetic origins and chemical structures, their innumerable biological effects, and their formation by an extensive number of diverse fungal species. MTs are often categorized by clinicians according to the organs they affect, thus classifying them as nephrotoxins, hepatotoxins, neurotoxins, immunotoxins, and so on. It should be taken into consideration that all toxic compounds synthesized by fungi are not MTs; the target and the concentration of metabolites should be kept in view. A vast literature on MTs with several monographs is available [69] and more than 300 MTs have been documented and recognized [71]. The utmost probable risk to humans and animals due to MTs is posed mainly by ergot alkaloids, aflatoxins, fumonisins, trichothecenes, zearalenone and ochratoxin A [68]. The adverse health outcomes of the mold-contaminated indoor environment, particularly MTs have been established by various studies [72].

Mycotoxicosis can be classified as acute or chronic diseases. Acute toxicity, in general, has a swift onset and toxic response, whereas chronic toxicity is because of the low-dose exposure over a longer time, thereby causing cancers and other irreversible consequences. It is essential to show a dose–response relationship between the MT and the disease to establish that the symptoms are related to mycotoxicosis. This correlation requires epidemiological studies for human inhabitants and

supportive evidence is achieved when the distinctive symptoms of suspected human mycotoxicosis are obtained reproducibly in animal models, by exposure to the alleged MT [69].

Severe toxic effects on human and animals have been reported due to the consumption of MT-contaminated foods, since these MTs can be mutagenic, teratogenic, carcinogenic and so on. These toxins are considered more hazardous than pesticide residues or food additives [73]. Overall, the scientific quality of the literature about MTs is varying. A high level of imprecision can be found in some of the reports due to the inclusion of information from former reviews of uncertain merit, hence presenting questionable hypotheses [69].

Mycotoxins and Polycarbonate Plastics

It is known that MTs may enter the food chain in the field, during storage, or at later stages. The harmful effects posed by MTs can be aggravated whenever handling, shipping and storage practices are more favorable (poor hygienic conditions, elevated temperature and moisture) to their growth [69]. The contaminants like pesticide residues, plant toxins and food additives are considered as chronic dietary risk elements but MTs have been ranked much more harmful [74]. The toxicity arising from both MTs and PCPs together can induce health hazards at a greater level; for example, the storage of food contaminated with MTs in containers made up of PCPs can be more hazardous than due to any one of them alone.

The dermal and inhalation may also be the other important route of exposure to MTs, apart from the usual route which is by ingestion of food or feed contaminants. Acute to severe disease conditions may exist due to MTs that may be due to exposure to high levels of MTs or from prolonged exposure to small quantities of these toxins [68]. Several in vitro studies have also revealed additive and synergistic toxic effects of MTs [75]. Furthermore, it is noticed that the stated studies aiming on the combined toxic effects of MTs are somewhat unmatched, owing to difference in experimental designs and conditions [76].

BPA is the most debated compound which is used to make clear and hard PCPs containers, and also reusable water and infant formula bottles [77]. BPA was apparent in dust, air particles and water, according to studies. Former studies have revealed that it can leach from PC plastics, epoxy resins and other products that are in contact with foods and drinks. Studies based on risk assessment proposed that canned food items may contribute to 10–40% of the daily BPA ingestion [78, 79]. It has been established that BPA has become a universal component in epoxy resins and PCP materials, used by the masses from dental sealants to plastic water bottles [80].

Role of Mycotoxins and Polycarbonate Plastics in Neurological Disorders

The pathophysiological and toxicological effects of MTs and PCPs, specifically containing BPA have been elucidated in different studies carried out on animal and tissue culture. There is substantial epidemiologic evidence about them and some of them are discussed below.

Evidences from Experimental and Epidemiological Studies for MT-Induced Neurological Disorders

It is well known that MT contamination has been threatening to humans and animals [73]. As mentioned earlier, MTs may enter the food chain at various stages and problems due to them can be aggravated whenever handling, shipping and storage practices are favorable to mold growth [69]. Although the main targets of MTs are diverse, a number of them have similar modes of actions and some have additive or synergistic effects.

The occurrence of MTs in foodstuff is intently related to the contamination by fungi from plants. Cereals (i.e., wheat, corn, rice, barley, etc.), oilseeds (i.e., cotton, sunflower, peanut, etc.), pulses, nuts and dried fruit, spices, coffee and cocoa are the foods that are directly exposed to MT contamination. The food products that are derived from animals, fed with contaminated feed, contain MTs as residues or toxic metabolites. MTs are usually heat resistant and normal cooking cannot destroy them totally. The impact of MTs on health depends on the ingested quantities through food, compound's toxicity, body weight of the individual and the presence of other MTs. The range of biological effects owes to diverse chemical structures of different MTs that can react with RNA, DNA, enzyme co-factors, functional proteins and membrane components [81]. It has been reported by the Food and Agriculture Organization (FAO) of the United Nations that about 25% of food crops globally are considerably infected by MTs [82]. Some guidelines have been set by regulatory authorities universally for MTs in food and feed; though the regulated MTs, supplies and maximum tolerable limits differ widely [83]. Therefore, highly sensitive and reliable determination techniques should be employed to evaluate food safety.

Cirillo et al. reported chemical contaminants as xenobiotics in food and feed that could have enduring toxic effects on individuals. One of them was BPA, which is recognized as an endocrine disruptor. It can alter receptors or protein expression in diverse important regions of brain. Different studies reported similar changes that indicate the effects of BPA on neurogenesis, neuroendocrine effects, morphology of certain brain regions, and so on [81]. Several other studies have also exhibited the adverse health outcomes of MTs [72, 84]. It has been stated several times in various studies that, overall, MT exposure is more probable due to frequent inadequate methods of food handling and storage, malnutrition and non-existence of

regulations for protection of exposed human populaces. Yet particular subgroups may be susceptible to MT exposure in the developed countries [69].

Some of the mold species, like *Trichoderma*, *Fusarium* and *Stachybotrys*, produce MTs which are absorbed from the airways, intestinal lining and skin, thereby affecting multiple organs, that is, lungs, musculoskeletal system and central and peripheral nervous systems. It has recently been found that exposure to mold and MTs can directly affect the nervous system or through immune cell activation, thus giving rise to neurodevelopmental disorders such as autism spectrum disorders [72]. Some earlier researches have also presented altered neurologic functioning in mold-exposed groups when compared with controls, that includes alterations in body balance, visual fields, blink-reflex latency, reaction time and color discrimination [85–88], and depression [89].

Recent studies, with patients and experimental models of multiple sclerosis (an autoimmune disease of the central nervous system), put forward that fungal infections are amongst the potential originators or aggravators of this disease [90]. Gliotoxin (GT) is the principal and the most effective MT, which is secreted by *Aspergillus fumigatus* sp. It can injure and kill astrocytes, microglial cells and oligodendrocytes. The harmful consequences can be due to a direct contact of the fungus with the central nervous system or by the toxin release from a non-neurological place. The effect of GT on experimental autoimmune encephalomyelitis development was studied in female C57BL/6 mice that was immunized with myelin oligodendrocyte glycoprotein and then injected intraperitoneally with 3 doses of GT (1 mg/kg b.w., each) on days 4, 7 and 10. GT intensified indications of the disease in a dose-dependent way and the results showed that GT given in a non-neuronal location increased neuro-inflammation in experimental autoimmune encephalomyelitis. Other MTs could also be harmful towards many neurological ailments by similar mechanisms [90].

A study in 2019 reported on MTs causing physiological, pathological and biochemical alterations in several species. Among animals and humans there is a wide range of harmful effects of MTs, which could be immune toxicity, carcinogenicity, teratogenicity, neurotoxicity, nephrotoxicity, hepatotoxicity, reproductive and developmental toxicity, and so on. It was further elucidated that MTs can exist in various essential agricultural and food commodities, largely reliant on moisture content of product, temperature, pH, relative air humidity, food matrix composition and the existence of mold spores. The industrial processing cannot reduce them, hence, food processing under standardized and well-controlled conditions is essential at every step of the food manufacturing and the storage chain should be controlled. For reduction of contamination to the least, preventative measures must be applied by all means [91].

The first review of contemporary knowledge concerning MTs illuminated that the MTs can affect enteric nervous system, that plays an important role not only in almost all regulatory processes within the GIT but also in adaptive and protective reactions, in response to pathological and toxic factors in food. Since MTs are present in food and drinking water, the GIT is the part of the body that first comes into contact with the toxic factors [92].

Recent studies have described the effects of MTs on the enteric nervous system. These studies have shown that enteric nervous system has a vital role to regulate most of the GI functions; it is involved in adaptive and protective processes against food pathogenesis and toxicity, but this can be compromised by the deleterious effects of MTs [93]. An investigation was made on male Wistar rats (aged 21 days) administered with low but different doses of deoxynivalenol (DV) for 42 days and the effects on the enteric nervous system were observed using immunohistochemistry and microscopic analysis [94]. DV in all concentrations decreased the area of the general population of not only myenteric neuronal cells but also nitrergic and cholinergic cell neurons. Additionally, the area of gliocytes in the myenteric plexus and the myenteric ganglia area were also decreased [94]. Apart from changes in the enteric nervous system, any other toxicity symptoms were not exhibited by animals [95].

T2 toxin is similar to DV, which belongs to the trichothecene family [96]. Even low doses of this toxin affect the GIT, resulting in histopathological changes of intestinal mucosal layer, disturbed intestinal barrier activity, inhibition of mucin production and effect on enzymatic activity of enteric cells [97–100]. T2 toxin exhibits neurotoxicity, leading to varied neurological symptoms like muscular weakness, ataxia, anorexia and pathological lesions in the brain with functional disturbances [101–103]. This is related with ROS and oxidative stress and inhibition of the mitochondrial membrane potential and apoptosis amplification [95, 104].

Another research has also provided evidence for T2 neurotoxicity. It is stated that human exposure to this MT is via dietary ingestion and in livestock due to contamination in feed [105]. This toxin can cross the blood–brain barrier (BBB) and store in the central nervous system hence leading to neurotoxicity. It induces oxidative stress and mitochondrial dysfunction in central nervous system, as demonstrated by in vitro and animal studies. The neurological symptoms (ataxia and muscular weakness) were obvious in mice or rats when exposed to T2 toxin [101, 106]. These toxins easily enter and harm the BBB, then store in brain tissue, causing neurotoxicity [107, 108]. Nakajima et al. established that T2 toxin exposure of mice, in developmental stages resulted in increased metallothionein expression in fetal astrocytes and hippocampal neural stem cells [109].

Oxidative stress induced by the generation of reactive oxygen species (ROS) is the primary mechanism of neurotoxicity for several prominent environmental pollutants and food contaminants. Reports on environmental pollutants and food contaminants, like T2 toxin, DV, citreoviridin (CV) and fumonisin B (FB), confirm oxidative stress as the primary mechanism of neurotoxicity [109–114]. Animal models and in vitro neuronal cell culture systems have revealed role of oxidative stress and mitochondrial dysfunction in neurotoxicity induced by T2 toxin [103, 115, 116]. Gaige et al. reported that in mouse primary cultured neurons, a marked increase of ROS was observed with T2 toxin treatment at 10 ng/mL for 20–30 min [117]. Agrawal et al. found that treatment of human neuroblastoma IMR-32 cells, with 40 ng/mL T2 toxin, brought in ROS production, as early as 15 min post-exposure and led to a marked increase in apoptosis [118].

The toxic effects of T2 toxin causing nervous disorders have been studied using female Wistar rats administered with only one dose of T2 toxin (2 mg/kg b.w.). Then, the rats were sacrificed at day 1, 3 and 7 for further studies. The damage to the brain and pituitary gland of the rats were observed by histopathological analysis and transmission electron microscope (TEM). At the molecular level, this was detected by real time-polymerase chain reaction, western blot, and immunohistochemical assays. T2 toxin concentration in the brain was assessed by liquid chromatograph-mass spectrometer/mass spectrometer (LC-MS/MS). Pathological lesions were seen in the brain, 3 days post-exposure, while pituitary lesions were seen at 7 days post-exposure. Only one rat was noticed with low concentrations of T2 toxin in the brain. It was hypothesized that brain damage was caused because the toxin directly crossed the BBB [102].

Another MT, zearalenone, is produced mainly by *Fusarium graminearum*, *F. culmorum*, *F. crookwellens* and *F. roseum* [119]. It is present in wheat, oat, barley and bread [120]. Zearalenone can cross BBB, thereby influencing CNS [121, 122]. Exposure to zearalenone leads to unusual synthesis of neuronal factors and enzymes in neurons, it induces neuronal apoptosis, surge oxidative stress, disturb nervous system development and perhaps lead to behavioral anomalies and alter the functions of glial cell [122–125]. The impact of zearalenone MT on intestinal nervous structure are found in only two studies, conducted on 8-week-old pigs of the large white Polish breed, using immunofluorescence method [126, 127]. The neurochemical coding of nerve fibers in the mucosal and muscular layers of the ileum were found affected when zearalenone was administered in very low doses of 10 μg/kg body weight/day [126] or 0.1 mg/kg of cho/day for 42 days [127].

The MT patulin is formed by different species of Penicillium, Paecilomyces, Aspergillus and Byssochlamys [128, 129]. It is found in fruits (particularly in apples) and vegetables [130, 131]. Patulin is neurotoxic and damages DNA in brain neuronal cells, produces mitochondrial and lysosomal malfunction, reduced ATP levels and amplified oxidative stress [132, 133]. This MT also disturbs calcium signaling in the enteric neurons and upsets neuronal morphology, thereby diminishing total neurite mass and neurite outgrowth [134].

Mailafia et al. in 2017 stated that humans are exposed to patulin mostly through infected food substances particularly, apples and apple-based food products. Patulin has been linked in the last decades to neurological, gastrointestinal and immunological adverse effects, mainly causing liver and kidney damages. Factors like temperature, humidity, chemical's availability, and so on affect the food fungal spoilage. Fungal growth and MT production are influenced by chemical and physical conditions. Above all, any unsuitable practices of manufacturing can be a probable contamination corridor, during any stage of processing [135]. The findings of many published studies regarding patulin are summarized in an article by Saleh and Goktepe [136]. Various animal models including hamsters, mice, chicken and monkeys have been employed to explore patulin toxicity. The exposure route was mainly through ingestion of infected food or infected water, for which gavaging technique was used. Patulin is heat stable and unlikely to be digested by animals; its environmental fate is also not well understood [136].

Studies have revealed that plants could protect themselves against xenobiotics, by altering the chemical structure of various toxicants, including MTs. It is difficult to manage the amounts of MTs, once they are formed, since they are very resistant to physical and chemical treatments and are stable under storage conditions. Hence, the best way to limit them is by restricting their formation in the first place [136]. The highly toxic fumonisin MTs are produced by *Fusarium proliferatum* and *F. verticillioides* [137]. The nervous system is most susceptible to their adverse effects. These MTs may increase neurodegenerative reactions and diseases like Alzheimer's disease, multiple sclerosis and Parkinson's disease. It damages neuronal developmental processes in the central nervous system [138, 139].

The most common MT, reported in some studies, is ochratoxin A (OTA) which is found in foods and water-damaged buildings that has been related to health problems [140] including severe neurologic problems in human beings [141, 142]. Neurotoxic effects of OTA were studied and the possible mechanism of toxicity along with the role of cytotoxic oxidative stress on neuronal cell line (Neuro-2a) was assessed in vitro. The results showed that ROS was elevated due to OTA toxicity in Neuro-2a cells; dose-dependent cell death in Neuro-2a cells was induced by this MT with 500 nM of EC_{50} value. Cell proliferation, signaling and apoptosis were induced as there had been disruption of the redox balance or oxidative stress due to generation of reactive oxygen species within the cell [143, 144].

A combined computational technique based on inverse and direct docking was applied in an investigation to detect alleged protein targets of different MTs and xenobiotic substances, which can contaminate food, giving rise to many harmful effects on human health. This procedure allowed in identifying various MTs like OTA, aflatoxins (AFT), DV and GT. Experiments comprising microscale thermophoresis and steady-state fluorescence confirmed the binding of various MTs to acetylcholinesterase and X-linked neuroligin 4, involved in synapse activity, neuronal plasticity and development. This combined "in silico" and "wet" methodology revealed the possibility of direct interaction between MTs and NLGN4X protein, which is vital for synaptic plasticity. The synaptic dysfunction results in neurodevelopmental disorders [145] and mutations in the NLGN4X gene can be associated with autistic spectrum disorders [146].

Determination of OTA, GT, zearalenone and sphingosine–sphinganine ratio was done by LC analysis, in sera and urine of children with autism and healthy controls. A probable role of OTA in autism's pathobiology was observed. In animal models, OTA was found to exert its neurotoxicity particularly in male animal models, in terms of autistic spectrum disorders. The in vitro assessment of OTA showed that it increased microRNA-132, which is decontrolled in patients of autism [147].

Amid xenobiotics, MTs are considered as global food contaminants producing toxicological effects, critically linked with the symptoms of autistic disorders, altering the immune and neurological systems, generating oxidative stress and induce injuries to the intestinal barrier [148, 149]. The presence of MTs in 60 samples of refrigerated pizza dough, in Spain, was investigated using extraction with methanol and determined by LC-MS. In the analyzed samples, the identified MTs were AFT B_1, B_2, G_1, zearalenone, enniatin A, A_1, enniatin B, B_1 and beauvericin. It was

observed that all the samples were contaminated with at least four MTs and all are from *Fusarium* species (zearalenone, enniatin A_1, enniatin B, enniatin B_1) [150].

Evidences from Experimental and Epidemiological Studies for PCP-Induced Neurological Disorders

As mentioned before, processed and packaged food can be considered as the main source of human exposure to MTs, plasticizers and BPA that can be very harmful to humans and may lead to various tissue and organ disorders. Different studies enlightening harmful effects connected with PCP materials are discussed below.

It is acknowledged that BPA can leach into food items from the internal coating of epoxy resin of canned foods and other end user goods (i.e., PCP tableware, food storage containers, water bottles, baby bottles, etc.). The degree of BPA leaching from PCP bottles into the liquid depends on the temperature of the liquid or bottle rather than the age of the container. One of the utmost concerns about BPA is its widespread human exposure. In 2003–2004, National Health and Nutrition Examination Survey (NHANES III) was conducted by the Centre for Disease Control and Prevention (CDCP). They found noticeable BPA levels (93%) in 2517 urine samples collected from people aged 6 years and above. The CDCP NHANES data are considered representative of exposures in the USA. Some animal studies also reported effects in fetuses and newborns exposed to BPA [151].

BPA has estrogen-like and anti-androgen effects and can enter the body through different routes like respiratory tract, digestive tract and skin. It is capable of damaging various tissues and organs, that is, immune system, neuroendocrine system and reproductive system. BPA can disrupt neuroendocrine system by disrupting the feedback control system including hypothalamic–pituitary–gonadal axis (HPG axis), hypothalamic-pituitary-adrenal axis (HPA axis or HTPA axis). At HPA axis, BPA competitively binds with corticoid receptors and controls receptor expression, resulting in sex-specific neurobehavioral disorders. At HPT axis, BPA can act on pituitary directly and disturb thyroid stimulating hormone (TSH) release, thus inducing neurodevelopment and metabolism disorders [152].

Animal models have suggested that BPA can also induce carcinogenesis and mutagenesis. Numerous studies have exhibited an association of BPA levels with the risk of certain neurodevelopmental diseases like autism spectrum disorder. BPA was also reported to activate insulin receptor mediated pathways in the brain tissues of mice that could enhance the risk of neurodegenerative ailments [152].

BPA exposure results in loss of sex differentiation in brain structures and behavior in both rats and monkeys [153]. Such animal studies can be linked to disease developments in humans, associated with a very low dose of BPA contact, leading to adverse health outcomes. A neurotoxicologist at North Carolina State University had been analyzing the nervous system of rats before they were born, after exposure to very small quantities of BPA. It was found by looking at messenger RNA levels

in the brain that BPA-exposed rats had signs of several estrogen receptors in the hypothalamus and amygdala, which are the structures that can impact reproduction and behavior. On the contrary, the neurological problems were studied in 2010, reporting no evidence of low-dose effects.

An extensive published literature has shown the adverse outcomes of BPA exposure at minute doses, based on administration through development to grown-up experimental animals [54]. Exposure to BPA has been found to induce anxiety, an increased risk of autistic behaviors, impaired memory and learning, and social behavior changes [154]. Studies on mice behavioral aspects have also discovered that female animals were presented with lower anxiety and reduced depressive behavior in elevated plus maze and forced swim tests. The impact on behavior was reliant on BPA dose and gender of animal. Some other experimentation demonstrated that maternal behavior was influenced by extended BPA exposure to a low dose, during pregnancy and lactation, suggesting affected neural circuits on maturity. European Food Safety Authority (EFSA) (2015) stated that existing studies were insufficient for drawing conclusions about BPA exposure and related neurobehavioral effects. The reasons might be study limitations, insufficient statistics, and inconsistent results from various studies [31, 154].

There are quite a lot of hypotheses that offer an elucidation for BPA effects on the nervous system. One is connected with a decline in total thyroxine (T4) in pregnant females and thyroid-stimulating hormone (TSH) in male neonates; another is linked to low-dose prenatal BPA exposure in pregnant rats, altering thyroid receptor expression in the fetal neocortex. They put forward that perinatal hypothyroxinemia may induce neurological deficits, induced by BPA exposure, during pregnancy [31].

Certain behaviors like anxiety were explained in a study that appeared due to a decline in the number of dopamine neurons [155], in addition to interference with thyroxine hydroxylase activity, by early exposure to BPA. As BPA may interfere with neuronal plasticity processes, the development of new memories may also be altered. It decreases synaptic density, increases the synaptic cleft length, decreases the active zone length, and reduces post-synaptic density in the hippocampus [156]. Long-term effects on brain function and behavior due to BPA exposure has been explained in research. This is by stimulation of insistent gender-specific epigenetic modifications like DNA methylation in the brain, which may also have transgenerational effects [157].

Several animal studies describe that perinatal or neonatal BPA exposure leads changes in brain sexual differentiation. BPA can cause violent behavior, anxiety, cognitive insufficiencies, and learning-memory deficiency. It can also impact the presentation of juvenile social behaviors in mice [158, 159]. Perinatal exposure to BPA increases anxiety like behavior and elevates dopamine levels in male, but not in female mice [160]. During lactation, BPA exposure in male rats is linked with hyperactivity and dopaminergic neuron degeneration. In rodents and nonhuman primates, BPA has adverse outcomes on the brain, even at fairly low levels [79]. Research studies on BPA have also been trailed by National Center for Toxicological Research, FDA. These studies are related to the fate of BPA in the body from different routes of exposure, safety evaluation of low doses of BPA and assessment of

certain new outcomes [58, 161–172]. In the above-mentioned studies, it has been found that after 8 h of oral ingestion of BPA, that was 100–1000 times more than people are exposed through food, very low and immeasurable amount of active BPA passed from the pregnant rodent to the fetus. BPA metabolism to inactive form is more rapid after oral ingestion than from other routes of administration (i.e., injections). It is much effectively metabolized and excreted by the primates including humans as compared to rodents. No effects of BPA were found at any low-dose range in the sub-chronic study [58, 161–172].

The surge in the neurobehavioral disorders has led to collection of evidence that BPA can disturb nervous system development. Many studies have reported that increased gestational urinary concentrations of BPA are interrelated with adverse behavioral effects in children [79]. A study in Japan has detected that more BPA can leach from PC stuff that has been scratched or is more than 4 years old or the used bottles that have been brushed or dish washed and sterilized. Thus, children may suffer from various ailments like adrenal stress, neurological disorders, gastrointestinal issues, and so on [173].

During gestation in human, BPA exposure was connected with hyperactivity and aggression in 2-year-old girls and with depression and anxiety in 3-year-old girls [174]. Still, certain studies have not been found any considerable links between infant neurobehavioral measures and gestational BPA exposure [175, 176]. It is stated that the behavioral effects of BPA exposure are different, depending on both the age of child and exposure time. Hence, BPA has proven to have damaging effects on neurological development, even other bisphenol analogues, which are used as substitutes for BPA, also suspect to have a wide range of biological activities [79].

The propagation of plastic production and dependence on them, principally for single-use or as disposable, is detrimental to our environment and ecosystem, with adverse outcomes on human health [177, 178], this also has been postulated and studied [177, 179]. Various studies may exhibit the existence of identified harmful bacteria and toxicants in produces or drinks as a final consequence. Significant amounts of plastic gathered in the natural surroundings and landfills require intense research to investigate the amounts and effects of plastic debris. Furthermore, it is important to explore how the plastic contaminants are conveyed to organisms in the natural environment, and also the level to which such chemicals could then be conveyed alongside food chains, from environmental plastics [54].

FAO (USA) indicated ~25% of food crops to be considerably infected by MTs globally [82]. It is established that the MTs may be formed in food commodities and crops, they along with components of PC plastic containers can pose more threat to human health especially the induction of neurological disorders [31, 68]. Furthermore, it was also notified that the plasticizers and BPA can leach from plastic packing [180].

Human Protection from Exposure of Polycarbonate Plastics

Human can be protected from PCP exposure via environmental and biological monitoring. At present, processed and packaged foodstuffs are among the foremost sources of human exposure to BPA and plasticizers. Exposure data from BPA biomonitoring is considered essential, for explaining the outcomes from animal studies and also for assessing health risks to humans [79]. Biomonitoring has revealed the presence of phthalates, BPA and other additives in plastics and their metabolites in humans. Exposures to such contaminants are through ingestion, inhalation and dermal contact [54]. Studies on biomonitoring have shown that both BPA and phthalates were found in more than 95% of urine samples globally. Various studies have concentrated on the ecotoxicology of BPA and phthalates in biota including rodents, mice and aquatic organisms [180].

A number of challenges in examining the association between plastic additives and adverse human effects are encountered. The exposure assessment is quite difficult due to the varying production patterns and the use of plastics and the additives they contain, along with the confidentiality of industrial specifications. Budding methodology, technology and statistical methods should aid to unravel the associations between such chemicals and health outcomes. Strategies for reduction or alternatives in the use of these chemicals in plastic manufacturing should be considered (e.g., use of citrates as a substitute of plasticizers) [181]. Globally, Governments are initiating policies for reducing the use of plastic in various sectors, and for improving disposal and recycling systems [178, 182].

PC containers are made of BPA and it is released over time into beverages or food stored in them as BPA polymerization leaves some monomers unbound [34, 183]. BPA is quickly leached after repeated washing of such containers and when the acidic or basic items are kept in them as they break down the polymer. Therefore, monomers from baby bottles, reusable water bottles and the inner linings of food cans, made from BPA, can leach into food, mostly at high temperatures [34, 183, 184]. There are the signs of occurrence of aminolysis of PCs by milk and ethanolysis of PCs by 50% ethanol, under pertinent test settings. The use of PCP (type 7) has been decreased recently to a greater extent due to proven health risks associated with BPA [185]. People should be aware of the chemical constituents of plastic products and their health outcomes [186].

In contrast to these studies, transport levels of BPA from PC bottles were analyzed in Korean food samples by high-performance liquid chromatography (HPLC) subjected to simulated usage by heating in a boiling water bath, with microwave, or filling them with boiling water. It was found that the level of BPA released from the bottles did not exceed the levels established under the European Union and Korea Food and Drug Administration (specific migration limits of 600 ppb). According to this data, the use of PC plastic bottles on daily basis in Korea is considered safe [187]. But recent studies have established that BPA absorption into the body can lead to the development of metabolic disorders, immune toxicity, interference of cellular pathway and neurotoxicity [188].

To avoid BPA exposure, its use in the manufacture of baby bottles has been put to an end by many countries, among which Canada is the first. The health organizations like FDA, WHO, the US department of health and human services and centers for disease control and prevention have also alarmed on the use of BPA [188]. At the present time, BPA is everywhere in our surroundings and humans come in contact with BPA continuously at different ages via packed foodstuff, drinking water, dermal exposure, and inhalation of household dusts [189]. Various guidelines can be followed to avoid the exposure to BPA and phthalates. They include avoidance of plastic use with numbers 3 (PVC) and 7 (PC) and prefer to use glass containers. However, if plastic use has to be opted, then use the ones that do not have BPA (i.e., plastic numbers 1, 2, 4 and 5). It is also recommended not to use plastic containers in microwave ovens and to keep hot liquids or food [190].

More studies, both in vivo and in vitro, are being conducted to further investigate side effects of BPA exposure on different body organs [191, 192]. Besides dietary ingestion, another substantial BPA source of exposure in humans is the use of thermal paper for supermarket and ATM receipts, that could well transmit BPA to the skin even while holding for as long as 5 s, it is generally extractable after 2 h, signifying skin perfusion so much that it could not be removed or washed off with ease [193]. It should be noted that EFSA fixed the standard tolerable daily dose of BPA as 0.05 mg/kg body weight and lately, the safe human limit to BPA exposure daily has been lowered to 4 μg/kg/day [31, 154].

Plastics constituents do not have noteworthy bio accumulatability, except when accidentally ingested and getting entrapped in the GIT. Biomonitoring studies have revealed the existence of a steady-state concentration of plastics' constituents in the human body [194]. This reflects the steadiness of continual exposure and metabolism and excretion of these chemicals. Confirmation of potential impairment has been considered enough by the FDA (USA) to state that "recent studies provide a reason for some concern about the potential effects of BPA" [195]. In reaction to such alarms, BPA also has been banned in the USA from usage in infant bottles and spill-proof cups for babies so as to protect a predominantly susceptible populace [196]. Recycling of plastics seems to be a great option after disposal as there can be partial retrieval of the material and energy used to create them. Yet all plastics cannot be recycled and it is challenging to yield recycled plastic of a similar quality. Biodegradable plastics are another possibility that should be thought-out but this can result in undesirable concerns for the environment [197].

Plastics have substantial benefits for the future, but it is obvious that the existing methodologies of their production, usage and disposal are not supportable and pose health concerns for wildlife and humans. The solutions can be achieved only by combined actions through proper use, disposal, recycling, material reduction, and so on. The governments and policymakers should set standards and goals, also by outlining suitable product labeling to notify change, and by funding the research and technical improvements [198].

Interventions to Prevent and Protect from Exposure of Polycarbonate Plastics

As mentioned earlier, BPA is in extensive use industrially as a monomer or additive to manufacture PCs, epoxy resins and other polymeric substances [199]. The PCs account for nearly 64% of the world's BPA demand, while epoxy resins account for 34%, these two are estimated to rise at average annual rates of almost 3% and 4%, respectively, over the next 5 years [200]. PCPs are desired for various technical applications due to their transparency, resistance and rigidity, and also to manufacture containers for foods and liquids [154]. However, the transmission of BPA from plastic containers to food has been described in many studies [201–203] which is intensified by heating, use of microwaves, material overuse and contact with alkaline or acidic substances, leading to BPA ingestion [204].

Attempts have been made to remove BPA from aqueous solutions through biological, advanced oxidation and membrane adsorption processes. The biological technique involves BPA biodegradation into removable, nontoxic components by applying biological agents (e.g., enzymes). Advanced oxidation methods use the oxidation mechanism by applying oxidizing agents for BPA radicalization into other composites. Membrane adsorption process can be achieved chemically by hydrogen bonding, or physically by hydrophobic interaction between BPA and membrane medium to remove BPA in aqueous medium [188].

An assessment of BPA exposure in adults was done by Lorber et al. (2015), where 204 samples of fresh, frozen and canned foods were collected in 2010 in two rounds. It was found in 73% of canned food samples but only 7% of non-canned foods had low concentrations of BPA [205]. Another study was performed to assess BPA distribution in humans, which determined that BPA is evident in all human tissues. The maximum free BPA concentrations were found in adipose tissue (1.12–12.28 ng/g), liver (0.77–3.35 ng/g), and brain (up to 2.36 ng/g). Besides, total BPA (1.1 ng/mL) and unconjugated BPA (0.4 ng/mL) in breast milk has also been found [63]. Some preventive measures have been pointed out by the National Institute of Environmental Health Sciences (NIEHS) and Mayo Clinic in order to reduce BPA exposure as it may leak from containers and can linings into food and liquids. Use of a HEPA-filtered vacuum is also advised as they can filter minute chemical particles, while other vacuums release such chemicals in the blown-out air [206].

Warning Signs of Bisphenol A Toxicity

Exposure to BPA toxicity from PCPs can be confirmed from urinalysis but apart from this, some warning signs that can be the indication of BPA toxicity:

Obesity

It is more of a function of hormonal or metabolic changes and many studies have established association of weight gain with BPA exposure [207, 208].

Early Puberty

BPA disturbs the hormonal balance and produces estrogen-like effects that can alter many hormonal pathways, hence causing early puberty in both animals and humans [209].

Hypertension

A study was conducted enrolling 60 individuals who had to drink the identical beverage from either the standard BPA lined or a glass container. Their blood pressure and BPA levels in their urine were measured after a couple of hours. The systolic blood pressure was found to be 5 mmHg higher and the BPA levels were more than 16 times higher in the urine of those who drank from the usual BPA-lined container. Thus, the use of such containers can raise blood pressure for some hours after ingesting food from them due to the possibility of BPA leaching [210].

Erectile Dysfunction

This was recognized in Chinese factory workers, who had high levels of BPA exposure at their work when compared with those who were not exposed to BPA in the same city. The exposed persons were found to be four times more probable for developing erectile dysfunction [211].

Cardiac Disease

BPA has been associated with cardiac diseases as per research. There was a threefold increased risk of cardiac disease linked to persons with maximum exposure to BPA, as revealed in a study. This may lead to the accumulation of plaques in cardiac arteries, cardiac arrhythmias, and even cardiac attacks [212].

Attention Deficit Hyperactivity Disorder

Several researchers have identified that the brain is affected by BPA and it may cause attention deficit hyperactivity disorders in both animals and humans. In a research enrolling 292 children, it was revealed that BPA levels in pregnant mothers and then later in children at 5 years of age are likely to influence the development of attention deficit hyperactivity [213].

Breast Cancer or Prostate Cancer

Cancer cells may arise in the breast or prostate if there is BPA exposure in elevated quantities in ingested foodstuff or water [214].

Treatment of Toxicity from Polycarbonate Plastics Containing Bisphenol A

It is crucial to plan and implement the handling, disposal and protection from the exposure of PCPs containing the harmful BPA. A variety of studies are published both against and in favor of use of BPA-containing PCPs. So additional research is needed and much effort is required to eliminate BPA from the environment securely, rather than its prohibition in the synthetic industries. An extensive exploration can be done to discover methodologies for the growth of probiotics that can provide health advantage to the host when administered in adequate quantities. Plausibly, probiotics can be helpful to securely eliminate accumulated BPA from live systems.

After ingestion, BPA is rapidly bound to glucuronic acid to form BPA glucuronide. As BPA is quickly soluble in water, it should be removed through urine by which its ability to interrelate with organic processes is reduced in the body. It was observed in a study on rats that when they were exposed to BPA with probiotics in their food, BPA concentrations in their blood were significantly dropped and they defecated 2.7 times steadfastly as compared to the rats which were administered non-supplemented food. Thus, intestinal consolidation was decreased by probiotics via enhancing the secretion of BPA, thereby decreasing the undesirable effects on the health of humans. Probiotic capsules are available that can be taken as supplements to stabilize the gut bacteria and help to remove poisonous chemicals from the body [215]. BPA in PCs is considered an endocrine disruptor interfering with the hormonal system in animals and humans. The alterations produced in serum parameters by BPA were investigated and they were significantly amended by quercetin, which owes to the antioxidant potential of quercetin [216].

A method has been developed which can help to remove more than 99% of BPA from water very quickly, effectively and economically worldwide. The system

employed catalysts called *tetra*-amido macrocyclic ligand (TAML) activators that imitate oxidizing enzymes. These TAML activators efficiently break down dangerous chemicals in the water when they combine with H_2O_2. A 99% reduction of BPA was observed after the addition of TAML and H_2O_2 to heavily contaminated water with BPA, within 30 min, at near neutral pH (i.e., pH used for the treatment of wastewater). Due to this treatment, BPA formed oligomers that precipitated out of the water after clumping. These oligomers were not found harmful themselves and the nature of bonding did not allow reversal of these oligomers to BPA. Moreover, these along with the decontaminated water were tested with Tiered Protocol for Endocrine Disruption assays. It has been noted that the TAML-treated BPA water had no estrogen activity or did not cause anomalies in developing zebrafish embryos and yeasts. The efficacy of TAML treatment on BPA-laden water was also tested at pH 11 and within 15 min more than 99.9% reduction in BPA was reported [217].

Preventive Measures

Preventive measures are recommended for the decrease of BPA exposure from PCPs. Some of them are given here.

Prevention for Infants

It is recommended to avoid infant bottles or containers with PC imprints and with recycling number "7" due to the presence of BPA. Additionally, BPA-free bottles that are recognized or licensed opaque bottles with recycling numbers "2" or "5" can be used. However, PC bottles should not be heated, used for boiling or washed in dishwashers; glass materials can be used and breastfeeding is suitable to reduce BPA exposure.

Prevention for Children and Adults

For the food and liquids, glass, paper, cloth, stainless steel, ceramic or clay containers can be used. Microwave in PCP containers and contact of PCPs with sour or oily foodstuff should be avoided. Clay or metal filters instead of synthetic filters for coffee should be used and the type of plastic used in food processors should also be checked [215].

Conclusion

This chapter outlines preparation, advantages and disadvantages of plastics made from different polymers including PC. BPA and MTs produce hazardous effects, specifically neurological disorders in humans and animals. Preparation of plastic materials containing PCs and for food storage should be avoided. Monitoring of BPA and MTs in the environment and biological system would be of great help to avoid hazardous outcomes. Governments, worldwide, should prompt setting and implementing standards and goals in order to decrease the use of PCPs.

Conflict of Interest Nothing to declare.

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Chapter 9
Bisphenol A and Neurological Disorders: From Exposure to Preventive Interventions

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Abstract Massive use of man-made chemicals has brought a lot of significant alterations in our environment as a whole. Among them, Bisphenol-A (BPA) is the most commonly used in the manufacturing of synthetic polycarbonates, plastics, thermal paper and epoxy resin. BPA is majorly found in the surroundings of human and particularly in drinking water. There is a lot of data and research studies which provide detailed data concerning the presence of BPA in water, food and indoor environment as well as in fluid and tissues of human body. The outcomes of BPA exposure on human behavior are relatively new issue and it has also become a special concern due to its potential effects on children. Although little data is available related to neurological disorders to BPA exposure, an association between BPA exposure with altered neurobehavior has been reported, including attention deficit, aggressive behavior, depression, hyperactivity and anxiety in children. It has been observed that BPA exposure during the critical window of development in children causes disruption of brain. Previous studies suggested that prenatal exposure of BPA may have negative impact on neurobehavioral functioning in children and it may be sex dependent. Therefore, it has become necessary to be watchful towards the potential adverse effects of pervasive exposure of low doses, although more studies are required in humans to rule out the correlation between exposure of BPA and its outcomes on humans. Meanwhile, it is prudent to inform and educate the women who are planning or undergoing pregnancy about the outcomes of BPA exposure and measures to avoid and reduce their exposure. The main objective of this chapter is to explore and summarize the neurological effects of BPA exposure, and from a public health perspective, preventive measures and policies have also been discussed.

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Introduction

Bisphenol-A (BPA) is one of the most extensively used man-made chemicals that are synthesized worldwide. Current epidemiological studies indicate that a grand total of eight billion pounds of BPA are produced annually [1]. BPA is used at industrial level for the manufacturing of epoxy resins and plastics that are pervasive in our daily life and environment [2]. The estrogenic activity of BPA has been confirmed by comparing it with structurally related synthetic diethylstilbestrol (DES) compound. DES is a more potent estrogen than BPA in a classical estrogenicity assay of vaginal cornification. BPA was used as a synthetic estrogen, therefore deserted in the favor of DES which was administered during pregnancy from late 1940s to 1971 for the prevention of prevent multiple pregnancy related problems including premature birth and miscarriage [3]. In the 1940s and 1950s, the first industrial use of BPA was identified in plastic manufacturing. BPA is commonly utilized in the manufacturing of beverages or food containers, such as baby bottles [4]. Being an important component of epoxy resins and polycarbonates, it is used for some dental materials such as dental sealants and for the lining of beverages and food containers as well as many other products. Other additional uses of BPA include coatings of CDs, DVDs, electronics and electrical equipment, sports safety kits, automobiles, carbonless papers and recycled papers often used in register receipts [5].

Regarding the prevalence of BPA in our surroundings, it is surprising that measurable levels have been detected in the majority of examined individuals. Recently, Center for Disease Control (CDC) has measured the delectable levels of BPA in urine samples (92.6%) of more than 2500 volunteers in cross-sectional study [6]. The adjusted mean level of BPA reported was 4.5 ng/mL in children of ages 6–11 years, 3.0 ng/mL in adolescents of 12–19 years of age and 2.5 ng/mL in adults. Based on some other researches, BPA has also been detected in the placenta of pregnant women, neonatal blood, human amniotic fluid, human breast milk and cord blood [7]. Recent studies measured the presence of BPA in urine but fewer have measured BPA in blood samples. According to these studies, internal quantities of unconjugated BPA were found to be approximately 1 ng/mL [8]. Ingestion is the main route of BPA exposure in humans and after ingestion, BPA is metabolized in a very short time and excreted from the body through urine [9].

Production and Uses of BPA

A Russian chemist, Alexander P. Dianin was the first scientist who synthesized BPA in 1891 in a condensation reaction of one acetone and two phenol molecules in the presence of ion-exchange resin and hydrogen chloride as catalyst. In 1930, the syn-

thesis of BPA was thoroughly analyzed [10]. All over the world, BPA is one of the most widely synthesized and used chemicals. In 2003, the manufacturing of BPA exceeded more than 2.7 million tons annually and now according to the literature, the figure has reached to 3.8 million tons [11]. BPA is most commonly utilized in the production of synthetic polymers including polycarbonates and epoxy resins [12]. Synthetic polymers of BPA have good mechanical properties, thermal stability and low adsorption of moisture. These polymers are used in the manufacturing of various items including bottles, dental products, water pipes, nipples, food containers, medical equipment, toys, CD/DVD discs and electronic devices [13]. BPA is also most widely employed as an antioxidant and stabilizer in the production of vinyl chloride [14] and it is also utilized in the manufacturing of thermal paper which is used in books, faxes and register receipts and it also used to produce brochures, food containers, mailing envelopes, newspapers, toilet paper and kitchen papers [15, 16]. Moreover, BPA is also used in the synthesis of polyacrylate lacquer coating of tins and polyester [11].

The major contributing sources of BPA contamination are either via sewage treatment plant or by direct discharge of industrial waste to the rivers. Lee et al. (2003) have reported that BPA is found abundantly in the rivers located in highly industrialized and urbanized areas where the concentration of BPA ranges from 0.01 to 44.65 μg/L. In drinking water, BPA has also been found at the concentration of 0.16 ± 0.03 μg/L which is similar to the median value detected in raw water and from particular locations where STP effluent samples have been collected. This is due to the dumping of wastewater into rivers from municipalities located nearby the city and from urban areas [17]. The presence of BPA in ground water is related to infiltration of leachates containing BPA in landfills [18].

Biotransformation

Other than human beings, some other living organisms also have the potential to degrade BPA. BPA may be biotransformed in plants, vertebrates, invertebrates and also biodegraded by microorganisms such as algae, bacteria and fungi.

Animals

Biotransformation of BPA in vertebrates occurs by oxidation and hydroxylation reactions and these reactions are catalyzed by microsomal monooxygenases in the presence of cytochrome P450 (CYP450) enzyme [19, 20]. In a study of orally administered BPA-^{14}C, the metabolic fate was determined by hydroxylated metabolites such as 2,2 bis(4-hydroxyphenyl) propanol and [21] isolated 3 hydroxy bisphenol A which are the most important metabolites of BPA biotransformation. Some scientists also revealed that BPA dimers and 4-isopropylhydroxyphenol are also

produced by cleavage of BPA. The results showed that in the presence of cytochrome CYP450, BPA metabolites have characterized showing stronger estrogenic activity as compared to that of BPA itself [22, 23]. BPA is biotransformed by microsomal enzymes CYP3A4, CYP3A5 and CYP2D6 in a series of reactions of ipso substitution to hydroxycoumaryl alcohol (HCA), ortho-hydroquinone (HQ) and 4-isopropylphenol (IPP).

Algae

It has been found that algae may destroy xenobiotics in dark period found heterotrophically but it has a lesser efficiency profile. Algae have found various applications in environmental cleanup as they can remove various poisonous substances from the environment, thus reclaiming polluted environments. They have the ability to synthesize their own food using carbon dioxide and can metabolize various chemical substances in addition to BPA [24]. BPA was degraded by various algae species at the concentration range of 10 to 80 M, particularly by *Chlorella fusca*. It has also been established that *C. fusca* has the ability to remove BPA at concentration of 40 M in just 7 days, not only autotrophically with 82% and also heterotrophically with 27% effectiveness [25].

BPA is also degraded by *C. vulgaris* with moderate effectiveness at the concentration of 20 mg/dm^3 within 7 days [26] and as a result of degradation, various new compounds are formed like hydroxyl Bisphenol and other potential derivatives having anti-estrogenic ability [27]. Surprisingly in biodegradation reaction, BPA lost its estrogenic ability and an intermediate product is formed known as 4-(1-hydroxy-2-methyl-prop-1-enyl) phenol. Another study conducted on *Monoraphidium braunii*, a green alga, has found that the alga has the ability to eradicate BPA at various concentrations of 2, 4 and 10 mg/dm^3 with a moderate efficiency profile of 39%, 48% and 35%, respectively [16, 28].

Fungi

Various species of fungi have also the ability to degrade BPA as shown by bacteria. The first one is *lignolytic* fungi obtained from soil and wood, among which *Trametes versicolor*, *Stereum hirsutum* and *Pleurotus ostreatus* can degrade BPA to a considerable degree at the range of 4.6 mg/dm^3 which is usually present in water [29, 30]. The possible reason of their effectiveness to significantly degrade BPA is that they can consume aromatic substances from natural sources like lignin and phenolics which are largely present in environment.

Cajthaml and colleagues have shown other lignolytic fungi that may cause BPA degradation. It was the keen observation of investigators that *I. lacteus* and *P. ostreatus* are considered as more effective BPA degraders [31]. They proposed that the

particular enzymes responsible for its degradation are lignolytic enzymes like lignin peroxidase, manganese-dependent peroxidase and laccase [30]. They also elucidated that BPA lost its estrogenic activity after the chemical reaction. Other fungi like *Trametes villosa* and *P. ostreatus* O-48 have the ability to degrade BPA within just 12 days up to 80% at a concentration of 0.4 mM.

According to another study which was conducted on 26 species of fungi that can cause the degradation of BPA, the investigators had found that there were 11 out of 26 species that have shown alteration to BPA up to 50%, remaining 4 out of 26 like *Fusarium sporotrichioides* NFRI-1012, *Fusarium moniliforme* 2–2, *Aspergillus terreus* MT-13 and *Emericella nidulans* MT-98 have shown BPA degradative products that are significantly effective [16, 32].

Another study has evaluated that *Aspergillus* sp. isolated from tannery effluents also biodegrades BPA at 20 mg/dm^3 having 77% efficacy within just 5 days [33]. BPA exhibited highest effective profile of degradation by *I. lacteus* which has the ability to degrade BPA at 50 mg/dm^3 within 12 h. It has also been noticed that *I. lacteus* uses laccases and manganese peroxidase for mineralization of BPA [34, 35]. Based on evidences from recent studies, the enzymes particularly laccase which are isolated from two Columbia forest white rot fungi, *Ganoderma stipitatum* and *Lentinus swartzii*, are capable of degrading BPA from 88.2 to 97.8% within 6 h [35]. It has also been noticed that these enzymes are responsible for the conversion of BPA into high-molecular weight oligomers, thereby reducing the estrogenic potential of BPA up to 90% [36].

Other fungal sources which can also biodegrade BPA at the range of 10 mg/dm^3 within 14 days include *Irpex lacteus* 617/93, *Phanerochaete magnoliae* CCBAS 134/I, *Pleurotus ostreatus* 3004 CCBAS 278, *T. versicolor* 167/93, *Pycnoporus cinnabarinus* CCBAS 595 and *Dichomitus squalens* CCBAS 750 [16, 37].

BPA Exposure and Human Diseases

Elevated levels of BPA in human adults have been associated with various ailments, medical conditions and health outcomes. An increased level of BPA exposure in humans is associated with several reported health complications that include diabetes which is related with the report that a low concentration of BPA inhibits adiponectin release from adipose tissue of humans [38] and alters liver enzymes and cardiovascular diseases (CVDs). In women, elevated levels of BPA may be associated with recurrent miscarriage [39] and is also correlated with an increased number of premature births [40]. DNA damage of sperms and decrease in semen quantity have also been found to be associated with elevated BPA levels in men [41, 42]. All of this shows a negative correlation between BPA levels and health outcomes in adults, but none of them can prove causality. Thereby, the first step is the identification of potential human health effects due to BPA exposure, which requires further confirmation. Additional data that assess association between BPA level in pregnant women, in newborn baby, in cord blood and medical complications in childhood

and later in life should be forthcoming from recently collected samples as well as current samples from human population [43].

Effects of BPA on Neurological System

As BPA has some effects on endocrine system which have recently been investigated [44–47], therefore, it was initially evaluated for its effect on sexual dysfunction, cancer of reproductive organs and malformation [48]. Epidemiological studies on population have linked metabolic disorders to BPA exposure, such as obesity, cardiovascular disease and diabetes [47, 49, 50]. The pervasiveness of neurodevelopmental disorders has been observed due to the production of toxic chemicals over the past few decades. It has been evidenced that accumulation of environmental toxic chemical, such as BPA, can cause neurodevelopmental disorders [48]. United States National Toxicology Program (NTP) concluded that "There is a main concern for effects on prostate gland in fetuses, infants, brain and behavior, and children at current human exposures to BPA". Thus, on the basis of these evidences, neurological systems are considered to be the most important target of BPA.

A number of BPA exposure studies on animals during gestational period reported its effects on brain growth and behaviors (Table 9.1). BPA exposure in prenatal and neonatal alters brain sexual differentiation [51, 52]. BPA exposure can persuade the cognitive deficits, anxiety, aggression and learning memory impairment [53–55]. BPA exposure has also been found to elevate the juvenile social behavior in mice. BPA exposure in prenatal rats increase anxiety-like behavior and increase dopamine level in males, but not in female mice [56]. Exposure to BPA in male rats during lactation is correlated with degeneration of dopaminergic neurons and hyperactivity [57, 58]. BPA exposure during breastfeeding and organogenesis upregulates dopamine receptor function, whereas at other gestational periods exposure of BPA does not elicit any effect, suggesting development of critical window of BPA toxicity [57]. In both nonhuman primates and rodents, BPA exposure has untoward effect on the brain at relatively low concentrations [58, 59].

In early life stage of humans, BPA exposure and its accumulation suggest that its low concentration can impact neural development (Table 9.2). It has been evidenced that the exposure of BPA during the gestation period is associated with the aggressive and hyperactive behavior in 2-year-old girls [60] and with depression and anxiety in 3-year-old girls [61]. Pereta et al. suggested that urinary BPA concentration during pregnancy was associated with elevated emotional reactivity and aggressive behavior in boys between 2 and 3 years of age [62]. Harley et al. reported that BPA concentration in prenatal urine was co-related with increase internalizing problems in boys, but not in girls [63]. Miodovnik et al. found that prenatal exposure of BPA was not correlated with childhood social impairment in 7–9-year-old children [64].

Surprisingly, BPA has been found to possess sex specific effect on behavior expressions correlated with activity, sociality and anxiety [56, 65]. Many neuroendocrine and behavioral pathways are sexually dimorphic. BPA exposure that dis-

Table 9.1 Effect of bisphenol-A on nervous system of experimental animals

Animal	Doses	Major effects	References
Mice	2 ng/g or 20 ng/g of body weight	Increase aggression in male rats	[80]
Mice	25 ng/kg/day	Number of tyrosine hydroxylase neurons decrease	[71]
Mice	25 ng/kg/day	Number of tyrosine hydroxylase neurons decrease	[53]
Mice	30 ng/g diet	Enhance morphine-induced hyperlocomotion and reward effect	[81]
Mice	30 ng/ g or 2 mg/g diet	Impairment of memory	[55]
Mice	2 and 200 μg/kg/ day	Increase anxiety like behaviors in female mice	[82]
Mice	2 μg//kg/day	Sex specific epigenetic disruption of brain	[71]
Mice	10 μg/kg/day	Increase anxiety in females	[83]
Mice	20 μg/kg/day	Perturbed migration and differentiation of neurons	[84]
Mice	20 μg/kg/day	Perturbation of neurotransmitter system	[23]
Mice	40 μg/kg/day	Change in the NO production	[85]
Mice	100 μg/kg/day	Anxiolytic like effects and induction of cognitive deficits in mice	[86]
Mice	2 mg/g diet	Enhanced hyperlocomotion and sensitized to methamphetamine	[87]
Mice	50 mg/kg feed weight	Impact on anxiety and social behavior	[67]
Rat	2 μg/kg/day	Increase hyperactivity and decrease attention	[88]
Rat	15 μg/kg/day	Increase immobility in the force swim test	[89]
Rat	20 μg/day	Hyperactivity	[90]
Rat	24 μg/kg/day	Increase depressive-like behavior	[91]
Rat	40 μg/kg/day	Increase cognitive deficits and anxiety	[92]
Rat	40 μg/kg/day	Alter brain monoaminergic function	[93]
Rat	50 μg/kg	Increase oxytocin immunoreactive cell number in para-ventricular nucleus of female rats	[75]
Rat	50 μg/kg/day	Elevate short term passive avoidance memory	[94]
Rat	100 μg/kg/day	Change in gender dependent memory acquisition	[95]
Rat	600 μg/pup/day	Increase spontaneous motor activity	[90]
Rat	1.5 mg/kg/day	Disruption of sexual differentiation in brain	[96]
Rat	40 mg/kg/day	Increase estrogen receptor's expression in the medial pre-optic nucleus	[97]
Monkey	50 μg/kg/day	Perturbation of the synaptogenic effect of estradiol	[58]

rupts hormone functions during critical period of prenatal development may perturb sex specific or hormone regulated behavior. Disruption in behavior may lead to impaired responsiveness and reduce social adaptation to environmental demand. BPA exposure may impact on sex of many child and externalizing behaviors.

The molecular mechanisms of BPA exposure on the nervous system mediating effects have now been clarified based on various studies. Disruption of maternal gonadal and thyroid hormones development may be due to the effect of BPA expo-

Table 9.2 Effect of bisphenol-A on nervous system on different age groups

Subject	Major effects	References
Infants of 5 weeks	No association with infant behavior	[68]
Girls age of 2 years	Increase aggression score and hyperactivity	[60]
Girls age of 3 years	Worse behavior	[61]
Infants age of 7 and 9 years	No association with social behavior	[64]
Boys age of 3–5 years	Association with increase emotional reactivity and aggressive behavior	[62]
Boys age of 7 years	Increase symptom of anxiety and depression	[63]
Infants age of 6–10 years	Increase behavior problems in boys but not in girls	[98]

sure. Chevrier et al. reported that the exposure of BPA during pregnancy was associated with reduced thyroid stimulating hormone (TSH) in males and decreased total thyroxin (T_4) in pregnant women [66]. Furthermore, prenatal BPA exposure in low doses in pregnant mice alters the expression of thyroid receptors in the fatal neocortex. BPA exposure in early ages of life has been shown to effect dopamine systems. In monkeys gestational BPA exposure reduces the number of midbrain dopamine neurons. Studies reported that rate limiting enzymes in dopamine synthesis and tyrosine hydroxylase is affected by exposure of BPA. Altered dopaminergic system due to BPA exposure may account for neurological disorders such as anxiety like behaviors [67].

Clinical studies suggested that BPA exposure during early life may affect the neural development in children (Table 9.3). During the gestational period, BPA exposure may be associated with aggression and hyperactivity among 2-year-old baby girls particularly [60]. In another study, BPA was also found to be associated with symptoms of depression and anxiety among 3-year-old baby girls. Notably, childhood exposure to BPA was found less important than gestational exposure. Gestational BPA exposure has more important role regarding the development of neural and behavioral defects [61].

Perera and colleagues have reported that maternal BPA exposure during the gestational period resulted in augmented emotional reactivity and aggressive behavior among boys of 3 or 5 years age [62]. In contrast to these, there are also few studies which exhibited that there is not a considerable relationship between maternal BPA exposure during gestational period and adverse behaviors among their offspring. When Miodovnik and his colleagues conducted a study to find the association between gestational BPA exposure and social behaviors in children, they resulted that there is no association between gestational BPA exposure and social impairment in children [64, 68]. This may have relevance for understanding the mechanisms of BPA induced neurodevelopmental toxicity [56, 65]. To clear controversies among these aforementioned studies, there is need to precisely monitor the time of exposure and level of urinary BPA. Such investigations may give some conclusive remarks on BPA induced health outcomes. It is well known that gonadal hormones

Table 9.3 Effect of bisphenol-A on nervous system conducted in USA and its different cities

Country/city	Sample size	Subjects	Detection technique	Observations	References
USA	249	2-year-old children	HPLC	Augmented hyperactivity and aggression scores	[60]
USA	244	3-year-old children	HPLC	BPA may induce worse behavior	[61]
California	292	5, 7 and 9 year-old-children	HPLC	BPA may promote depression and anxiety	[63]
New York	189	5-year-old children	HPLC	Augmented emotional reactivity and aggressive behavior	[62]
Southwestern Ohio	350	5 weeks infants	HPLC-MS	No effect on infant behavior	[68]
New York	404	5- and 7-year-old children	HPLC-MS	No relationship with social impairment	[64]
USA	153	6–19-year-old children	HPLC	Augmented behavior problems among boys but no such observations made in girls	[98]

have a great influence on sexual differentiation in the brain. Consequently, EC exposure causing alteration in gonadal hormone level may be a reason behind sex-specific changes in behaviors [69]. Galloway et al. investigated that the level of urinary BPA was correlated with serum concentrations of testosterone [70]. Remarkably, the latest studies reported that prenatal BPA exposure resulted in sex-specific disruption of epigenetic pathways in the brain [71].

It is evident from the literature that a rate-limiting enzyme involved in dopamine production, called tyrosine hydroxylase, is influenced by BPA exposure [72]. Hence, it may be concluded that alterations in dopaminergic system induced by BPA may be accountable for neurological deficits including anxiety [67, 73]. Moreover, BPA exposure during developmental stages may alter the functions or organization of oxytocin/vasopressin system [74, 75], resulting in impairment of behavioral responses governed by this pathway [74, 76]. Additionally, it is evident from the literature that prenatal BPA exposure has an impact on fetal neocortical development during the early stages of embryo development [77].

Longitudinal studies in humans to evaluate the cause–effect relationship between neurodevelopmental disorders and exposure of environmental chemicals are still insufficient. Therefore, it is need of the hour to conduct such studies for evaluating the childhood BPA exposure and its health outcomes and to make strategies in order to reduce the risk of neuro-endocrine disorders.

Prevention Strategy

Preventive measures in exposure to BPA is urgently required. This is based on the need of a political background to limit and, in fact, ban the manufacturing and utilization of these offending chemicals, and implementation of some remediation technologies. There should be adequate educational workshops conducted in hospitals and schools (especially in maternity, pediatric and endocrinology clinics) that will prove helpful in understanding ECs and especially the early life consequences of these pollutants. Clinical neuro-physicians and endocrinologists should be educated about BPA and its potential untoward effects on human beings. Exposure to BPA is most common among uneducated individuals and among those with a low income. Professional workers using chemicals, fungicides, pesticides and paints are at the highest risk of EDC exposure. In high-risk areas, individuals should be informed and preventive measures should be implemented to avoid high-risk exposure of these chemicals. Properly educated individuals can follow the safe and precautionary principles in order to avoid and reduce the exposure of these chemicals. The intervention of local governors and policy makers is essential in aspects beyond the scope of the individual. A large number of guidelines and recommendations toward preventive strategies and protection of individuals should be developed and implemented by authorities or policy makers (Table 9.4).

Conclusion

Although numerous studies of BPA effects on neurological functions have been published, but exact mechanisms are still unclear. BPA shows non-monotonic dose–response functions, and very different effects at higher levels than environmentally relevant doses [10]. Epidemiological studies have revealed that the general population's exposure to BPA may elevate the risk of metabolic disorders such as diabetes, obesity and coronary heart diseases. Furthermore, it is also unclear that BPA has such wide-ranging effects on neurological systems at low concentrations. Even BPA exposure at low doses during critical development windows may trigger major neurological perturbations [78, 79]. Duration of exposure and BPA concentration are key factors determining potential behavioral and developmental disorders. It is essential to understand the factors involved in the neuro-developmental toxicity of BPA exposure during pregnancy to prevent adverse neurological effects of these compounds. Due to significant toxicity of BPA exposure and leaching of BPA from epoxy resins and polycarbonates into water and food, several countries have banned bottles and packing products that are prepared by using BPA and replaced it with BPA analogues such as bisphenol S. Yet there are some precautionary measures that should be followed in order to avoid exposure to these toxic chemicals and their induced health outcomes.

Table 9.4 Recommendations for prevention of BPA exposure

Recommendations for individuals for prevention of BPA exposure
• Pregnant women should avoid exposure of BPA
• Children should be prevented from chemical insult
• Consumption of chemical contaminated food and water should be avoided
• Nonylphenols, petroleum products, plastics and industrial fluid should not be burned
• Plasticizer bleach into fluid when warm so should be avoided use of hot tea and coffee in plastic cups
• Should be avoided to served warm milk in plastic bottles
• For the consumption of warm drink and food use recommended glassware's
• Direct dermal contact to BPA should be avoided
• Individuals should be avoided to swim in contaminated water
• Warm pudding and similar food should be avoided to be served in plastic plates and cups
• Should be used glassware's rather than plastic
Recommendation for authority and policy makers for prevention BPA exposure
• Contamination of lakes, river and seas with chemical should be avoided
• Periodically drinking water should be checked in terms of organochlorine chemicals
• To detect and remove BPA from drinking water better water treatment technologies should be adopted
• Prohibition of burning of industrial chemicals, plastics and solvents should be regulated
• Epically at textile, plastic and paint manufacturing plants fire prevention should be provided
• Use and over production of plastic materials should be avoided
• Drinking water reservoir and pools should be avoided by over treated with chloride
• Environmental pollution of BPA should be avoided
• Recommendation technologies for EDCs should be developed

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Chapter 10
Volatile Organic Compounds and Neurological Disorders: From Exposure to Preventive Interventions

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Abstract A pollutant with the newly established toxic mode is categorized as an emerging environmental contaminant; many point and non-point sources introduce these contaminants in the environment. Volatile organic compounds (VOCs) are the compounds having a low boiling point, variable lipophilicity and volatility, and are being produced from anthropogenic activities and natural sources. With BTEX (Benzene, toluene, ethylbenzene, and xylene) compounds being most abundant (up to 60%), VOCs are used as a reference for the evaluation of VOC exposure and levels in the environment. VOCs may cause behavioral, neurological, dermatological, and respiratory symptoms in humans as evident from experimental and epidemiological data. Humans are exposed to VOCs through skin, GIT, and lungs. Due to the high lipophilicity of VOCs, they can cross biological membranes and the blood–brain barrier (BBB) and thus resulting in numerous neuropsychiatric disorders, comprising of diminished impulsive control, changes in the motor and cognitive functions, hallucinations, headache, dizziness, and dementia. The mechanism of neurotoxicity of single VOC has not been elucidated completely because VOCs are always present as a mixture, but the possible reason may be the oxidative stress and changes in the neurotransmitters and ion channels functions. Several epidemiological and experimental studies (in vivo and in vitro) have been conducted for assess-

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ment of neurotoxic mechanism, risk of acute and chronic exposure, and neurobehavioral changes. BTEX compounds are the most toxic environmental pollutants and cause several neuropsychiatric changes including dementia, headache, nausea, malaise, impairment in learning, and memory; toluene is also associated with leukoencephalopathy, fetal solvent syndrome, and sick building syndrome and targets white matter of the brain. Other VOCs having a higher potential of neurotoxicity include solvents containing chlorine, such as trichloroethylene (TCE), perchloroethylene (PERC) and dichloromethylene, formaldehyde, n-hexane and acetone. VOCs' occupational exposure level in workers is monitored through the measurement of biomarkers; a recent technique for assessment of environmental agents' exposure is the measurement of micro-RNAs in plasma/serum. Health risks from VOCs are inevitable due to their ubiquitous nature, and measures should be adopted especially in workplaces, urban and industrial areas to keep the level of toxic VOCs below the operational exposure limit (OELs).

Keywords Occupational exposure · Neurotoxicity · Neurobehavioral changes · Volatile organic compounds

Introduction

Emerging contaminants are defined as "any natural or synthetic chemical or microorganism which is not monitored commonly in the atmosphere, and potentially responsible to any familiar or hazardous health impact or/and human health effects by entering the environment" [1]. An important point to consider is that most of the emerging contaminants are not the new pollutants or those which are recently introduced in the environment, instead, the majority of the emerging contaminants are those which are already well-established pollutants but their toxic mode or effect is newly demonstrated. Thus, adding the word *emerging* with contaminant refers to its emerging concern in the environment, therefore sometimes referred to as dichloroethylene "contaminants of emerging concern" or "the chemicals of emerging concern" [2]. The categories of emerging contaminants are pharmaceuticals and personal care products (PPCPs), plasticizers, surfactants, flame retardants, and pesticides [3]. Several daily use products have been included in the list of emerging contaminants, such as by-products of drinking and swimming pool water disinfection, gasoline additives, nitrosamines, hormones, and some endocrine-disrupting compounds, drugs of abuse, organophosphate containing flame retardants, flavoring agents (acesulfame, sucralose, cyclamate, saccharin, aspartame), nanomaterials (nano-gold and nano-silver, fullerenes, carbon-based nanomaterials), perfluorinated compounds [perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and others], algal toxins, polar pesticides, and their transformation/degradation metabolites, siloxanes, benzotriazoles and perchlorate, and so on. This list is steadily growing by the addition of more compounds that are being reported in the environment and the number is expected to increase in the future [4].

Emerging contaminants enter the environment via the same sources as of other traditional pollutants such as wastewater, effluent disposals, emissions, and industrial processes [5]. The major source of many emerging contaminants is the wastewater effluent, as these are present in many household products, pharmaceuticals, fabric coatings, detergents, lotions, foam cushions, cosmetics, sunscreens, food packaging, beverages, and so on. Chemicals from these products are released into wastewater, and many of these are not completely removed in the treatment of wastewater, so they enter the supply of our drinking water and rivers. Other important sources of their entry into the environment are agriculture and surface run-off. Apart from these processes, contaminants can also enter the environment after transformation through the process of photolysis, microbial degradation, and hydrolysis, and thus there is a possibility of their reaction with the disinfectants present in wastewater treatment or drinking water resulting in the formation of disinfection by-products [6]. Contamination sources are majorly divided into two groups: point sources and non-point sources. The details of these sources are given below.

Point sources include contaminants released from a particular location and there are spatially distinct ways by which these contaminants are demarcated in the environment, for example, discharge from the sewage treatment plants, mineral extraction, and industrial activities.

Non-point sources are also called diffuse sources; they refer to the contaminants from diffuse, indistinct sources that are present over the large area. Examples include the runoff produced after the application of manure or bio-solids in soil and the excessive flow of rain in industrial or urban places. Overall, the diffuse sources are present in minor quantities, but to the process of the natural attenuation, these are more responsive as compared to point sources. It is difficult to link diffuse sources returning to their source of origin, called polluter. Thus, it is difficult to measure environmental effects and to control diffuse sources [5].

Volatile Organic Compounds

As characterized by the World Health Organization (WHO), volatile organic compounds (VOCs) are the substances having a boiling point lower than 250 °C when measured at 101.3 kPa standard atmospheric pressure [7]. These are the organic compounds that are easily evaporated at room temperature and also have variable volatility and lipophilicity [6]. In terrestrial environments, VOCs dissipate very fast. Several well-known VOCs are produced by industrial activities, but living organisms also produce many VOCs as a part of metabolic activities. VOCs enter the environment mainly by industrial activities and the evaporation or combustion process of the petroleum-based products. They are ubiquitous due to their use in a number of products like air fresheners, paint thinners, dry cleaning liquids, automotive products, plastics, and pharmaceuticals [8]. Volatile organic compounds include aliphatic and aromatic hydrocarbons, aldehydes, ketones, acids, alcohols, and ethers; having diverse functional groups (oxygen, sulfur, phosphorus, halogens, and

nitrogen, not including carbonates and carbon dioxide) [9]. However numerous compounds are categorized under VOCs but in the environment majorly occurring is benzene and few of its organic derivatives (o-, m-, and p-), such as toluene, ethylbenzene, and xylene, jointly called BTEX, they comprise about 60% of VOCs and present a threat to human health as environmental pollutants [7].

Sources of VOCs

Natural sources, such as forest fire and biogenic precursor's transformation mainly contribute to environmental VOCs, however, the anthropogenic activities are also contributing much to the production of toxic VOCs and their emission in the environment so that in the global atmosphere they account for about 25% [7]. Major contributors include natural gas and petroleum extraction, fossil fuels burning and petrochemical activities, mobile sources, such as automobiles, buses, trucks, motorcycles, and airplanes, followed by the industrial and chemical processes (oil derivatives, adhesives, lubricants, and paints manufacturing), commercial sources, mining, stove gas leakage, boilers and water heaters at homes, and pesticide use in agriculture [10]. Household products also contain many VOCs as their ingredients, such as aerosol sprays, paints, varnishes, paint strippers, waxes, disinfecting products, cosmetics, cleaning products, mouth repellents, degreasing products, automotive products, and air fresheners. Drinking water is a usual source of solvents exposure, as it may contain wastewater discharged from industries or household use or the by-products of the disinfection process like chloroform/trichloroethane ($CHCl_3$). A little amount of VOCs is also present in office use equipment like printers and co.

piers, correction fluids, carbonless copy paper, craft materials, and graphics, including adhesives and glues, photographic solutions, and permanent markers [11]. Toluene and perchloroethylene are being used to a great extent in the industrial processes and products. Toluene is present in gasoline sources, paint thinners, and paints while perchloroethylene is being used in degreasing of metals and dry cleaning processes [12]. Acetone is produced in large amounts in the manufacturing process of plastics, paper, paints, and pharmaceuticals, and it is used in the process of oil extraction as a solvent for fats and as a precipitant in starch and sugar purification process [13].

BTEX (Benzene, Toluene, Ethylbenzene, and Xylenes): Indicators of Toxic VOC Exposure

BTEX compounds constitute almost 60% of the VOCs in the urban area's environment, and these toxic pollutants are thus used as a reference for the evaluation of VOC exposure and level in the environment [7]. In the natural form, BTEX

compounds are found in diesel, crude oil, and gasoline, and are discharged in the atmosphere, either these fuels burn or not. Apart from this, BTEX compounds are widely used as precursors for the manufacturing of substances and as an additive too. For manufacturing of consumer products and synthetic materials, like nylon, plastics, paints, and insecticides, benzene is used; toluene as a solvent for coating of paint, oils, resins, and rubber; in plastics, pesticides, and paints ethyl-benzene is found; as solvent xylene is used in the rubber, printing, and industries of leather [14].

VOCs Toxicity

VOCs are inert and lipophilic compounds that are capable of crossing biological membranes, and their toxicity in the body depends on their biotransformation [7]. There are some instant symptoms like headache, fatigue, dizziness, respiratory tract infections, skin allergy, eye infections, and impairment of memory, which have been experienced by few people immediately following the exposure to some solvents. CNS activity depression is a common physiological outcome caused by high exposure of some VOCs. General anesthetic effects can be caused by VOCs, and as a most severe outcome unconscious, and in some cases, death may occur at the end. As the length of the carbon chain, halogen substitution, double bonds, and a number of functional groups increase, lipophilicity also increases; thus, the effects of VOCs on the central nervous system (CNS) also increase. Membrane and tissue irritation may also be caused by VOCs [11]. The International Agency for Research on Cancer (IARC) categorized a few VOCs as group 1 human carcinogens, like benzene, vinyl chloride, and 1,3-butadiene [7]. Epidemiological studies have reported that chronic exposure to high levels of VOCs may cause neurological, dermatological, and behavioral symptoms in workers and technicians. Cigarette smoke and daily use products at home can introduce benzene, formaldehyde, xylene, and toluene in the indoor environment. Learning inhibition and behavioral depression can be induced by gaseous formaldehyde in animals, as evident from some experimental studies [15].

Environmental Contamination and Exposure to VOCs

The US Environmental Protection Agency (EPA) has developed the National Emission Inventory for the determination of pollutant emission amounts in the atmosphere, and to make a comprehensive, detailed air emission estimate of environmental pollutants that are most hazardous in a specific territory [7]. Through the process of evaporation VOCs become a part of the environment, this happens when the products which contain VOCs are used and during the activities of production, storage, processing, and transportation. Inhalation, skin contact, and ingestion are the processes by which people get exposed to these solvents in the environment

[11]. The properties of VOCs including the absence of charge and small molecular size result in their rapid absorption across the gastrointestinal tract (GIT), skin, and lungs and also make the inhalation process a major exposure route [6]. Systemic absorption of the major portion of inhaled VOCs occurs in the deep regions of the lungs, that is, the alveoli; however, a little absorption also occurs in the upper portion of the respiratory tract. GIT is also a good site for the absorption of VOCs and within a few minutes of the oral dosing peek blood levels have been observed. The passive diffusion process results in the penetration of solvents across the skin barrier, the stratum corneum [11].

VOC concentration exceeds in the indoor environment as compared to outdoors, so the chances of exposure in people are more as they spend about 90% of their time indoors. Thus, exposure to VOCs in most people occurs through indoor environmental sources. Although most people get exposure to most of the VOCs below the levels set in health-based guidelines, a group of people experiences a high rate of exposure that exceeds guidelines. Thus, the environmental exposure of VOCs to individuals is a very crucial health concern. Currently, we do not have a complete understanding of VOCs. Concentration data of VOCs, especially that of exposure is limited, except for some compounds. There are multiple modes of VOC exposure data, low values to the extreme values, often a big segment of data is below the method detection limits (MDLs). There is significant interpersonal and spatial variability in field data and limited shreds of evidence also show high temporal variability. These characteristics of VOCs result in the complication of analysis and modeling which are aimed at assessment of risks, management of exposure, and policy actions. Apart from these statistical and analytical issues, the exposure of VOCs occurs typically as a mixture, and the components of a mixture may contribute jointly to the adverse effects. However single compounds are focused in most of the studies, guidelines, and the regulations, and thus cumulative risks and exposures occurring from mixtures are underestimated. In addition to this, an investigation about the VOCs mixture composition is still not complete, and the components of the mixture show varying effects [16]. The most significant potential of causing adverse health effects is of high exposure to VOCs. To analyze the exposure and concentration data lognormality assumptions are applied widely [17].

BTEX and Chlorinated Solvents

Not only air but water and soil have also been found to get polluted by BTEX compounds because they have a good dispersion capacity due to their physicochemical properties. When they are released in the environment, they can either be volatilized, adhere to soil particles, dissolve in the water, or are degraded biologically. Areas having intensive industrial activities are found to have a very high concentration of BTEX compounds; high levels are also reported in big cities due to traffic issues [16]. Toluene induced acute intoxication features were described in 1963 for the first time. Many neurological features are caused by acute intoxication depending

upon the level of exposure. Low-level exposure, that exceeding just 200 ppm, can result in headache, fatigue, slowed reflexes, and paresthesia. At the level of 600 ppm or above, confusion develops, while euphoria results when the level of exposure reaches to about 800 ppm. Toluene abusers expose them deliberately to the level of minimum 800 ppm, and sometimes higher, to get the desired euphoric effect. Many symptoms of toluene abuse resemble that of ethanol intoxication, as abusers use toluene to get the "quick drunk" effect [18]. The saturation of the CYP2E1 pathway for dichloromethane occurs in rats at the exposure level of 500 ppm or higher for a period of 6 h to 2 years. In a pharmacokinetic model based on the physiology of rat, the saturation of the CYP pathway was found at 200 ppm or higher concentration of trichloroethane (TCE) under the acute durations of exposure (less than 24 h). At a concentration of more than 500 ppm, the majority of the TCE effects were shown, thus, it was the prediction that either the parent compound or its metabolites (e.g., those from glutathione-S-transferase –mediated pathway) result in the neurological effects [19].

Volatile Organic Compounds and Neurological Disorders

VOCs inhalation in industrialized countries is a major health concern, as the volume of production and release in the environment is high in these areas [20]. VOCs can cause CNS changes, either reversible or irreversible. Changes in the motor or cognitive function including memory and attention deficit, gait ataxia, dysmetria, and tremor are found to be associated with VOC exposure [21]. It is evident from many pathological and clinical studies that VOCs after chronic abuse result in many neuropsychiatric problems, like a hallucination, dementia, distractibility, loss of controlling impulse, and also respiratory issues [22].

After entering the body, VOCs may cross the blood–brain barrier (BBB) and thus affects the CNS. However, it is still not clear that what will be the direct effect and toxicity of VOCs on neuronal function. Oxidative stress as a reason for neurotoxicity of few solvents has been suggested by some studies [22]. If there is excessive production of reactive oxygen species (ROS) and if they are not scavenged on time, there would be a possibility of accumulation of products of lipid peroxidation, damaged mitochondrial or nuclear DNA, and dysfunctional proteins [23]. Some volatile organic compounds are stored in the cerebral tissues due to their high lipophilicity [22]. The possible mechanism that can be involved in the neurotoxicity of a single VOC might be the impairment of intracellular calcium, oxidative damage, and changes in the metabolism of excitatory amino acids. The mechanism of a single volatile organic compound induced neurotoxicity is unclear because the VOCs present in the indoor environment is always in the mixture form, coming from various sources and may contribute jointly to the adverse effects [23].

Experimental and Epidemiological Studies Assessing VOCs-Induced Neurotoxicity

In Vitro Experimentation

The neurotoxicity mechanism of VOCs has been studied on many animal models and also on cellular levels using the in vitro preparations of cultured cells and Xenopus oocytes [23]. Complex dosimetry and absence of information regarding the mechanism of inhaled volatile organic compounds impede the understanding of chronic and acute effects of exposure to solvents. Bushnell et al. developed a model called Exposure Dose Response (EDR) for the prediction of acute exposure effects of VOCs on CNS using exposure data (the concentration and inhalation duration). The model was used for the quantification of inhibitory effects of VOCs on ion channels, using the pheochromocytoma cells. Solvents used were toluene, perchloroethylene (PERC), and trichloroethylene (TCE); all of them caused inhibition of current through the voltage-sensitive calcium channels. Toluene and PERC also caused inhibition of nicotinic acetylcholine receptors (nAChRs) in the Xenopus oocyte. Through this model, it is possible to relate the VOC induced in vitro acute effects on ion channels to the in vivo effects [20].

Due to the uncertainty of VOCs effects on humans like that of toluene and PERC, measuring the risk of VOC exposure to humans on exposure is also uncertain. Studies have shown ion channels such as nAChRs as toluene targets. Thus, Bale et al. conducted a study on Xenopus oocytes, using the technique of two-electrode voltage clamp for assessment of the difference of potential toxicity of PERC and toluene on the ligand-gated ion channels of human and rat. There was no difference in the inhibitory effect of toluene and PERC on nAChRs in both species (human vs. rat), but the receptors showed more sensitivity to PERC than toluene [12]. Workplaces are exposed to a number of neurotoxic VOCs. However, conducting studies for assessment of the cellular mechanism is very difficult due to the high volatility of solvents. Kanemitsu et al. conducted a study to expose slices of the brain to VOCs, and results showed a decrease in synaptic plasticity in dentate gyrus, caused by 1-bromocriptine [23].

Animal Studies

Animals models have been used for the quantitative prediction of the effects of VOCs in human beings [12]. Zhu and Minto conducted a study for exploring the neurotoxic effects of VOCs in the Kunming mice (control vs. exposed group). They exposed mice to the mixture of many main VOCs including formaldehyde. Tests performed to assess the neurobehavioral function were step-down test, spatial water maze, measurement of percutaneous activity, and step-through test. Results suggested that VOCs can damage the ability to learn and memorize in the Kunming mice [24].

Results from many epidemiological studies have suggested that the "sick building syndrome" or the "building related sickness" is caused by the presence of fungi indoors. Inamdar et al. conducted a study on *Drosophila melanogaster* for providing a reductionist approach about the toxicity associated with fungal VOCs. Some known fungal VOCs, like 1-octen-3-ol, 2,5-dimethylfuran, 3-, 2-octanone, and trans-2-octenal, were used in a low concentration. These compounds caused changes in the dopaminergic neurons and also locomotory defects in the experimental organism. Delay in the VOCs induced changes in dopaminergic neurons was observed after ingestion of vitamin E (antioxidant), which links toxicity of fungal VOCs with the generation of ROS [25].

Inamdar et al. conducted another study on *Drosophila melanogaster* for identification of the possible signaling mechanism involved in the dopamine related neurotoxicity induced by 1-octen-3-ol. There are many signaling pathways which are involved in the pathogenesis process of Parkinson's disease (PD) and cognitive dysfunction associated with it, two basic pathways that have been reported to take part in the survival and neuronal apoptosis process, that is, Akt and capase-3–dependent pathway and c-Jun N terminal kinases (JNK), were focused in the study. A heterozygous organism with the mutant alleles for over-expressed levels of abovementioned signaling pathways was exposed to the study solvent. Over-expression of these signaling pathways (JNK and Akt) improved the survival in flies with mutant alleles when compared with control; this depicts that these signaling pathways have a pro-survival role by protecting against the 1-octen-3-ol induced loss in the dopamine activity. The test solvent caused the activation of capase-3 signaling pathway resulting in apoptosis [26].

Metals aerosol is generated in the process of welding, which may affect the health of workers who inhale it, this welding fume be able to also result in the neurological dysfunction in welders akin to PD. The use of adhesives in the "weld-bonding" process in some industries increases the possibility of adverse effects. To investigate the neurotoxic effects associated with the weld-bonding process, Sriram et al. conducted a study on Sprague-Dawley rats. Whole body of rats was exposed to inhalation of an aerosol of weld bolding either with or without sparking (sparking has more VOCs and low metal). Results suggested that short-term exposure to the weld bonding aerosol can cause neurotoxicity due to differences in the levels of some neurotransmitters (like serotonin and dopamine) in the nerve cells of rats [27].

To assess the neurobehavioral changes and their possible mechanism by direct contact with VOCs, research was carried out in 2018 on the Kunming mice. The combination of VOCs containing benzene, xylene, toluene, and formaldehyde was exposed to mice at a low dose. Sub chronic exposure resulted in the damage of motor and physique functions and the impairment of memory and learning capacity of mice. The mechanism involved in neurotoxicity may be abnormal metabolism of the cholinergic enzyme system and neurotransmitters, oxidative damage, and NMDA receptor expression alteration [15]. Another study on Kunming mice was conducted by Wang et al. to assess the neurobehavioral symptoms of a mixture of VOCs (benzene, formaldehyde, toluene, and xylene) and carbon monoxide. The inhaled mixture impaired memory and learning in mice; a possible mechanism may be impairment of monoamine neurotransmitters [28].

Mosquitoes are known for having a neurotransmitter functions similar to that of humans at neural synapses, like acetylcholinesterase, oxidative enzymes, and esterases. Mosquitoes also have neurosensory sensitive olfactory cells at their antenna which are used for detection of organic compounds in the air while searching blood hosts. Thus, they are used for assessment of neurotoxic effects of environmental VOCs like that of acetone. Lash et al. carried out a study for evaluation of the suitability of using mosquitoes in conducting VOCs bioassay [29].

Human Studies

Due to the ubiquitous nature of VOCs in homes and workplaces, they pose a serious health concern to the public. They can enter the human system via inhalation route, through skin and GIT absorption, resulting in many ill health effects. Epidemiological studies have also suggested the negative effects of VOCs on human health [25]. A case report was presented that described peripheral neuropathy symptoms in the technicians of vehicle repair after inhalation of an aerosol formulated with acetone, toluene and hexane [30]. The literature describes that high-level exposure of VOCs to the workers in occupational settings (like shops of auto repair) can cause neurological dysfunction. Exposure to the general population can be low level or chronic while can be acute to the workers. It is difficult to estimate the changes in neurobehavioral function after infusion of VOCs in the common people, therefore the association of VOCs experimental exposure to the neurotoxic effect has not been elucidated yet. Subjective recall can cause biases in the determination of duration and levels of exposure to VOCs in the epidemiological studies [31].

Persistent changes in the function of CNS caused by previous events, such as that due to genetic factors and chemical exposure may stay dormant in showing clinical features until they get "unmasked" by a second natural or experimental process like a subsequent exposure to chemicals in older age. Exposure to chemicals that may share a common mechanism(s) of action to the disease of concern may unmask a latent neurodegenerative disorder. A case report of a 45-years-old male was presented, who developed the symptoms of the neurotic disease after unintentional exposure to VOCs at the workplace; he had no family history of motor neuron disease. Exposure to VOCs, like toluene, can cause an increase in oxidative stress and changes in motor function, resulting in the unmasking of latent amyotrophic lateral sclerosis (ALS) in susceptible people. The patient presented in the case report was exposed to the solvents (toluene and xylene) which can increase the risk of ALS type disorder [21].

Acute effects on health with solvents exposure are recognized in people at the occupational settings (e.g., nausea, lightheadedness, and headache), and unconscious, intoxication, and death in some cases have been reported with high exposure. Chronic effects of VOCs have been presented in studies too, such as concentration and cognitive deficits, sustained changes in the mood or memory, which sometimes can lead to the chronic solvent neurotoxicity (CSN) or chronic toxic encephalopa-

thy (CTE). CSN is more common in the spray painters of automotive shops or industrial workers. A study was conducted to assess the use of solvents at the workplace (the vehicle collision repairs factory). It was a cross-sectional study to assess the neurobehavioral symptoms in workers of factory vs. reference workers. An increased risk of psychosomatic, neurological, memory, concentration, and mood symptoms was observed in workers of a collision repair factory [32].

PCE has been known as a neurotoxic occupational or environmental contaminant. Widespread contamination of drinking water occurred between 1968 and 1983 in the Massachusetts region, Cape Cod, due to PCE. The contamination sources were the distribution pipes' inner surface that was coated with a vinyl liner. A retrospective, cohort study was conducted in 2016 by Aschengrau et al. for examining the health consequences of PCE exposure in early life stages. This study concluded the long-term neurotoxic effects of TCE exposure in early life; the association was more with bipolar disorder, illicit drugs use, and post-traumatic stress disorder [33].

BTEX compounds are used in many industries like paint, steel, electronics, oil, and petroleum and are classified as hazardous pollutants in the air. BTEX causes poisoning in the body by entering through the route of dermal absorption or inhalation, the main route being the respiratory absorption. These compounds get accumulated in the nervous system, fatty tissues, heat, and liver, resulting in adverse health outcomes. Mousavie et al. conducted a study on operational employees for assessment of neurobehavioral symptoms of the BTEX exposure among workers of oil refinery (exposure group vs. control group). The exposure group was having more positive neuropsychiatric symptoms as compared to the control and the frequency of symptoms was associated with the values of toluene and benzene measured at a particular location [34].

A well-known outdoor as well as an indoor pollutant is formaldehyde; thus, everybody is exposed to this from various sources, such as household products, cigarette smoke, exhaust gases, and other industrial and medical products. Formaldehyde has various ill effects on health and affects tissues like eyes, skin, gonads, respiratory tract, and GIT. Many studies have been conducted on the adverse health effects of formaldehyde, epidemiological studies have concluded that the workers and histology technicians having higher exposure to formaldehyde for a longer time period experience neurobehavioral and neurocognitive symptoms. Experimental model studies have also confirmed the neurotoxic effects of formaldehyde [35].

BTEX Compounds

BTEX compounds are derivatives from the organic material and gasoline combustion and are extensively used. In almost all the ecosystems, these compounds coexist in a mixture form. The composition of the mixture varies depending on the source, industry type, activities in a particular region, and also on the condition of

the environment [16]. When BTEX compounds enter into the body through skin or inhalation, they cause poisoning. The International Agency for Research on Cancer (IARC) classifies benzene in group 1 human carcinogen, while toluene, ethylbenzene, and xylene are neurotoxic agents and thus affect the CNS [34]. The direct effects of benzene exposure on behavioral changes are not known yet. Xylene being a neurotoxic can result in loss of memory when there is repeated exposure [15].

After inhalation of toluene in humans, it is found in the blood within 10 seconds. Moreover, it reaches to maximum blood levels after 1–3 h of GIT administration. In this context, its absorption through GIT is slow as compared to the respiratory tract [36]. Effects of BTEX can be either acute or chronic based upon exposure timings, exposure to BTEX in a higher concentration for a short time period results in throat irritation and dizziness. However, a low concentration exposure to solvents for a longer time may cause chronic effects like nausea and memory loss [34].

Toluene present in paints, cleaning solvents, and glues may result in sick building syndrome and is highly toxic to the nervous system [22]. Sick building syndrome is associated with symptoms like respiratory symptoms, eye irritation, headache, malaise, and GIT disturbances [15]. Toluene also affects the white matter in the brain and is also a solvent of abuse for a few people. Leukoencephalopathy is caused by intensive, long-term exposure in toluene abusers; symptoms include dementia, dysfunction of the corticospinal tract, cerebellar ataxia, cranial neuropathies, and brainstem signs. The most disabling feature is dementia, associated with a characteristic deficit pattern that consists of apathy, inattention, dysfunction of memory, preserved language, and visuospatial impairment, but before dementia, the most unobvious impairment in the neurobehavioral function can be detected. Neurobehavioral dysfunction has been seen after long-term toluene exposure, but it is not clear that what will be the threshold for the development of leukoencephalopathy. Teratogenic features have been shown in toluene abuse during pregnancy, such as fetal solvent syndrome, which has similarities with fetal alcohol syndrome [18].

Biotransformation of BTEX Compounds

BTEX are derivatives of benzene and are aromatic hydrocarbons (Fig. 10.1). Ethylbenzene and toluene are having an ethyl group and a methyl group respectively and are mono-substituted. While xylene has methyl groups and is di-substituted, the mixture of xylene comprises ortho, meta, and para compounds [37]. This structure and high volatility of BTEX facilitate them to enter the organisms through many routes, inhalation is most common, then skin and a lower percentage are absorbed through the oral route. Studies on toxicokinetics conducted in animals and human have shown that the high lipophilicity of these solvents lets them to be distributed in the vascular tissue that is rich in lipids, such as brain, adipose tissues, and bone marrow, and that they are excreted from the body rapidly [38].

The toxicity of BTEX is determined through their biotransformation in the body due to their reactive nature [9]. There are two phases of BTEX biotransformation,

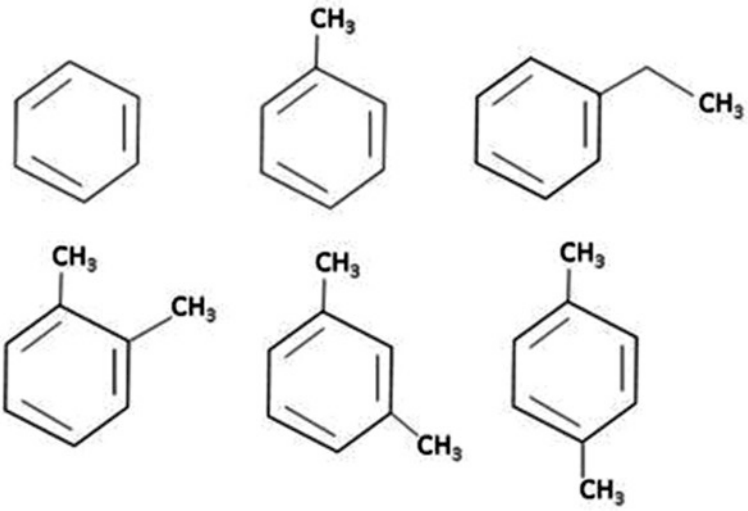

Fig. 10.1 Structural representation of BTEX. First row: Benzene, toluene and ethylbenzene. Second row: ortho-, meta- and para-xylene (Figure is adapted from [7] which is not copyright protected)

phase I and II. Benzene has the highest toxic potential as compared to other BTEX compounds due to an epoxide formation by the action of CYP2E1 on the compound [14, 39]. The biotransformation of benzene and toluene occurs in the liver after absorption. The metabolites of the biotransformation process are excreted through urine with a minimum amount of unmodified compounds (toluene less than 0.01% and benzene less than 0.1%). The Cytochrome P450 enzyme system, particularly, CYP2E1 is involved in the metabolism of toluene. After the formation of epoxide from benzene through the action of CYP2E1, S-phenylmercapturic acid (SPMA) and t,t-muconic acid (t,t-MA) is formed. Hippuric acid and S-benzyl mercapturic acid (SBMA) are formed from toluene, which after a secondary pathway form S-toluil-mercapturic acid and ortho- and para-cresol [40]. At higher levels of exposure, BTEX compounds show a competitive metabolism with inhibitory mechanism, thus these compounds show dose-dependent biotransformation while the first step in the metabolism of all compounds does not show saturation [14]. All BTEX compounds exhibit a neurotoxic effect through the physicochemical changes induced by parent compound in the CNS [14, 41].

Pathophysiology of Brain Damage by Toluene

The exact mechanism by which toluene causes damage to the white matter of the brain is not known. Being a highly lipophilic compound, toluene distributes in the lipid-rich areas of the brain in experimental animals. This observation suggests that

myelin that contains 70% lipids may be a target site for toluene induced brain damage. An autopsy study conducted on a patient exposed to toluene inhalation before death revealed that the concentration of toluene in the corpus callosum was highest while it was minimum in the hippocampus and cerebral cortex, a predilection for damage of corpus callosum was also seen in MRI. After white matter localization, further mechanism of brain injury is not certain. It is suggested that lipid peroxidation is caused by free radical formation; toluene or its metabolite benzaldehyde has been involved in the formation of ROS in CNS. With abstinence, the brain damage by toluene may be reversible [18].

Prevention of Toluene Toxicity: Evidence from Studies

A major part of the functioning of the brain and nervous system is carried out by omega-3 fatty acids. It comes up with the burgeoning of the brain, speedy verbal communication, up to mark coordination, and privilege from swatting dysfunctions in the child. Its neuroprotective effects in brain tissues have also been pass on. Contemporaneous studies manifested that omega-3 fatty acids enhance the activities of some antioxidant enzymes and intercept oxidative mutilation in tissues. As a result of experimental studies accomplished in rats, it is stipulated that omega-3 fatty acid therapy arrest the toluene-induced neuronal damage in the prefrontal cortex region [42]. *Nigella sativa* (NS), a plant with black seeds, belongs to the family Ranunculaceae is shown to hold >30% of fixed oil and 0.4–0.45% wt/wt of volatile oil. The volatile oil has been shown to contain 18.4–24% thymoquinone (TQ) and 46% monoterpenes. The material collected from the black seeds have pharmacological activities such as bronchodilation, immunomodulatory, antibacterial, hypotensive, antidiabetic, hepatoprotective, gastroprotective, antihistaminic, antioxidative, and neuroprotective effects that reveal by clinical and animal studies [43]. Thymoquinone is a crucial bioactive component of the essential oil and its presence in this plant is responsible for all therapeutic activities. Thymoquinone can be considered as a utilitarian surrogate in the treatment of illness affiliated with the nervous system. A study by Beheshti et al. concluded that NS, through inhibition of acetylcholinesterase enzyme and particularly due to its antioxidative effects, ameliorates nervous system diseases [44]. Mehmet Kanter oversaw a study concluding that NS therapy causes morphologic refinement on neurodegeneration in frontal cortex and brain stem after appalling toluene vulnerability in rats [43].

Chlorinated Solvents

Chlorinated solvents such as trichloroethylene (TCE), perchloroethylene (PERC), and dichloromethane (DCM) are capable of dissolving organic substances, for such characteristics, these solvents have been intended for a variety of industrial and

consumer cleaning means. Cumulatively for TCE, PERC, and DCM, exposure can occur through inhalation due to the volatilization of the solvent or ingestion predominately from groundwater pollution [12]. Since the beginning of the twentieth-century, Cl-VOCs have been released into environment media due to human activities [45]. PERC (also called tetrachloroethane) inhalation is the classic passage of entry in the human body, however, they have the ability to enter the body through skin layers. Neurological deficits happen when ingested including cognitive and visual impairments. 1,1,1-trichloroethane and TCE (also called chloroform) have been illustrated to inhibit the function of excitatory receptors [*N*-methyl-D-aspartate (NMDA)], nicotinic acetylcholine receptors (nAChR), and enhance the function of inhibitory receptors $GABA_A$ and glycine receptors. Neurotoxicological changes sketch the most noticeable health reviews backing exposure to these chlorinated solvents in experimental studies. Several central nervous system consequences disclose the following acute, sub chronic, or chronic exposure to each of these three compounds. In rodent studies, several neurological changes are commonly observed among TCE, PERC, and DCM. Changes in spontaneous activity, impaired motor coordination, and visual and auditory dysfunction included in these reverberations [12].

Biotransformation

For prognostication and exposition of adverse responses, TCE metabolism to toxic moieties remains a paramount thought. Furthermore, pivotal urinary metabolites from these pathways have an advantage for evaluating exposure in workplace areas. Two major pathways are there through which TCE metabolism transpires: cytochrome P450 (CYP)-dependent oxidation and glutathione [GSH] conjugation catalyzed by GSH *S*-transferases (GSTs).TCE undergoes cytochrome P450 (CYP)-dependent oxidation to form either a TCE-CYP intermediate or an epoxide intermediate. Additional processing through either non-enzymatic rearrangements or actions of aldehyde dehydrogenase (ALDH), alcohol dehydrogenase [ALDH], CYPs, or GSH *S*-transferase zeta (GSTZ) surrender various metabolites that expel through urine. By the GSH conjugation pathway TCE experience conjugation with GSH to relent the GSH *S*-conjugate DCVG (*S*-(1,2-dichlorovinyl) glutathione). After processing to yield the cysteine *S*-conjugate DCVC (*S*-(1,2-dichlorovinyl)-L-cysteine), three potential fates are detoxification to back down the mercapturate NAcDCVC or bio-activation by either the cysteine conjugate β-lyase to yield dichlorovinylthiol, which regroup to yield thioacylating species or the flavin-containing monooxygenase to give DCVC sulfoxide. The mercapturate can also be deacetylated to regenerate DCVC or it can undergo CYP3A-dependent sulfoxidation; metabolites are eliminated through urine [29].

The most subtle passage of non-cancer human toxicity is neurotoxicity associated with PERC subjection and is matched up with parent compound concentrations at the target site. Both cytochrome P450s (CYPs) and GSH S-transferases (GSTs)

are involved in PERC metabolism. Oxidative metabolism of PERC foremost to the formation of trichloroacetic acid (TCA) has been speculated to be assigned to CYP2E1 substrates based on analogy to trichloroethylene (TCE), while other enzymes (including other P450s) may be entangled. Although the liver is the leading sponsor to the oxidation of PERC, extrahepatic oxidative metabolism may occur in the kidneys and lungs [46].

Neurotoxic Mechanism

The pioneer-chlorinated solvent associated with distinct targets in the nerve cells is responsible for neurotoxicity. This theory is reinforced by in vitro studies with PERC and TCE. Based on the similarities in neurological effects and mechanistic consequences, there are hardly any studies with DCM, the neurological mechanisms may be identical to the finer characterized solvents of PERC and TCE. It is known that solvents interact with several ion channel targets in the central and peripheral nervous system, but the primary molecular targets are barely transparent. Challenges between correlating the mechanistic studies to the neurotoxicological outcomes are the difference in exposure duration. Acute or short-term exposure is used by most of the mechanistic studies, whereas various (but not all) neurotoxicological consequences as described below are because of a longer-term exposure (sub-chronic, chronic) duration [12]. Table 10.1 shows the TCE, DCM, and PERC induced changes in the brain [19].

Prevention Measures

Innumerable corrective methods have thrived for the abolition and decomposition of Cl-VOCs from polluted water, air, and soil media over the past decades because of their global existence in the environment and detrimental effects on the human health. Broadly, these methods can be classified as non-destructive or destructive. Non-destructive methods principally make use of the physicochemical properties of chlorinated compounds like high volatility and hydrophobicity to physically remove these impurities, and the nature of these compounds normally does not change (e.g., air stripping and adsorption methods). However, by breaking the C–Cl bond the contaminants are neutralized in destructive methods, changing the nature of these compounds. In destructive methods, as in the phytoremediation and biodegradation approaches, Cl-VOCs could be decomposed under natural conditions by plants and microorganisms during their metabolic activities. Cl-VOCs also can be broken down by chemical reactions with corresponding chemical additions. Cl-VOCs could also be destroyed by using energies as in thermal incineration, photocatalytic oxidation, electrochemical oxidation, and electrochemical reduction approaches (Fig. 10.2) [45].

Table 10.1 Comparison of reported neurochemical and pathological changes in animal studies with TCE, PERC, and DCM

Brain region	TCE	PERC	DCM
Whole brain	After exposure to 320 ppm of TCE for 5–90 days, no change was observed in the weight of whole brain of Sprague-Dawley rat	Changes were observed in Mongolian gerbils and rats (various strains) after exposure duration of 1–12 months; such as changes in enzymes levels in brain and decreased astroglia proteins (GHAP and S-100); decrease in RNA content in the brain; decrease in threonine, serine, and glutamine	No information
Cerebrum	No change was observed in the weight of cerebral cortex, after exposure to 320 ppm of TCE for 5–90 days duration, in the male Sprague-Dawley rat	No change in the weight of cerebral cortex of Mongolian gerbils after exposure to 120 ppm for duration of 12 months. Another study showed significant decrease in the weight of cerebral cortex of male Sprague-Dawley rat after exposure to 320 ppm of PERC for 30 days	Increase in the levels of succinate and NADPH diaphorase; increase in cerebral RNA and decrease in succinate hydrogenase was observed after exposure to 100 ppm + 2800 ppm peak exposure for 2 weeks (1000 ppm TWA) in the male Wistar rats. In another study there was increase in the levels of astroglia proteins in Mongolian gerbils at 210 ppm exposure for 3 months
Cerebellum	Increase in glutamate and GABA uptake at exposure of 50 ppm or higher levels for a duration of 12 months. Initially increase in astroglia proteins, S-100, was followed by a significant decrease at exposure of 170 ppm for a duration of 5 months	Considerable decrease in levels of taurine; no change in the levels of GABA or glutamine, no change in the uptake of glutamate or GABA after exposure to 120 ppm for a duration of 12 months in Mongolian gerbils	Decrease in succinate hydrogenase after exposure to 100 ppm + 2800 ppm peak exposure for 2 weeks (1000 ppm TWA) was observed in male Wistar rats in a study. Another study shows a decrease in DNA concentration per wet weight. Increase in GABA, glutamate after exposure to 210 ppm for a duration of 3 months in Mongolian gerbils

(continued)

Table 10.1 (continued)

Brain region	TCE	PERC	DCM
Frontal cortex	No information	Decrease in the DNA content was observed in a study, after continuous exposure to 600 ppm for 4 weeks, in Sprague-Dawley rats. Another study showed decrease in DNA content in Mongolian gerbils after 60 ppm exposure for 12 weeks	Decrease in levels of GABA, glutamate, and phosphoethanolamine after 210 ppm exposure for 12 months in the Mongolian gerbils
Medulla/ midbrain/ hypothalamus	No information	No information	In the serotonin and dopamine levels in the medulla, decrease in the norepinephrine levels in midbrain, decrease in levels of serotonin and norepinephrine in hypothalamus in male Sprague-Dawley rats after acute dose of DCM (534 mg/kg oral)
Hippocampus	40% decrease in myelinated fibers was observed in a study after a low level utero exposure of TCE 4 mg/day, in the Sprague-Dawley rats. Another study result showed decrease in response to titanic stimuli in mice at 24 h post injection after 300 mg/kg exposure i.p. no change in the weight of whole brain in male Sprague-Dawley rats after 320 ppm exposure for 5–90 days was observed in a study	Decrease in the levels of taurine and increase in levels of glutamine after 120 ppm exposure for 12 months in Mongolian gerbils. No change in levels of GABA or uptake of glutamate and GABA	Increase in the acetylcholine levels showed in a study after acute dose (534 mg/kg oral) in the male Sprague-Dawley rats. In another study decrease in the concentration of DNA per wet weight in Mongolian gerbils at 210 ppm exposure for 4 months
Substantia Nigra	Dopamine neurons degeneration at 400 mg/kg/day exposure for 4 weeks in mice; in another study dopamine neurons degeneration was observed at 1000 mg/kg/day exposure for a duration of 6 weeks in rats	No information	No information

(continued)

Table 10.1 (continued)

Brain region	TCE	PERC	DCM
Caudate nucleus	No information	No information	Increase in levels of catecholamine at 70 ppm exposure; decrease in the level of catecholamine at exposure of 300 ppm or high for 3 days in the male Sprague-Dawley rats
Striatum	No information	At 800 ppm exposure for 1 month in male Sprague-Dawley rats, there was decrease in acetyl choline levels	No information

Table is adapted from (19) after some modifications. (Table is not copyright protected)

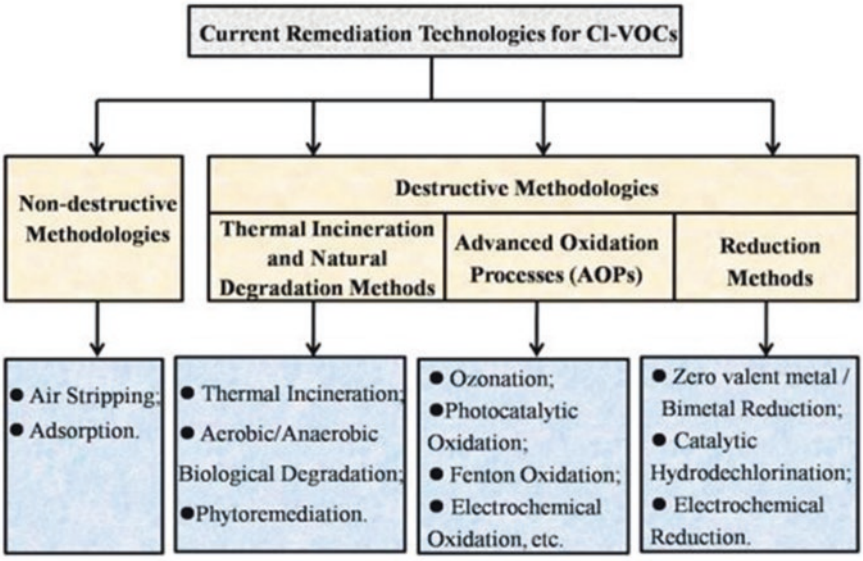

Fig. 10.2 Summary of current remediation technologies for Cl-VOCs (Figure is adapted from [45] which is not copyright protected)

Formaldehyde

Ordinarily, in both indoor and outdoor air, formaldehyde (FA) is present due to its copious and pervasive origin. Formaldehyde is familiar to prompt acute poisoning and cause irritation, as well as other immunotoxic effects. Chronic exposure to formaldehyde can be blameworthy for the manifestation of neurasthenia, which comprises of headaches, dizziness, sleep disorders, and memory loss. Chronic exposure to formaldehyde increases the chances of headache and dizziness by 30%–60%, which is stipulated by various reports. It is therefore postulated that inhalation of formaldehyde, during the early postnatal period, can cause some neurological diseases with aging [47]. Formaldehyde exposure instigates behavioral depression and learning inhibition, illustrated as a result of many animal experiments [15]. Foisting concentration limits for formaldehyde and paraformaldehyde in cosmetics is a regulation embraced by the European Union. These substances are granted at a maximal concentration of 0.2% by weight or volume [41].

Biotransformation

Nearly every tissue in the body is capable of foundering formaldehyde after immersion [47]. Catalysis of formaldehyde oxidation in tissues is ensured by many enzymes, the supreme one being DPN-dependent formaldehyde dehydrogenase. Formic acid engendered by this process, which is enough expelled through urine as sodium formate but substantially further oxidized via reactions with glutathione and along with a pool of one-carbon compounds up to CO_2, which is exhaled by the lungs. This alteration being capricious, the spin-off of this process is methanol [48].

Mechanism of Neurotoxicity

The subjection of rats to formaldehyde roots copious morphological changes in the brain and damages the prefrontal cortex together with the hippocampus, as it is a restricted animal study related to the neurotoxicity of formaldehyde in rats and mice that inhaled FA marshal to learning and memory disorders. Furthermore, plentiful affirmations confirm that rise in endogenic FA levels by upregulation of semicarbazide-sensitive amine oxidase (SSAO), one of the enzymes in the pathway producing FA, and a shortfall of aldehyde dehydrogenase class 2 (ALDH-2), one of the enzymes that degenerate FA, the pathology of Alzheimer's disease. Comprehensive mechanisms underlying the neurotoxicity of FA have not been well illuminated due to the extensive dissemination of FA in the environment and its serious effects on the brain. The oxidative damage is one of the censorious outcomes of FA exposure. Depletion of viability, inhibition of CBS expression, less endogenous

H_2S production, and NO production are due to exposure of PC12 cells to FA. Nerve cells are guarded against oxidative stress by its antioxidant effect with the help of hydrogen sulfide (H_2S), an endogenous gas transmitter [35].

Preventive Strategies

The lineup of safeguard effect from interventions is intensifying the enzymatic capabilities to catalyze the oxidation of formaldehyde into formic acid (despite a doable concomitant elevation in the production of the highly toxic methanol) and the only reason is oxidation which is an alternative to the participation of formaldehyde in reactions with bio-macromolecules. Hence, it is the basis of its toxicity. A salient function of this enzyme system is lessening glutathione, and it is not astonishing that the administration of exogenous GSH at sub-acute inhalation with formaldehyde escort to expanding survival of experimental animals. Bio protective activity of a combination of amino acids is even more practical interest that participates in the biosynthesis of GSH that is glycine, glutamate, and cysteine, where the latter may be replaced with its more attainable metabolic predecessor, that is, methionine [48].

The pineal gland in mammals produces an endogenous neurohormone known as melatonin. Modern studies have shown that melatonin functions constructively as an antioxidant, that is, a hydroxyl radical and a peroxyl radical scavenger. The protective effect of melatonin in opposite to formaldehyde-induced neurotoxicity in the prefrontal cortex at immune histochemical and biochemical levels has been looked over by Ismail Zararsiz. The inference of this study is melatonin treatment intercepts formaldehyde-induced neuronal damage in the prefrontal cortex of rats [49].

n-Hexane

A multitude of complications involved with n-hexane due to intended and work-oriented exposure has compelled pharmacists to study this toxic chemical. Central and peripheral axonopathy, peripheral neuropathy, paranodal axonal inflammations, and demyelination can be seen in humans and animals caused by continued exposure [50]. Also, acetone in combination with n-hexane produces dangerous products that show neurotoxic effects [30]. In Nagoya, the first case of n-hexane polyneuropathy was seen among Japanese laborers working in polyethylene factories. The common symptoms were muscle weakness and affected sensory functions. Biopsy of nerves of leg muscles has shown the myelin loss and axon degeneration. However, patients have undergone recovery taking many years after the exposure ended [51].

Biotransformation

The metabolism of n-hexane has been studied on laboratory animals and humans. The metabolic mechanism involves a series of hydroxylation and dehydrogenation reactions. n-hexane undergoes a hydroxylation reaction in the first step that occurs by the transformation of cytochrome P-450 and cytoplasmic dehydrogenase enzymes oxidize the metabolites of this reaction to respective ketones. The main metabolites of n-hexane include methyl n-butyl ketone, 2,5-hexanedione, 2-hexanol and 4,5-dihydroxy-2-hexanone. Further, 2-hexanol is converted to 2-hexanone and 2,5-hexanediol following the bioactivation pathway. Both of these products are again metabolized to 5-hydroxy-2-hexanone and 4,5-dihydroxy-2-hexanone which are further oxidized to 2,5-hexanedione. 2,5-hexanedione is the actual foremost toxic metabolite formed by a human body due to n-hexane. N-hexane can be eliminated by exhalation of non-metabolized compounds and volatile agents, and also by urinary excretion. The level of 2,5-hexanedione in urine is the mean of determination of n-hexane exposure towards a person [51].

Neurotoxicity Mechanism

It has been clarified that neuropathy is caused by oxidation of a metabolite of n-hexane, that is, 2,5-hexanedione. After its formation, 2,5-hexanedione gets converted into dimethyl pyrrole adducts by binding with lysine ε-amine groups of proteins, and further produce pyrrole dimers by autoxidation. Subsequently, inter and intramolecular crosslinking appear in the protein structure. In this way, post-translational adaptations in protein structure may cause functional loss to the protein and damage to the nervous system. N-hexane-induced neuropathy can be protected by a possible tactic, that is, to prevent the formation of 2,5-hexanedione and pyrrole adducts. Garlic, with its great medicinal significance, is a natural source of a phytochemical compound diallyl trisulfide (DATS), which protects rats from this neuropathy. Also, regulatory agencies along with research groups have set occupational exposure limits (OELs) to establish conventional standards [50].

Acetone

Several anthropogenic means can expose human beings to acetone. It is also endogenously produced by the body itself in the liver, lungs, and kidneys. Meanwhile, the decarboxylase enzyme releases acetone as an intermediate metabolite during the breakdown of acetoacetate. Regrettably, sociological sources increase the body's work to also eliminate the excessive acetone from the body. It is done by urination, exhalation, and enzymatic metabolism (cytochrome P450 isozymes) [13].

Biotransformation

The metabolism of exogenous acetone generally involves a three-step mechanism. The very first step that is also the rate-determining step encompasses the intrahepatic P450IIE1-dependent oxidation of acetone to acetol which is catalyzed by acetone monooxygenase. This reaction controls the overall elimination of acetone from the body. The second step of the reaction follows two pathways: (1) methylglyoxal pathway which involves intrahepatic oxidation of acetol to methylglyoxal and (2) propanediol pathway which includes the extrahepatic reduction of acetyl phosphate to 1,2-propanediol using propanediol phosphate dehydrogenase enzyme. Finally, in the third and last step, the products of both pathways of the second step are further oxidized to pyruvate which is the most significant building block of several biochemicals. In the case of a very large amount of absorbed external acetone, 1,2-propanediol undergoes cleavage into formate and acetate. Acetone can be removed from the body in urine as acetol, methylglyoxal, or as D-lactoyl-GSH when conjugation of methylglyoxal occurs with glutathione. The products of intermediary metabolism are also exhaled as carbon dioxide in the air [52].

Neurotoxic Mechanism

Interestingly, acetyl Coenzyme-A which is involved in the production of acetone endogenously is also responsible for the generation of acetylcholine, a neurotransmitter in the human nervous system. Plus, the acetate formed from acetone degradation is also produced by the breakdown of acetylcholine by the esterase enzyme. This acetate is the raw material for acetone formation. Both coenzyme-A and acetate play a prominent role in the malfunctioning of the nervous system in the body. Therefore, excessive exposure to acetone can lead to an imbalance of acetyl coenzyme-A and acetate concentrations in the neurons and eventually disturb the functioning of acetylcholine activated neural signal transmission. Such sort of chemical imbalance in the nervous system can be the reason behind dizziness, headache, and sometimes unconsciousness in case of prolonged exposure [13].

Preventive Measures to Reduce VOC Exposure Among Workers

Biomarkers as Tools in Bio-Monitoring Chemical Exposure

In bio-monitoring measurements are done of different toxic materials, their metabolic products, or molecular signatures of resulting effect in the specimens of living organisms including humans and animals, encompasses urine, blood, fecal material,

excreted breath air, the protein of hairs, hand or toenails, bronchial lavage, breast milk, and the body's adipose tissues. Certain detectors are termed as biomarkers, and can also be designated as "any material, constituent or procedure that can be calculated in the living organism or its resulting material and indicator may forecast the prevalence of any ailment or any odd behavior" [51]. For the detection of exposure of volatile organic compounds in an occupational aspect, biological monitoring is the most reliable and precise method for assessment [53].

Biological monitoring is done by comparing the difference between two individual variables like absorption, distribution, biotransformation, elimination, and amount of chemical exposed in 10 doses and comparing it with the biological exposure index (BEI), which is used as a standard. Biological examination of toluene in case of workplace exposure could be monitored by examining the concentration of O-Cerosol in urine and direct serum concentration of toluene. Some experts considered the urinary hippuric acid as a preferred biomarker for measuring the toluene concentration at a toxic level of exposure [53]. Along with hippuric acid, trans, trans-muconic acid (*t,t*-MA) and S-phenyl-mercapturic acid (SPMA) are urinary biomarkers of benzene [40]. At the end of the workweek, the recommendation was given by the American Conference of Governmental and Industrial Hygienists (ACGIH) about the utilization of urinary trichloroacetate (TCA) levels as the biomarkers for the assessment of workplace TCA exposure, and they restricted a limit of 100 mg TCA/l [51].

As the nervous system has complex nature, its characteristic eccentricity, along with the complication linked with prompt and easy evolution of sensitive, particular, and authentic biomarkers indicate its neurotoxicity. For instance, the activity of Monoamine oxidase B (MAO-B) could be preferred. MAO-B is used as a clinically active biomarker to check the pharmacological effect of MAO inhibitors, specifically in the treatment of Parkinson's disease. The activity of MAO-B in platelets has been taken as a biomarker to check the response of occupational exposures of styrene and perchloroethylene, which are involved in dopamine depletion. Any change in MAO-B concentration could surely indicate the recognizable feedback to the consumption of dopamine and, in other words, styrene, and their metabolic products might pose an undeviating inhibitory effect on the activity of the enzyme [51]. In past, by using biological exposure index (BEI), the Hippuric acid (HA), methyl hippuric acid (MHA), and mandelic acid (MaA) were used as biomarkers for the vulnerability of toluene, xylene, and ethylbenzene [54].

A few examples explain that the consistent physiological processes or metabolic processes of food preservatives and flavor enhancers may alter the excretion of metabolic products through the urine and may influence the precision and sensitivity of that procedure. Moreover, if there is a need to determine the exposure of a single compound, urinary metabolites assessment is the most reliable method, and VOCs are almost all present in the industrial area settings. In this situation, the unmetabolized compounds in urine can be determined by this technique. Another study results indicate that the amount of unaltered VOCs in the excretory material of urine may be an authentic biological marker for detecting the small exposure of these toxic materials in the workplace environment [55].

Micro-RNAs represent a specific type of RNA; they have an integral function in the regulation of translational mechanisms. Many kinds of research reveal that any abnormal behavior in the function of miRNA which may be the result of hazardous chemicals and contaminants in the environment that exert an injurious effect on health. For interpreting the infective process pathway triggered by the toxic environmental material, the analysis of miRNA is an applicable method. However, RNA is present in both blood constituent serum and there is equilibrium in the movement of miRNA between the blood and extracellular fluid. Hence, it makes the assessment easy. Mostly the circulating miRNA can be easily identified by polymerase chain reaction as compared to the protein-based biomarkers in blood, and the low amount of some protein-based biomarkers can remarkably obstruct the process of identification. Furthermore, another reason that challenges the precise assessment of protein-based biomarkers is the difference in post-translational changes while miRNAs are homogeneous after activation. The detection procedure of miRNAs which is present in blood can be conducted by using either whole blood or serum or plasma component. The findings of another study illustrated those distinctive molecular signatures of volatile oils present in circulation. And the toxicants present in response to different types of VOCs' specific miRNA signature were able to differentiate the different toxicants present in circulation. These biomarkers are considered as a predictable and detectable substitute for measuring the miRNA in response to environmental exposure of VOCs [54].

Occupational Exposure Limits

Occupational exposure limits (OELs) are created to forestall and control potential health problems in the working environment. It is expected that at the degree of the OEL for a given concoction, all or almost the entirety of the uncovered workers will not experience antagonistic health impacts [56]. OELs are built up as norms by administrative offices or as rules by research groups or trade organizations [51]. OELs that are established as standards by regulatory agencies or as guidelines by trade organizations or research groups are described in Table 10.2 [51].

Computerized Fluid Dynamic to Prevent VOCs in Industrial Environment

To control VOC exposure among laborers, LEV frameworks are planned and manufactured to eliminate contaminants. Computerized fluid dynamic (CFD) is the arrangement on preventive technique in planning LEV framework and before the LEV frameworks are created [57]. Flynn and Sills directed an investigation to recreate breathing zone fixation for a basic portrayal of spray-painting a flat plate. The

Table 10.2 The standards of OELs as established by research organizations and regulatory authorities

EU (European Commission) SCOEL: Scientific Committee on Occupational Exposure Limits	
OEL	Occupational Exposure Limits
BOELV	Binding Occupational Exposure Limit Values
BLV	Biological Limit Values
USA OSHA: Occupational Safety and Health Administration	
PEL	Permissible Exposure limits
TWA	Time Weighted Average
USA ACGIH: American Conference of Governmental Industries Hygienists	
OEL	Occupational Exposure limits
TLV	Threshold limit value
BEI	Biological exposure indices
UK COSSH: Control of Substances Hazardous to Health and HSC, Health and Safety Commission	
OES	Occupational Exposure Standard
MEL	Maximum Exposure Limit

Table is adapted from (51) after some modifications. (Table is not copyright protected)

outcomes exhibit the ability of CFD to follow accurately changes in breathing zone fixation related to work rehearses demonstrated beforehand to be noteworthy in identifying exposure. CFD is the best approach to decide the effectiveness of the ventilation system [58]. Kassomenos et al. used the CFD model PHOENICS to explore VCM accumulation in work environments. The outcomes indicated that the utilization of a CFD is a promising procedure to examine the occupational exposure in the known carcinogen VCM and to plan the best possible ventilation framework to lessen the results of an inadvertent arrival of VCM in a work environment. Estimation likewise made and found that the computational outcomes are reasonable and in great concurrence with the trial estimation [59].

Wong conducted a study to check the influence of the mechanical ventilation system in a hawker center of Singapore, where CFD simulation was used for ventilation. It was concluded that the installation of fans should assist in hot air flow out of the closed area and the most effective fan is an exhaust fan because it can improve stack ventilation in the building [60].

Conclusion

Due to lack of information about the relative sensitivity of VOCs, their risk assessment is uncertain. The high volatility of solvents and their presence in the form of the mixture in the environment make it difficult to conduct studies on assessment of

cellular mechanisms involved in neurotoxicity. The ubiquitous nature of VOCs makes their exposure inevitable and poses continuous health risks to humans, particularly at workplaces where the concentration is relatively high. There is a need for new methods for risk assessment of individual compounds, epidemiological studies to elucidate neurotoxic mechanism at the cellular level, and strategies for remediation of VOCs at workplaces to keep the exposure limits below the threshold.

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Chapter 11
Persistent Organic Pollutants and Neurological Disorders: From Exposure to Preventive Interventions

Hammad Ahmed, Ali Sharif, Sahar Bakht, Faraza Javed, and Waseem Hassan

Abstract Persistent organic pollutants (POPs) are organic compounds that are nondegradable by chemical, biological, and photolytic processes. Because of their continuous bioaccumulation in the environment, they impart drastic effects on human health. The hazardous effects of POPs are so impactful that a special "Stockholm Convention on POPs" was organized in 2001 to highlight the emerging problem. As an early measure, the convention banned or restricted the production of some 12 pollutants worldwide. Besides the endocrinological, gastroenterological, and dermatological complications, these POPs also exert their harmful effects on the nervous system. Clinical signs of Parkinson's disease, Alzheimer's disease, stroke, epileptic seizures, multiple sclerosis, dementia, and attention deficit hyperactive syndrome are observed in POPs exposed people. Moreover, in vitro and in vivo studies reveal that organochloride and organophosphate both can cross the blood–brain barrier and damage the dopaminergic, cholinergic, and serotonergic neurons. Additionally, these pollutants can increase or decrease the levels of neu-

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rotransmitters and exert oxidative damage to neuronal cells. Certain POPs can activate neuroinflammatory pathways by disrupting expressional levels of proinflammatory and anti-inflammatory cytokines. Presence of a few selective studies with limitations and lack of conclusive outcomes, the exclusive epidemiological studies focusing on the effect of POPs on neurological disorders are lacking in modern-day literature. There is no antidote available in the treatment of organochloride exposure as yet, however for organophosphate exposure, pralidoxime is used. On chronic exposure of POPs, symptomatic treatment is recommended. Such endeavors should be encouraged that highlight the ways of controlling the exposure of pollutants.

Keywords Environmental pollutants · Neurological disorders · Biotransformation · Treatment of POPs

Introduction

Persistent organic pollutants (POPs) are chemicals of global significance due to their extended spread capacity, environmental durability, and the tendency to biomagnify and bioaccumulate in the ecosystem. They impart extremely hazardous impacts on human health and the climate [1]. Humans are exposed to POPs in several ways: primarily through the edibles, through polluted air, outdoors, indoors and at workplaces. Routine household items contain POPs that are used to improve product characteristics. POPs are found essentially everywhere in quantifiable concentrations. As a result, the highest concentrations of POPs are found in edible organisms [2]. The central nervous system (CNS) is the most important target of organochlorinated (OC) and organophosphorus (OP) pollutants [3].

Human beings come across with the commonly used POPs like OC, such as dichloro diphenyl trichloroethane (DDT), most notably polychlorinated biphenyls (PCB), as well as unintended industrial waste processes, especially polychlorinated dibenzo-p-dioxins and dibenzofurans, famously known as “dioxins” [4, 5]. POPs bioaccumulate in the food and organisms. Even a very small amount of exposure to POPs can cause the detrimental health problems in human beings like cancer risk, reproductive disorders, alteration of the immune system, neurological disorders, neurobehavioral impairment, endocrine disruption, genotoxicity, and increased birth defects. Moreover, these POPs can be the predisposing factor to cause certain neurological disorders [6]. POPs were commonly used during the post-world war II industrial revolution era when thousands of synthetic chemicals were brought in commercial usage. Some of these substances are useful for insect and disease management, crop growth and manufacturing but had unintended impacts on human health safety, and climate. Some of the well-known POPs include PCBs, DDT, and dioxins [7]. These manufactured chemicals are used in livestock, disease prevention, and construction or production processes [8].

Exposure of POPs

Accidentally generated pollutants such as dioxins generally arise from the manufacturing processes of certain industries, kilns, and combustion (municipal and medical waste incineration and garbage burning in the backyard) [9]. The rapid growth of population, the emerging need for processed foods, and widespread application of pesticides are increasingly resulting in the bioaccumulation of POPs [10]. Increased usage of pesticides in agriculture and household has contaminated the natural and developed climate, leading to bioaccumulation of toxicants and adversely influencing human health [11].

Presently, about 200,000 compounds have been reported and registered in the database of the European Chemicals Agency. Although chemicals used in pharmaceuticals are under strict regulatory control, other substances require minimal regulatory control before reaching the market. Approximately 20% of these chemicals have been checked for toxicity, which requires a proper assessment of their health hazards and environmental impact. POPs is a broad term that includes an extremely long range of chemicals having very similar toxicity and resistance to degradation. Furthermore, owing to the extensively lipophilic characters these chemicals are deposited in adipose tissue and have a half-life from 1 month to several years. Nonlipophilic compounds are also widely spread and quantifiable amounts of these can be traced in the circulation of all inhabitants of the industrialized world.

Stockholm Convention

Stockholm Convention on POPs is an international environmental treaty, signed in 2001 and effective from May 2004, that purposes to eliminate or restrict the production and use of POPs [12]. The steps should be taken to prohibit the manufacture of the chemicals mentioned in Annex A. Efforts should be made to limit the manufacture of the chemicals listed under Annex B, and steps shall be taken to minimize the unintended release of the chemicals listed in Annex C with the objective of persistent minimization and, if viable, eventually eliminating it [13].

Persistent Organic Pollutants Associated with Neurological Disorders

In the Stockholm Convention, 12 POPs were listed that are known and reported to cause toxic effects in humans and the environment. These POPs were classified into three categories, as shown in Table 11.1 [14].

Aldrin is used to kill the pests like termites, grasshoppers and corn rootworms. It has the potential to kill birds, amphibians, and *Homo sapiens*. Aldrin was tested in

Table 11.1 Classification of POPs according to Stockholm Convention

Category	POP	Included in annex	Chemical nature
Pesticide	Aldrin	A	OC
	Chlordane	A	OC
	DDT	B	OP
	Dieldrin	A	OP
	Endrin	A	OC
	Heptachlor	A	OC
	Hexachlorobenzene	C	OC
	Mixer	A	OC
	Toxaphene	A	OP
Industrial chemicals	HCB	A&C	OC
	PCB	C	OC
By products	Hexachlorobenzene	C	OC
	Polychlorinated dibenzo-*p-dioxins*	C	OC
	PCBs	C	OC

rice plants for pest control which resulted in the slewing of many birds along the gulf coast of Texas. The lethal dose of aldrin is about 5 g for humans. Humans are exposed to aldrin by milk products and livestock. The average daily ingestion of aldrin and its by-product dieldrin is approximately 19 μg per human in India [15]. Chlordane is a broad-spectrum insecticide used comprehensively to control termites. The remnants of chlordane stay for a very long time in the body as it has a half-life of 1 year. Chlordane is exposed via air and has carcinogenic potential [16].

DDT was used during the World War II to protect armed forces and citizens from the insects-borne diseases like malaria, and other diseases. It was also used as a pesticide besides its utility to kill the mosquitoes [17]. Although it is banned worldwide, it has been spotted in the eatables. Traces of DDT are also identified in the breast milk, which is alarming for infant health [18, 19]. Long-term chronic exposure to DDT causes detrimental health effects.

Dieldrin is primarily used to control termites and textile pests. It is also used to kill insects growing on agricultural soils. In soil, its half-life is about 5 years. As aldrin is also converted into dieldrin, the concentration of dieldrin is relatively higher in the environment. Deposits of dieldrin are present in the natural environment and human serum but edible items are the foremost source of contact [20].

Endrin is sprayed on agricultural crops. It is also used to control rodents like rats. It usually does not accumulate in the adipose fatty tissues as compared to other related substances, though it has an extended half-life and can stay in the body for 12 years. Food is the chief source of its exposure [21].

Heptachlor is used to eradicate soil insects, termites, crop pests, and mosquitoes. It is implicated in killing endangered bird species that are on the verge of extinction. Experimental in vivo studies have shown that its high doses are lethal to mink, rats, and rabbits, whereas its low doses result in adverse behavioral issues and reduced reproductive success. Like other pollutants heptachlor also possesses carcinogenic potential [22].

HCB is a by-product of various industrial chemicals that target agricultural crops. In 1954–1959 the inhabitants of eastern Turkey ate HCB-treated seed grain that led to various adverse symptoms including photosensitive skin lesions, colic problem, and debilitation. Several thousands developed a metabolic disorder called porphyria turcica, and 14% eventually died. HCB is injurious to living organisms even at lesser quantities, influences the reproductive health of humans. Approximately all the foods have HCB contents [23].

Mirex is frequently used to control fire ants, termites, and other types of pests. In industries, these are used to control fire in plastics, rubber, and electrical goods. Its direct contact appears to cause injury to humans and animals. It is one of the most stable pollutant with half-life up to 10 years. It is exposed to human via food [24]. Toxophene is applied to agricultural crops and vegetables to control pesticides. It can kill ticks and mites produced in cattle and livestock [25].

These biphenyls are used in the manufacturing industry for heat exchange fluids, electric transformers and capacitors, and as additives in paints, carbonless copy paper, and plastics. Thirteen of 209 polychlorinated biphenyls (PCBs) show dioxin-like toxicity [26]. Their potential to remain in the environment depends on the number of chlorines in the compound. Their half-lives can fluctuate from a few days to years. PCBs are toxic to animals and humans alike. Reproductive failure and immunosuppressant potential are associated with PCB toxicity [27]. In Japan, exposure of contaminated rice with PCBs caused significant hazardous effects including pigmentation of nails and mucous membranes, swelling of eyelids, fatigue, nausea, and vomiting. PCBs are also labeled as a probable human carcinogen [28]. Dietary measures can be enacted that will reduce PCB half-lives in humans by increasing its excretion [29].

Metabolism of POPs

POPs are metabolized by the CYP450 family. Phase-I metabolism includes hydroxylation or oxidation of chlorinated POPs substrate via several processes [30]. Phase-I augments the elimination of POPs, as hydroxylation enhances the water solubility and hence increases its rate of removal via kidneys or intestines. Phase-II metabolism entails the synthesis of the Phase-I metabolite, either hydroxylated or by conjugating it with certain functional groups, such as glutathione, glucuronic acid, or methylsulfonyl, resulting in far more water-soluble metabolites that are eliminated at a much quicker rate than their parent compounds [31].

OC usually induce isoforms of the CYP4501 that initially activates the free-floating aryl hydrocarbon receptor located in the cytoplasm, and then transfer to the nucleus in an aryl hydrocarbon nuclear transporter complex and at last it forms an adduct, thereby upregulating CYP4501A mRNA [32]. Moreover, these substances are consecutively metabolized by the isoforms from the CYP P4501, predominantly CYP4501A [33], though cytochrome P450 1, 2, and 3 families all are involved in the metabolism of at least some forms of POPs.

Several OC pollutants induce CYP450 2B and 3A families [32, 34]. DDT isomers are metabolized by the CYP450 2B1, 3A1, 2B6, and 3A4 [35], though DDT and their foremost metabolites, that is, DDE and DDD are the inducer of CYP450. Owing to the highly lipophilic nature and resistance to further metabolism, DDE is selectively retained. However, DDD is easily metabolized in most animals. Most OC and OP pollutants induce CYP4502B and 3A. Chlordane is hydroxylated to 3-hydroxychlordane, which is subsequently dehydrated to 1,2-dichlorochlordene [36]. It then metabolized to oxychlordane by epoxidation [37]. Dieldrin also induces CYP P4502B [38] and CYP P4501A and 2A [39]. Mirex also induced CYP4501A, 2B, 2E, and 3A [40].

POPs-Associated Neurological Disorders

Parkinson's Disease

PD existed even before the formation or production of POPs. It is believed that exposure of pollutants is not the sole reason of the disease. Nevertheless, POPs can aggravate and actively participate in the pathogenesis of such substances known to be accelerators of PD pathogenesis. It is known that POP exposure can be the aggravating factor for disease progression [41].

These hazardous compounds affect the nigrostriatal dopamine system, upon chronic exposure. POPs have the potential to produce subtle toxic effects. These substances aggravate the likelihood of dopamine cell death. Additionally, acute exposure of POPs can affect the mitochondria and exerts oxidative damage that leads to the cell death. They can also initiate the neuroinflammatory processes by disrupting the cytokines that lead towards further cell damage [42].

OCs are associated in the development of PD. Dieldrin has the best reported dopaminergic associated neurotoxicity. It interrupts the ubiquitin proteasome system by producing oxygen radicals, activating the caspases and accumulation of fibrils of synyclein [43]. Both dioxin-like and non–dioxin-like compounds has the potential to induce neurobehavioral modifications in animals. It alters the neurotransmitters levels in the various brain parts observed in monkeys, rats, and mice. Among all the changes, the most notable is significant reduction in dopamine content at basal ganglia and prefrontal cortex [44, 45]. It is observed that acute administration with DDT 600 mg/kg causes hyperexcitability, tremor and hyperpyrexia. All the observed symptoms are due to significant reduction in cortical and striatal ACh and norepinephrine concentration. In brainstem, there was a markedly enhanced concentration of 5-hydroxyindoleacetic acid. However, no change was observed in the levels of dopamine in the striatum of male and female rats [46]. Altered metabolism of brain 5-HT and NE might be the underlying cause of DDT-induced hyperthermia, while the seizures are observed subsequently after the acute lethal dose [47]. α-chlordane and HCB in equivalent doses lack the chronic effects

on the central nervous system [48]. In comparison, it can be found that DDT has lesser dopaminergic effects than the dieldrin. DDT exposure does not show nigrostriatal and behavioral abnormalities [49]. The acute and chronic exposure of few pesticides has been involved in the development of PD, such as maneb, paraquat, and rotenone [50, 51]. Mirex is also associated with the induction of PD in humans on occupational exposure [51, 52]. Maneb, rotenone, and paraquat all displayed the potential to show the signs of PD in experimental animals [53]. Extensive studies are required to explore the mechanistic mysteries of these compounds in disease progression [54]. Despite the neurotoxic potential of OP and pyrethroids their exposure may not lead to the development of PD. It may be attributed to their failure to actively destroy the dopamine neurons or their brief half-lives. However, several tests showed Cyclodies is validated. Keep it as such based pollutants are elevated in post-mortem PD brains [55]. Therefore, while cyclodies are not extremely toxic to dopamine, they do show possible biological plausibility and environmental significance [56].

Pathogenesis of the PD induced by the POPs targets multiple molecular mechanisms. These targets are decreased levels of dopamine, oxidative damages, synuclein, and proteosomes, may kill or escalate the susceptibility of dopamine neurons. Besides that, there are multiple molecular targets that can trigger neurodegeneration, it is particularly important to consider how mixtures of pollutants acting at different sites of nervous system work together to destroyneurons [57].

Alzheimer's Disease

POPs have shown the capability to cause neurological disorders including AD [58]. At limited doses, some of the POPs do not exert hazardous effects to the humans, but their combination can be lethal and poisonous. Many chemicals possess the potential to act as cholinesterase inhibitors, this specific effect has long-term adverse effects on the CNS [59]. If humans are exposed to OC via food or drinking water, the slow metabolism and excretion of these pesticides, along with their strong hydrophobic influence, facilitates the bioaccumulation. Experimental studies demonstrated that these POPs cause oxidative stress-mediated neurotoxicity. Likewise, OP pollutants have been shown to induce the cellular morphological alterations and stimulates non-cholinesterase–associated drug targets including motor proteins, neuronal cytoskeleton, and axonal transport [60].

Both OC and OP pollutants have been reported to influence carbohydrate and fat metabolism. At a cellular level, reduced cellular viability owing to lipid peroxidation and genotoxicity can ultimately escalate the risk of developing AD [60]. Experimental studies have proved that carbamates exert their neurotoxicity by targeting AChE. As a result, it can cause long-term nervous system damage [61]. Paraquat induces oxidative instability in the prefrontal cortex, which in turn is believed to facilitate the decreased cognitive performance with increased amounts of Aβ protein [62]. The connection of rotenone-induced AD requires further

research. Although, the mitochondrial damage associated with rotenone can be a detrimental factor to induce AD [63].

Pyrethroid pesticides are largely utilized in cultivation and industries as they are known neurotoxicants and may be converted into neurotoxic degrades. These pollutants cause neurological defects and altered tau phosphorylation. In vitro studies on human cell lines showed pathological cell death and neurotrophic impacts [64]. Maternal occupational sensitivity to pyrethroids and OP causes physiological neurotoxicity during infancy, a significant risk factor for compromised neurobehavioral growth of offspring including the development of CNS conditions such as AD [65].

Dioxins possess a lipophilic nature; hence, they can modify the neurotransmitter functions and induce oxidative damage that influences Ca^{2+} homeostatic processes. Dioxin and its related compounds are reported to raise calcium levels in the neuronal cells and tau phosphorylation via the upregulation of phospho-glycogen synthase-3 β. Certainly, these in vitro findings are similar to the postmortem neuronal cellular pathologies observed in AD patients [66]. Moreover, PCBs are associated with the pathogenesis of PD; however, AD pathogenesis is not well established. Further research is needed to establish the relation of PCBs with AD [67].

Stroke

High serum levels of POPs are correlated with an elevated likelihood of stroke formation or worsening in the elderly. Taken together with previous laboratory and epidemiological research, POPs may play a key role in the development of stroke. The risk of stroke is increasing significantly worldwide. POPs are associated with an increased risk of hospitalization for a stroke with comorbid hypertension. Further research is required to explain the functions of particular contaminants in the development of atherosclerosis and atherosclerosis-related diseases and to elucidate the important causal pathways and biological mechanisms. Occupational exposure to dioxin is correlated with the occurrence of atherosclerotic lesions in carotid arteries [67]. Serum levels of PCBs and some pesticides are directly related to self-reported hypertension and heart disease [67].

Both experimental and empirical studies suggest that POPs are implicated in the pathogenesis of atherosclerosis and POPs may affect the liver and interfere with the synthesis of lipids by encouraging the production of atherogenic dyslipidemias. POPs and an advancement in hospitalization levels for strokes with comorbid hypertension are important to ensure that the findings of the research cannot be solely due to the adverse impact of demographic features that are considered to be as risk factors for the outcome of a concern. The key possible explanatory variables that should be addressed in our analysis are race, age, class, and gender [68].

Increased serum POPs rates are associated with an increased risk of stroke growth, especially ischemic stroke. Nonetheless, cross-sectional results show that more empirical analysis of the impact of POPS will be rather worthwhile. Likewise,

given the existence of less recorded trials, more prospective PAC research, including bisphenol A and phthalates, should be considered [69].

Epilepsy

Chronic DDT administration induces random and stimulus-sensitive myoclonus in mice and rats. It is notable that serotonergic medications raise DDT-induced myoclonus. DDT-treated rats had elevated concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in seven geographical areas, but serotonin was raised only in the midbrain and cerebellum. This may be due to the deficiency of serotonin at the receptor site [70]. Nonetheless, when DDT was applied to pargyline-treated rats, a slightly higher rise in serotonin was detected in cerebral region. The concomitant administration of DDT and chlorophenylalanine not only reversed the reported spike in 5-hydroxyindoleacetic acid but also almost entirely prevented the neurotoxic effects (hyperpyrexia, tremor, and convulsions) associated with the pesticide. On the other side, DL-6-fluorotryptophan (a more common serotonin production inhibitor) reverses the DDT induced hyperpyrexia. HIAA did not affect the frequency of tremor and convulsions. Increased brain serotonin levels can indicate DDT-induced hyperpyrexia [71].

In pargyline rats, DDT induced elevation in 5-HT levels was higher than the monoamine oxidase (MAO) inhibitor alone. Treatment with 6-fluorotryptophan or methyl-p-tyrosine, 5-HT or NE synthesis inhibitors stopped DDT-induced hyperthermia but not tremors and convulsions. Pretreatment of rats with hydantoin has proconvulsant potential. Additional studies have showed that pretreatment with piperonyl butoxide enhanced tremor, while chlordane also aggravate the tremor threshold. Hydantoin-induced attenuation of DDT-induced neurotoxicity may be due to the ability of hydantoin to block repetitive nerve burning by binding to sodium inactivation gates [72].

The neurotoxic insecticides endrin, dieldrin, aldrin, lindane, and deltamethrin inhibited γ-aminobutyric acid–dependent Cl^- uptake [73]. The $MgCl_2$ administration decreased the neuroexcitability induced by aldrin and increased the survivability [74].

Chlordane causes mild tremor, hind leg stiffness, convulsive symptoms, and a dose-dependent decrease in rectal temperature. Quantification of neurotransmitters in brain at different time intervals confirmed a steady decline in cortical and striatal ACh, and reasonably enhanced levels of AChE function. The hypothermic reaction is associated with pronounced significant reduction of NE in the brain stem accompanied by an increase of 5-HIAA, whereas 5-HT stayed unchanged [75].

Tremors and convulsions are symptoms of severe chlordane poisoning in humans. Convulsive chlordane serum levels are of 3 ppm and lethal serum rates are of more than 5 ppm in humans. Chlordane toxic activity is swift, happening within 2 h of an acute dosage with progress and regeneration after 24 h. Chlordane overdose does not induce residual neurotoxic symptoms [76].

During the administration of chlordane EEGs, random electrocortical activation and brain potential changes have been shown to exist without clinical symptoms of persistent toxicity. The random operation in all assemblies has improved dramatically. Elevation of amplitude and substitution of sinusoidal waves by fast, complicated discharges was observed. These variations were proportional to the length of treatment, suggesting that chlordane is a chronic neurotoxin. Chlordane is a chronic neurotoxin and electrocerebral disruption is an early and responsive indication of chlordane intoxication [77].

Other Neurological Disorders

Organophosphorus substances, that is, chlordane and heptachlor cause neurological problems such as multiple sclerosis. The results are not in consistent with the toxicity of chlordane [78]. The higher concentration of POPs is reported to induce attention deficit-hyperactivity disorder (ADHD). Different findings were observed in the research groups for PCBs, hexachlorobenzene and chlordane. The concentration of DDE, the key metabolite of DDT, was increased in these people. Additionally, neurodevelopmental dysfunction was recorded for dioxins and PCBs, but DDT seems to have been less examined in this regard [79].

Associations have been identified regarding serum concentrations of POPs in the groups of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans and the prevalence of ADDH. Prospective experiments continue to explain the existence of these interactions [80]. Prolonged use of aldrin has major negative effects on muscle function, thinking and memory. Aldrin impaired muscle synchronization in both groups; however. Greater degradation occurred in the male group. Unlike aldrin, endosulfan inhibited both cognitive capacity and a conditioned avoidance reaction. These symptoms are triggered by shifts in brain monoamines or by suppression of vision and reflexes, or both have been suggested for such behavioral consequences [81].

Treatment Strategies and Preventive Interventions

Organochloride Poisoning

Supportive treatment and identification of symptoms of end-organ injury (e.g., CNS, heart, kidney, liver) are the cornerstones of rehabilitation. No antidotes are available for OC poisoning but OP poisoning can be managed with antidotes [82]. Generally, patients of obvious nonsignificant and nontoxic contamination are required to stay in the emergency department for 6–8 h. If any signs or effects of toxicity occur during this period, the patient is usually admitted to the hospital.

Intensive care unit treatment is suggested for those with severe involvement or indications and effects of intoxication [83]. Attend to the ABCs (Airway, Breathing, and Circulation) and secure the airways at all times. Another key guideline is to allow skin decontamination by scrubbing with soap and water. Skin decontamination is better performed in the isolated and open area [84]. It is suggested to avoid emesis as the patient may have a drastic shift in mental state and there may be suctioning for gastric material. It is also recommended to avoid intense external stimulation to the patient that can precipitate seizures. It is best to initiate calming operation if the individual becomes hyperthermic [85].

Repeated evaluations of ABCs and vital signs of the victim are of severe significance in situations of acute poisoning. In addition, the safety of airways must be confirmed. It is suggested to allow early quick intubation to promote excessive benzodiazepine use. Seizures may begin without any paroxysmal symptoms. When the patient becomes unconscious during intubation, electroencephalogram monitoring is required. Attempt to stop seizure activity should be ensured by using conventional medications, beginning with benzodiazepines if clinically possible. Other symptomatic relief drugs can also be considered at this stage such as phenytoin, propofol and barbiturates if deemed required. Rhabdomyolysis may occur in patients with sustained convulsions or acute renal failure with or without hyperkalemia [86].

Incessant cardiac monitoring is advised for the intoxicated patient. β-blockers can be used if ventricular dysrhythmias are observed. If hypotension persists and the patient remains nonresponsive to fluids, IV phenylephrine, an alpha-adrenergic agonistic drug, should be considered [87].

Irrespective of the route of administration, it is recommended to consider activated charcoal because it can facilitate fecal removal of toxins. Patients treated with charcoal have more risk of epilepsy and eventual aspiration [88]. Cholestyramine can be used to interact with these lipophilic metabolites. Cholestyramine diminishes the reabsorption and keeps the binding agent in the GIT for fecal elimination [89].

Sucrose polyester is known to enhance the excretion of fat-soluble POPs. Whole-bowel irrigation may be indicated. Induction of diuresis, hemodialysis, and hemoperfusion enhances the elimination techniques [90]. In case of liver damage due to POPs, we can administer N-acetylcysteine that may prevent irreversible hepatic injury [91].

Organophosphorus Poisoning

Antidotes for OP poisoning are atropine, 2-PAM, and benzodiazepines (e.g., diazepam). Prompt treatment of the recommended dose of atropine should be initiated [92], as a large dose of atropine is essential to treat OP poisoning. For adequate and timely atropinization, doubling methodology of dosing is used, with cumulative dosing (1 mg to 2 mg, 4 mg, 8 mg, 16 mg,) and so on. On comparison, it is revealed that alone atropine cumulative dosing is found to be equally effective as atropine plus 2-PAM for OP poisoning [93].

Table 11.2 Specific antidote and treatment of POPs

Type	POPs	Antidote	Treatment
OC	PCB, Chlordane, Heptachlor, HCB, PCDD, PCDF, Toxaphene	No specific antidote	Activated Charcoal, Bile acid sequestrant, Cholestyramine, Beta blockers, Alpha adrenergic agonists, Anxiolytics, Anticonvulsants, General anesthetics, Beta 2 agonists, Anticholinergics
OP	Parathion, Malathion	2-PAM	Anticholinergics, Benzodiazepines

Symptomatic treatment along with the respective antidote is recommended in the early course of treatment [94]. A high dose of 2 PAM can be lethal, so a low dose (1–2 g slow IV) is suggested. Studies have proved that in the case of intermediately severe toxicity continuous infusion is found to be more effective as compared to intermittent bolus dosing [92]. In order to enhance the delivery of atropine and midazolam to achieve rapid atropinization, intraosseous administration is recommended [95]. Unlike IV administration, intraosseous administration requires professionally trained personnel to administer [96, 97]. The sublingual route of administration of atropine can also be used for intoxicated patients. This route can be useful in case of mass causality [98].

Glycopyrrolate can be used if the atropine is not available. Additionally, glycopyrrolate does not cross the blood–brain barrier [99]. Few studies have shown the benefits of adjunctive magnesium therapy in intoxicated patients [100, 101]. Furthermore the addition of ketamine in the standard therapy can protect the neurobiological symptoms of the poisoning [102]. Moreover, modern interventions include neuroprotective agents and bioscavengers that are expected to activate AChE, thereby enhancing the ACh elimination [103, 104]. Specific antidotes and treatment are shown in the Table 11.2 [105].

Conclusion

POPs are lipophilic compounds and they tend to bioaccumulate in fatty tissues for a very long time. Owing to their long half-lives, POPs remain concentrated in the human body for an extended period of time. POPs are poorly metabolized and have the hydrophobic nature that provides basis for its bioaccumulation in humans. POPs can cause neurological disorders by crossing the blood–brain barrier. Symptomatic treatment of the POP poisoningis recommended. It is a need of the hour that prompt actions be taken to minimize the exposure and production of these pollutants.

Conflict of Interest The authors declare no conflict of interest.

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Chapter 12
Polychlorinated Biphenyls and Neurological Disorders: From Exposure to Preventive Interventions

Mutayyba Fatima, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Polychlorinated biphenyls (PCBs) are industrially synthesized compounds that can produce hazardous reactions and diseases in human beings. They can cause multiple toxic effects in human beings ranging from mild effects such as some behavioural changes to severe effects such as neurotoxic reactions. Humans can be exposed to these PCBs in multiple ways such as combustion and burning of coal or wood or either via accidental exposure, for instance fire in buildings. PCBs are one of the most studied pollutants in the environment and have various congeners that differ from one another in positions and numbers of chlorine atoms. Metabolism of these PCBs occurs via cytochrome P450 mediated transformation that depends on their structural properties. There are many uncertainties in assessing PCBs-associated health risks as it involves a number of extrapolations and each extrapolation introduces uncertainty in the risk assessment. According to the mechanism of toxicity, the toxic congeners cause adverse effects at cellular level including effects on intracellular absorption**,** cell membrane, gap junctions and neurotoxic effects. Epidemiological studies suggest that nutrition and exercise can play a major role in the prevention and protection of human beings from the potential adverse health effects of PCBs.

Keywords PCBs · Neurotoxic effects · Persistent organic pollutants · Biotransformation

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Introduction

Polychlorinated biphenyls (PCBs) are commercial compounds in which biphenyl undergoes the process of chlorination and then these compounds are marketed based on their chlorine contents. These are also called as persistent organic pollutants (POPs). PCBs are toxic substances that were primarily used as dielectric fluids in electrical devices such as capacitors and transformers because of their chemical stability and physical properties. These are synthetic chemicals which are used as coolants and insulators in multiple electrical pieces of equipment. Even after getting banned for several decades, they still continue to exist in the outer environment as a result of their long half-life and also poor disposal practices. PCBs can accumulate in human beings and lead to a number of disorders including hypothyroidism, behavioural and cognitive problems. PCBs were the first among those industrial compounds which were banned worldwide because of the toxic effects they have on humans. Despite of the fact that their production on an industrial scale is banned, these compounds are still present in our bodies as they are present in the food mainly in poultry that we consume in our daily life. Once these compounds get into the body, they bind with fat and cause effects for the long term. Because of the toxic effects of PCBs, high bioaccumulation potential and persistence in the environment, they have received much attention. They have 209 congeners of varying degrees of chlorination. These include both less chlorinated congeners that undergo hydrolysis in the human liver upon ingestion and highly chlorinated congeners which are metabolically inert and upon ingestion leads to the accumulation of parent compound in body fat [1, 2].

Pure PCBs are crystalline, odourless compounds with colour varies from yellow to colourless. Commercial products mainly contain viscous liquid mixtures of PCBs. Their viscosity depends on number of chlorine atoms, the more the number of chlorine atoms, the more viscous liquid will be and depending on viscosity, the colour of the liquid will also be changed from light yellowish colour to dark colour [3]. At low temperature, instead of crystallization, PCBs are turned into solid resins. PCBs are inert in nature and they resist oxidants, alkalis and acids [4]. However, under some specific environment, PCBs can be destroyed by various biochemical and thermal processes.

PCBs possess remarkable insulating and thermoelectric properties because of which they are used in number of applications all over the world. Mainly, PCBs are used in capacitors and transformers as dielectric fluid, coolants, lubricants and as heat-transfer fluids [5, 6]. PCBs are highly stable and their mixtures are also used as plasticizers, in construction of industrial buildings as additives in sealant materials and as fire extinguishers [7]. At present, because of persistent and bioaccumulative properties of PCBs, they are widely distributed in environment and are known to cause various ecological and environmental issues [8, 9].

Types of PCBs

Depending on the pattern and structure of enzyme induction of PCBs, they can be divided into two groups.

Coplanar PCBs

This group of PCBs which are also known as dioxin-like (DL) PCBs does not have chlorine atom substitutions on ortho positions of both phenyl rings. They have dioxin like planar structure and consist of 12 congeners and are polychlorinated non-ortho and mono-ortho biphenyls. These types of PCBs are referred as DL-PCBs because of the two reasons. First, they bind with the same receptor to which dioxin binds, that is, aryl hydrocarbon receptor (AhR) and second they possess similar toxic properties as that of the dioxins [10, 11]. Humans get exposed to these DL-PCBs mainly through the animal fat present in the food [12].

Non-coplanar PCBs

Introducing two or more than two chlorines atoms at ortho position of PCBs, leads to a decrease in coplanarity among the two phenyl rings because of the steric interactions. These PCBs are called as ortho-substituted or non–dioxin-like (NDL) PCBs. They do not possess binding affinity for AhR. Although NDL-PCBs, such as PCB153, sometimes show a high percentage of total PCB congeners which are present in the environment, most of the adverse effects caused by complex PCB mixtures occur because of DL-PCBs [10].

Congeners of PCBs

PCBs are biphenyl derivatives which are formed by substituting the hydrogen atoms from one to ten with chlorine atoms. Each group of congener has a definite number of isomers: decachlorobiphenyl 1, nona- 3, −chlorobiphenyl 3, di- 12, tri- 24, penta- 46, tetra- 42, hexa- 42, hepta- 24, octa- 12. Total number of congeners of PCBs is 209 and a coding system having numbers from 1 (mono-Cl) to 209 (deca-Cl) is commonly used for these homologue's or chlorobiphenyls. PCBs are usually tasteless, odourless, colourless or light-yellow solids or oily liquids and some of them are volatile. Physicochemical properties of PCBs usually depend on the number of substituted chlorine atoms and their position of the attachment in biphenyl rings. PCBs are insoluble in water; however, water solubility increases with an increase in

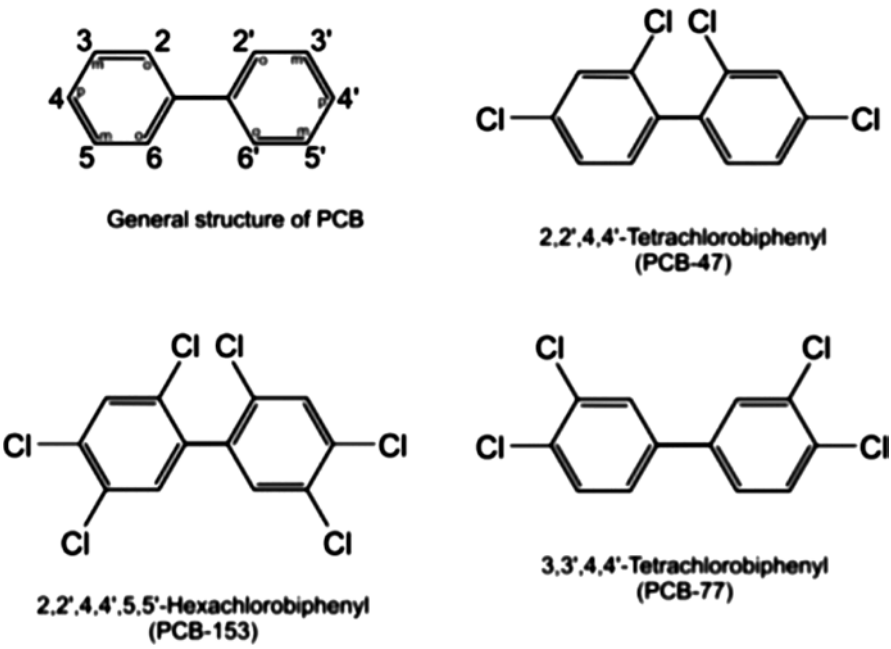

Fig. 12.1 General structure of PCB and some congeners

the number of chlorine atom [13]. The general structure of PCB along with the structure of three congeners is shown below in Fig. 12.1.

Sources of PCB Spreadability

Because of their broad range of application, they are widespread in the both abiotic and biotic environments, from where they get released into air during the following processes [14].

- Coal combustion.
- Burning of wood and coal.
- Incineration of waste material.
- Incidental events such as the fire in buildings.

PCBs are also released into the environment as a result of [15] the following.

- Migration of material from fireplaces or landfill sites.
- Illegal burning of plastic and other refuse in a domestic fireplace.
- Emission from some industrial procedures such as paper bleaching.
- Leakage from vehicles, machines and damaged transformers or heat exchangers.

PCB Exposure

Humans can be exposed to PCBs through the consumption of edible items such as dairy products, eggs and fish contaminated with PCBs. Human beings can also be exposed themselves with PCBs through the air or by drinking contaminated water or through direct contact with PCBs. The following are the three main ways through which humans can be exposed to PCBs.

Environmental Exposure

PCBs are environmental pollutants which have been released in the environment as a result of human activities. Although their manufacturing was banned years ago as these substances were lipophilic, bioaccumulative, degradation resistant, they are still present in significant proportions in the environment [16]. We can get exposed to PCBs through the food we consume, the air we breathe and the land we live (Fig. 12.2). The main sources of environmental PCBs are described below.

Airborne PCBs

PCBs belong to the class of organic compounds that are listed as POPs and banned worldwide due to their side effects. PCBs are emitted through various sources into the atmosphere. Indoor air, industrial and highly populated urban areas contain the highest proportion of airborne PCBs. A study investigated the indoor concentration of PCB in school buildings and blood levels of PCBs in teachers from these schools to get information about the potential health hazards posed because of PCBs present in indoor air. The result of blood analyses suggested that in spite of the high indoor PCB concentration level in the schools, the blood concentration of PCB in teachers showed only a moderate increase. The reason behind this can be the presence of only low levels of chlorinated PCB congeners [17].

Reported levels of PCBs in ambient air are generally more in urban areas majorly due to the different industrial processes resulting in the release of PCBs into the environment. A study conducted in the Indian city Kanpur has found that more than 50% of PCBs were present in ambient air. Human health risk via inhalation was estimated in terms of incremental lifetime cancer risk (ILCR) and lifetime average daily dose (LADD).The result of this study shows that the ratio of PCBs in the air is lower than guideline values and health risk obtained via inhalation are in the acceptable range which indicates that risk because of PCB exposure present in ambient air is minimum to adults [18].

Fig. 12.2 Sources of environmental exposure of PCBs

Eggs

Eggs are consumed on daily basis worldwide. Eggs also contain some proportion of PCBs through which the human body can be contaminated with PCBs. Eggs are one of the essential components of human diet all over the world. Although nutritional value is obtained from eggs, eggs can be contaminated with organic resistant pollutants. A study conducted in 2019 compared the effect of various types of chicken husbandry system on bioaccumulation of selected POPs. This study proves that the husbandry system affects the composition and levels of PCBs and other POPs in eggs. The presence of dioxin and dioxin like PCBs in foods such as eggs should be a subject of concern [19]. In 2013, a study was conducted in Turkey to find out the ratio of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), DL-PCBs and indicator PCBs in eggs and egg products. The concentration (pg/g fat) of these PCB congeners is presented in Table 12.1. The level of these contaminants in egg and egg products consumed in Turkey is less than the accepted levels of PCDD/Fs, PCDD/Fs and DL-PCBs and indicator PCBs as per Turkish Legislation [20].

Table 12.1 Level of environmental pollutants (PCDDs and PCDFs in (pg WHO-TEQ (2005) g^{-1} fat) and indicator PCBs in (pg g^{-1} fat) in eggs and egg products

Samples	Levels of contaminants		
	PCDDs	PCDFs	DL-PCBs and indicator PCBs
Eggs and pasteurized egg samples	0.247–1.527	0.282–1.762	202–1235
Egg yolk powder samples	0.122–0.494	0.214–0.640	217–1498

TEQ toxic equivalency

Soil

Soil represents an interesting reservoir of PCBs. Deposition of PCBs in the surface soil may lead to contamination of fruits, vegetables and food chains. The close proximity of surface soils to human beings can also result in human exposure via consumption of contaminated fruits and vegetables, and the occupational exposure through inhalation while breathing, ingestion and direct skin contact pathways. As a result of this exposure, PCBs will induce the detrimental effects on human health. Studies have shown a continuous increase in the ratio of PCBs in the environment of India [21]. First attempt in order to investigate the occurrence of PCBs in the soil and to determine the diffusive air-soil exchange, at both regional and local scales within the metropolitan Indian environment was made in 2016. For this study, different cities were selected from north and south India. As a result of this study, quantity of 33 PCB homologues were evaluated in the soil collected from surface and then possible sources of these congeners were derived using "positive matrix factorization" model. Mean σ33 PCB concentration in the surface soil (12 ng/g dry weight) was approximately two times the concentration found in the global background soil but almost equal to findings from Pakistan and urban sites of China. Heavier PCB congeners (6CB-8CB) were prevalent mostly in urban centres. Data collected from these cities provide evidence that surface soil is acting as a reservoir for heavy-weight PCB homologues and as a source for lighter-weight PCB homologues [21]. Another study was also conducted in India in order to estimate the daily intake of PCBs and their corresponding increased risk on various health conditions. This baseline study provides the database in the tropical countries and may also be useful in the risk assessment of industrial PCBs on the human population. This study concluded that proportion of POPs including DL-PCBs were less as compared to the recommended guidelines of the soils for the protection of environment and human health [22]; however, in estimated levels of PCBs, tri-chlorinated and tetra-chlorinated biphenyls were prominent. The sources of PCB contamination in the industrial city Korba can be emissions from local industries and long-distance transport depositions [22].

Fish and Seafood

Fish and seafoods are also one of the major contributors in exposing humans to PCBs. When living organisms consume fish and seafoods intoxicated with POPs, these PCBs enter the human body through ingestion. The ratio of PCBs and their deleterious effect on health depend on the concentration of PCBs present in fishes consumed by other fishes. A study has been conducted in order to check the distributional patterns of PCBs in the wild fish of Hong Kong and to estimate the health hazards related to their consumption. Two types of organic environmental pollutants, dichlorodiphenyltrichloroethane (DDT) and PCBs, were determined in 31 types of wild fish, which were caught from the coastal areas of Hong Kong. The findings of this study show that the proportions of DDT and PCBs in the wild fish were at a level which exists at the low end of the global ranges. Feeding habits as well as marine environment of fish may have some effect on DDT and PCBs bioaccumulation in them. Assessment of human health risks suggested that the increase in lifetime cancer risk of paediatric and adult inhabitants exposed to DDTs and PCBs through consumption of wild fish was higher. Because of this, the local residents of Hong Kong should decrease their daily consumption of wild fish, which they caught from the surrounding coastal areas [23].

Similarly, in another study, the level of PCB congeners was estimated in the coastal waters in Bangladesh. Although, at present, the use of PCBs at industrial level is severely restricted, findings of this study depict that contamination of these congeners is widespread in the coastal environment of Bangladesh and it is assumed that continued use or historical usage are the main reasons behind this. According to the results, PCB ratio in the Bangladeshi coastal waters is more than existing national and international guidance levels and can potentially damage the ecological environment as well as human health [24].

Accidental Contamination

Accidental contamination with PCBs can also result in high levels of POPs inside the human body. This exposure can occur through an incidental event such as fire or by consuming food items that are accidentally contaminated. The best known example of this type of contamination of edible items is Yusho (Japan) and Yu-Cheng (Taiwan) food poisoning. This pandemic occurred because of mass food poisoning which was caused by the consumption of commercial brand rice oil which was contaminated by PCBs. A similar incident occurred in Taiwan in 1979. The diseases caused are named as Yusho disease and Yu-Cheng disease, respectively. The main signs and symptoms of the diseases include increased discharge from eyes, numbness, and pigmentation of the skin, nails and conjunctivas [25].

An incident of accidental contamination of PCBs of animal feed is Belgian PCB incident that occurred at the end of January 1999. In this incident, a mixture of PCB congeners was accidentally added into the stock of recycled fat which was used to

manufacture the animal feed. PCB food monitoring program was implemented after this incident, which provided the information that contamination was limited and affected only 0.5% of farms of the country [26].

Occupational Contamination

Many investigators, who evaluated the levels of PCBs in workers by analysing the adipose or blood samples, have reported the occupational exposure of humans to PCBs. However, the intensity of this exposure is directly related to the duration of exposure and toxic potency of the PCB congener [27]. Some industrial activities which contain unintentionally produced 2, 3, 7, 8-TCDD such as the manufacturing of chemicals and pesticides and waste incineration may also result in additional human exposure to PCBs.

In an experimental study, industrial exposure to PCBs and internal dose was investigated in 80 workers who were exposed to PCB mixtures with 42% chlorine content for many years. Liquid gas chromatography was used to determine the PCBs in samples that were taken from air, surfaces and tools of the workroom and from the palms of hand and blood of the workers. All tested surfaces, tools and air collected from the workroom were heavily contaminated. In blood samples of the workers, total PCB concentrations in the range of 88 to 1319 μg/kg were observed [28]. These findings provide the result that PCB absorption mainly occurred via skin in these workers and because of this, the industrial preventive surveillance should take this route of PCB exposure into account.

Levels of PCB Exposure

Acute High-Level Exposure

Acute high-level of PCB exposure can cause different types of skin rashes and acne in adults or children exposed to PCBs. The type of acne which is caused by PCB exposure is known as chloracne and in appearance, it is almost same to that of the regular acne [29]. However, the major side effects of PCBs were normally experienced by the children who were born by the exposed mothers. Based upon the follow-up studies of two incidents that occurred in Japan and Taiwan, it was concluded that pregnant mothers exposed to high levels of PCBs can have children having the following problems that lasts from months to years after birth: darkening of skin colour, abnormal behaviour, facial abnormalities, nail changes and altered IQ [30].

Chronic Low-Level Exposure

Chronic low-level exposure can cause the following effects in children born by PCB-exposed mothers: altered thyroid function; problems with the immune response; increase in certain forms of cancer [31]. A study was conducted in order to focus on the reconstruction and prediction for China for long-term emission trends of intentionally and unintentionally produced PCBs and PCBs re-emissions from the secondary sources such as soils and vegetation. From the results, it was suggested that primary sources still dominate; however, many unintentional sources are predicted to become a main contributor till 2035 for PCB-28. E-waste that is imported from other countries is also thought to play an increasing role until 2020–2030 on a national scale because of the decrease in intentionally produced emissions. Hypothetical emission conditions estimate that China could become a potential source of PCBs to neighbouring countries with a total output of ~0.4 ton/year by around 2050 [32].

PCBs-Induced Disorders

PCB exposure can result in serious diseases. PCB exposure can increase the risk of several diseases notably cancer, cardiovascular disease, reproductive and metabolic disorders, recurrent infections, neurobehavioral effects and Parkinson's disease.

Cancer

According to the International Agency for Research on Cancer, PCBs have been identified as Group 1 known human carcinogens. The specific cancer type with strongest documented evidence is malignant melanoma. However, there are many other types of cancers for which strong associations with serum PCB levels have been found [33–35]. PCBs which have been found in human tissues for decades are tumour promoters but their contribution to cancer risk now starts to appear that is because of the long human cancer latency and nature of tumour progression. Epidemiological associations have been seen between the PCB exposure or tissue content and cancer [36]. Mechanistically, the agent which alters the DNA sequence irreversibly such as a genotoxic compound is called initiator while an agent that alters the expression of genetic information (epigenetic changes) in the cell is known as a promoter [37]. The administration of PCB mixtures and certain congeners for the long term may lead to the development of hepatic tumours. PCBs by definition act as both initiators and promoters. Except liver tumours, many PCB mixtures and PCB homologues were reported to promote the lung tumours in mice model. It has

been reported that PCBs can also cause the lung tumours in experimental animal models [36].

Cardiovascular Disorders

Cardiovascular disease (CVD) is still the main cause of death in many developed nations. Multiple factors including environmental and chemical exposures contribute to CVDs. Evidences from epidemiological, in vitro and in vivo studies relate the CVDs with PCBs present in the environment [38]. It has also been reported that there is a dose-dependent relationship between the serum levels of PCBs concentrations and CVDs [39]. Rate of hospitalization of patients suffering from coronary heart disease and myocardial infarction in New York State residents living in a zip code was examined. This study compared the rates of hospitalization of patients living in zip code having landfill or PCB waste site with those living in a zip code without any hazardous PCB waste site after the adjustment of factors like age, sex, income and health insurance coverage. These results show that people living in a zip code having a PCB hazardous waste site (it can be either a landfill or a contaminated body of water) are directly associated with an increased incidence of coronary heart disease and myocardial infarction [40].

Reproductive Disorders

PCBs can also have an effect on human reproductive health. The study described here focuses on the side effects of PCBs on reproductive health in humans from four diverse populations, including the following.

1. Inuit population from Greenland.
2. Swedish population of fishermen and their wives.
3. Urban populations from the cities of Warsaw in Poland.
4. Kharkiv in Ukraine.

These populations represent the considerable variations in the exposure levels of PCBs due to the differences in the consumption of contaminated food items. Due to bioaccumulation of PCBs and their long half-lives in humans, these substances are still ubiquitously detected in various populations. The results of this study have suggested that PCB-153 can affect both male and female reproductive functioning in Arctic and European populations at the level of PCB exposure currently experienced in these populations [41]. PCBs are highly persistent organic substances that bioaccumulate in the food chain and can cause a variety of side effects in humans including alterations of reproductive function. However, the exact mechanism by which PCBs can exert side effects is not completely understood yet [42].

Metabolic Disorders

PCBs have potential to cause various metabolic disorders such as hepatic steatosis, obesity, diabetes mellitus and dyslipidemia [43]. Diet containing antioxidants may help to overcome the toxic effects of PCBs. Gut microbiome is sensitive to the environmental pollutants and diet and regulates the metabolism of host. Exposure to dioxin like PCBs occur mainly through the food consumed and can increase the incidence of developing various cardio-metabolic disorders [44]. A possible indication of altered gut health is gut or systemic inflammation which increases due to the presence of PCB 126 [45]. PCB exposure can also play a crucial role in increasing the chance of hospitalization of diabetic patients. Kouznetsova et al. analysed New York State hospitalization data admissions for diabetes of adults in relation to residence in a zip code having PCB-contaminated landfill site. Living in a polychlorinated biphenyl contaminated zip code was related to 23% increased chance of hospitalization for diabetic adult patients as compared to the rates of residents of zip code without a landfill, after adjustment for race, age, sex, urban/rural residence and median household income [34].

Recurrent Infections

Immune system suppression is a critical factor because individuals with weak immunity show more susceptibility towards infections and autoimmune diseases. PCB exposure can suppress both cellular immune response and immunoglobulins. Repeated reoccurrence of infections can occur because of the PCB exposure. In the past, it was considered that immune suppression is the only biologic effect that occurred at the lowest PCB concentration; however, now, it is believed that neurobehavioral effects occur at even lower doses than the doses required for immune suppression. Findings from human studies have suggested that individuals who are exposed to PCBs have a greater risk of all types of infections because of the suppression of immune system [35]. It is reported that family earnings of people who live along the Hudson River in New York is high as compared to the other upstate residents. Data from Behavioural Risk Factor Surveillance System shows that most people there smokes less, do more exercise and consume healthy food as compared to other New York inhabitants but still they show higher hospitalization rates for chronic respiratory infections. It is suggested that the reason behind this is, they have suppressed immune system due to higher rate of exposure of inhalation PCBs from the river nearby [35].

PCBs-Induced Neurological Disorders

Brain has been identified as a vulnerable target of persistent environmental pollutants in many preclinical and epidemiological studies [46]. Though the production of PCB is banned, it is still a potential risk factor for human health. PCBs are associated with neurodevelopmental disorders and neurotoxicity. Epidemiological studies relate PCB exposures with increased incidence of neuropsychiatric deficits in children [47]. Many neurotoxic PCB congeners show axial chirality and affect cellular targets resulting in PCB neurotoxicity [48]. The following are the neurological disorders whose risk of incidence increases with PCB exposure.

Impact on Intellectual Function

Exposure to PCBs has been associated with toxic impact on intellectual function in both geriatrics and young children. In a study conducted by Schantz et al. in order to determine the effect of PCB exposure on intellectual functioning during adulthood, he studied memory function in total of 572 adults of the age between 49 and 86 years old, who consumed a large proportion of contaminated Great Lakes fish and 419 people who did not eat fishes. He used three memory tests and a number of visual tests to assess the side effects of PCBs on intellectual function. The serum level of PCBs and a number of other contaminants were detected in those adults. According to the result of this study, adult performance of all three memory tests were reduced as the PCB dose elevated but PCB exposure did not have any effect on the visual tests. This experimental study is very significant as it shows that even adults can have a particular loss of intellectual function and memory upon PCB exposure [49]. The conclusion of this study is that if in early life, the child's PCB exposure level is higher, the child will have low intelligence quotient and possess more anti-social behaviour such as depression and attention deficit hyperactivity disorder symptoms. In adults who are exposed to PCBs, a decrease in the intelligence quotient is paralleled by reduction of memory [50].

Parkinson's Disease

Various epidemiological studies have identified the exposure to PCBs as a major risk factor for Parkinson's disease and are more prevalent in women. Patients already suffering from neurodegenerative diseases can exposed to these substances as early as in their adolescence. The presence of these substances in the brain provides the cumulative and toxic kinetic features which are the indication of chronically acting neurotoxicants [51]. PCBs possess many features such as chemical stability, low volatility and lipophilic properties which not only allow them to

remain persistent in the environment but also enable them as ideal candidates for being involved in the risk of developing Parkinson's disease. Additionally, PCBs' tendency of bioaccumulation and biomagnification can further increase the chances of their toxic level accumulation [51].

In order to determine the relationship between the Parkinson's disease risk and PCB exposure, a study was conducted in which 594 PCB exposed subjects were selected among which 369 were females and 225 males. On these subjects, transcriptome gene expression analysis was applied. As a result, it was observed that non–co-planar PCB blood levels of males showed no association with the expression levels of Parkinson's disease-specific genes; however, non–co-planar PCB blood levels in females somehow was associated with the expression levels of Parkinson's disease-specific genes. Out of 131 Parkinson's disease-specific genes which were affected, 39 Parkinson's disease–specific genes showed similar changes in their expression level in substantia nigra of deceased Parkinson's disease patients [52].

In another study which was conducted to determine the link between PCB levels in the post-mortem human brain tissue and Parkinson's disease, findings showed an association between the brain PCB levels and risk of Parkinson's disease. Females were more susceptible and had a higher risk of Parkinson's disease from PCB exposure when compared to males [51].

Alzheimer's Disease

From the outcomes of a cohort study which evaluated the mortality among a cohort of 24,865 workers who were manufacture capacitors at plants in various cities and get exposed to PCBs, it was observed that Alzheimer's disease showed no positive relationship with PCB exposure and this disease did not elevate the mortality rate in workers [53].

Dementia

Human exposure to PCBs can lead to various neurologic disorders including PCB-induced dementia. This type of dementia can be characterized by abnormally fast rates of forgetting on verbal and nonverbal memory tests and impairments in confrontation naming. Many epidemiological and clinical studies indicate that patients have many neurological complaints such as headache, depression, vertigo when exposed to PCBs but only a limited number of patients can show these complaints on objective neurological measures. A study which included neuropsychological test data of patients exposed to PCBs highlighted the following three points [54].

- If humans remain exposed to PCBs for longer duration, they can develop a rapidly progressing dementia which can be complicated by an organic affective syndrome.
- Dementia secondary to PCB-exposure can have some same features which dementia of the Alzheimer's type possesses.
- Neuropsychological testing can provide an early index of PCB-induced neuropathology even in cases when other studies such as radiological studies are negative.

Amyotrophic Lateral Sclerosis (ALS)

Neurotoxic substances including PCBs have been suggested to play crucial role in the aetiology of amyotrophic lateral sclerosis (ALS). A study was conducted in order to determine whether PCBs and other POPs affect ALS. From the findings of this study, it was concluded that higher concentrations of PCBs are associated with reduced ALS survival and this reduction in survival rate is not dependent on age, gender and other covariates. This study provides a supports to the idea that exposure of POPs and PCBs can play a role in the disease pathogenesis [55].

Another study was conducted in Michigan to determine the link between occupational exposures of various POPs including PCBS and development of ALS. The findings suggested that blood levels of these pollutants were associated with ALS and can represent a modifiable risk factor in ALS [56].

Mechanism of PCBs-Induced Neurotoxicity

PCBs are metabolised via microsomal monooxygenase system to phenols (through arene oxide intermediates) and this process is catalysed by CYP450. These phenols can be further hydroxylated into catechols. These intermediates are electrophilic in nature and can bind to the nucleophilic cellular macromolecules (e.g. protein, RNA, DNA) by covalent bonding and after binding, cause DNA strand breakage and DNA repair, which contributes to the toxic response of PCBs. In addition, arene oxide intermediates can also form conjugates with glutathione and after undergoing further metabolism form methyl sulphonyl metabolites. Binding of these metabolites to some proteins may contribute in adverse impact of PCBs. It has been proposed that hydroxylated PCB metabolites can also contribute to PCB toxicity [57, 58].

Mechanism of PCBs-Induced Neurotoxic Effects

PCBs are among the most experimented environmental pollutants and through the intensive research; it has been suggested that PCBs act on a variety of neurochemical and neuroendocrine targets. The most likely targets of PCB exposure are summarised in Table 12.2 [59] and are described in the following subheadings.

Neurotransmitter Systems

Ortho PCBs induce the release of biogenic amine in dopaminergic cell cultures and brain preparations. The effect of PCBs on dopamine depends on whether animals are exposed to PCBs in developmental stage or in adulthood. PCB exposure will result in inhibition of plasma membrane dopamine transporter (DAT) in synaptosomes and inhibition of the vesicular monoamine transporter (VMAT). This will lead to the reduction in brain serotonin levels and alteration of DA level and its turnover in brain [59].

Calcium Homeostasis

Ortho PCBs increase the intracellular level of calcium by releasing the calcium from both intracellular and extracellular stores. The increased calcium level will affect the calcium haemostasis in synaptosomes and other cells. Calcium signalling is essential for proper functioning of the cells and this sustained increase in the intracellular level of calcium will have a detrimental effect on neurons [59].

Table 12.2 Mechanisms of neurotoxic effects of PCBs

Targets of PCB exposure	Types of PCB	Toxic effects	Mechanism of action
Neurotransmitter system	Ortho-PCB	• Alters DA levels • ↓ Serotonin brain levels	Inhibits VMAT in synaptic vesicles and plasma DAT in synaptosomes
Calcium homeostasis	Ortho-PCB	• Alters calcium homeostasis • Sustained increases in intracellular calcium are detrimental for neurons	↑ Skin intracellular calcium level
Oxidative stress and cell viability	Non-coplanar PCBs	• Induces cell death • Induces oxidative stress	PCBs ↑ ROS formation ↑ Intracellular calcium level Neurotransmitter receptor activation

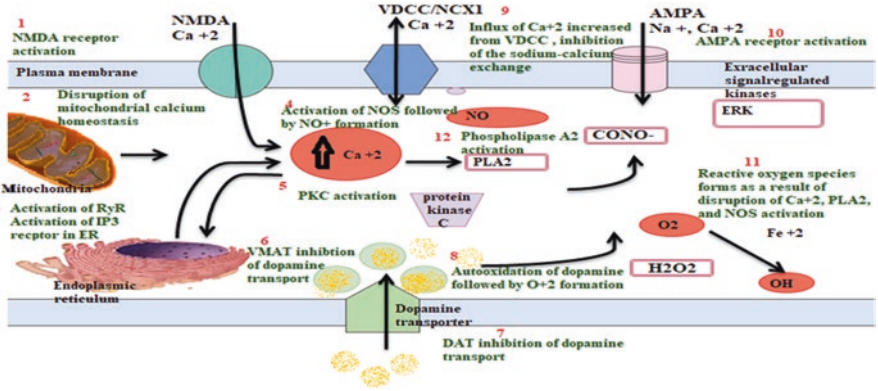

Fig. 12.3 Summary of PCBs-induced neurotoxic effects

Oxidative Stress and Cell Viability

Non-coplanar PCBs induce in vitro cell death by apoptosis and necrosis, the major causative factor of which is oxidative stress. Non-coplanar PCBs increase the formation of ROS in cerebellar granule cells. PCBs effect the cell viability and oxidative stress by increasing the intracellular calcium levels, alternating neurotransmitter compartmentalization and by neurotransmitter receptor activation. Elevation of intracellular levels of calcium can activate various signalling pathways, from which many pathways can induce oxidative stress [59, 60]. All of these effects may result in the activation or inhibition of number of signal transduction enzymes such as protein kinase C, nitric acid synthase activity, synaptic plasticity for instance long-term depression or long-term potentiation and decrease cell viability [59]. A summary of possible neurotoxic effects caused by PCBs is shown in Fig. 12.3.

PCB Congener–Specific Effects at Cellular Level

PCB Congener–Specific Intracellular Absorption

Congener specific cellular absorption of PCBs is crucial for PCB bioaccumulation and toxic activity in organs. In order to gain the knowledge related to the nature and rate of PCB absorption, Ghosh and co-workers exposed hepatic and renal cells to two PCB congeners (PCB-153 and PCB-77). Within 30 min, almost 40% of PCB-153 congener was identified in hepatic G2 cells and it attained its peak level after the 6 h, along with PCB depletion in the medium. For PCB-77 congener, the peak levels within liver cells were reached after 3 h. And in renal cells (HK2), the absorption level of both congeners, PCB-153 and PCB-77 attained their highest concentrations at 3 and 6 h respectively. It was found that hepatocytes can start the

absorption of PCB congeners much rapidly as compared to that of the kidney cells, regardless of the fact that the level of PCB congeners attains its peak level much earlier in the renal cells. This variation in the uptake rates of kidney and liver cells can occur because of different lipid composition of the hepatic and renal plasma membranes, and the rates of dissolving of two polychlorinated biphenyl congeners in them [61, 62].

PCB Congener-Specific Cell Membrane–Related Toxic Effects

PCB congener can also cause specific toxic effects on cell membrane. PCB 52 can cause death of thymocytes by elevating the level of calcium ions, reducing mitochondrial membrane potential and increasing cell membrane permeability, leading to the loss of integrity of cell membrane [63]. PCB 153 can cause attachment of leukocytes to brain endothelial cells and stimulation of NADPH oxidase complex formation in raft domains. This leads to an increase in superoxide production [64]. It also stimulates Src/JAK/EGFR redox signalling and cause the upregulation of CAM expression. PCB 153 through this mechanism, activates the endothelial cells of human brain. PCB 128 can kill neurons in cerebellar granule cells by increasing level of calcium ion, decreasing mitochondrial membrane potential resulting in loss of cell membrane integrity rapidly, resulting in death of neurons [63]. The toxic effects of such types of PCBs are summarised in Table 12.3.

PCB Congener-Specific Impact on Gap Junctions

The toxic adverse potential of PCBs results in numerous deleterious effects on human health. One among the various presented mechanisms of PCBs carcinogenicity is the downregulation of gap junctional intercellular communication (GJIC) and/or Cx expression in a broad range of tissue and cellular models, including human keratinocytes and epithelial cells of human breasts [65]. Phosphorylation of connexin is involved in the regulation of communication of gap junctions at several stages in the Cx “life cycle” including the following.

- Hemi channel oligomerization.
- Protein export to the plasma membrane.
- Hemi channel activity and assembly of gap junction.
- Gap junction channel gating and Cx degradation.

PCB-153 interferes with proper transport of connexin-43 to cell membrane, which can be related to the direct lysosomal degradation of endoplasmic reticulum (ER)/Golgi compartment–trapped connexin-43. PCB-153 can also interfere with the restoration of gap junction plaques [66]. NDL-PCB congeners with 2,2′6 substitution including PCB-19, PCB-51, PCB-53, PCB-95, PCB-104 and PCB-136 had

Table 12.3 PCB congener–specific cell membrane related toxic effects

PCB congener	Cellular module	Toxic effects	Mechanism of induction	Ref.
PCB-52	Thymocytes	Cell death	• ↑ of Ca^{2+} levels • ↓ Mitochondrial membrane potential • Loss of cell membrane integrity • ↑ In cell membrane permeability	[63]
PCB-153	Human brain endothelial cells	PCB-153 activates human brain endothelial cells	• Leukocytes adhesion to brain endothelial cells • Stimulate formation of NADPH oxidase complex • ↑ Superoxide production • Stimulate Src/JAK/EGFR redox signalling • Upregulation of CAM expression	[64]
PCB-28	Cerebellar granule cells	Kill neurons	• ↑ Ca^{2+} level • ↓ Mitochondrial membrane potential • Cause loss of cell membrane integrity rapidly	[76]

moderate potencies for GJIC inhibition [67]. PCB-153 decreases connexin-26 (*Cx-26*) mRNA expression along with PCB-126 and PCB-77. PCBs also reduce the mRNA expression *of Cx-43*. *Connexin-32* mRNA expression decreases under the influence of both PCBs 126 and 77 [68]. PCBs inhibit GJIC and reduce the expression of connexion 43 in neural stem cells [69]. Figure 12.4 shows the PCBs disturbed regulation of gap junction intercellular communication at various steps during the life cycle of connexion.

Biotransformation of PCBs

PCB congeners vary in the number and position of chlorine atoms. Metabolism of PCBs mainly depends on the position and number of chlorine atoms within the molecules which means biotransformation depends on the structural properties of PCBs [70]. PCB metabolism is inversely proportional to the number of chlorine atoms on biphenyl; less the number of chlorine atom on biphenyl ring, the rapid would be the metabolism of PCB. Moreover, the presence of vicinal non-chlorine substituted sites, mainly at the meta and para positions of the biphenyl moiety of PCB elevates the incidence of transformation by CYP450-mediated transformation. Eventually, the fate of PCB depends on its structural properties inside the human body. PCBs containing higher chlorine numbers are resistant towards the process of

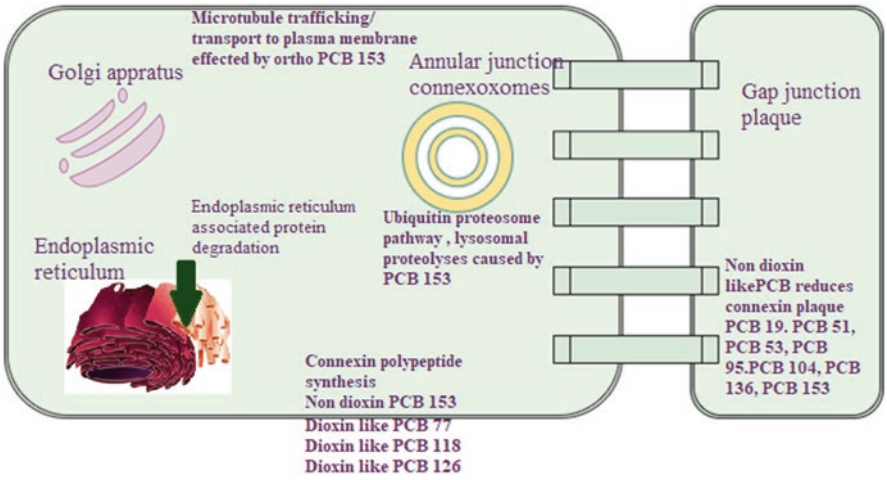

Fig. 12.4 Schematic representation of PCBs disturbed regulation of gap junction communication at various stages of the life cycle of connexion

biotransformation reactions and because they are highly lipophilic they tend to retain in plasma or adipose tissue [70].

Steps Involved in the Biotransformation of PCBs

A general scheme of metabolism of a PCB homologue (CB-101) is shown in Figs. 12.5 and 12.6 along with enzymes involved in different steps of the metabolism of PCB.

Activation

It is the first step in the biotransformation PCB. This step is catalysed by CYP450, which causes the oxidation of PCB congener to form arene oxide.

Deactivation

In the second step, the arene oxide is deactivated to a PCB. The hydroxyl group can also be inserted through a direct mechanism. The formed arene oxide intermediate may undergo 1, 2 shifts.

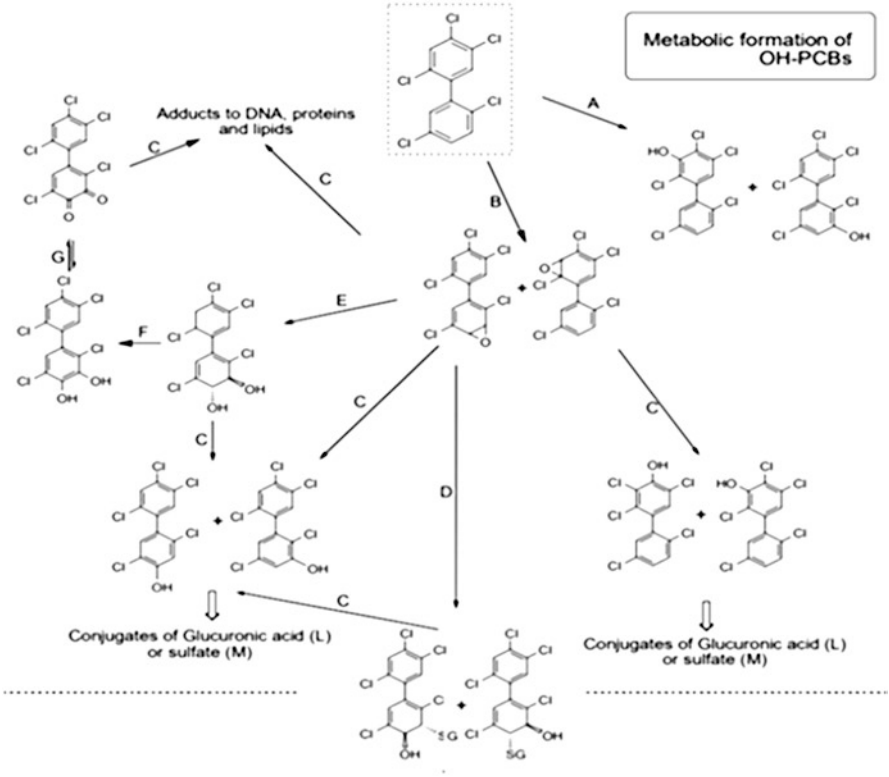

Fig. 12.5 General scheme of PCB congener (CB-101): Metabolic formation of OH-PCBs; Enzymes involved in the metabolic pathways labelled as A, B, C, D, E and F are A: CYP450 enzyme system, CYP_{2B} (rodents); B: CYP450 enzyme system, CYP3A4 (humans); C: Non-enzymatic reaction; D: Glutathione S transferase; E: Epoxide hydrolase; F: Dihydrodiol dehydrogenase. (Adapted from [57])

Conjugation

This step is done to improve the water solubility of intermediates. A huge number of hydroxylated PCBs are excreted out from the body directly or after forming conjugate by reacting with some endogenous compounds such as sulphate or glucuronic acid. Another way by which deactivation of PCB arene oxide occurs is through conjugation with glutathione. Glutathione conjugate is cleaved to polychlorinated biphenyl cysteine. For the formation $MeSO_2$-PCB, thick cysteine conjugate is cleaved by an enzyme which is present in intestinal microflora known as C-S-lyase enzyme and thus forms PCB thiol. This metabolite can either by methylated to form PCB methyl sulphide or excreted without conjugation or after it. The PCB methyl sulphide formed in the intestinal tract is absorbed and then undergoes oxidation to form $MeSO_2$-PCB in the liver [57].

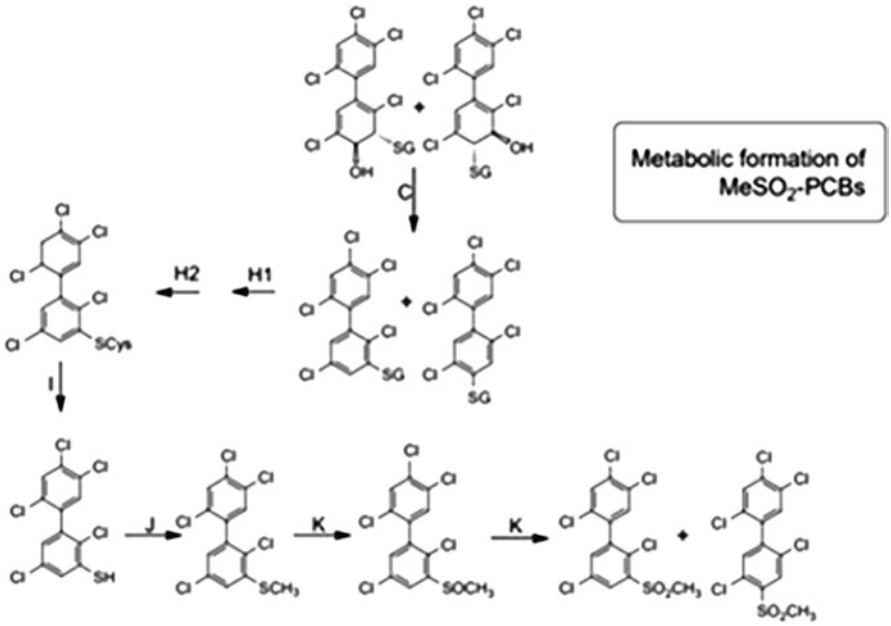

Fig. 12.6 Metabolic formation of $MeSO_2$-PCBs: Enzymes involved in the metabolic pathways labelled as G, H, I, J and K are G: Autoxidation and peroxidase, H: Mercapturic acid pathway 1) glutamyl transferase and 2) cysteinyl glycinase, I: C-S-lyase, J: S-adenosylmethionine S-Methyltransferase (SAM), K: CYP-mediated S-oxidation. P450 or FAD containing mono-oxygenase. (Adapted from [57])

Tolerable Daily Intake of PCBs

In 1990, the Joint FAO/WHO Expert Committee on Food Additives concluded that it was not possible to establish an accurate numerical figure for a tolerable daily intake (TDI) of PCBs for humans because the data available was very limited. Generally, PCBs were classified as carcinogenic to human beings. However, at the national level, government starts employing TDI for PCB congeners for the purpose of risk management. Tolerable daily intake of polychlorinated biphenyls for human has been set at 20 ng/kg body weight/day (over the whole life). This has been calculated from the Lowest Observed Adverse Effect Level (LOAEL) of one specific PCB mixture which is Aroclor 1254, on the immune systems of rhesus monkeys. In this case, for calculating TDI for human the minimum level of polychlorinated that gave rise to adverse toxic impact in animals from LOAEL was divided by an overall uncertainty factor of 300, which depicts possible differences in susceptibility among experimental animals and human [71].

Health Policy Regulations for PCBs

For the protection of the public and workers from the potential adverse health effects of PCBs, the US government has developed some standards and regulations for PCBs which have been summarized in Table 12.4.

Uncertainties in Assessing the PCB Health Risks

Assessment of health risks of PCBs usually include a number of extrapolations [72], such as the following:

- Experimental animals to human beings.
- Higher doses to lower doses.
- One route of exposure to another.
- Short-term to lifetime exposure.
- Healthy adults to children.

Table 12.4 Standards and regulations for PCBs

Standards		Organization	Limit of PCBs	
Workplace standards	Air	OSHA	PCBs having 42% chlorine	1.0 mg/m^3 for average molecular formula of $C_{12}H_7Cl_3$
			PCBs having 54% chlorine	0.5 mg/m^3 for an average molecular formula of $C_{12}H_5Cl_5$
		NIOSH FDA		10-h time-weighted average of 1.0 μg/m^3
Environmental standard	Drinking water	EPA	For drinking water's maximum contaminant level	Zero
			For PCBs in public water systems maximum contaminant level	0.0005 ppm
	Food	FAO WHO	Daily PCB intake	6 μg/kg per day
		FDA	All foods	0.2–3.0 ppm
			Fish	2.0 ppm
			Food-packaging materials	10 ppm

OSHA The Occupational Safety and Health Administration, *NIOSH* National Institute for Occupational Safety and Health, *FDA* Food and Drug Administration, *FAO* Food and Agriculture Organization, *WHO* World Health Organization

Every extrapolation incorporates the uncertainty in the assessment of risk of PCBs because every extrapolation makes a likely assumption to complete the lacking data.

Uncertainty in Extrapolating the Data from Animals to Humans

During risk assessment, it might be assumed that results from animal studies can be equally applied to humans which means that the risk is directly proportional to the total dose regardless of exposure scenario. Laboratory animals used in experimental studies on which the calculation of TDI is based can be more sensitive to PCB exposure than humans.

Human Variation in Biologic Susceptibility

Studies regarding risk assessment can also assume that children and adults both are equally susceptible. Children can be more susceptible to PCB exposure than healthy adult populations.

Uncertainties Due to the Nature of PCBs

PCBs are very complex mixtures having 209 congeners which have different physicochemical and toxicological properties. The lack of proper information on the extent of lot differences and topological implications has contributed much to the uncertainty in assessing the potential health risks associated with PCBs. Most of the studies on PCBs consider mixtures of PCBs for study rather than individual homologues which might have different mechanisms of action.

Uncertainty Because of Environmental Processes

Environmental processes (Fig. 12.7) can also alter the PCBs mixtures after their release in the environment and in this way, people can be exposed to polychlorinated phenyl mixtures of PCBs that might not resemble those mixtures which were the subject of human observational studies or animal experiments.

The combined effect of environmental processes results in the substantial uncertainty. From the data in the past four decades, it can be seen that new studies allow for better health risk assessment in humans. New studies have responded to the unavailability of proper database on commercial PCBs and related compounds of

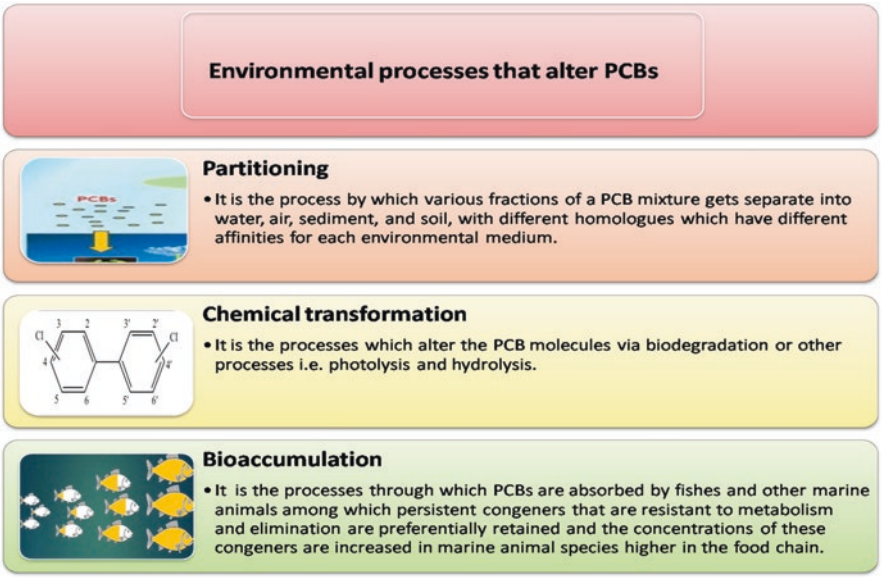

Fig. 12.7 Environmental processes that alter PCBs

different composition and on PCB mixtures which resemble the mixtures present in the environment. In the case of human studies, in which health outcomes were first seen for PCBs with high levels of PCDFs, later studies investigated other populations exposed to much lower PCDF levels. With the establishment of new testing methods for obtaining mechanistic information, it is thought that our understanding of polychlorinated biphenyls toxicity will continue to increase further and new data can reduce the uncertainty in assessing health risks [72].

Preventive Interventions Against PCB Exposure and Associated Disorders

The following are the most important interventions which can help in the prevention and protection of human beings from toxic effects of PCBs.

Impact of Nutrition on PCBs-Induced Toxicity

Awareness about the diet-derived molecules that can modify and possibly help to prevent the of toxicity of environmental pollutants including PCBs is increasing. Well-defined modulators of chronic disorders mainly include nutrition and lifestyle

and collected pieces of evidence are suggesting that dietary component may be able to modulate toxic effects related to POPs, such as PCBs. It is necessary to explore the impact of nutritional factor regarding the protection from environmental toxicology and to improve the understanding and knowledge about the relationship between nutrition and lifestyle, exposure to environmental toxins including PCBs and disease. Strategies to completely reduce these toxins and pollutants from environment are extremely difficult and costly. Dietary interventions act as an efficient, safest and most sensible way to prevent or decrease the harmful effects of these environmental toxicants such as PCBs. Multiple recent studies have suggested that some particular dietary fats can elevate the risk of PCBs-induced diseases however other dietary factors for instance omega-3 fatty acids can provide protection from such environmental toxin-induced diseases [16]. It is well recognized that the diet in Western countries is omega-3 polyunsaturated fatty acids deficient but possess increased amounts of omega-6 polyunsaturated fatty acids. Adjusting these ratios of omega-3 fatty acids towards higher levels can help improve endothelial dysfunction induced by PCBs and other environmental toxicants [16].

Role of Exercise in Protection Against PCBs-Induced Disorders

Experimental evidences suggest that exercise is extremely helpful to protect the vasculature against oxidative stress and inflammation induced by PCBs. Coplanar and non-ortho-substituted PCBs are persistent and a major risk factor for endothelial injury and CVD is associated with it. Exercise plays an important role in reducing the systemic oxidative stress and in the upregulation of antioxidant enzymes. Exercise has also been well established for atherosclerotic CVD as an effective primary and secondary intervention.

In a study, the effects of exercise on coplanar PCB-induced cardiovascular risk factors such as oxidative stress, impaired glucose tolerance, inflammation, hypercholesteremia and endothelium-dependent relaxation were examined on mice. Exposure to non-ortho-substituted or coplanar PCB increases risk factors associated with cardiovascular disease. As a result of this study, it was examined that exercise reduces cardiovascular disease risk factors in PCB-77-treated mice and has also upregulated antioxidant enzymes such as phase II demodification enzymes. It is suggested that lifestyle modifications including exercise especially aerobic exercise can be utilized as a therapeutic approach for the prevention of PCBs and other environmental pollutants induced adverse health effects [73].

Protective Effect of Ginseng Extract on PCBs-Induced Disorders

Oxidative stress plays a significant part in the pathological processes of neurodegenerative diseases. PCBs are persistent organic environmental contaminants, among which some are neurotoxic. PCB-52 is well known in inducing death in human neuronal SK-N-MC cells via apoptosis. In a recent study, Panax ginseng extract was investigated for its ability to protect human neuronal SK-N-MC cells from PCB-52-induced apoptosis. Evidence suggests that Panax ginseng exhibits protective effect of neuronal SK-N- MC cells against PCB-52-induced apoptotic death through the free radical and anti-oxidative scavenging activities [74]. The elucidation of intracellular signalling cascades in response to PCB-52-induced oxidative stress and modulation of these signalling cascades by ginseng extract or its single component provides further insights into the molecular basis of its neuroprotective effects against PCBs-induced neurological disorders.

Bioactive Compounds Prevent PCB-126-Induced Endothelial Cell Inflammation

Bioactive compounds for instance polyphenols can exert their protection mechanism by modulation of inflammatory pathways which are regulated via nuclear NF-κB signalling. Anti-inflammatory polyphenols such as epigallocatechin-3-gallate (EGCG) have been shown to provide protection against toxic effects induced by environmental pollutants. EGCG has been reported to inhibit NF-κB activation and PCBs-induced vascular toxicity can be reduced by EGCG-induced epigenetic modifications. It has been demonstrated that EGCG, the major bioactive polyphenol present in green tea, can reduce PCBs-induced vascular inflammation through a repressive epigenetic effect on NF-κB signalling pathway [75]. The results of this study show that EGCG exhibits anti-inflammatory properties in vascular diseases, which may, in part, occurs through epigenetic modifications of NF-κB target genes. Thus, epigenetic regulation of vascular inflammation by EGCG can explain its protective mechanisms and in this way support the consumption of green tea as a potential candidate for the prevention and treatment of vascular inflammation and atherosclerosis against environmental pollutants such as PCBs.

Conclusion

PCBs are environmental pollutants that contain chlorinated biphenyls. PCBs are mainly of two types: dioxin-like and non–dioxin-like PCBs which differs in the position of chlorine atoms. Production of PCBs is banned, yet a high percentage of

these pollutants is present in air and water which indicates large-scale production of these pollutants in the past decade. Humans can be easily exposed to these pollutants through various sources. As a result of PCB exposure, the incidence of various diseases such as hypertension, cancer, diabetes, recurrent infections, neurological disorders including Parkinson's diseases, Alzheimer's disease, ALS, dementia and cardiovascular diseases increases. Biotransformation of these PCBs in human body depends on CYP450 enzymes, and there are many uncertainties in measuring the health risks posed by PCBs. The USA has also developed some regulations and standards for the protection of the public and workers from the side effects caused by PCBs and these standards should strictly be followed to avoid the exposure to PCBs. Exercise and nutrition play crucial role in the protection and prevention of PCBs' side effects. Ginseng extract has protective effects against PCBs-induced toxicity, while EGCG prevents endothelial cell inflammation induced by PCB-126.

Conflict of Interest Nothing to declare.

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Chapter 13
Phthalates and Neurological Disorders: From Exposure to Preventive Interventions

Asma Ashraf, Shumaila Kiran, Saima Muzammil, Sumreen Hayat, Muhammad Umar Ijaz, and Aqsa Muzammil

Abstract Phthalates are organic compounds that are used in cosmetics, food packaging industry, toys and paints, and, most commonly, as plasticizers. Phthalates are classified as low and high categories according to their molecular weight. Human health issues, especially neurodevelopmental problems, are significant consequences of exposure to phthalates. Both low- and high-molecular weight phthalates like MBP (monobutyl phthalate) and DEHP (di-ethylhexyl phthalate) metabolites are associated with different cognitive and behavioral issues. It may cause severe asthma, affect motor neurons and cause many neurological disorders. Prenatal phthalate exposure is related to behavioral problems in children. In this chapter, we have discussed the pharmacokinetics of phthalates in association with neurodevelopment disorder in humans. Due to its potentially harmful nature, this ubiquitous environmental contaminant has gained considerable attention. The most common plasticizer used globally was phthalate acid esters (PAE), also known as phthalate.

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Later on, many organizations have imposed restrictions on phthalate use in children's toys or products. However, products used by adults still contain phthalates, such as low-molecular weight phthalates, whereas DEP, DnBP and DiBP phthalates are used in medications, solvents and cosmetics.

Keywords Phthalate exposure · Neuro problems · Plasticizers · Autism

Introduction

Phthalates are well-known organic compounds that are typically used in many products like toys, foods, paints, varnish, cosmetics and thinners [1–5]. They are used as plasticizers, which means these chemicals are embedded in plastics for increasing their transparency, flexibility and durability. Phthalate is mainly used to soften polyvinyl chloride (PVC). These are the class of chemicals that are associated with neurological and developmental disorders like autism, reduced mental IQ, and psychomotor development upon exposure [6, 7]. There are many ways of phthalate exposure. It can penetrate the human body through various routes such as inhalation, oral route and dermal contact as they are widely used in many industrial products [4]. Phthalate is metabolized rapidly to monoesters approximately 3 to 18 h and excreted out of the body through urine [4].

The European Parliament (Directive 2005/EC) decided to prohibit the production and distribution of phthalate-containing toys and cosmetics for children in 2005. But still, there are no legal regulations regarding the use of phthalate in products used by adults. The use of phthalates in packaging materials is not regulated yet. Consequently, many consumers are not aware of whether a product contains phthalates or not. Phthalates may cause health problems because these are effortlessly absorbed into the body, and their prolonged exposure is dangerous [8–11].

Phthalates are classified into two categories, one is lower-molecular weight phthalates and the other is higher-molecular weight phthalates. Lower-molecular weight phthalates are those that originate from C3-C6 alcohols. These are being progressively substituted in various products in the European Union, Canada, and the USA, as a result of their health issues [12, 13]. Subsequently, low-molecular weight phthalates are substituted by the high-molecular weight phthalate, which have more than 6 carbons in their backbone. The backbone containing more than 6 carbons gives them durability and permanency, and also make them an alternative plasticizer that is not based on phthalic anhydride. High-molecular weight phthalates dominated the market of plasticizers until 2010. Later on, producers were progressively forced to use non-phthalate plasticizers, and legal provisions against phthalates have been approved and also environmental awareness has grown. This transition to phthalate-free plasticizers has prohibited producers from using post-consumer recycled plastic because recycled content would likely comprise phthalates. Hence, manufacturers have been encouraged to use only new plastic in their products.

Classification of Phthalates

Phthalates are phthalic anhydride esters, which are obtained by the process of esterification of phthalic acid using alcohol. Reacting alcohol will define the physical and chemical properties of the resulting product. These alcohols may contain long alkyl chains or short alkyl chains. The long-chain alcohols form high molecular phthalates, while short-chain alcohols form low-molecular weight phthalates. The classification of phthalates into low-molecular weight and high-molecular weight categories is shown in Fig. 13.1 [14, 15].

Phthalates having a high molecular weight consisting of 9 to 13 carbon atoms in their chain, which enhances their durability and permanency. The most common types are DINP, DIDP and DPHP, which constitutes more than 80% of phthalates used in the world. They are commonly used in flooring, wall coverings, synthetic fibers, wire, cables, automobile applications, synthetic leather, self-adhesive films, coated fabrics and roofing. They mostly do not cause harm to human health.

Phthalates of low molecular weight consist of 3 to 8 carbon atoms in their backbone. The important phthalates are DEHP, DBP, BBP and DEP. They are primarily present in medical devices, inks, cosmetics, the lining of PVC and adhesives. These are mostly considered as more dangerous substances to human and animal health. They mainly disrupt the endocrine system. Therefore, they are prohibited from being used in toys, cosmetic products, medical devices and childcare equipment [16–18].

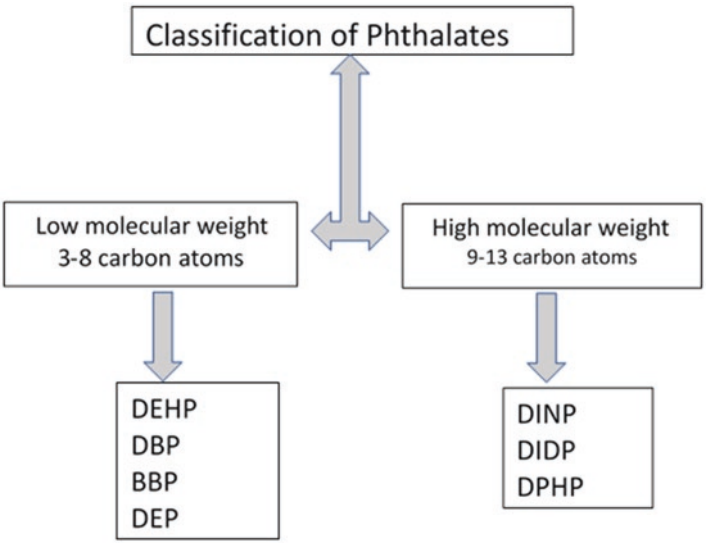
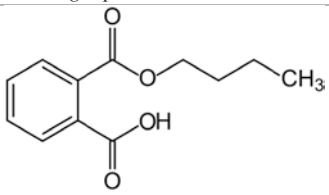
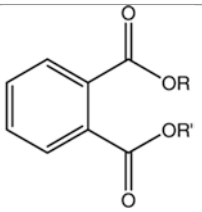
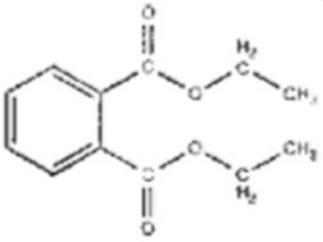
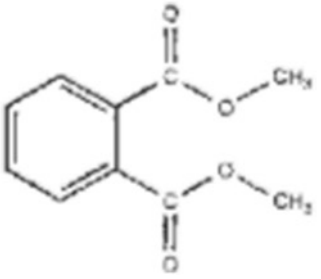
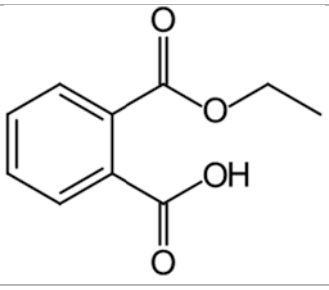


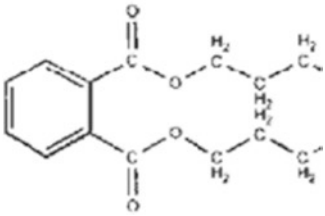
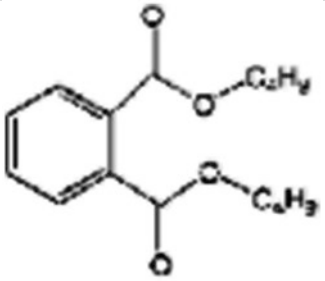
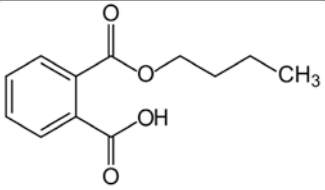
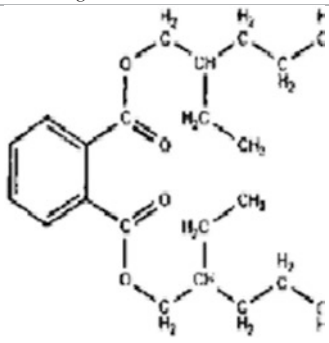
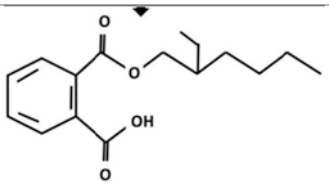
Fig. 13.1 Classification of phthalates according to molecular weight

Table 13.1 Structure, molecular weight and usage of phthalates

Phthalates	Structure	Molecular weight (g/mol)	Usage
Low molecular weight phthalates			
MBP		222.24	–
MMP		180.15	–
DEP		222.4	Solvent in personal care products, cellulose acetate plasticized films for food packaging
DMP		194.18	Used as plasticizer, also used in insect repellents
MEP		194.18	–

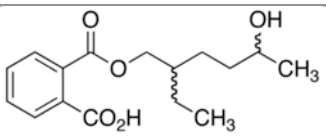
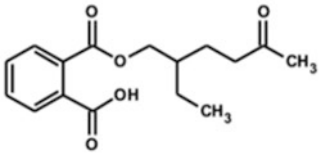
(continued)

Table 13.1 (continued)

Phthalates	Structure	Molecular weight (g/mol)	Usage
DBP		278.34	Enteric coating of medications and food supplements and nitrocellulose-coated regenerated cellulose film
DIBP		278.34	Used as a substitute for DBP due to the similarity in their application properties
MIBP		222.24	–
High molecular weight			
DEHP		390.56	Production of polyvinyl chloride (PVC) plastics. Used in PVC-based medical products retail packed food items
MEHP		278.34	–

(continued)

Table 13.1 (continued)

Phthalates	Structure	Molecular weight (g/mol)	Usage
MEHHP		294.34	–
MEOHP		292.33	–

Phthalates and its compounds are discussed in Table 13.1. These are divided by their molecular weight, low molecular weight and higher molecular weight. Their uses are also listed in Table 13.1.

Sources of Phthalates

Phthalates are ubiquitous in the general population and widely distributed throughout the world. Numerous consumer products contain phthalates in them due to their remarkable property of plasticity. They impart various favorable characteristics to the products to make it valuable. Therefore, these are part of pharmaceuticals, dentures, clothing, nutritional supplements, cosmetics, food packaging, children's toys, medical devices, automobiles, lubricants, building materials, insecticides, household furnishings, glow sticks and cleaning material waxes. Phthalates render plasticity to the rigid household materials such as PVC and other products [19–21].

The molecular weight of phthalates determines its use in different industries and household materials. High-molecular weight phthalate esters (PAEs) such as diisononyl phthalate (DiNP), di-isodecyl phthalate (DiDP) and di-(2-ethylhexyl) phthalate (DEHP), and are used in high magnitude in furnishings, construction material and clothes. However, the immense utilization of phthalate esters in PVC to impart flexibility. In contrast, low-molecular weight PAEs such as dimethyl phthalate (DMP), diethyl phthalate (DEP), and dibutyl phthalate are mostly used in waxes, adhesives, inks, lubricants, cosmetics, insecticides and pharmaceuticals. They are used as solvents too. They also act as dissolving agents in personal care products, for example, in nail polish, shampoos, soaps and hair sprays [22, 23].

It is estimated that more than three million metric tons of phthalate are manufactured every year globally [24]. Table 13.2 describes various phthalate and their source of exposure. Because of their massive use in our daily life, every person encounters various PAEs several times a day. Therefore, our lifestyle is dependent on phthalate products [25].

Table 13.2 Sources of phthalate exposure

Phthalate (abbreviation)	Sources of exposure
Low molecular weight	
Di-n-butyl phthalate (DBP)	Paints, adhesives, personal care products (perfumes, aftershaves, nail care, makeup)
Dimethyl phthalate (DMP)	Personal care products (deodorants, fragrant aftershaves, shampoos, hair styling)
Di-iso-butyl phthalate (DiBP)	Paints, adhesives
Diethyl phthalate (DEP)	Personal care products (deodorants, fragrant aftershaves, shampoos, hair styling, skin care, nail care, makeup, baby preparations)
High molecular weight	
Di-iso-nonyl phthalate (DiNP)	Household products (toys, floor tiles, wall coverings, furniture, paints, adhesives, gloves), clothes and footwear, car interiors, food packaging, medical devices
Butyl benzyl phthalate (BBzP)	Paint, adhesives, car care products, toys, food packaging, synthetic leather, deodorants
Di (2-ethylhexyl) phthalate (DEHP)	Household products (toys, floor tiles, wall coverings, furniture, paints, adhesives, gloves), dust, food packaging, medical devices
Di-n-octyl phthalate (DnOP)	Household products (floorings, carpet tiles, vinyl gloves, garden hoses, wire and cable insulation, adhesives), food applications (package sealants, bottle cap liners)

Routes of Exposure

Phthalates are present everywhere in our environment. They are lipophilic, which influences their property of leaching. Some potential routes of exposure to phthalates are inhalation, ingestion, intravenous injection and skin absorption [26]. Human exposure to phthalates occurs through three means, direct exposure to phthalates, contact with phthalate-containing products and leaching of phthalates into ingestible products [27]. Figure 13.2 describes the route of phthalate exposure; sometimes intravenous fluids could be contaminated by phthalate esters [28].

Phthalate ingestion occurs via food is through various sources. The intake of contaminated food is considered most significant source of exposure to phthalate in the population. However, phthalate concentration is widely variable in foods. The donut wrapping, tablet and food packaging are major PAEs contaminants. Similarly, pharmaceutical preparations are also coated with a polymer that determines the location and extends the duration of drug delivery.

DBP and DEP are important plasticizers for enteric coatings of tablets. These coatings are commonly present on antibiotics, anti-histamines, laxatives, herbal preparations and nutritional supplements. As far as children's exposure is concerned, polymer toys containing phthalates is a common risk in children. These toys contain DEHP, DBP, BBP, DiNP, DnOP and DiDP. Estimates about average exposure in kids by mouthing activities range from 5.7 to 44 μg per kg per day [29].

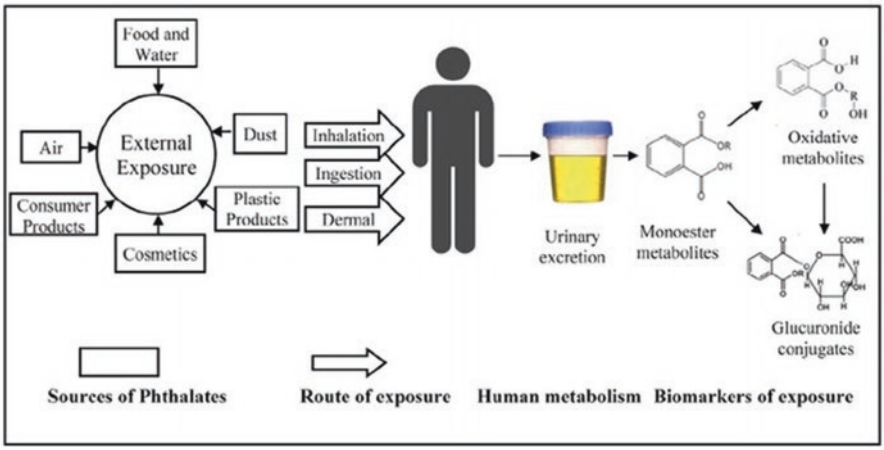


Fig. 13.2 Route of exposure to phthalates

Phthalates may be acquired through inhalation. DEHP may be transferred from PVC tubing during the passing of respiratory gases. In the same way, house dust and indoor air also carry phthalate particles. These phthalates leach from household furnishings, building products, toys, clothing and inside automobiles from plasticized components. These impurities cause an undefined level of contamination in the food, water and air [21].

Becker et al. [30] conducted the study and took a house dust sample of 254 children whose urinary metabolites of DEHP are also examined. The average contamination level is 508 μg DEHP/g of dust. Therefore, it is a minute contributor in exposure to phthalates through dust approximately 76 μg/day. These little figures are not counted in total exposure.

Intravenous exposure is commonly associated with medical care. A variety of medical equipment are made of PVC and plasticized with DEHP. Bags and IV tubing deliver intravenous drips, injections, nutritional formulas and blood. Similarly, dialysis also uses a similar sort of apparatus. Leaching of DEHP from these apparatuses depends upon lipid content in the fluid, temperature, storage time and agitation. However, exposure level among individuals is variable because of specific conditions of the individual, duration of exposure and choice of equipment [31].

The skin may come into direct contact through cosmetics, clothing, sunscreens, insecticides, modeling clay, personal care products, waxes, yoga pads and cleaning products. Females are prone to it due to the use of cosmetics. However, absorption depends upon various factors involving chemical structure, formulation vehicle, chemical concentration, water and lipid solubility, and anatomic area of application. The skin absorption of substances from the face and axilla is tenfold higher than that in the arm. Studies show that phthalate absorption from the skin is generally slow [21].

Exposure may occur across the whole life span from fetus to infancy, childhood and adult in both humans and animals. Phthalates can cross the blood–brain barrier

and enter into the placenta; therefore, we can measure its concentration in amniotic fluid. Similarly, it is also present in breast milk. However, its high concentration is reported in urine about 5–20 times than in blood or milk. In contrast, the exposure and oxidized metabolites may vary in relation to age, gender and race [32].

Preventive Measures to Avoid Phthalate Exposure

Exposure to phthalates is widespread and causes many health problems. There are some practical solutions to protect and reduce direct contact with these chemicals. Some preventive measures are discussed in Fig. 13.3.

- Avoid storing food and heating it in plastic containers using microwave. Use glass, ceramics or stainless-steel containers for leftovers [33].
- Avoid storing fruit and vegetables in plastic bags. Prefer using reusable beeswax wraps and biodegradable paper bags to wrap sandwiches. This creates a kind of raincoat that keeps the food fresh.
- Instead of plastic bottles, use glass or stainless-steel bottles.
- To cover the leftovers, use bowl covers, dishes and glass jars [34].
- Reduce consumption of canned products.
- Prefer fresh, frozen, or food in glass jars.
- It is advised to keep the traceability of phthalate material in manufactured products according to Regulations (CE) n 1935/2004 and (UE) n 10/2011.
- Read the label and avoid personal care products containing fragrances or perfume. Avoid nail polish that has phthalates. These are labelled as DBP free or Toxic Trio Free.
- Be aware that paper cups for takeaway coffee or tea are often lined with plastic, and the lid is made of plastic.
- In some coffee bars, you can bring your cup and even get a price reduction.
- The less you handle receipts and aeroplane tickets, the better.
- Buy in bulk or without plastic packaging.

Fig. 13.3 Preventive measure to avoid phthalate exposure

- Avoid plastic bags and their accumulation.
- Use natural material in home construction; avoid vinyl shower curtains, vinyl flooring and plastic windows.

Phthalate Metabolites as Biomarkers

Phthalate metabolites are reactive chemicals that can be found in everyday life products. Among these metabolites, some common metabolites are shown in Fig. 13.3 including p-hydroxybezoic acid and 2-hydroxy-4-methaoxybenzophenone or benzophenone-3 [35, 36]. Phthalate exposure is widely associated with many disorders such as insulin resistance [37], DNA damage, sperm reduction and premature thelarche [38]. The ten most commonly used phthalates in consumer products are dicyclohexyl phthalate (DCHP), diethyl phthalate (DEP), di-isobutyl phthalate (DiBP), dibutyl phthalate (DBP), dimethyl phthalate (DMP), di-n-octyl phthalate (DnOP), di-isodecyl phthalate (DiDP), benzyl butyl phthalate (BzBP), DEHP, and diisononyl phthalate (DiNP) [39]. In Fig. 13.4, some of the major phthalate diesters and their metabolites are shown.

The metabolism of phthalates generates a variety of chemical species containing monoesters and oxidized metabolites. The long-chain phthalates generate oxidized metabolites as the primary metabolite [40]. Oxidized species have distinct advantages as a biomarker. The PAEs are ubiquitous in the environment and contaminate many biospecimens by photolysis, hydrolysis through esterases or leaching.

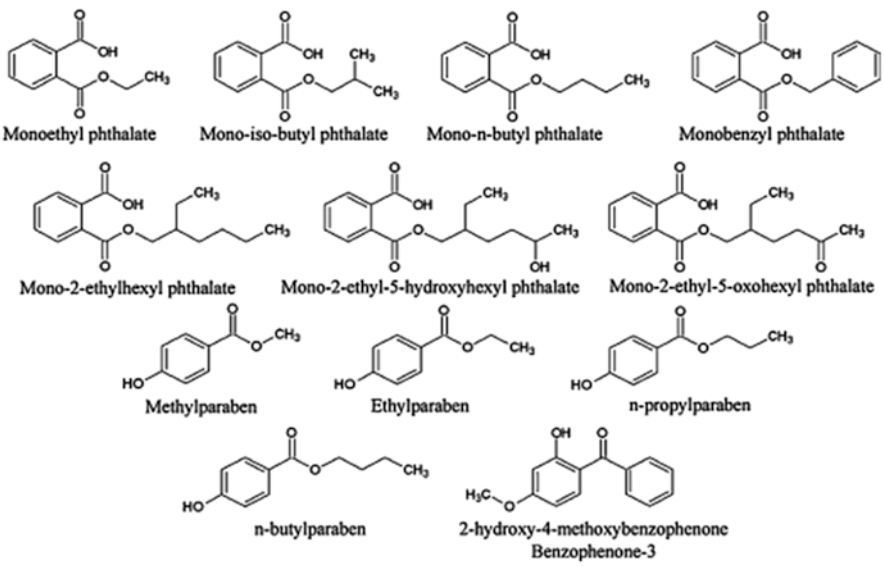


Fig. 13.4 Most common phthalates used in daily life products

Therefore, sample collection, storage and analysis can be contaminated. However, secondary metabolites are not vulnerable to external contamination because they can be made only from monoesters via hepatic metabolism only [41].

Furthermore, monoesters have a very short life span and they quickly get oxidized while secondary substances have long half-lives. Accurate reading can be altered if monoesters are rapidly degraded or externally introduced. However, oxidized metabolites are said to be extra reflective of mean exposure than monoesters, at least in the case of PAEs with five or more carbons in alkyl side chain [42].

To measure the exposure level, a method uses urinary phthalate monoester metabolites acting as biomarkers [43]. The benefit of using phthalate monoesters as biomarkers is biologically active monoester molecules [44]. Phthalate monoesters can be detected in samples such as urine, serum, seminal plasma, saliva, ovarian follicular fluid, breast milk and amniotic fluid using different chromatography techniques. Of several chromatography techniques, the most common is high-performance liquid chromatography (HPLC) [41]. But after conversion to volatile derivatives, gas chromatography can also be used to measure phthalate monoesters [45].

Pharmacokinetics of Phthalates

Pharmacokinetics is defined as the mechanism of any compound that follow ingestion to elimination. This includes chemical absorption right after its administration to its distribution in the body, and lastly, its excretion from the body via urine or feces. Many studies have been conducted related to phthalates pharmacokinetics [46, 47]. Phthalate exposure to humans can occur via many routes comprising ingestion (via contaminated food and water) or inhalation and dermal contact [48, 49]. These studies concluded many findings such as that high phthalate diesters are highly metabolized in the gastrointestinal tract; that they are absorbed as monoesters and that DEHP and MEHP are highly binding agents of plasma proteins. Minor differences in metabolic pathways are observed among different species. Generally, these diester phthalates are metabolized in two steps: first, hydrolysis of diesters to monoesters, and second, conjugation [50].

Absorption

The process of absorption starts after the administration of any substance. The ingested substance is digested in the gut and absorbed into the bloodstream through villi and microvilli. The initial degradation of one alkyl group may be in the saliva, but the major digestion occurs in the gut. Diesters are readily hydrolyzed by esterases, leaving behind monoesters. These esterases are present in intestinal mucosal

cells. Short alkyl chain PAEs are rapidly metabolized than long alkyl chain PAEs. Pancreatic secretions also contribute to the intestinal digestion of phthalates [51].

The degree of absorption of PAEs from the gut has been estimated by monitoring the metabolites in urinary excretions. The absorption of phthalic acid itself seems to be incomplete unless it is metabolized into simpler units. In an experiment, 3 mg and 1 g are administered in 4 days and 24 h. Around 40–50% of concentration is recovered from urine. Phthalates present in the food are well absorbed from the intestine. However, dermal or pulmonary absorption would not bereported due to the lipophilic nature of phthalates [52].

Distribution

Distribution is a process in which a substance passes into the interstitial fluid from the blood. The distribution is directly proportional to the blood flow and capillary permeability. The structure and chemical nature of diffusing substances largely influence the distribution within tissues. The hydrophobic substances readily cross the membranes, while hydrophilic substances require a particular junction to penetrate the cell [52].

DEHP circulates in the blood with the aid of various solubilizing agents. Most of DEHP binds to lipoproteins, and the rest loosely attach with the albumin [53]. Phthalates can cross the placenta and enter into the fetus. Radioactivity is also recovered from the fetus showing the maternal transfer of phthalates to the fetus. Its presence is also reported in breast milk [32].

Metabolism

Metabolism is a process in which molecules are modified for energy generation and easy product elimination. The main arena of metabolism is hepatic metabolism. Absorbed phthalates are further metabolized in the liver in a two-step process. In the first step, diester phthalates are hydrolyzed into monoesters in intestinal or hepatic metabolism. Catalyzation occurs through enzymes such as esterases and lipases. The second phase involves the formation of hydrophilic glucuronide conjugates by UDP-glucuronosyl-transferase [40].

Low-molecular weight phthalates commonly generate monoesters such as DBP and DEP. These chemical species are excreted in urine as a parent metabolite. However, monoesters having five or more than five carbons in their side chain undergo ω-oxidation to yield oxidized metabolites. Thus, the esters with long alkyl chains are considered as oxidized primary metabolites in urine. At the same time, long-chain phthalate esters produce more metabolites. The proportion of numerous oxidized species depends upon the parent chain length. The oxidized products can

further lose two carbons at the terminal ester side chain via β-oxidation. Therefore, longer alkyl chains would result in a greater variety of metabolites [54].

After initial oxidation of PAEs, the carbon atoms undergo successive oxidations to produce alcohols, aldehydes, ketones and carboxylic acid. Compounds with six or more carbons in a chain may undergo β-oxidation to create two-carbon fragments. Generally, the metabolism of phthalates remains unaffected regarding the path of administration [26].

Excretion

Excretion is a process of elimination of the drug from the body. The substances to be eliminated require sufficient polarity for efficient excretion. Because the nonpolar drugs are reabsorbed in convoluted tubules. But excretion through urine is not the ultimate route; drugs are also excreted in feces, sweat and breast milk. The primary route for clearing of PAEs is urinary excretion. Other elimination routes are quite uncommon for phthalates. Monoesters are excreted as free or conjugated with glucuronides along with oxidized species. Low-molecular weight phthalates produce an enormous proportion of free non-polar esters, while toxidized species have a greater percentage of conjugated monoesters. Excreted phthalates are low-molecular weight (90%) and high-molecular weight phthalates (10%), eliminated in urine. Therefore, we can assess the concentration of low molecular weight phthalates from the excretory monoesters. In contrast, we cannot estimate the concentration of phthalates of high molecular weight in the body from urine [55].

The proportion of excretory monoesters along with its oxo, hydroxy and carboxy products decreases with the increase in alkyl chain. This indicates that the higher percentage is excreted via feces. The bulk of chemicals is eliminated within 24 h, and almost none is left 3–5 days after exposure. A 61-year-old healthy male took three oral doses of DEHP; the resulting oxidized metabolites are 5OH-MEHP, MEHP, 5cx-MEPP5oxo-MEHP, and 2cx-MMHP. The amount of all these products constitutes to 65–70% of the administered dose, while the rest is eliminated in feces [56].

Human Health Issues

The high level of exposure to some phthalates causes developmental and reproductive toxicities in both male and female animals [57]. Although abnormalities like shortened gestation, changing semen quality, premature breast development in young girls and reduced anogenital distance in baby boys are also reported due to these phthalates, data is limited [58].

Neurodegenerative Effects of Phthalates in Adults

In general, there are lots of evidence from the literature to develop neurodevelopmental problems due to exposure to phthalate exposure in humans. The effects on motor neurons are observed by phthalate exposure [59]. By assessing the biological phthalates impact on developing organisms, it is estimated that phthalate exposure are significantly greater in infants and children in comparison with adults. It is observed that overall, there is a significant effect on children as compared to adults [60]. It has been verified by research that phthalates affect reproductive and developmental organisms and have toxic effects on animals and humans [61]. Moreover, diethylhexyl phthalate has been evidenced to affect neurodevelopment both in vitro and in vivo [62]. Their exposure is closely associated with the intelligence of school-age children [63].

Reorganization of neurocircuitry and extensive growth of neurons that occur during the developmental stage leaves the brain susceptible to environmental abuses. Hippocampus is a brain region (localized) that exhibits extensive structural and functional changes during developmental periods and at adulthood. It has long been studied for its vital role in memory and learning [64]. It has been examined that due to high exposure to phthalates, widespread disruptions in functional and structural plasticity of hippocampal occur. However, it is still an open research topic of how these changes occur. Is it direct or indirect? In direct effect, phthalates have a neurotoxic effect, while in indirect effect changes are due to disruptions in endogenous endocrine functions [65].

Bayer [66] showed that in the hypothalamic/preoptic area, aromatase enzyme action is affected due to exposure to DEHP at a low dose of 0.135 mg/kg, in the brain of both genders. This enzyme activity is crucial for masculinization of the brain as it converts testosterone into estradiol. Therefore, decrease in the aromatase enzyme activity could be a severe problem for brain masculinization during the neurodevelopmental stage, resulting in a more feminized form of the male brain after phthalate exposure [67].

Kuliński reported a case study of 37 years of a male patient with severe nervous system damage [5]. This was due to continuous exposure to diisononyl phthalate (used in paint thinner) at the workplace at least for 10 years. Brain MRI of the patient showed scattered lesions in cerebral hemispheres. The patient was observed with symptoms of decreased cognitive function and memory loss. His disorders were identified during clinical examination and connected with long time exposure to phthalates that have toxic effects on the central nervous system. This prolonged exposure was caused by phthalates contained in the chemical used at work. Therefore, it is reported that continuing contact with phthalates causes severe damage to the nervous system.

Many studies have shown an association between neurological damages like cognitive, motor and sensory problems and neurodegenerative disease with expo-

sure to phthalates. It has been reported that there exists a connection between exposure to phthalates and neurological disorders [68–71]. It is also known that phthalates can persist in the human body for many days after absorption and can cause damage to the blood-brain barrier.

Neural changes have also been reported due to exposure to DEHP (phthalates). The exposure to DEHP or DEHP metabolites in adults expressively mitigates activity in membrane Na+ /K+ ATPase that is connected with neuronal damage by disruptions in ion homeostasis [72]. Na+ /K+ ATPase is an essential enzyme to transport cations and when its activity is interrupted, it can cause neuronal cell death [73]. Moreover, Ca^{+2} levels increased in minutes in neurosecretory and pheochromocytoma cells after DEHP exposure [74].

Phthalate Exposure and Health Problems Related to Children

In the recent decade, a large number of epidemiological studies have been reported that showed associations between phthalate exposure to parents and, ultimately, to children. These studies reported that due to phthalate exposure, neurodevelopmental issues arise among children at the age of 10 years [75–84]. Braun et al. [85] evaluated different phthalate metabolites that vary with children's sex. In a study by Ejaredar et al. [86], an association between prenatal phthalate exposure during childhood and adolescence was established, as this information is important to evaluate the long-term effect of phthalates. An association of phthalate exposure in prenatal with cognition problems and behavior outcomes at ages 7–16 years has been examined. The study found associations of prenatal phthalates with neurodevelopment and weak associations of LMW phthalates with internalizing and externalizing behaviors in adolescence.

In infants and adolescents, phthalate exposure, various phthalate sources and routes of exposure are related to developmental problems. This is very important to aware of the parents regarding potential exposure. Usually, kids' goods and indoor air are the largest sources of DiDP, BBzP, DEP, DiNP and DMP, whereas food is the primary source of DEHP and, in some cases DBP. Because of more requirements of food and water (per unit body mass) and higher hand-to-mouth activity, infants and children have more phthalate consumptions.

There are many health problems associated with phthalate exposure in children that disrupts average growth and development. A study to find the toxicity of phthalates has been conducted in rats and it has been found the anti-androgenic activities of phthalates in male rats that were exposed in utero [84]. Phthalate exposure with several childhood health outcomes has been discussed here.

Physical Growth and Asthma

Many cross-sectional studies in Germany and the USA assessed the relationship of concentration of urinary phthalate metabolite and anthropometry in children and as well as in adolescents. Author links open overlay panel [55]. Higher DEP metabolite concentrations were found to be a cause of higher BMI among adolescent girls [87]. In a study, a positive relationship between BMI and DEP metabolites was observed among children in New York by Teitelbaum [88]. While at the same time, another study in Denmark by [89] testified the inverse relationship of urinary phthalate metabolites and anthropometric measurements in children. The reason for this positive correlation among urinary DEP metabolites and BMI may be that individuals with high BMI have larger body surface areas and use more quantity of personal care products containing phthalates.

Several studies also showed the association between respiratory and allergic diseases as well as phthalate exposure in children. In a study in New York, during pregnancy, increased urinary BBzP metabolites were associated with 50% increased eczema in children at 24 months of age [90]. Different studies in Bulgaria, Sweden, and Taiwan found a relationship between the concentration of settled dust phthalate and asthma and eczema in children [8, 91, 92]. Studies showed that increased DEHP dust concentrations in the homes might be the reason for all these health problems in children [91, 92]. Children with higher exposure to DEHP dust concentrations were more prone to have an allergy (2.7 times), asthma and wheezing symptoms in comparison with children that are less exposed. Some of the studies also associated higher dust BBzP concentration with increased incidence of asthma and allergy [92, 93]. It is evident that exposure to DEHP and BBzP in childhood is related to allergic disease development [94, 95]. However, clear evidence can only be found by longitudinal studies to identify its association with susceptible stages of development.

Neurodevelopmental Problems

There are lots of studies conducted to assess the relationship between phthalate exposure and children's neurodevelopment. Cho et al. [96] reported in a cross-sectional study of 667 children, a decrease in IQ level by 2 points with a higher urinary concentration of DBP and DEHP metabolite in children. In another cross-sectional study, a higher concentration of urinary DEHP metabolite was observed in 48 children with autism disorders [97]. Similarly, a cohort study was conducted with 417 infants born to Korean mothers with high concentrations of urinary DEHP and DBP metabolite and observed lower mental and physical health in infants. Whyatt et al. and Kim et al. [76, 98] also reported the same findings who studied the children's growth in New York City-born to women with high DBP urinary concentration. Data of 296 mother–child pairs showed reduced physical development at the age of 3 years. In Table 13.3, the sources and tools for measurement of children's neurodevelopment are discussed.

The relationship between exposure to phthalates in pregnancy and infant behavior was observed using the Brazelton Neonatal Behavioral Assessment Scale. It was found that urinary phthalates concentration in mothers was associated with low alertness quality in girls [71, 99]. Therefore, a significant number of studies suggested a link between neurodevelopment and gestational phthalate exposure (Table 13.3).

Therapeutic Interventions for Neurological Disorders

It has been estimated that hundreds of millions of people are suffering from neurological disorders around the world. Neurological disorders of central and peripheral nervous systems are of various kinds and heterogeneous. Overall, 10.2% of the total disease are of neurological disorders in 2015, and the cause of death due to neurological disorders was estimated at 16.8% in 2015 [100]. In the USA alone, the annual cost to manage neurological disorders was $800 billion [101].

The therapeutic intervention for neurological disorders includes stem cell therapy, gene therapy, dietary changes, and histamine treatment. Stem cell therapy treats the brain where neurons are damaged or defective, through stem cell therapy, these neurons were aimed to repair or replace the damage. It repairs the injured part via paracrine effects and even it can generate new neurons to mitigate the adverse effects of neurological disorder. The stem cell used in therapy are Neural stem cells (NSCs), hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). The advantages and disadvantages of different stem cells are mentioned in Table 13.4.

Ketogenic diet are used for utilizing instead of glucose for the central nervous system, and for this purpose, less strict variant of the ketogenic diet has been developed, such as the modified Atkins diet (MAD) and combine it with medium-chain triglyceride oil (MCT). Many studies have examined the use of ketogenic dietary supplements and found it to be useful for epilepsy treatment [102, 103]. Alzheimer's disease has been studied for using a more ketogenic diet and lessens the use of glucose. A high level of glycemic diets is linked with the cerebral amyloid burden [104]. In 2015, a study demonstrated that patients using keto monoester (R)-3-hydroxybutyl (R)-3-hydroxybutyrate for 20 months without an alteration in their diet has improved their cognitive performances and also increase circulating serum β-hydroxybutyrate levels [105]. Other neurological disorders can also be treated with ketogenic therapies, including Parkinson's disease, ischemic brain and mood disorders and multiple sclerosis. It is demonstrated in one study that it improves in forelimb motor functions [106].

For the treatment of many CNS diseases, H3R is used as a potential treatment because of its pharmacological features. However, no histaminergic dysfunction was observed directly in neurological disorders. H3R is effective because of its autoreceptor characterization and also it release neurotransmitters such as dopamine, acetylcholine (Ach), 5-hydroxytryptamine, GABA and peptides [107].

Table 13.3 Type of phthalate exposure and tools used to assess children's neurodevelopmental outcomes

Phthalate type/level	Neurodevelopment measurement tool	Exposure measurement time	Outcome measurement time	Reference
LMW mean (pg/L) MnBP: 48.9 MEHP: 21.3, MEOHP: 18.0	KEDI-WISC	9 ± 0.7 years	9 ± 0.7 years of age	[96]
LMW median (pg/L) MnBP: 36.2, MMP: 1.7, MEP: 385.8, MiBP 6.2 HMW median (mg/L) MBzP: 23.8, MECPP: 35.8, MEHHP: 19.6, MEOHP:17.9, MEHP: 6.1, MCPP: 3.4	Brazelton Neonatal Behavioral Assessment Scale (BNBAS)	25–40 weeks of gestation	1–5 days after birth	[99]
LMW median (mg/L) MnBP: 36.2, MMP: 1.7, MEP: 385.8, MiBP 6.2	Behavior Rating Inventory of Executive Function (BRIEF) Behavior Assessment System for Children–Parent Rating Scales (BASCII-PRS)	25–40 weeks of gestation	4 and 9 years of age	[82]
LMW mean (mg/dL) MnBP: 46.7 HMW mean (mg/dL) MEOHP: 23.4, MEHP: 34.0	Teacher-rated ADHD scores Computerized Measurements of Inattention and Impulsivity	8–11 years	8–11 years of age	[109]
LMW mean (mg/L) MnBP: 12.4 HMW mean (mg/L) MEHHP: 8.9, MEOHP: 7.4	Bayley Scales of Infant Development—II (BSID-II)	35.7–41.7 weeks of gestation	6 months of age	[98]
LMW median(mg/L) MnBP: 33, MMP: 1.8, MEP: 372, MiBP: 6.5 HMW median (mg/L) DEHP (MEHHP aMECPP): 125	Social Responsiveness Scale (SRS)	31.2 weeks of gestation	7–9 years of age	[77]

(continued)

Table 13.3 (continued)

Phthalate type/level	Neurodevelopment measurement tool	Exposure measurement time	Outcome measurement time	Reference
LMW mean (mg/dL) MnBP (boys): 19.4, MnBP (girls): 23.0, MiBP (boys): 4, MiBP (girls): 4.1 HMW mean (mg/dL) MEHP (boys): 5.2, MEHP (girls): 8.7, MEHHP (boys): 16.0, MEHHP (girls): 18.3, MEOHP (boys): 14.3, MEOHP (girls): 15.3	Pre-School Activities Inventory	28.3 weeks of gestation	4–7 years of age	[110]
LMW mean(mg/L) MnBP: 85.61, MMP:MEP:138, MiBP: 2.3 HMW mean (mg/L) MBzP: 3.54, MECPP: 39.65, MEHHP: 22.08, MEOHP: 14.23, MEHP: 6.56, MCPP: 1.75	Bayley Scales of Infant Development—II (BSID-II)	27–40 weeks of gestation	2–3 years of age	[111]
HMW median (mg/L) MEHP (cases): 55, MEHP (controls): 28	Autism spectrum disorders using Diagnostic and Statistical Manual of Mental Disorders (DSM IV)	11 ± 0.5 years	11 ± 0.5 years	[97]
LMW mean (mg/L) MnBP: 38.0, MiBP: 9.3 HMW mean (mg/L) MBzP: 19.0, MECPP: 40.2, MEHHP: 23.0, MEOHP: 19.2, MEHP: 5.1	LMW mean (mg/L) MnBP: 38.0, MiBP: 9.3 HMW mean (mg /L) MBzP: 19.0, MECPP: 40.2, MEHHP: 23.0, MEOHP: 19.2, MEHP: 5.1	33.1 weeks of gestation	3 years	[76]
LMW median (mg/L) MnBP/MBP: 24.0, MiBP:4.5, MnBP/MBP: 20.3, MiBP:3.6 HMW median (mg/L) MECPP: 38.0, MEHHP:26.9, MEOHP: 19.9, MEHP: 4.9, MECPP:29.9, MEHHP: 20.4, MEOHP: 16.5, P: 4.2	NICU Network Neurobehavioral Scale (NNNS)	16 weeks of gestation 24 weeks of gestation 16 weeks of gestation 24 weeks of gestation	5 weeks	[71]

Table 13.4 Different types of stem cell for therapeutic intervention of neurological disorders

Stem cells	Disadvantages	Advantages
HSCs	Limited experience for a neurological disorder It requires donor and recipient to be genetically matched, therefore generally limited to autologous therapy	Established industry for preparation and harvesting Globally accepted
NSCs	Ethical implications around procurement Poorly understood and least explored in clinical studies Tumorigenic risk	Prototype stem cells neurological disorder NSCs can be derived from other stem cell types
MSCs	Poorly understood mechanism Unregulated clinics globally	No need for genetic matching Evolve into off the shelf allogeneic products

Table 13.5 Histamine H3R antagonists in clinical trials for the treatment of CNS disorders

Disease	Antagonists	CNS disorder status
Alzheimer disease	PF-03654746	Mild/moderate
	GSK-239512	Mild/moderate
	MK-0249	Mild/moderate
Schizophrenia	MK-0249	Cognitive impairment
	GSK-239512	Cognitive impairment
	Pitolisant (BF2.649)	Cognitive impairment
Weight loss	PF-03654746	–
ADHD	JNJ-31001074	Adult and pediatric patients
Parkinson disease	Pitolisant (BF2.649)	Sleepiness
Narcolepsy	Pitolisant (BF2.649)	Cataplexy
	GSK-189254	Sleepiness
	PF-03654746	Sleepiness
	Pitolisant (BF2.649)	Sleepiness
	JNJ-17216498	Sleepiness

Table 13.5 discusses the histamine compounds for CNS disorder treatment. H3R plays a vital role in histamine synthesis and inhibit the cAMP-dependent protein kinase cascade as well as the calcium/calmodulin [108].

Conclusion

Neurological disorders, including autism and behavioral problems, are increasing rapidly throughout the world. Evidence has suggested that this increase is due to high exposure to phthalates chemicals. Usually, phthalates are eliminated from the

body rapidly, but our body is continuously exposed to them through polluted air, water and contaminated food. It is reported that phthalates may cause nervous system damage. Exposure to phthalates could be through ingestion, inhalation and absorption through normal skin. Phthalate exposure in children is associated with low IQ scores and cognitive behavior. It is clear that even constant exposure to the low level of phthalates is responsible for the alarming increase of neurodegenerative diseases. There is an urgent need to study thoroughly to evaluate the effects of phthalate exposure on the human body so that a healthy lifestyle could be realized.

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Chapter 14
Perfluoroalkyl Chemicals and Neurological Disorders: From Exposure to Preventive Interventions

Samia Gul Niazi, Chanda Javed, Taiba Suleman, Samra Sadiq, and Imtiaz Mahmood Tahir

Abstract Perfluoroalkyl substances (PFAS) are the member of that class of compounds which includes at least one fluorine atom in their structure, are being used in various industrial and consumer products due to their unique chemical properties. Perfluorooctanoic sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are the most important and well-known components among PFAS. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) exert various kinds of effects on living organisms, but the most serious ones are the metabolic effects. However, PFAS are inert metabolically itself, but they interfere with endogenous metabolic pathways and reactions, and indirectly affect the metabolism of the body. Unluckily, there are many other PFAS to those humans are exposed throughout their life which not only imparts harmful effects on adults but also in whole life. It has been quantified that PFAS are present in amniotic fluid, fetal tissue, breastmilk, lung, heart, umbilical cord, and brain, blood, and placenta which indicates PFAS exposure in infants from the very start of life. PFAS exposure to Nematodes for 72 h shows the evidence of neuropathology during the inspection of GABAergic, dopaminergic, serotoninergic, and cholinergic neuronal morphologies. Ingestion of mycotoxins causes com-

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plex problems to human health. Physio-chemical processing aimed to destroy and mineralize contaminants into carbon dioxide and water or less toxic products.

Keywords Perfluoroalkyl substances · Mycotoxins · Perfluorononananoic acid · Perfluorooctane sulfonate · Perfluorooctane sulfonic acid

What Are Perfluoroalkyl Substances

Perfluoroalkyl substances (PFAS) are the member of that class of compounds which includes at least one fluorine atom in their structure, are being used in many commercial and consumer products due to their unique chemical properties, for example, oil-repellent capability. The whole world is being polluted with these dangerous chemicals. It has been verified from various animal studies that PFAS exposure can affect the homeostasis of lipids, alter the fatty acid composition, and change differentiation of adipocyte. PFAS have properties helping in their long-range transportation and allow longer residence time in the atmosphere and all together they are readily converted into carboxylic acids and other compounds because of their high reactive properties [1].

Sources and Types of PFAS

Perfluoroalkyl substances, a large class of synthetic compounds that persists as an alkyl moiety with one fully fluorinated carbon atom, are the source of contamination since many years and considered as important issue towards global threats to health. Perfluoroalkyl chemicals which remain in the environment for a longer period are considered or referred to as “forever chemicals” which persists in the environment. They are highly mobile in the given environment and some of them have been found as bioaccumulate in humans and animals. These compounds are also famous for producing fluoropolymer Teflon and Scotchgard (stain-resistant coating), the chemicals which are used in industrial goods where they need grease or waterproofing is required or surfactant effect is needed. Other industrial products included cosmetics, water- and stainproof textiles, packing of eatables, nonstick cookware, and lastly aqueous film-forming foam (AFFF) to act against class B fires and as a matter of metal plating processes. Due to vigorous use of PFAS now a day they are largely found in different sources of water like rivers, groundwater sources, lakes, drinking water and present in the soil, air, house dust, and food. The level of PFAS in humans all over the world, especially in America where its use is very high, reached to a detectable level in blood serum where they are causing many problems in human body (CDC 2018). PFAS are linked with many pathological conditions like immune system dysfunctions, liver problems and most importantly develop-

mental, reproductive, and hormonal imbalance. PFAS can directly mimic the actions of endogenous ligands thus acting as agonist or antagonist this is considered their primary action however their secondary action is not well researched and harder to elucidate.

Types of PFAS

Perfluorooctanoic sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are important as well as well-known components among PFAS. They are also well-studied chemicals these days [2]. The research data has been found abundantly when we talk about PFAS and it is increasing exponentially therefore now it is easy to understand its shortcomings related to its exposure on common man life [3]. For PFOA and PFOS, now its considered as alarming situation, that causes negative health effects on and various agencies warned about its serious impacts on human [4]. There are many types of PFAS are now available as the time is passing and research is being done. Some common types of PFAS are as follows:

- Trifluoroacetic acid (TFA)
- Perfluoro hexanoic acid (PFHxA)
- Perfluoro heptanoic acid (PFHpA)
- Perfluoro pentanoic acid (PFPnA)
- Perfluoro propanoic acid (PFPrA)
- Perfluoro butanoic acid (PFBA)
- Perfluoro butane sulfonate (PFBS)
- Perfluoro hexane sulfonate (PFHxS)
- Perfluorooctanoic acid (PFOA)
- Perfluorooctanesulfonic acid (PFOS)

Human Exposure to PFAS and Mechanism of Induction of Neurodegeneration

Human Exposure Pathways

The main source of exposure among human beings is drinking water, house dust (indoor air inhalation), and interaction with other contaminated surfaces or media [5]. The most important properties which PFAS possess are their nonstick nature and surface tension–lowering ability, due to which they can repel, fixed essential oils and water and modify the surface chemistry of the products we are dealing with. The ability of PFAS to reduce surface tension makes possible its use in metal plating, provide aids in fluoropolymer manufacturing and the preparation of semiconductors [6, 7]. Direct human exposure to such chemicals can be ruled out by shifts

in chemical production and it is also for a short time, but accumulation of PFAS in the ocean and thereby marine food chains and groundwater AFFF contamination persist for a longer time [8, 9]. Exposure of these pathways is important to interpret drivers of sequential changes in concentrations of PFAS in serum measured in biomonitoring studies and for assessing future risks of exposure [10].

Consumer Products, Dust, and Indoor Air

In a household or daily routine materials, PFAS have been found in winter kinds of stuff like sweaters and jackets, upholstery, room carpets, different types of papers, raw building materials, food materials, impregnation agents, cleansers, polishes, paints, and ski waxes, including many other items commonly found in offices, households, and cars [11, 12].

Another important which need to be discussed is that PFAS can move from fluorochemical treated papers which are in contact with food stimulants like butter, vinegar, water, and water–ethanol mixtures, shows direct exposure routes to human being [13, 14]. Exposure of PFOS and PFOA from skin related products are considered less as compared to direct route [5]. In a study of 41 Norwegian women, Haug et al. [15] reported that food was considered as the main pathway for exposure to these chemicals, although the home or in the house (dust, air) could participate for up to ~50% of the total PFAS intake. Exposure or biotransformation of PFAS precursor's within the human body is another threat we are facing which leads to additional problems related to these chemicals and it is also increasing uncertainty about its effects [16]. Another pathway is Inhalational route of these precursors which occur in indoor environments where PFAS containing goods or products are present [17, 18].

As PFOS and PFOA have been phased out "(from 2002 by the primary US manufacturer and then in 2006 eight companies decided to rule out these chemicals till 2015 (Technical fact sheet PFOA and PFOS November 2017)" and their precursors have led to the highest production of compounds and some other structurally alike compounds with short chains [19, 20], an additional holistic approach is required to check human exposure to these fluorinated chemicals. For this purpose, Robel et al. [21] determined total concentration of fluorine fraction that can be transferred from specific consumer goods and is available for exposure to humans daily. The researchers reported that typical techniques of measurement for chemicals like PFAS only make 16% of the total fluorine measured using particle-induced gamma ray emission (PIGE) [21]. However, discussing all the abovementioned data, we still need to establish a link between presence of PFAS in consumer products and their presence in dust, air, and food and their overall contributions to human exposure in populations with diverse product use patterns.

Drinking Water

Drinking water is considered as the most common source of exposure of PFAS to human population particularly among the people living near the area contaminated with such chemicals [22, 23]. The United States Environmental Protection Agency (US EPA) published lifetime health-related advisory level for PFOS+PFOA of 70 ng/L in drinking water in 2016 [22]. The US Agency for Toxic Substances and Disease Registry (ATSDR), in 2018, lowered the minimum risk levels (MRLs) for PFOS and PFOA compared to the reference dose (RfD) given by the Environmental Protection Agency (US EPA) when they developed lifetime advisory in the year 2016 [23]. So, for drinking water, minimum risk levels for PFOA and PFOS (given by ASTSDR) should be 7 ng/L for PFOS and 11 ng/L for PFOA. Some other lifetime drinking water advisories published by other countries and international agencies comprises 11 to 12 PFAS (Sweden and Denmark) and range from less than 10 ng/L up to hundreds to thousands of ng/L for different PFAS in Canada [24]. Grandjean and Budtz-Jørgensen [25] determined that lifetime drinking water advisory level for children should be minimum than 1 ng/L on the bases of specific dose-related to immunotoxicity (that is associated with PFAS) exposure in the Faroe Islands. Contamination of drinking water with PFAS was first shown in the USA in public and private drinking water supplies near a fluoropolymer manufacturing facility in Washington, WV in 1999 [26]. Then in 2010, again drinking water contamination was detected near army base in Michigan. Other than these some additional cases of drinking water contamination have also been reported in the USA, and most of them focused on little or unprivileged communities which use a single source of water (which is thought to be contaminated). The first nationwide research related to PFAS presence in the US drinking water was done in New Jersey, where 59% of PFOA was detected in public water supplies and their level reached to 190 ng/L [27]. The first statewide survey for the occurrence of PFAS in public water supplies was carried in between 2013 and 2015 by the USA. EPA under the third Unregulated Contaminant Monitoring Rule (UMCR3) [28]. Hu et al. [29] noted that levels of PFOS and/or PFOA in drinking water, exceeding the US EPA 2016 health advisory levels in large public water supplies serving up to six million American citizens. However, there is no data available for more than 100 million Americans who use their water from small public water supplies, representing a critical research need for the future. Recent data shows that a high concentration of the latest type of PFAS, such as GenX (hundreds of ng/L), has been found in North Carolina, downstream of a PFAS manufacturing plant in the Cape Fear River watershed [30]. Some data has been found about population who often eat marine mammals and seafood, like Inuit men in Greenland [31], whaling men in the Faroe Islands [32], and commercial fishery employees in China [33]. This data shows seafood elevated serum concentrations of PFAS. The level of PFAS in seafood depends upon the level of contamination in the water they are found so Seafood PFAS concentrations vary considerably with highest concentrations measured next to contaminated sites [34, 35]. Environmental level of long-chain compounds is considered the main driver of

variability in tissue concentrations across sites and species [34, 35], so higher concentrations of these long-chain chemicals increase the risk of their presence in the human body. These long-chain chemicals and PFAS can bioaccumulate at a higher degree than shorter chain length chemicals and PFCAs [36, 37]. If we assess previous studies keeping this in mind, they were based on assays which were designed for lipophilic (highly) substance [38]. Unlike the literature there is specific variability in exposure of PFAS through seafood because after cooking concentration of chemicals like PFOS has been shown to decrease [34].

Biosolids and Agriculture

The products made up of PFAS are used in the industry responsible for the collection of wastewater, so these wastewater treatment plants are itself a source of PFAS contamination of water [35]. It is also reported that the presence of more than three wastewater treatment plants within a specified area is believed to increase the likelihood of PFAS detection in that area's water sources [39]. Discharge of PFOS at higher level comes to light in 1995 before it was phased out at the start of 2000 [6, 9]. This wastewater discharge becomes the part of regional river networks and which indirectly becomes the source of pollution for marine ecology. Almost 85% of the exposure of PFOS at the continental scale is due to wastewater, however at local scale industrial sites are responsible [36, 37]. Not only wastewater but sewage sludge from wastewater treatment plants is commonly used as a fertilizer in fields and crops from an agricultural perspective, which is considered as another potential vector for exposure to humans. Different research works show such concerns about the presence of such material in biosolids also several data shows that PFAS were present in such biosolids [40, 41]. The 2001 US EPA National Survey of such biosolids (Sewage Sludge) showed that a load of these chemicals (PFAS) in US biosolids was 2749–3450 kg per year based on the 13 PFAS measured. So if we talk about total US load, an estimated 1375–2070 kg per year was applied for agriculture and 467–587 kg per year was transported to landfills [41]. Researchers worked on this and studied in detail the absorption of PFAS into crops and earthworms from sewage sludge which was used as biosolids in these crops [42, 43]. Therefore not only crops but dairy products like milk, cheese, yoghurt, and meat have been investigated and elevated PFAS concentrations have also been reported [35, 44], which suggests that farm animals that were fed crops which were contaminated with PFAS due to use of such biosolids which were discussed above, and this is one of the most dangerous threats as regards exposure of PFAS ins humans. So additional research on the significance of human exposure to PFAS, focusing on biosolids and agriculture, is the need of the hour.

Metabolic Effects of PFAS

PFAS exert various kinds of effects on living organisms, but the most serious ones are the metabolic effects and have attracted considerable attention in PFAS studies in vitro and in vivo. However, PFAS are inert metabolically itself but they interfere with endogenous metabolic pathways and reactions and indirectly they affect the metabolism of the body. As PFAS act as the cause for metabolic effects in the human body, they also affect the other toxicities related to metabolic pathways due to which PFAS may be the cause of secondary metabolic abnormalities also. In this chapter, we will discuss briefly the effects of PFAS on metabolic system and especially how PFAS causes neurodegeneration. Although neurodegeneration is the major area focused in this chapter, organ-specific and systemic toxicities related to metabolic effect are also discussed. There are specific PFOS which are found in blood and their long-chain fatty structure shows that a major role is played by hydrophobic interactions in binding of these chemicals with their molecules. During PFAS-receptor hydrogen binding and polar interactions are contributed by carboxylic acid groups and sulfonic acid and carboxylic acid. One of the main target identifiers is peroxisome proliferator-activated receptor alpha (PPARα), the main controller of liver lipid metabolism [45].

Molecular Targets Involved in the Metabolic Effects of PFAS

PFAS have very specific interactions with the molecule in the body and according to human anatomy their main target are receptors so PFAS stimulate metabolic effects by combining with various molecular targets, including receptor-specific and receptor nonspecific as given below.

Receptor Specific Metabolic Effects of PFAS

Receptor specific metabolic effects induced by PFAS are well characterized and it is believed to be induced by primary or secondary actions. PFAS can directly mimic the actions of endogenous ligands thus acting as agonist or antagonist this is considered their primary action however their secondary action is not well researched and harder to elucidate so proper data is not available according to that hence they don't show action by mimicking the endogenous ligands but they affect the signaling pathways by interference with the levels of ligands or receptors (see the Table 14.1).

Table 14.1 Receptor specific and nonspecific metabolic effects of PFAS

Name	Nature or location	Mechanism of action	References
PPARα	PPARα plays a role in lipid metabolism regulation and is called a nuclear receptor	The fatty acid is an endogenous ligand for activation of PPARα. PPARα, when activated, causes dimerization with retinoid X receptor (RXR), and then combine with peroxisome proliferator hormone response elements (PPREs), and various genes are regulated, that are responsible for fatty acid metabolism, for example, acyl CoA oxidase (ACOX) and fatty acid-binding proteins (FABPs) a	[128]
PPARγ	PPARγ is a member of the PPARs family, but the endogenous ligands are principally eicosanoids	The very important action of these receptors are that they regulate the storage of fatty acid and metabolism of glucose. PFAS, for example, PFOS and PFOA, are be capable to activate PPARα and PPAR γ	[129]
Estrogen receptor	They are known to endocrine disruptors	If PFAS interact with estrogen receptor they lead to profound metabolic and can interact with estrogen receptors directly	[130, 131]
Thyroid hormone receptor	Located in the hypothalamus	When the body is exposed to PFOA, the gene responsible for thyroid biosynthesis has been inhibited NHANES 2007–2008 data shows that there is a connection between increased circulating T3 levels and PFOA exposure	[132]
Leptin receptor	Act as an appetite regulator	When the body is exposed to PFOAS, one of the pathways disrupted is the leptin signaling pathway that leads to increased body weight and obesity	[133]
Nonspecific metabolic effects of PFAS	Obesity Developmental retardation Environmental	1. There is no specific mechanism of action has been known for PFAS induced increase in body weight however it is believed that may be interference with fatty acid metabolism is the reason 2. Effects are usually difficult to determined completely and can be widely considered due to metabolic effects. Therefore, additional studies are required to determine molecular targets and mechanism behind these effects	[133]

Laboratory Data on the Metabolic Effects of PFAS

Laboratory evaluations on metabolic effects have been described in this section. For explanation, indirect and direct metabolic effects have discussed separately.

Direct Metabolic Effects

Effects on Fatty Acids

Metabolism of fatty acids is one of the most well-known and well-studied effects analyzed in laboratory animals or other experiments like cultures of cells after PFAA exposure. The mechanism for increased fatty acid metabolism is that PFAS activates PPAR alpha which is the main element involved in the regulation of fatty acid metabolism so indirectly, this way exposure to PFAS causes metabolic effects in the body. A large number of studies have been conducted to analyze the effects on the metabolism of fatty acids following activation of PPARα [46–49]. However, it is also observed that PPARα may also have independent effects on other biological activities, as described by [45]. Research data shows the effect of exposure to PFAS may interfere with enhanced metabolism of fatty acid and the synthesis of cholesterol in the liver [50]. In addition to changes in genes, responsible for cholesterol metabolism, some direct effects on the cholesterol level in body are observed. In certain research works, reduced serum cholesterol level has been observed in male Sprague-Dawley (SD) rats [51]. Another study, which has been taken place earlier, shows that relatively highest exposure of PFOA in Wistar rats could be the reason for the accumulation of cholesterol in the liver [52]. As two effects observed side by side, that is, reduced serum cholesterol and increased liver cholesterol, we can explain these two facts by the fact that transportation of cholesterol to liver increased by PPARα agonism [53]. Guruge et al. [54] anticipated an attractive hypothesis related to PFOS. As cell membrane fluidity and membrane potential are affected by the incorporation of PFOS into cell membrane [55], PFOS plays a similar role as cholesterol, and hence the level of cholesterol decreases by functional replacement with PFOS. Thus, PPARα interference is considered one of the main and important causes of reduction in cholesterol level, and the cholesterol-lowering effect could be explained by the functional substitution hypothesis in PFAS lab models. However, further work is required to draw consolidated conclusions.

Effects on Carbohydrates

Carbohydrates are important components of food and in the body too however less data is available for exposure of PFAs induced effects on carbohydrate levels but available for glycogen mostly in animals. In one study, PFOA exposure to PFOA

decreased level of glycogen in livers of zebrafish, which indicates that PFAS affect the glycogen levels, more importantly deposition of glycogen [56]. More work is needed to know how carbohydrate level is affected by PFAS.

Effects on Other Metabolic Substances

Other than above-discussed substrates, another important endogenous compound is Carnitine that is responsible for fatty acid beta-oxidation. Peng et al. [57] stated that exposure to PFOA may cause disruption of carnitine metabolism in L-02 cells. Unlike others, the concentration of carnitine was reduced when exposed to PFOA, while the other metabolic carnitine analogues including acetylcarnitine, propionyl carnitine, butyrylcarnitine, and valerylcarnitine, were all believed to be increased. The enzymes responsible for carnitine metabolism,

Indirect Metabolic Effects at Genetic Level

Not only does PFAS directly affect the levels of lipids (fatty acids), thyroid hormones, and cholesterol, but it can also affect the genetic data that is related to the metabolism of these compounds. Primarily PPARα agonism mediates these effects, but independent effects of PPARα can also be present. They can also affect the metabolism of cholesterol, carbohydrates, nucleic acids, and alcohol. Guruge et al. [54] also described exposure to PFOA induced mutation in multiple genes of peroxisomes and mitochondria at expression levels. The genes responsible for this contain enoyl CoA hydratase, acyl-CoA oxidase, acetyl-CoA dehydrogenase, and carnitine palmitoyl transferases. This enhanced level of expression of these genes indicated that the metabolism of fatty acids promoted by PFOA. Other researchers also found the same results, including Krøvel et al. who reported that acyl CoA and PPARα expression enhanced by PFAS. In summary, changings in the expression of metabolic genes by PFAS exposure are the main parts of metabolic effects [58] of PFAS. These mutations in gene expression could be the reason or result alternations substrate level of metabolism.

Body Weight

Bodyweight usually is lowered in adult animals when they are exposed to higher doses. Lefebvre et al. [59] described a considerable decrease in body weight after dietary exposure of PFOS in adult Sprague-Dawley rats. This reduction in body weight thought to be a sign of general toxicity and was observed only at higher doses than the level of human exposure. However, bodyweight can be influenced by PFAS through signaling pathways interference in very lower doses. As mentioned in the table, PFOS exposure affected the animal models and led to increase in body weight, but at lower doses.

Human Data on the Metabolic Effects of PFAS

Accessible human data on PFAS metabolic effects are described in this section. The effects of PFAS on levels of uric acid, lipids, and thyroid hormone have been summarized (see Table 14.2).

Neurodegeneration by PFAS

PFAS have now polluted the whole world [60–62]. Moreover, measurable levels of PFAS are present in humans, from 2016 to 2018 as a whole serum mean concentration of PFAS are 2.04 ng/mL PFOA, 0.79 ng/mL perfluorononanoic acid (PFNA), 2.94 ng/mL PFOS and 1.10 ng/mL PFHxS [15, 16]. Unluckily, there are many other PFAS to those humans are exposed throughout their life which not only imparts harmful effects on adults but also in whole life. It has been quantified that PFAS are present in amniotic fluid, fetal tissue, breastmilk, lung, heart, umbilical cord, and brain, blood, and placenta which indicates PFAS exposure in infants from very start

Table 14.2 Parameters of human data on metabolic effects

Parameters	Level	Research attributes	Reference
Serum lipid level	Elevated	In occupational studies, different associations between PFOA exposure and HDL or triglyceride have been reported. There is an association of PFOA with increasing level of LDL but not HDL [134], increased total cholesterol but not triglycerides or HDL [135], and increased triglycerides but not LDL [136] The mechanism of action identified in animal studies, plays a role in changes in lipid levels in humans, given the discrepancy between human and animal studies on the associations between PFAS and serum lipid levels. Therefore, additional studies are needed to get the full picture on the effects of PFAS on serum lipids level in humans [137]	[134–137]
Uric acid (a by-product of purine metabolism) levels	Elevated	Recent studies in the general population additionally demonstrated that the association of PFOA and PFOS with an enhanced level of serum uric acid did not depend on race, body mass index, age, ethnicity, hypertension, diabetes, and cholesterol level of serum The positive associations between PFAS exposure and elevated serum uric acid levels have been reported in four studies in adult populations highly exposed to PFAS [135, 138, 139]; and two studies in the general population at lower "background" exposure levels of PFAS [55, 140]	[141]
Thyroid function	Elevated	1. Exposure of these chemicals causes impairment in the homeostasis of thyroid hormones by decreasing T3 and T4 in experimental animal models like rats and monkeys [137] 2. A significant association found between the level of PFOA and PFOS and thyroid disease in females while a very less association found between PFOS and thyroid disease in males	[137, 142]

of life [63, 64]. Many forms of toxicity have been identified in a model system of mice, rats, and cynomolgus monkeys; conversely, rodents require larger exposure to attain similar internal PFAS doses as observed in human because of the shorter half-life of PFAS in rodents. Sentinel species are useful to determine toxicity as these organisms are exposed to the chemicals of interest naturally and capable to show toxicity earlier than in humans. Moreover, various types of sentinel species have physiological similarities to humans for example (*Ursus maritimus*).

It has studies that mice that were exposed to PFOA or PFOS at postnatal tenth day showed enhanced activity at the age of 2 months and lesser movement at the age of 4 months, representing impacts on motor function [65]. Amusingly, PFOS exposure to mice during developmental stages had decreased the movement significantly after treating with methamphetamine [66]. Moreover, decreased myelination in the brain observed in mice that were exposed to 20 mg/kg PFOS per day for 28 days initiating at second month is also indicative of neurotoxicity [67].

PFOS Produces Dopaminergic Neuropathology

PFAS exposure to nematodes (*Caenorhabditis elegans*) for 72 h shows the evidence of neuropathology during the inspection of GABAergic, dopaminergic, serotoninergic, and cholinergic neuronal morphologies. Aldicarb and 1-nonanol assay was used for cholinergic, dopaminergic, and functional analyses. Mitochondrial contents, superoxide ions, and total reactive oxygen species were assessed through mechanistic studies. Lower levels of exposure (25 ppm, ~50 μM) can cause dopaminergic neuropathology, whereas neuropathology in serotonergic, GABAergic, and cholinergic neurons required high doses (100 ppm, ~200 μM). Furthermore, PFOS exposure produced dopamine-dependent functional loses, without changing acetylcholine-dependent paralysis. Lower doses of PFAS (1 ppm, ~2 μM) affected mitochondrial content rather than pathology induction which required high dose. Mutations in mitochondrial superoxide dismutase produced more adverse effects in animals [68].

Role of Mycotoxins in Human and Animal Nutrition and Health

Most of the toxic syndromes of human and animals involve mycotoxins. These toxins are mainly derived from oils seeds crops and cereals and products derived from them [69]. Through direct or indirect pathways mycotoxins enter the human and animal dietary system. Feeds or foods can indirectly be contaminated when an ingredient of a process has been contaminated previously with toxin-producing fungi or when fungi may be removed during processing but mostly mycotoxins

remain in finals yields. On the other hand, direct contamination of feeds or foods occurs when it is contaminated with toxin-producing fungus which ultimately produces toxins [70].

Human ingests mycotoxins in the form of mycotoxins in plant-based foods and by the consumption of metabolites and residues in animal-derived foods, for example, cheese, milk, and meat. Mycotoxins greatly affect the health of farmed animals as their fodder is plant-based. Mycotoxicosis exhibit difficulties in diagnosis as it can be confused with many other diseases caused by nutrient imbalances or pathogenic microorganisms [69].

In acute mycotoxicosis, animals may present marked signs of pathology but in severe cases, animals may die. Humans are exposed to mycotoxins when they consume mycotoxin-contaminated animal or plant-based foods. In chronic mycotoxicosis no macroscopically visible changes are found in infected animals and symptoms such as reduced growth rate, low market quality, decreased reproductive ability, decreased production of milk and decreased egg production. Diagnosis of such kind of disease is difficult but in farmed animals, it is the most common form mycotoxicosis [71]. As a result of their diverse chemical structures and different physical nature, mycotoxins show a wide range of biological effects. Moreover, individual mycotoxin may be estrogenic, embryotoxic, teratogenic, mutagenic and genotoxic. Many mycotoxins have been found to cause carcinomas in animals and perhaps in humans [69].

Effects of Mycotoxins on the Immune Systems

Host exposure to particular chemicals can cause immunosuppression consequently host becomes more susceptible to the risk toxins, microorganisms and tumor cells. Along with ochratoxin A and Aflatoxins, some trichothecenes can also cause immunosuppression and attack specific immunoglobulins if exposed to more mycotoxins. However, chief effects are involvement of nonspecific humoral and cellular immunity. Such responses result into delay cutaneous hypersensitivity, inhibit phagocytosis by macrophages, thymic aplasia, leukocyte migration, and lymphocyte proliferation. Particular mycotoxin involvement in an infection depends upon the agent of a disease, the toxin constitution and dose, animal species and probably the test sensitivity [69].

Health and Well-Being of Man

Ingestion of mycotoxins causes complex problems to human health. Historically, mycotoxins are known as ergotism. This pathology resulted due to the growth of *C. paspali* or *Claviceps purpurea* on rye and following the formation of toxic alkaloids and the baking process could not inactivate them. When used in rye bread

many alkaloids were capable of causing necrosis, limb loss, gangrene, nervous disorders along with dangerous effects on human fertility. Population regulation was considerably affected by the regular presence of fungal toxins in rye bread due to the high dependence of US population on it as a staple food [72].

Moreover, in the late 1600s in the USA, Salem witchcraft trials have been unexpectedly related with nervous disorders described for ergot alkaloids. Interestingly it is of great concern to note that when we use controlled doses of a specific ergot derived alkaloid pharmacologically much of the toxicity could be used to relieve migraine headaches and postpartum hemorrhage control. Mycotoxins got pharmaceutical value in this way [73]. Another human toxic syndrome related to consumption of mold-infected food also has historical importance. Particularly there has been frequent epidemics of acute aflatoxin poisoning throughout the world, such as alimentary toxic aleukia (ATA) in china and India, stachybotryotoxicosis in Russia, and yellow rice disease in the Far East. Other important human toxic syndromes associated with the ingestion of mold-contaminated foods have also had considerable historical and geographical relevance. Strong correlations of highly infected food consumption have been reported in each of these epidemics [74]. This problem has been lessened by using good agricultural practices, safe transport facilities, and better storage methods, thus reducing toxin-producing mold growth in raw materials [74].

Although mycotoxins are usually considered as diseases resulted by mycotoxins contaminated food ingestion, inhalation of mycotoxins spores through the respiratory system is also a great health issue [75]. Particularly this is applicable in long-term exposure to these spores in damp, mold domestic or occupational environments within fermentation industry. Aflatoxins have been related with genotoxicity resulting in teratogenicity or mutagenicity, on the other hand, other mycotoxins carcinogenicity, for example, ochratoxin A, patulin, T-2 toxin, sterigmatocystin, and zearalenone has been proven on animal tests, not in human. To assess carcinogenicity in humans, three types of epidemiological studies are employed, namely, case–control studies, cohort studies, and correlation studies [76].

Case-control and cohort studies are associated with individual exposure under investigation to the incidence of cancer in individual to give an estimated risk. In correlation studies, investigation units are usually whole population (in a specific time or specific geographical area) and carcinoma incidence is associated with a summary of population exposure to an agent under examination. On the whole, supposed mycotoxin evaluation indicates the evidence strength derived from experimental studies from animals and humans [76]. Conversely, it is difficult to establish a relationship between human exposure and aflatoxin exposure because of various associated uncertainties related to human epidemiological studies [77].

Physicochemical Processes for Treatment of PFAS

Two PFAS that have attained more attention due to their toxicity, persistence, potential of bioaccumulation and for presence in the environment are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS). Water treatment processes are mostly based on phase separation; frequently residual wastes are produced during this process which requires expensive treatment and handling causing enhanced costs. Physiochemical processing aimed to destroy and mineralize contaminants into carbon dioxide and water or less toxic products [78]. The following are some physiochemical processes discussed in this chapter.

Chemical Oxidation Processes

Transfer of electrons from one electron donor to another electron acceptor is called chemical oxidation. Chemical oxidation leads to chemical transformation of pollutants directly or by free radicals (uncreative species), which readily break contaminants [79]. PFAS are less vulnerable to direct electron transfer oxidation; It has been discovered that free radical oxidation process is the most aggressive and nonspecific approach of treatment.

Heat-Activated Persulfates

Most of the studies analyzing PFAS oxidation by free radicals have paid attention to activated persulfate. Most of the groundwater pollutants are degraded by activated persulfate, including herbicides [80–83], chlorinated solvents [84, 85], pharmaceuticals [86, 87] pesticides [88], and some PFAS [89, 90] and volatile organic compounds (VOCs) [91]. The redox potential of persulfate is 2.01 V, which reacts either by activating into free radical or by electron transfer to degrade pollutants. Many methods have been utilized for activation of persulfate in during treatment of groundwater to produce free radicals in situ chemical oxidation [92, 93]. When persulfate becomes active, it generates hydroxyl free radicals (2.7) and sulfate radicals (2.6 V) [79].

Maximum number of sulfate-free radicals are formed at low pH, though hydroxyl radicals are still produced. Park et al. [90] have recently studied the oxidation of PFOS and PFOA, 6:2 fluorotelomer sulfonate (6:2 FTSA) for in situ remediations of groundwater by heat-stimulated persulfate under favorable conditions. They specified that oxidation of 6:2 FTSA produced PFHxA and PFHpA and oxidation of PFOA followed by unstopping deteriorating pathway of producing short-chain compounds and fluoride. PFOS was not transformed even at the high temperature specified the similar regular loss of CF2 and formation of degradation intermediates [94].

Electrochemical Oxidation

Due to the ability to degrade an extensive range of recalcitrant organic compounds electrochemical oxidation is getting greater importance in recent years for the treatment of polluted water; Indirect or direct anodic pathways are used for electrochemical oxidation [95]. Direct electrolysis is performed by direct adsorption of contaminants onto the electrode and degraded directly, whereas indirect electrolysis is performed by degrading contaminants in a bulk of liquid in reaction with oxidizing agents which are produced at the electrodes [96]. Various materials have been utilized as electrodes but most of the studies have utilized electrodes made of boron-doped diamond (BDD) due to its thermal, mechanical and chemical stability [97]. Several other electrodes also have shown the capability to degrade PFAS for example titanium oxide (TiO_2), lead dioxide (PbO_2), and tin oxide (SnO_2) [98] in comparison with some other inactive materials, for example, platinum (Pt) and iridium (VI) oxide (IrO_2) [99]. Electrochemical oxidation of PFAS is also affected by some other factors such as temperature, initial concentration of PFAS [100], type of electrolyte, current density [101], and pH [102, 103]. The reason to prefer boron-doped diamond, TiO_2, SnO_2, and PbO_2 for electrochemical oxidation of PFAS is their high ability to transfer electron [99] and their atoms ability to stay in the same state of oxidation during electrochemical reactions and atom in the electron continuously recycle [104]. There are several advantages of electrochemical oxidation for example waste material is not produced, can operate at ambient temperature, no specific chemical requirements [105]. However, some cost and environmental risks are related to electrochemical oxidation. Various by products produced during the reaction are toxic for example perchlorate, hydrogen fluoride, lead and bromate. Schaefer et al. [106] analyzed the perchlorate formation BDD anode based electrochemical oxidation of PFAS. Usage of toxic metallic anodes results in the release of metallic by-products in the environment [105].

Photolytic/Photochemical Oxidation

Incomplete mineralization of pollutants through chemical oxidation produces more persistence and toxic by-products in the environment, causing higher operating cost as these by-products are more toxic than parent substances.

The use of ultraviolet (UV) irradiation (UV lamps or natural sunlight) has helped in lessening this problem through oxidation reactions between free radicals and contaminants, and subsequent complete oxidation of compounds [107]. The radiation output of most of UV lamps is 254 nm; pollutants absorb ultraviolet energy in the range of 200–300 nm, thus getting activated and further reacting with oxidants. Direct or indirect photolysis can degrade contaminants [108]. Direct photolysis occurs by the transformation of contaminants through UV light absorption, whereas in indirect photolysis degradation of contaminants occurs through their reactions

with generated reactive species [109]. PFAS do not absorb energy less than 220 nm; therefore, direct photolysis is not effective for PFAS degradation, and for efficient degradation of highly fluorinated compounds a wavelength of less than 190 nm is required [110].

Chemical Reduction Processes

Just like in oxidation processes, reduction processes also work by electron transfer to degrade contaminants or production of free radicals which break down contaminants. For groundwater treatment, reductants include ferrous ion, zerovalent iron (ZVI), and sodium dithionite which are capable to either directly transfer electrons or produce reducing radicals, for example hydrated electron and hydrogen radicals [111]. Factors on which reduction processes depend upon are contaminant concentration [112], concentration of reductant, presence of groundwater ions, and temperature [113].

Zerovalent Iron (ZVI)/Nanoscale Zerovalent Iron (nZVI)

ZVI or nanoscale zerovalent iron (nZVI) is a relatively cheap method of groundwater remediation; it can act as a reductant or sorbent. In situ remediation of groundwater mostly use ZVI as a reductant because it has high reducing ability and remediate groundwater successfully, for example, chlorinated groundwater [114], groundwater polluted with heavy metal field-scale tests and in the laboratory [115].

In general, reduction by ZVI involves the transfer of pollutants on the surface of ZVI, adsorption, and then conversion into less toxic substances, and later on, desorption, and by-products are transformed in the solution. Surface properties of ZVI have a great influence on the reactivity of contaminants [116].

Advanced Reduction Processes (ARPs)

Groundwater contaminants can also be degraded by advanced reduction processes (ARPs). A group of activation methods is involved in ARPs; for example microwaves, ultrasound and ultraviolet rays are involve in combination of activation methods such as ultrasound, ultraviolet, electron beam, microwaves with reductants, for example sulfide, ferrous iron, iodide, dithionite, and sulfite to produce a highly reactive chemical that covert pollutants to less dangerous products [113]. Hydrated electron, hydroxyl free radical, and hydrogen-free radicals are usually formed during ARPs. The oxidizing hydroxyl radical (OH), the reducing hydrogen radical (H), and the hydrated electron (eaq) are the most reactive free radicals pro-

duced during ARPs. ARP-induced degradation rates depend upon concentration of reductants and pH of the initial solution [113].

Ultrasonication

PFAS are successfully degraded by ultrasonication (sonolysis) to CO_2, F^-, and SO_4^{2-} [117]. The process of sonolysis depends upon propagation of sound waves in liquids at the frequency ranging from 20 kHz and 1000 kHz [118], which consequences in cavitations. Two mechanisms are involved in sonolytic degradation (1) reaction of hydroxyl radical because of the hemolytic breakdown of water under specific conditions (2) pyrolysis [119]. During the process of cavitation, cyclic production, growth, and fall of microbubbles cause a tremendous increase in pressure and temperature and free radicals are generated [120]. Different stimulated regions are present in cavitation bubbles where chemical reactions take place: The cavitating bubbles have different active regions where chemical reactions occur: (1) within bubble gas (2) interface in bubble gas-liquid and (3) in the region of bulk liquid. More frequently pyrolysis occurs in bubble gas and due to greater surface activity water repellent compounds, for example, PFOS and PFOA collect at the bubble water interface, going through in situ prolific degradation [121]. Pyrolytic degradation and defluorination od PFAS is greatly affected by the factors for example frequency [122], the temperature of the solution, sparge gas type, and PFAS initial concentration and power density [123]. Vibration amplitude is increased by increasing power, which increases cavitation generation rate and number also affecting the size of bubbles before falling down [124]. On the other hand, the rate of the reaction decreases at a certain power level [125]. The rate of sonolytic breakdown depends upon molecular adsorption sites, the intensity of the bubble collapse, and the oscillating frequency of bubbles. Therefore, the degradation rate increases by increasing frequency as more adsorption sites are created [125]. The rate of degradation also may be enhanced by the addition of catalyst [123]. Moriwaki et al. [126] analyzed PFAS (20 lM) sonolytic breakdown at a 200 kHz frequency in the atmosphere of argon. Successful removal of PFOS and PFOA was reported and the rate of degradation remains constant.

Lin et al. [127] reported complete removal of PFOA and more than 99% of defluorination observed by addition of sulfate ions during ultrasonic treatment. US-sulfate system reported that increased removal of PFOA occurs through two reactions, (I) destruction of PFOA in direct reaction in a bubble water interface and (II) SO_4 formation which then indirectly degraded PFOA to CO2, SO_4^{-2}, and F. These two reactions increased the rate of degradation. Efficiency of removal not affected by solution's PH, whereas degradation promoted by ambient temperature in comparison to raised temperature. Rate of degradation and defluorination of PFOA were highly dependent on the dose of sulfate [127].

Conclusion

Worldwide human beings are exposed to harmful effects of PFAS. Various in vivo and in vitro studies have been conducted; however, further work is required to draw consolidated conclusions.

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Chapter 15
Polycyclic Aromatic Hydrocarbons and Neurological Disorders: From Exposure to Preventive Interventions

Ajab Khan and Ali Raza Jahego

Abstract Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental toxic chemicals which include more than 100 chemicals, mainly produced as a result of improper combustion of organic substances like wood, coal, petrol and oil. These pollutants are released into the environment due to various activities including open air burning, natural losses, leakage of various chemicals, accidental fire and many more. The most common sources of PAHs production are house hold heating systems, plants using coal for gasification and liquefaction, various industries and factories manufacturing different livelihood products, petroleum refineries and automobile exhaust. PAHs metabolites (especially 1-OHP) in urine, and PAH–DNA adducts with DNA, RNA and proteins in WBCs and other tissues, which are part of PAH toxic mechanisms, are used to measure PAH exposure in humans. Despite of different biological barriers such as placenta and blood–brain barrier, brain still has unique susceptibility to environmental risk factors during its developmental period compared with the mature nervous system. Benzo(a)pyrene is one of the most toxic PAHs known which is often used as an indicator of PAH exposure in various epidemiological studies. PAHs combat and interfere with the functions of cellular membrane and its enzyme systems to cause cytotoxicity. Chronic exposure to even low concentration of these chemicals cause ever-lasting damages including infertility, cancer and neurotoxicity to humans as well as wild life. Epigenetic effects, oxidative stress and endocrine disruptions are some of the mechanisms investigated for PAHs neurotoxicity. As brain is the most vulnerable organ to oxidative damage due to low oxygen level which may cause alteration in gene expression, impairment in cellular signaling, membrane integrity disruption, altered neurotransmission and ultimately neuronal cell death. The oxidative stress (due to ROS) pro-

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duced in the CNS causes reduction in the antioxidant enzymes activities which are crucial for the behavioral effects induced by PAHs especially B(a)P. Adsorption, volatilization, photolysis and chemical degradation are some of the important processes in the removal of PAHs from both the atmosphere and environment. Among these, microbial degradation is considered to be the major PAHs degradation process.

Keywords Polycyclic aromatic hydrocarbons · Pollutants · Metabolites · Neurotoxicity · Oxidative stress

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are toxic chemicals which are universally produced due to improper combustion of organic substances like wood, coal, petrol and oil because of open air burning, natural losses and leakage of various chemicals, accidental fire and many more [1]. PAHs are white, colorless or pale yellow organic compounds with two or more aromatic hydrocarbons arranged in certain configurations [2]. The structures of some commonly found PAHs in the environment are shown in Fig. 15.1. The number of PAHs aromatic rings are directly proportional to its structural angularity, electrochemical stability, resistance to biodegradation, carcinogenic index, persistency and hydrophobicity while volatility of PAHs have inverse relation with molecular weight [3]. Environmental PAH (ePAH) are PAHs related to environmental medium such as water, sediment and soil etc. [4], mostly present in the forms of mixtures and are deposited in soil [2]. Among hundreds of PAHs, 16 are considered as pollutants of high concern by the U.S. Environmental Protection Agency and their structures are shown in our previous book entitled as "*Endocrine Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies*" [5].

Most of the PAHs are endocrine-disrupting chemicals (EDCs) which have a direct and strong blow on the regulation of endocrine system functions (metabolism, growth, immune system, and reproduction) as well as have toxic, mutagenic and carcinogenic effects [1]. PAHs being highly lipid soluble get absorbed through the gastrointestinal tract (GIT) of mammals and localized in body fats (due to its high tendency towards body fats), and are thus rapidly distributed in a wide variety of tissues. Cytochrome P450-mediated mixed function oxidase system with oxidation or hydroxylation is a first step in PAHs metabolism [6]. PAHs combat and interfere with the cellular membrane functions and its enzyme systems associated to cause cytotoxicity [7].

Although PAHs are not chemically synthesized for industrial purposes, still they are used for some commercial purposes including intermediaries in pharmaceuticals, agricultural and photographic products, lubricating materials, thermosetting plastics and other chemical industries [8]. In this chapter, we will discuss in detail

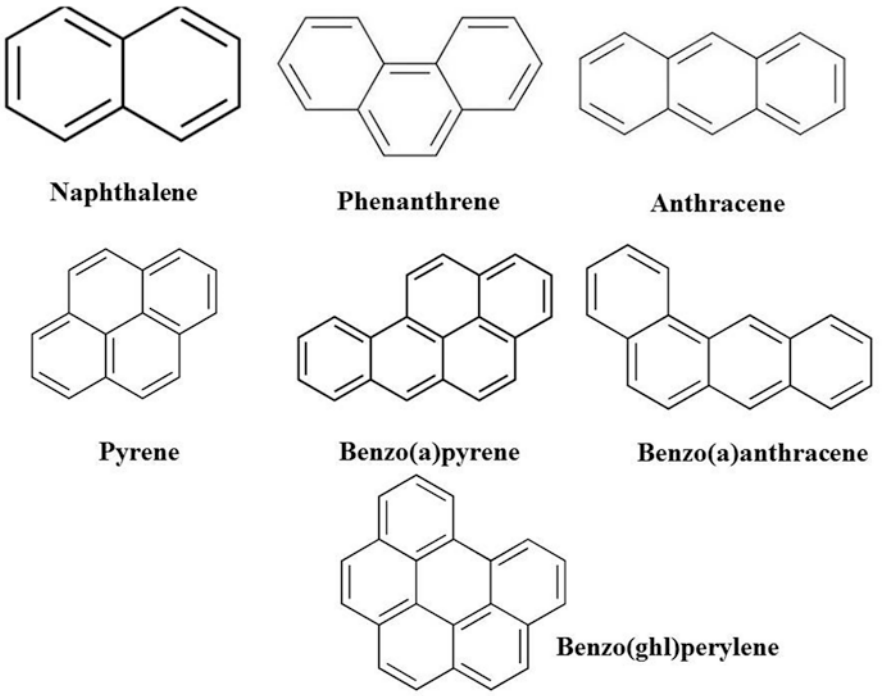

Fig. 15.1 Common representative of PAH compounds

the exposure sources of PAHs, their types, route of entry into the body and mechanism of PAHs-induced neurodegeneration. Moreover, data from epidemiological and experimental studies conducted to investigate the role of PAHs in neurological disorders will be discussed. At the end of this chapter, protection of human beings from its exposure and the therapeutic interventions which can play their role in the treatment will also be discussed.

Occurrence and Sources of PAHs

The sources of PAHs can be broadly divided into three categories such as petrogenic, pyrogenic and biological. Pyrogenic PAHs are produced by the pyrolysis process in which the pyrogenic PAHs are produced during combustion of organic materials at a high temperature (from 350 °C to more than 1200 °C) in the absence or low quantity of oxygen (anaerobic combustion). This may be an intentional process such as conversion of coal into coal tar and coke, and petroleum residues into lighter hydrocarbons, or an unintentional procedure due to incomplete combustion of various organic substances such as motor/truck fuels, wood in forest fire and improper fuel oils combustion in the heating systems. Some PAHs can also be

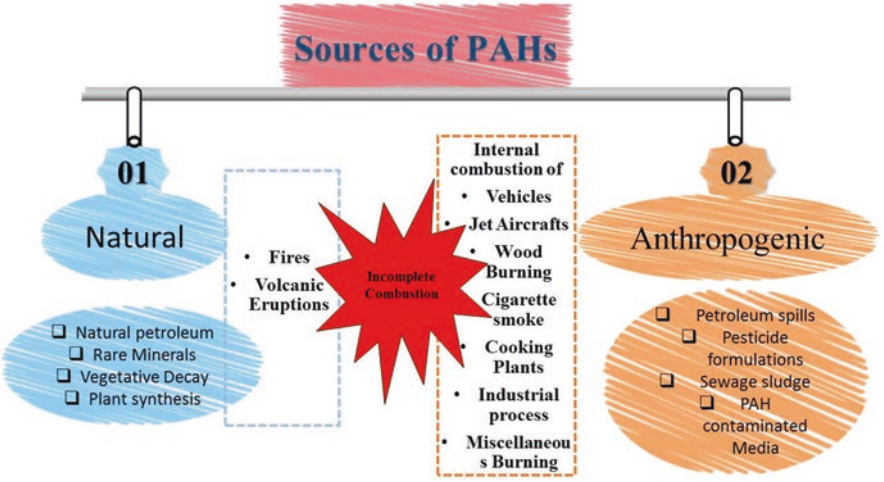

Fig. 15.2 Natural and anthropogenic sources of PAHs. Incomplete combustion is the main contributor of PAHs addition to the environment

formed at low temperature over a long period of time for example, PAHs present in crude oils are formed over million years at 100 to 150 °C temperature [6].

Petrogenic PAHs are commonly produced during maturation and other similar processes such as widespread transportation, storage and use of crude oil as well as their products, oceanic and fresh water oil spills, leakage of storage tanks (underground or above ground), accumulation of gasoline, motor oil and released substances related to transportation [6]. Biological PAHs are still under investigation to know either these PAHs are synthesized by certain plants and bacteria or produced as a results of vegetative matter degradation. Broadly, sources of PAHs can be divided into natural and anthropogenic as summarized in Fig. 15.2.

Emission, Transportation and Deposition of PAHs

As mentioned above, incomplete combustion of organic substances (both natural and anthropogenic) are the definite sources of PAHs which are continuously emitted, transported and deposited in the environment (Fig. 15.3). Compared with the rural, urban environment is the largest source of PAHs emission as most of the PAHs production sources are found in or around urban areas. The emitted PAHs can be found in two phases, that is, vapor phase (sorbet form) and solid phase (particulate matter) [9, 10]. Various factors are involved in the relative distribution in these two phases such as vapor pressure, molecular weight, ratio of vapor pressure and molecular weight. PAHs compounds have difference in their vapor pressure and thus are distributed with different concentrations in the sorbet [11] and vapor phases

Fig. 15.3 Emission and sources of exposure to environmental PAHs

[12]. Lower pressure PAHs such as benzo(a)pyrene tend to be sorbet to particulate compared with high pressure PAHs such as naphthalene which will tend to be in vapor pressure. The lower molecular weight PAHs with high vapor pressure are found in the vapor phase while the high molecular weight and low pressure PAHs are not. In contrary, compared with the particulate phase, the vapor phase has much lower concentration of the higher molecular weight PAHs [6]. With increasing molecular weight, the characteristics of PAHs become more pronounced, such as increased melting point and lipophilicity, and decreased aqueous solubility and vapor pressure. In summer, the concentration of PAHs increases in the gaseous phase especially in the tropical regions. Similarly, in winter or in arctic region in general, the concentration of PAHs are higher in particulate phase [13, 14]. Moreover, humidity and type of suspended particulates (metal oxides, pollen, soot, fly-ash, etc.) also affect the adsorption of PAHs [15].

PAHs are continuously deposited and distributed on the earth (soil) by dry or wet deposition from various adjacent or distant sources. When deposited, the majority of PAHs binds to soil particles and thus become mobile in the soil [16, 17]. Mobility of PAHs in the soil depends on both the properties of PAHs and soil, such as the sorbent particle size and the pore throat size of the soil [18]. Similarly, PAHs can also be deposited on the sediments of environment such as when PAHs sorbet to atmospheric particles, become settled on various surfaces including lakes, streams and oceans by the same wet and dry deposition method. Road runoff, storm and

sanitary sewer effluents also have PAHs which become sorbet to particles, settled and sediment into the soil [13, 19].

The concentration of PAHs in various food items depends on the areas where they have been grown, for example its concentration is tenfold higher in industrialized area or its surroundings or along the highways than in rural areas. Food processing such as smoking, drying and cooking at high temperatures including frying, grilling and roasting are main sources of PAH generation. It also depends on the duration of time, distance from the heat source, type of fuel used, drainage of fats and number of cooking items. The PAH concentration of barbecue meat is 130 μg/kg, and smoked fish and meat 200 μg/kg [20]. Generally, PAHs are lipophilic in nature and are therefore more soluble in lipids as compared to water. Vegetables with large leaves and plant surfaces (peel, outer leaves) compared with internal tissues have generally higher level of PAHs.

PAHs and Human Exposure

Generally, the population is exposed to PAHs primarily via inhalation (aerosols/fine particulate matters resulted from incomplete combustion), ingestion (smoked or grilled food products), dermal exposure (petroleum products) and accidental ingestion (house dust) [4]. Smoking, especially cigarette smoking (both active and passive, reported to be 20–40 ng/cigarette^3 of PAHs), and food contaminated with particulate PAHs are the primary sources of PAH exposure [21]. High-molecular weight PAHs are less volatile in nature which are mainly deposited on crops and food products located near major industrial areas or roadways, are also sources of human exposure.

As lipophilic in nature, PAHs upon exposure, becomes readily absorbed and metabolized by the organisms and causes their harmful effects. 1-hydroxypyrene (1-OHP) is a commonly measured biomarker of PAH exposure found in urine [22]. Children living in polluted areas (heavily trafficked road, industries, smoke) have higher level of PAH metabolites (especially 1-OHP) in their urine [23]. PAH–DNA adducts with DNA, RNA and proteins are also used to measure PAH exposure in human WBCs and other tissues [24]. PAHs are also monitored in air/atmosphere to estimate PAH exposure to humans without internal PAH concentration. PAH exposure ranges from 0.02 to 1.2 ng/m^3 and 0.15 to 19.3 ng/m^3 in rural and urban areas, respectively [25]. Major industrial cities and homes using low efficiency fuels (indoors) are at high risk of exposure of PAHs.

PAH and Neurodegeneration

Neurological impairments or neurodevelopmental disorders are dramatically increasing throughout the world. From 1990 to 2010, mental and behavioral disorders, Parkinson's disease, autism and attention deficit hyperactivity are increased by

37%, 75%, 30% and 16%, respectively, while the Alzheimer's disease has become doubled [26]. Emerging neuroimaging has showed evidences that particulate matter has a strong impact on the structures of brain including, reduced total brain volumes, frontal gray matter and deep gray matter [27–29]. The suggested neurotoxic mechanism for some of these particulate matter include epigenetic effects, oxidative stress and endocrine disruption [30–33]. Moreover, the lipophilic compounds (including PAHs) may induce neurological disorders as the lipophilic membranes such as blood–brain barrier allow them to entre in the brain [34–36].

As discussed, PAHs possessed a variety of hazardous health effects in humans and wildlife [37, 38], including cancer, altered hormonal levels, internal organ damage, nutritional deficiency (vitamin A), impairments in development or reproduction and possible neurodegeneration (4–13). Several clinical studies have shown that due to their neurotoxic properties, PAHs are involved in neurodevelopmental disturbances in children which causes neuropsychological symptoms including depression, anxiety and attention defects [39–41], structural abnormalities in the brain (reduced caudal volume) [39] and reduction in white matter areas (frontal, temporal and parietal lobes) [42]. In adults, higher exposure of PAHs leads to lower digit-span score and plasma concentration of various neurotransmitters such as aspartic acid, dopamine, nor epinephrine and gamma-aminobutyric acid [43], and also increase anxiety and digital span-score [44]. PAH is an environmental neurodegenerative risk factor for the adults which are associated with cortical thinning and thus reduces memory functions including verbal learning [45]. However, the knowledge about neurotoxic effects of PAHs in adults is still limited especially, in those which are at high risk of PAH exposure.

Among different PAHs, toluene is a neurotoxicant used in glue, benzo(a)pyrene (B(a)P) has both neurotoxic and carcinogenic activity and naphthalene has hemolytic properties and is an active substance used in mothballs. Among 16 PAHs identified as priority pollutants by US Environmental Protection Agency, cigarette smoke possessed several of them including B(a)P and phenanthrene [46], still the exact relation of PAH exposure and neurodegeneration needs to be evaluated. One of the most toxic known PAHs is B(a)P which is often used as an indicator of PAH exposure in various epidemiological studies. The wide range of PAHs present in cigarette smoke accumulate and deposit in the lungs as cigarette tar, get absorbed and due to their lipophilicity cross the blood–brain barrier membrane to enter into the brain. After multistep reactions (epoxides and polar hydroxyl-derivatives), the metabolized PAHs are absorbed and thus leads to an end product that the body can readily excrete [47]. PAHs have well known synergistic properties which can cause far more toxic effects in combination than alone [48].

PAH and Oxidative Stress

An adequate oxygen supply to the brain is crucial for the normal physiology of brain to control all functions of the body. As brain is the most vulnerable organ of the body to oxidative stress which may cause alteration in the gene expression, cellular sig-

naling impairment, disruption of membrane integrity, altered neurotransmission and ultimately neuronal cell death [49]. Neurons have none or very low capability of cellular regeneration as well as have high metabolic rate, and that is the reason why brain is the most prone organ to reactive oxygen species (ROS) [50–52]. These molecular oxygen metabolites (ROS) have antioxidant properties and thus inhibit the antioxidant enzymes activity to demolish the oxidative stress [53]. Lipids are the most susceptible biological molecules to ROS which causes peroxidation of the lipid molecules [52]. The main function of antioxidants is its scavenging property towards free radicles to vanish the oxidative stress produced in neurons, which is responsible for many pathological changes [54]. PAHs (especially B (a) P) have been reported to act against the antioxidant defense system and thus regulate the oxidative stress in neurons, resulting in the reduction of potential properties of various neurotransmitters, secondary and self-perpetuating damage from oxidative cellular injury, activate inflammatory response and DNA damage at the end [55]. The details of free radical formation, its neutralizing mechanism and cell injury is shown in Fig. 15.4.

PAHs Induce Cytochrome P450s

Endogenous as well as exogenous compounds (xenobiotics) are metabolized by a ubiquitous enzyme family called cytochrome P450. From organisms, PAH excretion is mediated by the enzymatic oxidation by these enzyme superfamily. PAHs, especially B (a) P induce CYP1A1 (an isoform) to metabolize a wide range of substrates including PAHs. In the first step of PAH metabolism, P450 enzymes are activated which add oxygen atoms to the aromatic rings of PAHs, making them more water soluble to get easily attached with lager groups (sugar or glutathione) and thus aiding in their elimination. However, there are some intermediate forms of PAHs which are harmful and cause damage before elimination [56]. Research has shown that high CYP1A1 activity can cause toxicity during PAHs metabolism. CYP450s metabolize B(a)P (PAHs) and change it into B (a) P-7, 8-DHD, which acts as a substrate for CYP-dependent oxidation reaction to produce B (a) P-7, 8-dihydroxy-9, 10-epoxide (BPDE), a carcinogenic and neurotoxic metabolite. BPDE binds covalently to DNA in the nucleus and form deoxyguanoside–DNA adducts [57], which starts misreplication and mutagenesis [31]. Therefore, a high level of CYP1A1 can cause deleterious activity within the neuronal cells due to oxidative stress generation and subsequent oxidation of biological molecules which can lead to irreversible injury as well as degradation of cellular macromolecules, and necrosis or apoptosis [58, 59], as shown in Fig. 15.2. As discussed, compared with the parental compounds, some of the intermediate products which are produced during B (a) P metabolism are chemically more active, toxic and electrophilic in nature [60].

There is also another possible mechanism of PAH metabolites' action. B(a)P acts as a ligand and become neurotoxic when it interact with the cytoplasmic aromatic hydrocarbon receptors (AhR) [61], and is translocated (Ligand-bound AhR) into the nucleus to form a heterodimer with aryl hydrocarbons receptor nuclear translocator (ARNT). Ligand-activated AhR-ARNT complexes interact with xenobiotic-

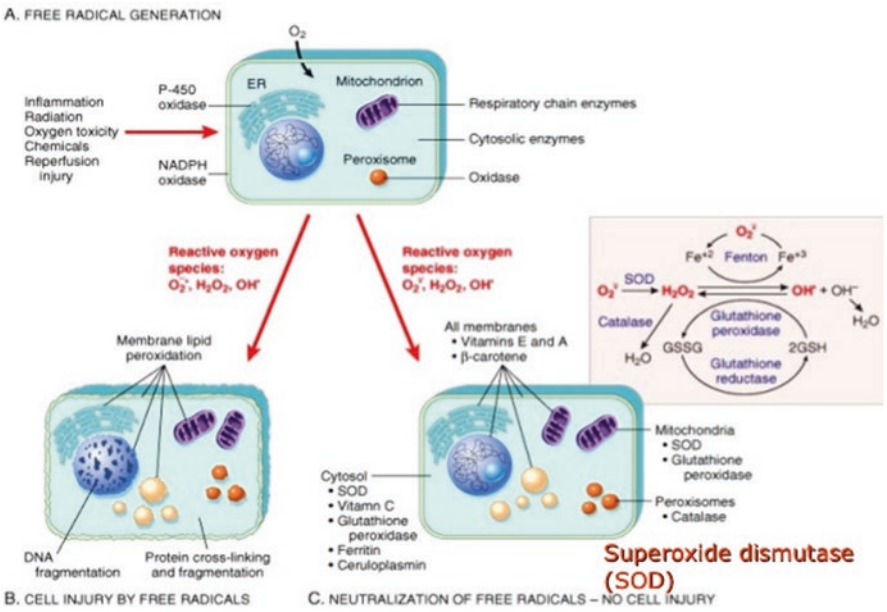

Fig. 15.4 The production, neutralization and role of reactive oxygen species (ROS) in cellular injury. With the help of oxidative enzymes present in the mitochondria, endoplasmic reticulum (ER), peroxisomes, plasma membrane and cytosol, molecular oxygen (O_2) is readily converted to superoxide (O_2^-). O_2^- is converted to H_2O_2, and H_2O_2 into OH by dismutation and Cu^{2+}/Fe^{2+} catalyzed Fenton reactions, respectively. In peroxisomes, H_2O_2 is also derived directly by oxidases. The produced ROS radical causes damage to proteins, lipids (peroxidation), DNA and ultimately cell injury. By Fenton reaction, O_2^- catalyzes the reduction of Fe^{3+} to Fe^{2+} and thus enhancing OH generation. SOD (superoxide dismutase), catalase and glutathione peroxidase are the major antioxidant enzymes. *GSH* reduced glutathione, *GSSG* oxidized glutathione, *NADPH* reduced form of nicotinamide adenine dinucleotide phosphate. (Adapted from [115] after some modification)

response elements (XREs) to promote transcription of various genes such as CYP450s enzymes (CYP1A1, CYP1A2 and CYP1B1) [62]. The high intracellular activity of these enzymes (especially CYP1A1) are deleterious because they can generate intracellular stress followed by oxidation and damage of biological molecules, which can ultimately lead to irreversible injury and necrosis of the cell [60].

Neurological Effects

Prenatal exposure to air pollutants (produced due to incomplete combustion) has adverse effects on fetal life and neurodevelopment. As discussed, the oxidative stress (due to ROS) produced in the CNS reduces the antioxidant enzymes activities resulted in abnormal behavioral effects by PAH especially B(a)P [63]. Similarly, a close relationship was observed among oxidative stress, locomotor behavior and

striatal function, and between hippocampal oxidative stress and age-induced cognitive decline [64, 65]. PAHs are neurotoxic, effecting nervous system including reduced motor activity (neuromuscular, physiological and autonomic deficits) as well as responsiveness to sensory stimuli [66–68], to which fetuses and infants are more susceptible than adults [69]. Loss of coordination and neuromuscular weakness, reduced responsiveness to sensory motor stimuli, polyuria and increased defecation are some of the signs and symptoms of acute exposure to PAHs, especially B(a)P and fluranthene [63]. Epidemiological studies have shown that prenatal exposure to PAHs is associated with PAH–DNA adducts in cord blood which causes reduced birth weight and head circumference [24, 70–72]. Reduced weight or head circumference are correlated with low IQ level and poor cognitive functions and school performance in early childhood [67, 73].

The development of human brain which include neurogenesis, migration, neuronal differentiation, synaptogenesis, myelination, apoptosis and synaptic plasticity in a tight controlled frame and perfect sequence, starts in the early gestation and completed after several years of neonatal life [74]. Despite of different biological barriers such as placenta and brain–blood barrier, brain has unique susceptibility to environmental risk factors during its developmental period compared with the mature nervous system [74–76]. The adult neuronal cell of brain lacks replication potential to replace the damaged DNA, have low level of protective enzymes (glutathione peroxidase (GSH-Px) and catalase) and high level of superoxide dismutase (SOD) [77, 78]. The cycling proper balance between GSH and GSSG enzymes are crucial for an effective antioxidant defense (Hunter and Simic 1983), because excess SOD compared with GSH-Px and CAT (enzymes of peroxidase metabolism) result in brain pathology [79]. Reduction in GSH is linked with number of CNS disorders including Alzheimer's and Parkinson's diseases [80]. Similarly, decrease in SOD leads to bipolar disorders while an increase causes manic and depressive episodes, while a decrease in CAT is involved in other psychiatric disorders [81, 82]. The brain is more prone to oxidative damage because of its high use of oxygen contents, and presence of oxidizable polyunsaturated fatty acids (PUFAs) and redox-active metals (copper and iron).

Removal of PAHs

PAHs can be removed from the atmosphere and environment through biodegradation, photochemical degradation and several other processes [6, 83, 84].

Removal of PAHs from the Environment

PAH Degradation

Environmental PAHs can be degraded by biodegradation, photooxidation and chemical oxidation, adsorption to soil particles, leaching and bioaccumulation [85]. As each PAH possesses a unique structure with a set of physical, chemical and bio-

logical properties, so these processes affect individual PAHs in a different manner. Some of the important PAHs degradation processes are discussed as under.

PAH Biodegradation

From literature review, the most frequent and commonly studied PAH degradation method is biodegradation, which may be either aerobic or anaerobic [86, 87]. For bacterial biodegradation, the PAHs must be first made available for bacterial uptake [85, 88, 89]. Solubility of PAH is strongly dependent on their molecular weight, an important factor for the bioavailability of PAHs. PAHs are bioavailable both in the dissolved and vapor forms while PAHs sorbet onto soil or other particles cannot be degraded readily by bacteria because at this form PAHs lack the enzymes used by bacteria for biodegradation [90–92]. There are also some other factors which effect the biodegradation and adsorption of PAH such as age or time duration of PAH in the soil.

Freshly deposited C-14 labeled phenanthrene and chrysene are adsorbed rapidly [90] compared with phenanthrene and chrysene exposed to soil for a long time are adsorbed very slowly [93]. Similarly, PAH degradation rate is reduced if bacteria involved in PAHs degradation find a chemical which is utilized more easily as an energy source. Competitive inhibition (by chemicals) of bacterial enzymes which are used to breakdown PAHs is another factor to reduce the degradation rate [94].

Degradation Through Photolysis

The breakdown of compounds by a series of reactions which are initiated by light is defined as photolysis [95]. During this process, the light absorbed by PAHs excite electrons of a molecule and convert them into an unstable form, ready for several physical and chemical processes. PAH photolysis degradation is more effective when they are present in the vapor or aqueous phase [96]. These reactions become stronger with increasing particle surface and light colored particles such as alumina or silica gel (half-life of anthracene is 0.5 h) compared with dark particles such as carbon black (half-life of anthracene is 310 h) [6]. Similarly, structure of PAHs also effect the process of microbial photodegradation process such as linear, 2-ring and some clustered PAHs are degraded easily and rapidly under direct light compared with angular PAHs because of their structure stability [97]. Moreover, low-molecular weight PAHs (naphthalene) are readily bioavailable and are therefore easily degraded by photolysis compared with high-molecular weight PAHs.

Chemical Degradation

Chemical degradation is a process of chemical oxidation (natural or part of treatment technologies) and is minor contributor of PAH degradation process in most of environmental conditions [98]. Several factors such as molecular weight, structure and physical state of the PAH, and environmental temperature as well as oxidizing strength of the compound can affect the oxidation rate [99]. Fluoranthene has been reported as the most stable PAH tested for oxidation by ozone [100], and that is why it is the most available PAH which is present at a high concentration in the atmosphere.

Removal of PAHs from the Atmosphere

Atmospheric PAHs can be removed either by dry or wet depositions or through various other pathways [101–103].

Dry Deposition

Once PAHs become sorbet to atmospheric particles and settle down to earth without precipitation, they can be degraded through dry deposition [104, 105]. The properties of PAH and sorbent particles as well as atmospheric condition are some of the factors which can affect the dry deposition rate. High-molecular weight PAHs tend to settle quickly as strong atmospheric currents are required to keep them suspended compared with small ones. The atmospheric currents and wind in unstable atmosphere have enough energy to prevent particles from setting down, and that is why particles settle down faster in a more placid atmosphere. Similarly, high atmospheric temperature distribute the total PAHs into more fractions in the vapor phase while lower temperature increase sorption of PAHs and thus can affect the dry deposition of PAHs [106].

Wet Deposition

The scrubbing of contaminants sorbet onto particulates and get dissolved into vapor phase contaminants out of the atmosphere through precipitation [107, 108]. Wet deposition rate depends on the phase in which PAHs are present such as sorbed PAHs are removed very easily from the atmosphere compared with the PAHs in the vapor phase. Dickhut and Gustafson [109] reported that out of the total atmospheric phenanthrene, most are associated with particulates and a considerable amount of the atmospheric phenanthrene is removed through precipitation as particle based, suggesting that precipitation of sorbed PAHs are more efficiently removed compared to vapor phase PAHs [110, 111].

Controlling PAH Concentration in the Environment

- Standards are established and regulated by the US governmental agencies relevant to PAH exposure in workplaces, environment and drinking water.
- The Occupational Safety and Health Administration (OSHA) have also established various standards relevant to PAH exposure in working areas which allow the employers to use engineering controls and work practices to reduce exposure and keep it under the permissible exposure limit which is estimated to be 0.2 mg/m^3 for 8-h TWA (time-weighted average).
- National institute for Occupational Safety and Health (NIOSH) [112] have proposed recommended exposure limit (REL) for PAHs which should be set at the lowest detectable concentration, that is, 0.1 mg/m^3 for coal tar pitch volatile agents for a 10 h working day or 40 h workweek.
- EPA has established ambient water quality criteria to set a non-detectable level or zero concentration for carcinogenic PAHs in ambient water. As benzo(a) pyrene is the most carcinogenic PAH known, EPA has set an MCL (maximum contaminant level) for it, which is 0.2 ppb [113].
- For lung cancer, World Health Organization (WHO) has also established unit risk of B(a)P at 87×10^{-6} ng m^{-3} for lifetime exposure with the guideline values of B(a)P at 0.1 and 0.3 ngm^{-3} [114].

Conclusion

From the present literature reviewed in this chapter, the following points can be concluded about the susceptibility of developing brain when exposed to polycyclic aromatic hydrocarbons.

- Extreme vulnerability do exist during early development of brain with long-term or even lifelong neurobehavioral disturbances.
- Due to industrialization, air pollution has now become a major problem and possible contributing risk factor for neurodevelopmental and neurodegenerative disorders.
- Although PAHs have carcinogenic and genotoxic properties, its anti-neurological effects still need to be evaluated.
- Research has now shown that PAHs have significant neurotoxicity during prenatal, neonatal and early childhood life. Thus, more investigations are needed to improve human health protection especially for fetuses, newborns and children.
- PAH metabolites (especially 1-OHP) in urine, and PAH–DNA adducts with DNA, RNA and protein in WBCs and other tissues are used to measure PAH exposure in humans. Benzo(a)pyrene is a known toxic PAH, which is often used as a biomarker for PAH exposure in various epidemiological studies.
- PAHs are suggested to cross the blood–brain barrier during prenatal, neonatal and early childhood and thus induce neurological damage. The mechanisms

behind PAHs-induced neurological disorders include epigenetic effects, oxidative stress and endocrine disruption.

- PAHs may undergo volatilization, photolysis, adsorption and degradation (especially microbial degradation). The degradation process depends on various factors such as nature and structure of the chemical compound being degraded, number and type of the microorganisms, and environmental conditions.
- Indoor fires (unvented) should be avoided and must be replaced by efficient, well-vented combustion devices; passive smokers should be protected from the risk of exposure from active smokers; monitoring of air pollution/year and filtration of industrial emission should be strictly regulated.

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Chapter 16
Nanomaterials as Source of Environmental Contaminants: From Exposure to Preventive Interventions

Shagufta Kamal, Muhammad Junaid, Ismat Bibi, Amna Kamal, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Claims of nanomaterials in environmental fortification have shaped the conditions to remediate environment and control pollution, which have brought about advances in environmental science and engineering. Using nanomaterials to resolve environmental matters will become an inevitable propensity in the future. Applications of nanomaterials in chemistry, degradation of organic pollutants, redressing of polluted soils or water, sensing and detection have been considered important. However, the potential risks of nanomaterials are not neglectable. The structure of nanomaterials imparts strong adsorption capacity of toxic heavy metals (copper, lead, mercury, cadmium, and others) in the soil, air, and water. These metals are considered highly toxic and can generate ROS, leading to multiple disorders including neurological disorders. Case studies related to neurotoxicity due to nanomaterials are discussed in the present chapter. The knowledge presented in this chapter will assist to envisage environmental hazards, evaluate impacts, and develop approaches to mitigate harm while encouraging advantageous practices involving nanomaterials.

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Keywords Organic pollutants · Toxic heavy metals · ROS · Neurotoxicity · Environmental risks

Introduction

Nanoparticles are a significant and the most important category of nanotechnology research, with structural dimensions ≥100 nm [1], while nanofibers are other important subsets of nanoparticles with structural dimensions ≤100 nm [2]. Nowadays, these nanoparticles or nanofibers have extensively been implemented in numerous industries in order to expand the eminence of their products (Table 16.1). Unrivaled characteristics of nanoparticles have aroused much interest in their applications; however, their inevitable influence on human health and environment should never be neglected [3]. Until now, many reports have been published which state the toxicity of nanoparticles for humans and generally all living organisms [4]. Due to their industrial applications (Table 16.1) in hygienic products, cleaners, medical diagnostic industry, polymer industries, and food products, they can easily contaminate ambient air and water. Therefore, lately they are overwhelmingly common in our routine lives. There are two large groups which express concern over possible implications of nanotechnology. The first group includes workers who work in industries while the second includes general consumers [5]. Due to all the loss besides the benefits related to nanotechnology, it seems important to anticipate the professional health threat of nanoparticles for employees exposed to them.

We must be aware of all side effects of nanomaterials when they come in contact. In 2004–2005 a new research was started to find out their physiochemical effects and examine their interactions at the cellular level in vivo [6]. Estimating the toxicity of nanomaterials is quite difficult as it relies on various parameters such as functional group, concentration, structure, and size. Nanomaterials destroy tissues by generating ROS and act as catalysts [6]. Despite a vast body of research on production of nanomaterials and their benefits, there is hardly anyway to overcome their side effects and hazards [7]. In this chapter, we discuss the toxicity and hazards of nanomaterials, control methods, instrument and protocols for identification of nanomaterials, occupational exposure issues, and available federal legal policy.

Types of Nanomaterials (NMs)

It is important to know bioavailability mobility and specificity of NMs with other compound to find out the chance of hazard related to production of NMs. For this reason, principal engineered NMs can be divided (Fig. 16.1) as carbon NMs, zero-valence metal nanoparticles, metal-oxide nanoparticles, quantum dots, and dendrimers [8]. Nanoparticles having desired shape, structure and surface properties

Table 16.1 Application of nanomaterials in various fields

Sr.#	Nanoparticles	Nanomaterial based products	Applications	Ref.
1.	SiO_2, AgCl, Ag	Textile/fabrics/ nonwoven	Surfaces-processed textile, smart clothes	[5]
2	Pt, Cu, Au	Energy	Fuel cells, solar cells, batteries capacitors	[2]
3	ZnO	Cosmetics	Sun protection, lipsticks, skin creams, toothpaste	[1, 2, 5]
4	Ag_2O, FeO, SiO_2, TiO_2	Food and drinks	Package materials, storage life sensors, additives, clarification of fruit juices	[1]
5	Silver	Household	Ceramic coating for irons, odor catalyst, cleaner for glass, ceramic floor, windows	[1, 2, 5]
6	TiO_2, ZnO	Sports/outdoor	Ski wax, antifogging of glasses/ goggles, antifouling coatings for shipped/boats, reinforced tennis rackets and balls	[1, 2, 5]
7	CNTs and ceramics NMs	Electronic equipment	Printed electronics mass production process for new types of electronic equipment sensors and photonic materials	[181, 182]
8	TiO_2, SiO_2, $CaCO_3$, $AlPO_4$, $Ca(OH)_2$, C^{4-}, SiO_2. $2H_2O$	Mechanical industries	Coating, lubricants, adhesive applications	[183]
9	Semiconductor NMs, ZnO, ZnS, CdS, CdSe, CdTe	Electronics	Water splitting applications, bandgap and band-edge positions	[184]
10	Noble metals	Dechlorination	TCE and chlorinated benzene-contaminated water	[185]
11	Silicon-based drug nanomaterials	Biomedical	Delivery vectors for cancer therapeutics and imaging	[186]
12	Liposomes	Biomedical	Drug delivery particles to target	[187]
13	Nano silica, Nano alumina, Nano kaolin, Nano clay	Concrete	Improve the binding effect, reduce the formation of micro pores	[188]
14	Ag^+, SiO_2, K^+, Ca^{2+}, iron, Zn, P^{3+}, B^{5+}, ZnO and Mo^{4+}	Agriculture	Food production, resistance to insects, soil management	[188]
15	Ag^+, Ti, sodium silicate, ZnO, Au, C^{4-} and hydroxy acid	Cosmetics	Skin lightener Antiaging	[189]
16	Toner	Printing	Deposited by a printer onto paper or other substrates	[190]
17	Ag^+, Aluminum, Palladium, SiO_2	Electronics	Light spectrum, conductor, LED, LCD, light beam	[191]

(continued)

Table 16.1 (continued)

Sr.#	Nanoparticles	Nanomaterial based products	Applications	Ref.
18	Ag^{+}, C^{4-}, Clay, Polyethylene, Sulfide, SiO_2	Textiles	Coating materials, abrasion resistant, flame-retardant fibers, improve heat conduction	[191, 192]
19	Ag^{+}, gold, C^{4-}, TiO_2, clay	Sports and fitness	Superstrong handlebars for mountain bikes, durable tennis racquets, ultralightweight bicycle frames, footballs/tennis balls, silver	[193]
20	Palladium, BaO_4SrTi, Ag^{+}, Ni^{2+}, Rh, CoO, clay, graphite, tungsten	Renewable energy	Utilized for improved wind and geothermal power generation, energy storage, lighting, and hydrogen fuel cells	[194]

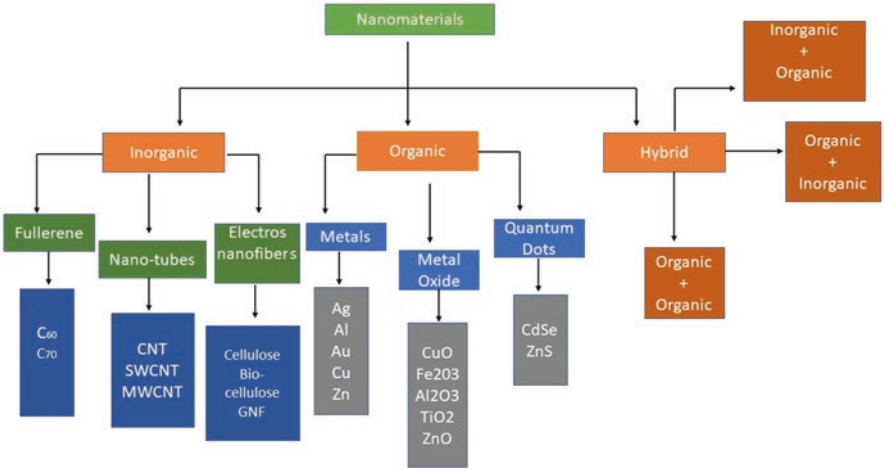

Fig. 16.1 Classification of nanomaterials (NMs)

are manufacture by nanotechnology and available. These nanoparticles play a vital role in drug delivery system, DNA-transfecting agents, chemical sensors, and modified electrodes and polymer materials, among others [9].

Environmental Fate and Behaviors of NMs

Manufactured or engineered NMs generally exist in the surroundings because they may be eliminated incidentally by human activities, or accidentally released during fabrication or application, and they may originate from the residues generated after utilization of compounds having these NMs [8]. It is assumed that NMs will be released into the surroundings after their utilization. Figure 16.2 represents the fate

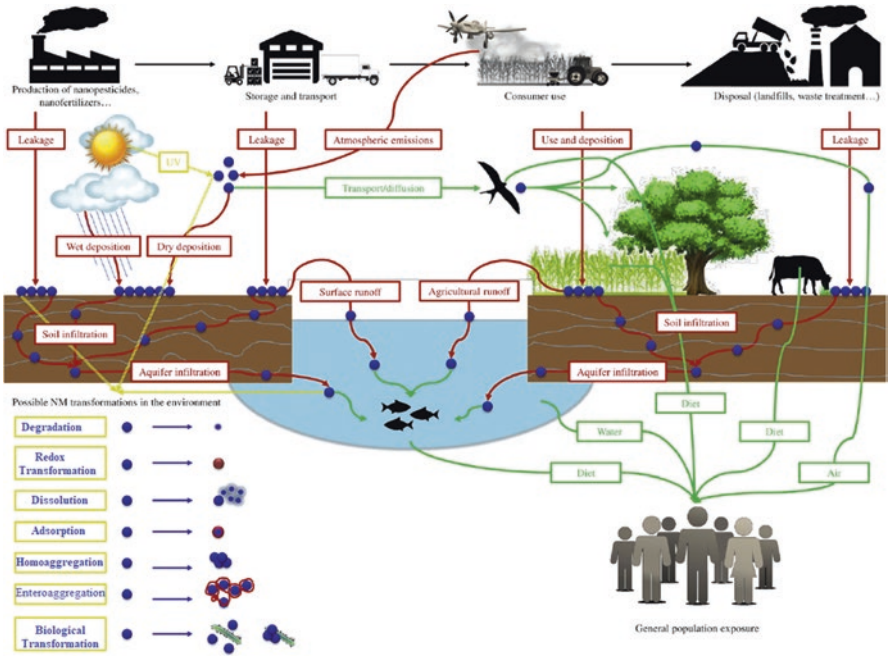

Fig. 16.2 Schematic representation of fate and behavior of NMs in the environment. (Adapted from (230) after some modifications)

of nano-materials (NMs) in the environment [230]. That is why hazardous effects of NMs on various life forms such as terrestrial organisms and aquatic life and on human health has garnered considerable attention among researchers. If NMs are released into the environment, they form clusters and interact with soil, sediments and go in drinking water and food product, pileup in living organism [10]. These mechanisms rely on characteristics of environment as well as characteristics of particles. Latest studies exhibited that the fate of NMs in the environment relies on the nature of their elimination, which influences all biotic and abiotic factors in the ecosystem [11]. The action of nanomaterials in the environment is hard to recognize due to infusion of complex chemical reactions. Sometimes, NMs act as colloids in the environment and that is the reason they are scattered across all the environmental phases [12].

Behavior and Fate of NMs in Aquatic Systems

Very limited knowledge exists related to the behavior and fate of NMs in aquatic ecosystems. Unbound NMs in the surroundings may form clusters. Bound and unbound NMs are released by sedimentation [13]. NMs are less mobile if they are

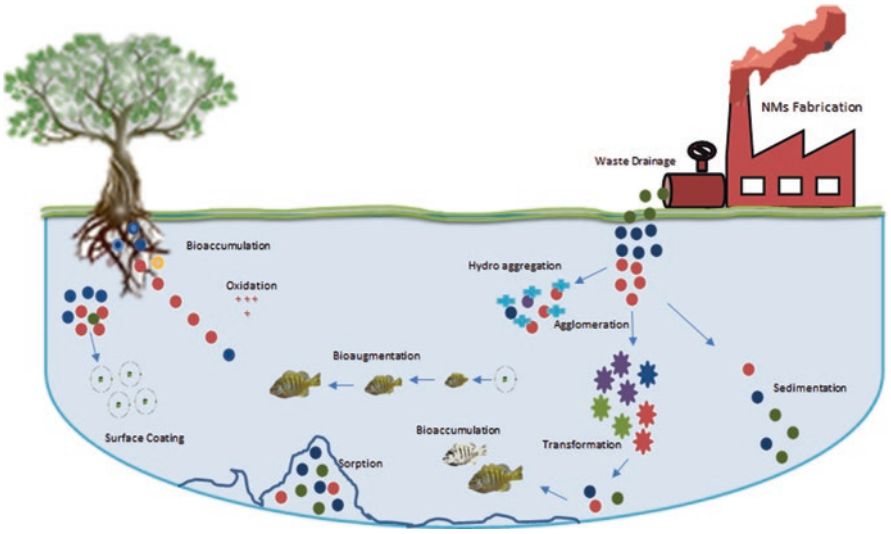

Fig. 16.3 Behavior and fate of NMs in aquatic system. The system includes positive and negative aspects of engineered NMs

formed in clusters or sorbed yet can undergo uptake by sediment-dwelling animals and filter feeders (Fig. 16.3). That is why bioaugmentation is achievable in food chain, but still there is no related data available. Accumulation depends on size; however, firmness of NMs is inversely proportional to their liability of aggregation. The process of cluster formation in natural system is correlated to the physical process for natural emulsion (e.g., fluid motion, gravity, and Brownian diffusion) [14, 15]. However, various environmental factors such as tendency of n-C_{60} to clump and C accumulation play a vital role in determining its solidity in aquatic environments, resulting in dormant exposure and risks posed by these NMs [16]. Nanotechnologists suggested that absorption of biomolecules i.e., proteins, polysaccharides, organic acids etc., and NOM onto the CNTs influenced their stability. SWCNT aggregation rate was significantly decreased in the order of; alginate < LB mixture < HA < BSA by the presence of biomacromolecules. This order of stabilization is observed due to more affirmed steric repulsion deriving from the absorbed layer of macromolecules as globular serum albumin presents denser barrier than linear alginate. Adsorption of NOM onto MWCNTs mainly due to π- π and hydrophobic attractions would increase 10 to 100 times water accommodation capacity. More hydrophobicity of CNT, greater will be the NOM adsorption capacity; similarly, more aromaticity of NOM, greater would be its affinity with CNTs [11]. The effects of interaction between engineered nanomaterial (ENMS) and edible plants depend on the type of NM (inorganic vs inorganic), shape, surface charge, size, aggregation properties and size. Different mechanisms of toxicity such as oxidative stress via uptake and accumulation in plants especially in their roots, overproduction of reactive oxygen species, physical adhesion of ENMs to biological molecules (e.g., corona around

NMs and proteins etc.), effect on root associated microbiota and release of toxic ions had been observed [17]. Functional groups that are attached or associated with the matrix of NMs are destroyed by these environmental factors, and these functional groups are also responsible for the chemical and biological alterations as a result of NM dissolution; for example, fulvic and humic acids inhibit accretion of CNTs [18].

In different environmental situations, clusters of nC_{60} are photochemically modified. Accumulation of TiO_2 NMs increases when pH range close to the zero point of charge, the aggregation process rises as ionic stability increase at any pH [19]. As steric revulsion rises, it will decrease TiO_2 NM aggregation and support absorption of fulvic acid [20]. TiO_2 NM diffusion was steady under environmentally related conditions of fulvic acid, pH, and ionic strength, indicating that, in the natural environment, TiO_2 diffusion may occur in a large area than it has been supposed [20]. Latest experiments have shown properties of metal-oxide ENMs and their cluster in the presence of liquid surroundings. Scientists call attention to collective methodologies to define the fate and properties of ENMs in liquid medium to recognize metal and metal oxide NMs (Au, TiO_2, ZnO, and Fe_2O_3). We combine SEM technology with energy-dispersive X-ray spectroscopy (EDS) [21, 22]. Using fluorescence spectroscopy we can estimate Au NMs and humic substance clusters [23]. Petosa et al. [24] found that in aquatic ecosystems, physicochemical interactions for accumulation and deposition of engineered NMs are increased and concluded that surface alterations such as polymer or surfactant layer enhanced steric stabilization resulted in slow nanomaterial downfall or accumulation [24]. Moreover, unexpected structure of particles, like in the case of CNTs, provides an extra property of capturing mechanisms (e.g., straining) which influences the transport patterns of nanomaterials. Lastly, the most frequent theoretical proposal and experiment used to estimate the deposition and accumulation of nanomaterials only apply for spherical particles; however, there are some drawbacks for even very minute spherical NMs [25].

Fate and Behavior of NMs in Soils

Several types of organic derivatives of plants and animals incorporate into the soil either in living form or dispersed on its surface as soil organic matter (SOM). These organic matters have a direct effluence on various properties of soil [26]. This soil organic matter can be divided into two types of segments, one is hydrophobic and the other one is hydrophilic depending upon their variability of the environment. The hydrophobic part of SOM consists of carboxylic and tannic acids, carbohydrates, and proteins, while the hydrophilic region contains humic substances (i.e., $C_6H_9O_6$, $C_{135}H_{182}O_{95}N_2S_2$, and C_6H_5. $C_{18}H_{37}$ to C_6H_5. $C_{22}H_{45}$ n-alkyl benzenes) comprising 60–80% of the SOM composition [27]. They are also named as dissolved organic matter due to their hydrophilic behavior of humic substances. When SOM interacts with NMs through various types of bonding forces they form a coating on

the surface known as eco-corona [28]. That is why nanomaterials may require new identity that can influence their characteristics and impact on environment to biological systems [29]. Due to a lot of variability of environmental conditions, there is less understanding between interaction of nanomaterials and SOM [30].

The adsorption of dissolved organic matter (DOM) on nanomaterials depends on reactive surface area and surface charge and intrinsic properties such as its charge, pH, ionic strength, cations and the structure of the formed coating (mono/multilayer, conformation) also affect this interaction. Nanomaterials also interact with the aqueous portion of the soil having dissolved organic carbon through various types of interaction forces such as van der Waals forces, Coulomb forces, hydrophobic forces, H bonding, cation bridging, and surface ion chelation [28, 31, 32]. It also has been seen that increase interaction of SOM with NMs can also increase the retention of nanomaterials in the soil [33]. These nanomaterials may stick on the upper layer of the soil by steric hindrance; therefore, NMs are retained in the upper-soil layer by steric hindrance, causing entanglement of these materials [34] (Fig. 16.4) indicated the fate of different NMs in soil [231]. But it also has been reported that this retention can also be irreversible in a number of cases [35]. It has been observed that addition of silver nanomaterials to soil with humic acid increases the absorption of silver nanoparticles in the soil [36]. Additionally, this study also detected that silver nanomaterial suspension is lower in organic soil than that in the mineral soil [37].

The toxicity and antimicrobial activity caused by a wide range of these nanomaterials affects the quality of the soil. Thus, these nanomaterials have a strong impact on the enzymatic activities of the soil [38]. Enzymes present in soil act as catalysts in decomposition, transformation of soil organic matter, detoxification of soil, nitrogen fixation, growth, and denitrification and also plays a key role in carbon, nitrogen, and sulfate cycles. These enzymes can act as a biological balance for soil quality [39]. These nanomaterials can influence the activity rate of these enzymes that can disturb availability of nutrients, nitrogen and sulphate cycle thus controlling the survival of microorganisms and plants that depend on this nutrition for growth,

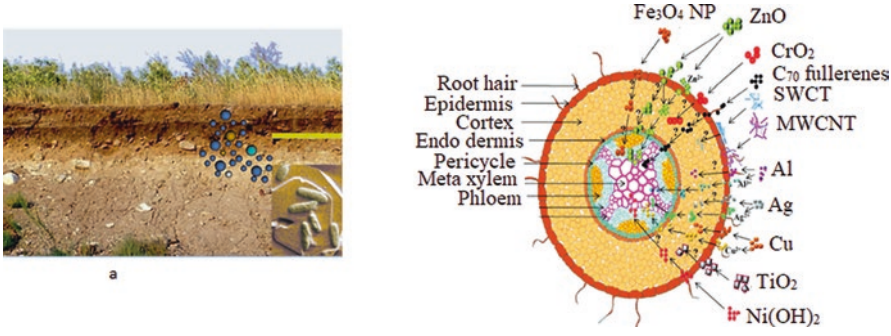

Fig. 16.4 Schematic representation of fate and behavior of NMs in soil (**a**) Biogeochemical transformation of NMs in environment (**b**) Nano toxicity in food chain. (Adapted from (231) after some modifications)

and survival [40]. That is why checking enzymatic activity is a significant implement for measuring the changes that arise in soil due to anthropogenic factors like the use or disposal of these nanomaterials in soil. Moreover, these soil enzymes also act in biotransformation of nanomaterials. Due to limited in vitro studies, there is a need for further data on nanomaterials' enzymatic biotransformation on soil.

Toxic Effects of NMs on Human Health

There is a thriving concern about the exposure and toxic effects of NMs because of their ability to absorb or pass through mammalian cell membrane. Their absorption rate within different cells depends upon sedimentation characteristics, size and aggregation [41]. Phagocytosis or endocytosis is involved for cellular absorption of NMs [42]. Diverse routes (Table 16.2) such as dermal (skin), gastrointestinal tract (pulmonary), oral, and inhalation are involved in NM exposure; however, coated products, food colors, health supplements, skin care products, paints, food additives, and sunscreens are another source of NM exposure to humans because these routes are not applicable for all NMs [43–45]. Therefore, biokinetics involving distribution, absorption, and excretion of foreign particles could be applied to assess toxicological influences of NMs [46]. Here we discuss some detailed mechanisms of NM exposure in the human body with their toxic effects.

Table 16.2 Different routes of entry of NMs in human body with their sources

Sr.#	Route of entry	Sources of exposure	References
1	Respiratory system	Handling Ag NMs in manufacturing or research facilities, aerosols directly applied in nasal or oral cavities; air filters, breathing masks; ambient airborne Ag NMs	[22, 195]
2	Skin	Wound dressings; antibacterial textile (e.g., sheet, towels, socks, underwear, fitness wear); antibacterial surfaces, paints; cosmetic products (e.g., lotions, roll-on deodorants, hair products); computer hardware and mobile devices	[5]
3	GIT	Food packaging, cooking utensils and coatings; water filters; health supplements; oral hygiene products (e.g., toothpaste, toothbrushes)	[196]
4	Reproductive system	Contraceptive devices; women's personal hygiene products	[45, 50]
5	Circulatory system	Intravenous injection AgNP-enabled drugs or drugs delivery/ diagnostic system implant, medical catheters	[49, 50]
6	Genetic instability	Cross the pores of nuclear envelop and make direct contact with nuclear proteins that leads to formation of protein aggregation	[197]
7	Ocular syndrome	Interact with epithelial layer of eye that could induce several inflammatory responses, affect lacrimal and ocular surface of the eye	[198]

Dermal Absorption

Skin provides first line of defense and barrier against foreign invasive agents, yet the absorption of NMs through skin is very low, might be accidental or occupational contact is involved through this route [47]. Absorption via skin or dermal absorption, which may be due to direct contact, accidental injection, contact with contaminated surface, or deposition from air, causes the entry of NMs into systemic circulation from different layers of skin [48]. Four pathways, that is, transepidermal, transappendageal, transcellular, and intracellular, are generally responsible for penetration across skin depending on the size of NMs; for example, NMs of 4–20 nm size can easily penetrate or permeate only damaged skin, while NMs ≤45 nm cannot penetrate or permeate [22, 49]. Literature reports that ZnO and TiO_2 NMs cannot penetrate the skin, hence unable able to exert pathological effects; Ag and Au NMs can penetrated, but results regarding their permeation potential are conflicting, whereas NMs of metals like Co, Pd, and Ni having a high potential to release ions and their capacity to localize into hair follicles has made them more hazardous. According to another study, quantum dots with different surface coatings, sizes, and shapes can penetrated intact skin at sporadically pertinent dosages [50]. Furthermore, surface chemistry and size influence dermal absorption more effectively.

Pulmonary Absorption

The main route of NM exposure is inhalation. NMs damage the lungs and respiratory tract (alveolar region, tracheobronchial, and nasopharyngeal) by different mechanisms after plonking on them and may also translocate to other cells or organs via blood and lymphatics [51]. Generally, hazardous effects of NMs depend on their physicochemical properties therefore evaluated under the new term "nanotoxicity." Furthermore, size, aggregation, agglomeration of NMs, and their size distribution in airways specify their penetration depth in respiratory tract. Wet size of NMs in airways or in saturated air due to their hygroscopic nature is another important factor for the determination of their deposition in respiratory tract [52]. NMs of 20 nm TiO_2 having 100 nm aggregated size and having 8 mg/m^3 concentration are found to reduce expiratory flow rate while larger size NMs of TiO_2 induce a very minor effect on the respiratory tract [5, 53]. The comparative analysis of aerosol effect of CeO_2, Al_2O_3 TiO_2, and ZnO (with 12 nm primary size except TiO_2, for which the size was 10 nm) on DNA and bronchoalveolar lavage (BAL) cell composition indicated increased respiratory rate and reduced tidal volume. However, 24 h post-exposure cell analysis of BAL presented lymphocytic inflammation to all NMs except TiO_2 and can be ranked as ZnO >> CeO_2 > Al_2O_3 = TiO_2 for induction of acute lung inflammation [5]. Acute phase response and long-lasting pulmonary inflammation was observed by the pulmonary exposure of carbon black (CB), TiO_2, and CeO_2 NMs [54]. The risk of vascular diseases is high after infiltration of these NMs into

endothelial cells of lungs [55]. Translocation of these NMs to liver has also been reported as hepatic DNA strand breaks has been observed following pulmonary exposure to CB [56]. NMs of aerosolized amorphous silica did not produce any adverse effect on histopathology, genetic makeup of lungs, or pulmonary inflammation [54]. Ag NMs may deposit on lungs after inhalation and may translocate directly from lungs to brain via pharynx or nasopharynx, kidney, spleen, GIT, olfactory bulb, liver, and heart [57]. Inhalation of MgO NMs (up to 30 nm) via nostrils is enhances the chance of olfactory bulb tumor, necrosis of factor-α mRNA and other regions of brain [58].

Eye Absorption

NMs in dust or with contaminated hands via enter the body. Very limited data is available regarding hazardous effects of NMs absorbed by eyes while theoretical assessment indicated that NMs are distributed to blood and translocated to first synapse from vitreous humor [59]. The present reports and knowledge about absorption of nanoparticles into the eye and evaluation of the possible eye toxicity are very limited [5].

Different Detection Methods of NMs

The sampling strategy based on aerosol space-time changes is required for appraising the personal exposure of workers or in workplaces instead of stationary sampling; therefore, occupational hygiene does not measure NMs continuously due to lack of standardized measurement methods and sampling techniques [60]. Proper instruments are essential for personal exposure samplings from breathing zones [61]. The key factor for decisive NMs in the workplace is reproducibility of measurements. The major hurdles [62] in sampling of NMs are as follows.

I. Lack of proper guidelines, instrument standardization procedures for measurement below 3 nm.
II. Periodic and fast distance sampling.
III. Lack of availability of standard and reference materials for some NMs.
IV. No differentiation between background levels of ambient and manufactured NMs in workplaces.

Currently, disparate procedures and instruments are being followed to gauge the aerosol denunciation in the workplace whereas these procedures are also applied to estimate NM exposure risks [63]. These procedures are generally categorized into direct and indirect methods (Table 16.3). Different techniques like electron microscopy, diffusion charger (DC), optical particle size (OPS), size selective static sampler, condensation particle counter (CPC), electrostatic low-pressure impactor

Table 16.3 Different methods of detection of NMs with their application and techniques

Sr.#	Methods for detection	Application	Size range	Techniques	References
1	Optical particle size (OPS)	Evaluating large agglomerates of nanomaterials	300 nm	Photo detector	[199, 200]
2	Condensation particle counter (CPC)	Determining nanoparticles	5.5 nm–9 μm	Optical detection, supersaturating aerosol laden-air, condensation of supersaturated vapors	[201–204]
3	Fast mobility particle sizer (FMPS)	Measuring aerosol particles	5.6–500 nm	Electrical mobility technique	[205]
4	Size-selective static sampler	Analyzing sample	100 nm	Gravimetric weighing or by chemical analyses	[206]
5	Diffusion charger (DC)	Measures the active surface area concentration of an aerosol	20–400 nm	Electrometer	[207, 208]
6	Electrostatic low-pressure impactor (ELPI)	Automatically measuring the number of particles	28 nm and 10 μm	Electrometer	[209]
7	Electron microscopy	Determining number and surface area	20–100 nm	Electron microscope	[210]
8	Aerosol particle mass analyzer (APM)	Particle mass	30–580 nm	Aerosol sample with particle density approx. 1 g/cm^3	[211]
9	Aerosol time of flight mass spectroscopy	Particle size and composition	100–3000 nm	Aerosol	[212]
10	X-ray diffraction (XRD)	Average particle size for a bulk sample	Below 1 nm	Larger crystalline samples required	[213]
11	Nanoparticle tracking analysis (NTA)	Particle size and size distribution	10–1000 nm	500 μl suspension, temp 5–50 °C, wide range of solvents can be used	[214]
12	Scanning mobility particle sizer (SMPS)	Particle size distribution	3–1000 nm	Uses an electrostatic classifier and a CPC, can also add DMA	[215]
13	Differential mobility analyzer	Particle size distribution	Below 3 nm	Can be combined with other techniques to create tandem DMA or DMPS	[216]

(continued)

Table 16.3 (continued)

Sr.#	Methods for detection	Application	Size range	Techniques	References
14	Nanoparticle surface area monitor (NSAM)	Human lung deposited surface area of nanoparticles	Below 10 nm	Similar to an electrical aerosol detector (EAD)	[217]
15	Photon correlation spectroscopy (PCS)	Average particle size and size distribution	1 nm–10 μm	Based on dynamic light scattering, an extension of the technique is photon cross correlation spectroscopy (PCCS) for high-concentration opaque suspensions giving particle size and stability of nanoparticles	[218]
16	Atomic force microscopy (AFM)	Particle size and characterization	1 nm–8 μm	A form of scanning probe microscopy (SPM). Requires less time and cost than SEM and TEM	[219]
17	Scanning electron microscopy (SEM)	Particle size and characterization	Below to 1 nm	Can be used in situ as environmental SEM	[220]

(ELPI), diffusion charger (DC), and fast mobility particle sizer (FMPS) are employed in the direct method category.

Management of NMs and Risk Assessment

Superlative objective of risk assessment is to rend quantitative information for the improvements of occupational exposure limits and other hazard management procedures (Tsang et al. 2017). European Commission of Regulation, Evaluation, Authorization and Restriction of Chemicals (REACH) reported that risk assessment is helpful for industrial employees to assess manufacturing conditions, appropriately to build better decisions about different parts of the process presenting progressively potential risk to workers in workplace as well as to the environment during the whole life cycle of NMs [64]. Risk assessments and threats may define the activities and careers that might be improved the likelihood of NM exposure. The risk of NM exposure could be increased during their fabrication processes such as drilling, mechanical disruptions of NMs, cleaning of instruments required for fabrication processes as well as working with NMs in liquid media or in gas phase having potential of inhaled or airborne formations [65]. Finding answers to the following questions is the main objective of performing risk assessment procedures [66].

- What are the consequences of toxic effects of NMs posed to environment and human bodies?
- What is the quantitative correlation between probability of inauspicious effects in windswept population with toxicant dose?
- What is the influence of different conditions on the exposure of NMs?
- What is frequency, percentage probability, and severity of hazardous effects in exposed population?

The most effective method to address all these questions is to manage a plan including a hierarchy control (Fig. 16.5). Only those strategies should be adopted that minimize or eliminate the exposure of NMs through their whole life cycle to the applications of personal defensive equipment. WHO recommended the following suggestions to assess NM exposure [67, 68]

1. They suggest adopting previously reported methods identical for specific occupational exposure limit (OEL) values of NMs to workers in workplaces.
2. Due to absence of precise monitoring OEL values for NMs in working places, select least OEL protective value that should be legally assigned OEL for bulk form of substances.
3. Stepwise approaches such as assessment of the potential for exposure → conduction of rudimentary exposure evaluation → conduction of comprehensive assessment following procedures of Comité Européen de Normalisation (CEN)

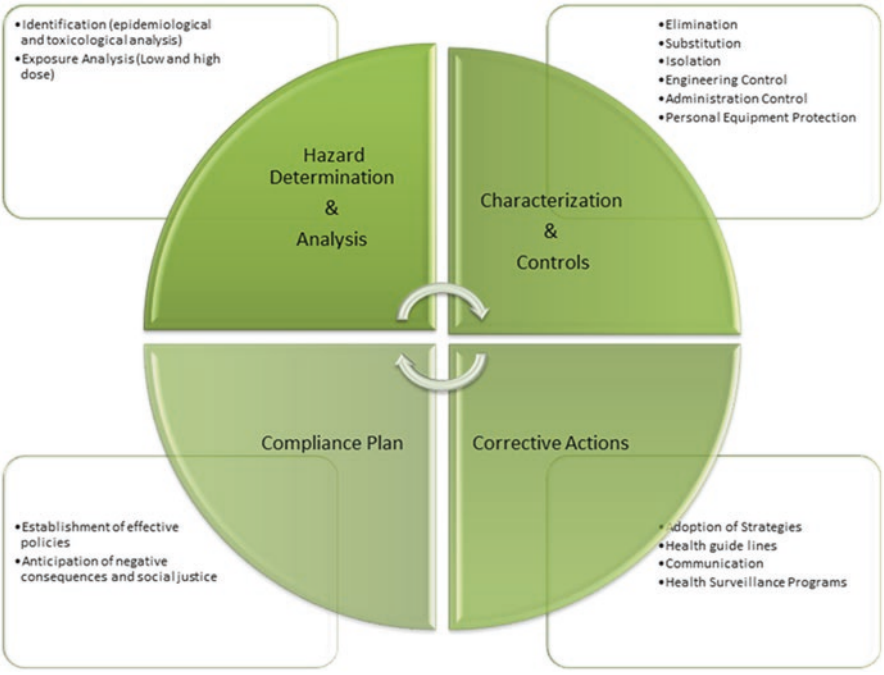

Fig. 16.5 Summary of risk assessment and management of NMs

or protocols of Organization for Economic Cooperation and Development (OECD) should be followed where specific OELs of any NMs are not available.
4. Insufficient evidences are available for preferences of any method over the other for dermal exposure assessment. However, multiple technical reports like ISO/TR13121 and ISO/TR12855 have been established by International Organization for Standardization (ISO) as a framework to assess hazards of NMs [69].

Another report considering engineered NMs used in industrial appliances, consumer product applications, and chemical manufacturing presented the framework to handle the potential risks associated with the disentangle of NMs during their life cycle [70]. Generally, researchers working in research laboratories and universities, and industrial workers are usually more prone to NM exposure. Due to presence of different strategies for every NMs, the exposure assessment of NMs is extremely complicated. Generally, NMs are fabricated in a fastened reaction cell and their aerosols cannot contaminate the air [71]. Human exposure to NMs occurs after their synthesis, drying, and application of these NMs in the synthesis of other NMs or during the cleanup operation of the reactor [72]. Literature informs that relocating nanopowders (dry) from a beaker to another can result in the release of airborne NMs from the fume hood, which are hazardous for researchers working with NMs as well as the laboratory environment. Many variables affect the release of NMs including work practices, hood design and operations, room conditions, type and quantity of NMs, and adequacy of room exhaust [73]. The Working Party on Manufactured Nanomaterials (WPMN) of the Organization for Economic Co-operation and Development (OECD) provided the list of manufactured nanomaterials that can be used commercially. The list includes single-walled carbon nanotubes (SWCNTs), fullerenes (C60), multi-walled carbon nanotubes (MWCNTs), Fe NMs, Ag NMs, carbon black, Al_2O_3, TiO_2, CeO_2, SiO_2, polystyrene, nanoclays, and dendrimers [74]. Risk management program for NMs should give directions about the general safety while working with NMs and also work as health program for all the workplaces and companies that synthesize and utilize NMs. As the consequence of new emerging risks, it should be able to modify the new technology, equipment and materials [75]. There is also the need of a cyclic set of processes that may provide feedback on problems, their corrections, and solutions as well [5].

The Demonic Side of Nanoparticles

NMs have good superpowers but having darker side as well. To improve the working of NMs, we have made some efforts to synthesis the NMs that have stable composition, size, shape, and diverse dimension that leads to their higher impact applications [76]. But we ignored the toxic effects associated with NMs when they come into the contact with living beings and environment. If we study their whole mechanism from synthesis to application, they are synthesized in industry by fol-

lowing the patented synthesis procedures that are discovered by the scientists associated with the field of nanotechnology and synthesize NMs by taking mandatory precautions. But when they are assembled, they incorporated into objects/drugs and other materials which are supplied to consumers who are mostly unaware of their toxic effects [77]. During this whole route, different people at different times are exposed to these NMs either directly or indirectly such as the workers may inhale these NMs at their job sites during their construction jobs [78]. In this chapter we have discussed the darker side of these NMs and what precautionary measures must be taken while dealing with NMs to avoid their damaging effects. To study the harmful effects of NMs many assessment methods, in vivo and in vitro studies and remediation process have been introduced including "nanotoxicology study" that was used to investigate the risk of toxicity of NMs at different levels [79]. In nanotoxicology, one can study the effect of size, morphology, surface charge, and chemical composition of NMs on the cells and tissues of living system and their detailed mechanism of interaction [80]. Incidental NMs are more harmful as compared to the manufactured nanoparticles because they contain higher redox organic chemical content, high penetration power and prolonged stay in respiratory tract after their penetration [81]. As incidental NMs have high surface area, the environmental pollutants such as heavy metals, organic chemicals, and oxidants can easily adsorb on their surface and resulted in unexpected hazards. Depending on their source of origin, incidental NMs can be classified into two types: primary INMs and secondary INMs. Primary INMs directly originate from their emission sources but when they get mixed with pollutants in air, such as nitrogen oxide, sulfur oxide, ozone, and organic molecules, they become secondary INMs [82]. We cannot easily control the self-formed NMs, but we have control over the prepared NMs because of knowledge about their mechanism of interaction with living system, their impact on different organs and diseases resulted by their toxicity. However, all kinds of NMs are harmful, but some types of engineered NMs that can cause hazardous effects are as follows: metal sulfide particles (e.g., FeS_2, ZnS, CuS), metal oxide NMs (for example, TiO_2, ZnO, Fe_2O_3), metal NMs (like Au NMs, Ag NMs, Zn NMs, Cu NMs), polymer NMs (including alginate, chitosan) and carbon nanotubes [83–85]. To study the impact of these NMs we have to discuss some important parameters, as NM toxicity assessment depends on various physiochemical factors that are listed here: (1) size, (2) chemical composition, (3) Morphology, (4) phase and crystalline structure, (5) surface area, roughness factor, porosity, and (6) hydrophilicity and hydrophobicity of nanomaterials [85]. Each parameter is discussed in detail in the following subsections.

Size of NMs

The toxicity of engineered NMs is influenced by the particle size that is an important parameter. Some NMs are nontoxic in bulk form but become toxic when they reach at nanometer level [86]. In general, NMs when ingested and exposed to cells,

absorbed on skin, and inhaled from air, they become toxic. The smaller size of NMs helps them to penetrate easily and quickly inside the body [87]. The size of NMs is analogous to the size of biological components that make them able to penetrate inside the human body. Similarly, NMs with increased surface area and decreased size can have great interaction with biological molecules with large surface area. Small NMs with large surface area always provide the sites for the generation of ROS which plays an important role in cell damage [88]. NMs with the size less than 1 μm can penetrate the respiratory system and cause fatal effects by taking their place in the alveoli. If size of nanoparticle is in the range of 500–200 nm, it can puncture the cell membrane and disturb the cellular mechanism by entering cytoplasm and other cellular organelles [88, 89]. Small NMs when enter the nucleus they can damage the DNA also. These NMs can interact with proteins by forming nanoparticle-protein complex which results in the interference in protein folding and causes the disturbance in cellular signaling that leads to neurodegenerative ailment [90, 91].

Morphology of NMs

The toxicity of NMs is also influenced by the aspect ratio and shape of NMs; for example, NMs that are of spherical shape have large aspect ratio and are the most common shape, thus imparting higher toxicity [92]. Many studies in literature have shown the impact of morphology of NMs on their toxicity. Carbon nanotubes have symmetrical and similar morphology as that of asbestos and is responsible for the inflammation of respiratory system [93]. Doshi and Mitragotri [94] in their study reported that needle-shaped NMs when inhaled cause disruption of cell membrane by introducing the cellular instability of ionic concentrations. Salahuddin and Galal and Chithrani [95, 96] conducted toxicity studies of gold NMs on mammalian cells in relation to their different shapes and sizes. This study concluded that when the shape of NMs is changed from rod to spherical shape, there was an increase of 500% in cellular uptake [97]. Liu et al. [98] studied the shape-dependent toxicity of NMs and synthesized two types of NMs called ceria nanorod and ceria nanowire. They reported that nanorods are nontoxic in nature while nanowires have a high aspect ratio, which resulted in maximum toxicity when their toxicity was tested on human leukemia cells [77].

Composition of NMs

The chemical composition of NMs also influences their toxicity to greater extent. NMs that have different compositions also have different accumulation time and place as well [52]. The NMs which accumulate in different places are responsible for different health hazards such as the NMs which accumulate in blood vessels

have an impact on blood clotting while those NMs that are accumulated in in lungs and liver that are associated with internal damage. According to Geiser and Kreyling, carbon NMs that are of smaller size can more quickly translocate in the secondary organs as compared to iridium NMs in a small time. If we take a glance on literature, many articles showed that metal and metal oxide NMs have high toxicity as compared to metal-free NMs. Cappellini et al. [99] have investigated the toxicity of many NMs including CuO, CNT, ZnO, Fe_2O_4, CuZn, Fe_2O_3, TiO_2, Fe_3O_4, and carbon nanotubes. They have explored the efficiency of their ROS formation and their impact on human A549 cells or alveolar epithelial cell adenocarcinoma [100, 101]. According to their studies, CuO NMs have shown the maximum toxicity followed by ZnO NMs and carbon nanotubes. This study suggests that composition of NMs have great impact on their toxicity [102].

Surface Charge of NMs

Surface charge plays a main role in cell membrane penetration, while NMs must have to pass the lipid bilayer in order to interact with living systems, which modifies the components of cells involved in cell damage. For example, if the surface of NMs is positively charged and the charge on cell membrane is negative, NMs can easily penetrate or attach to the cell membrane by electrostatic interaction. But if the surface of NMs is negatively charged, it cannot get easily ingested or pass through cell membrane because it is less attracted by cell membrane surface due to same charge on both surfaces [103] have synthesized and studied the cellular adsorption of Au NMs on the cell membrane [104]. They investigated that the positively charged Au NMs can get easily pass through the cell membrane due to their higher kinetics of passivation through the cell as compared to neutral or negatively charged Au NMs. Magrez et al. [105] have prepared the CNTs and investigated that those CNTs that are nonfunctionalized, are nontoxic in nature. But when these nonfunctionalized CNTs undergo acid treatment they become functionalized due to presence of organic groups such as carboxylic (-COOH) and hydroxyl (-OH), the surface of CNTs become charged that resulted in their increased toxicity [77].

Interaction of Nanoparticles with Living Systems: Its Effects and Mechanism

Nanomaterials influenced on living system because NMs incorporate into the cell and destroy the cell as well as membranes of organelle by the production of reactive oxygen species through oxidative stress [106]. Organelles such as heart, spleen and lymph nodes become enlarges due to accumulation of these NMs [107]. Movement of nanomaterials inside the cell increase when the surface is charged and linked with

cellular protein because of its electrostatic interactivity. Myocardial ischemia, destruction of endothelium, vasodilation, and inflammation of bronchi occur with the liability of human being toward chemical and mixture of chemical [108]. Most common antioxidant in the body are glutathione molecule and cytochrome C that shift electron from nanomaterials and generate ROS while the high level of ROS cause cancer and cell destruction [109]. Some other destruction due to nanomaterials are inactivation of cellular protein, disturbance in cardiovascular system, swelling of respiratory tract, enzyme denaturation, and change in gene sequences. We are exposed to nanomaterials via environment, nanodrugs, and food systems. Various health issues are due to high interactions of nanomaterials. Various consequences of nanoparticles on health are classified and discussed here.

Generation of Reactive Oxygen Species (ROS)

Normally in cells ROS are generated in little amounts for the normal activity of cells, regulate the normal metabolic function of cells, and maintain a balance in antioxidant defense system; ROS do not have any toxic effects on cells under normal conditions [110]. There is imbalance between oxidants and antioxidants when the production of ROS increases, leading to oxidative stress and high chances of disorder [111]. Nanomaterials have an electronic effect, so it can be used to produce ROS [31]. ROS are generated when nanoparticles of metals or metal oxides interact with components of cell redox potential of cell overlap with conduction band (Fig. 16.6). During oxidative stress, the concentration of antioxidants like glutathione (GSH) is low and ROS increase in concentration in the cell [112]. Concentration of chemokines and cytokines is balanced by GSH because it is defense antioxidant when level of ROS increase then level of GSH decrease and its increase the permeability of plasma membrane, cause inactivation of protein, concentration of cytokines increase and destroy cell DNA and ultimately leads to cell death [113].

Inflammation in the Exposed Body Part

The protection mechanism of body against pathogens, xenobiotics, and infectious antigens is inflammation. Ordinary swelling affects the growth of healthy tissues, but chronic situation leads to various disorders like skin problem, arthritis and lung disorders [114]. Swelling could take place in those tissues that have receptor mediators and effectors. Different types of receptors are present on the plasma membrane; nanoparticles act as a inducer; and cytokines, chemokines, and eicosanoids are the mediators [115]. Neutrophils, macrophages, and defensive proteins are turned on when they come in touch with contaminated cells and release defensive molecules such as elastase, proteinase 3, and reactive free radicals [116]. For time to time, persistent swelling and unrepairable destruction due to inflammation cause respira-

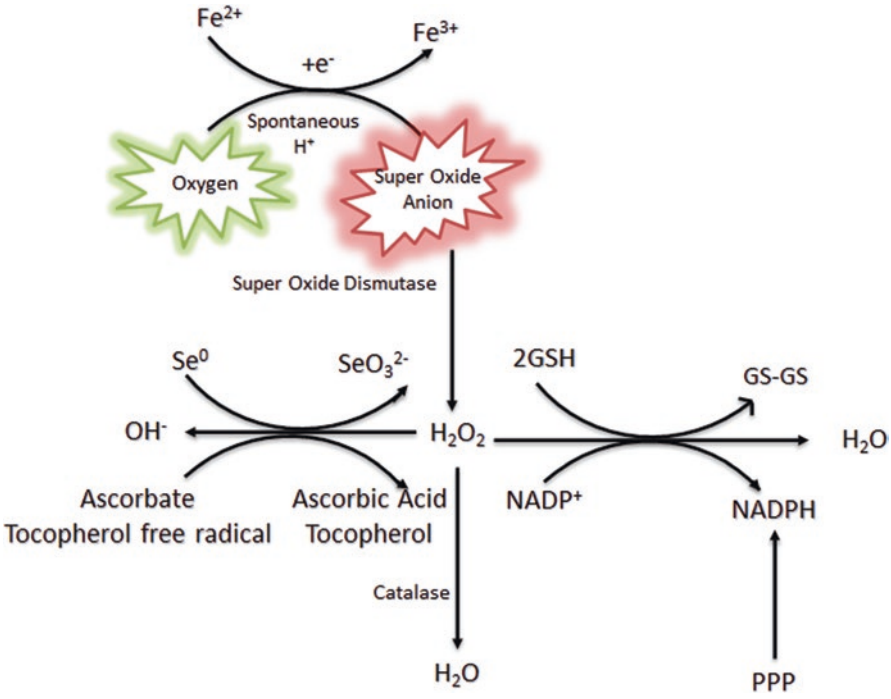

Fig. 16.6 Mechanism of ROS generation; GSH is glutathione reductase

tory and cardiovascular dysfunction. Neutrophils and macrophage activate the phagocytosis of nanoparticle and production of ROS collectively, cause inflammation [117]. Release of cytokines and interleukin-1β that attribute to the generation of ROS and disturbance of lysosome is caused by some nanoparticles such as silica, Ag, and Al_2O_3 [77].

Genotoxicity

The toxic effects of foreign substances on the cell which cause alterations in genetic material are referred to as genotoxicity. Nanoparticles have genotoxicity effect; in cells, these can destroy DNA, change the base sequence, or delete some bases. DNA destruction cause tumor in cell and abnormality in reproductive cell which leads to hereditary diseases like hemophilia, diabetes, and cystic fibrosis [118]. Many in vivo and in vitro studies have been done to check the genotoxicity of single-walled carbon nanotubes (SWCNTs) and shown destruction of mitochondrial DNA in mice [119]. The genotoxicity of nanocobalt on A549 epithelial lung cells was studied by Wan et al. This study showed this nanoparticle elevated phosphorylation process

and activated ataxia telangiectasia mutated protein, which is responsible for the breaking of double-stranded DNA [77].

Probable Mechanism for Nanoparticle Toxicity

Toxicity of specific NMs depend on the series of factors such as concentration, time of exposure, quantum properties, solubility, chemical structure, surface to volume ratio, shape & size, surface functionalization and degree of aggregation. Inflammation, allergy, oxidative stress generation, and epithelial tissue injury are the most common outcomes of nanoparticle toxicity [120].

Entry of Nanomaterials into the Cell

Endocytosis and diffusion of nanoparticles inside the cell produces oxidative stress and generates ROS and lowers the concentration of antioxidant, also activates macrophages, endothelial cells, and leukocytes), nuclear factor kappa B (NF-κB), transcription factor like activating protein 1 (AP-1), and increases the concentration of cytokines, causing swelling and changes in DNA sequences. If nanoparticles are incorporated in high amounts they can cause tumor and cell death [121, 122].

Nanoneurotoxicity

Nanomaterials have benefited mankind in a myriad ways for many years. Potential risks of NMs began to garner attention with its growing applications in all aspects of life. Overload of phagocytic cells may cause defensive fever, leading to reduced body immunity due to NMs [123]. Usually, NMs may accumulated in organs due to their slow degradation rates. NMs due to their high surface area may disturb biochemical mechanisms by influencing the proteins and enzymes of exposed persons. However, sensory cells cannot be repaired by regeneration like other damaged tissues [124]. Furthermore, most of the drugs are unable to cross the blood–brain barrier, making it very difficult to control sensory damage. Thus, a systematic and comprehensive evaluation of NMs' neurotoxic effects is imperative for prevention or reduction of sensory damage. Extensive research is being carried out all over the world on neurotoxicity of NMs [83]. Hazard assessment of CeO_2 depends on its potential application and biodistribution. Subcutaneous injection of Ag NMs in rats caused blood–brain barrier destruction, swollen erythrocytes and neural degradation, resulting in distribution throughout the whole brain after translocation from brain. A high dose of anatase TiO_2 could cause brain injury, leading to transformation of some glial cells into filamentous ones while others into inflammatory cells.

Anatase TiO_2–induced brain injury is dosage dependent while brain lesions and fat deposition in hippocampus was observed in ICR mice after GIT injection of nano sized TiO_2 suspension [125]. Mirsattari et al. [126] reported that 4-month continuous therapy of Ag in 71-year-old man suffering from myoclonic status epilepticus (MSE) squealed in comma with high levels of Ag in plasma, RBCs and CSF leading to death only after 5.5 months without availability of plasmapheresis. Ag in this patient caused irreversible neurological damage. Ze et al. [127] investigated the accumulation of TiO_2 NMs causing spatial recognition impairment and hippocampal apoptosis after intragastric injections of TiO_2 NMs in the mouse hippocampus. TiO_2 NMs affected homeostasis of enzymes, neurotransmitter systems and trace element concentrations, instigating neurotoxicity [128]. Subcutaneous injections of Ag NMs in rats damaged the blood–brain barrier and astrocytes, leading to neuronal degeneration [129]. Influence of nanomaterials on the brain of children is another predicament because the central nervous system has high elasticity in early life stages, and could significantly be affected by environmental incursions faced during fetal period. Unfortunately, direct or indirect mechanisms are involved in harming the fetal development on exposure to NMs during gestation period because a tiny amount of NMs can translocate to the fetal compartment from the maternal blood. The exposure of NMs presented differential phenotypes in both female and male offspring [130]. Recent studies revealed that prenatal exposure of TiO_2 NMs in mice fetuses resulted in elevated levels of dopamine, and its metabolites in prefrontal cortex and neostriatum. These indications in mice offspring highlighted abnormal growth of the central dopaminergic system [125]. Moreover, maternal administration of TiO_2 NMs during pregnancy reduced spatial memory, decreased hippocampal cell proliferation and inhibited learning ability in offspring [131]. The results of another study indicated that rats exposed to (100 mg/kg body weight equivalent to ~6000 mg/60 kg man, much lower than that recommended by WHO guidelines 1996) TiO_2 NMs regularly produced many side effects in hippocampus. Consequently, indelible applications of NMs, that is, TiO_2 NMs in expectant women for dentistry purposes, should be considered with substantial caution. NMs may ruin not only the mother but also the offspring. These types of influences are harmful and may last for a lifetime.

Possible Mechanisms of NMs Neurotoxicity

NMs having small size can easily reach the brain and be taken up by the cells of brain like glia and neurons by well-developed uptake mechanism such as caveolae and lipid raft dependent endocytosis, clathrin-dependent phagocytosis and endocytosis, and pinocytosis, whereas intracellular localization of NMs may vary depending on cell types and uptake mechanism [132]. Entry of NMs in the endothelial cell monolayer and their accumulation along the endolysosomal pathway influence the function of blood–brain barrier by altering its normal morphology while its intracellular interaction with biological molecules such as lipids, proteins, and DNA may

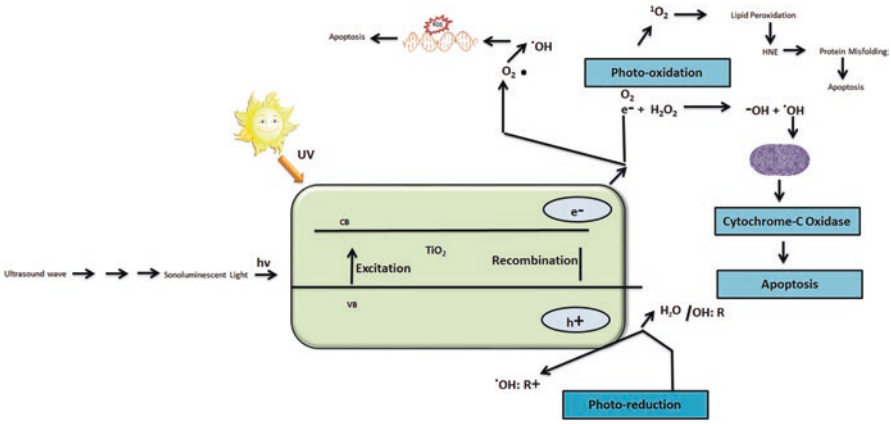

Fig. 16.7 Illustration of the formation of ROS and its impact on different organs

result in ion exchange disorder, new protein epitope exposure, enzyme failure, oxidative stress, signaling pathway activation, conformational changes, mutations, and elevated membrane permeability [133]. Oxidative stress, inflammation, and apoptosis consequences of astrocyte and microglia release after interaction of NMs with different mediators (Fig. 16.7) as neural cells regeneration power is very limited, utmost nervous tissue damage is irreversible [45]. Due to this perspective, it is critical to determine the underlying mechanism of neurotoxicity and lots of studies and research is going on to investigate. Type of NMs determines their interaction with biosystem. Hard NMs like metal oxides and soft NMs like liposomes influence differently on biosystems. The most common proposed mechanism in the latest literature includes immune system dysfunction, autophagy, and oxidative stress [134].

Oxidative Stress

Potentially extremely reactive molecules having an oxygen atom, that is, hydrogen peroxide (H_2O_2) and superoxide radical are reactive oxygen species (ROS). ROS are generally present in all cells produced by mitochondrial and cytoplasmic oxidation processes because their low to moderate concentration in every cell is vital for maintenance of normal physiological processes. Nevertheless, extreme accumulation of these ROS because of oxidative stress would significantly be damaging [135]. Frail antioxidant ability, terminal differentiation feature of sensory cells, and high oxygen consumption ability make CNS more prone to oxidative stress as it impairs cerebral cell viability; therefore, oxidative stress is considered as a crucial factor in acute CNS injury related neurodegenerative disorders (e.g., DNA damage, PD, and AD). ROS regulates the neuronal apoptosis with regulation of different transcription factors, ion channels, and kinases, a key mechanism involved in brain development [136]. Long-term memory loss is induced by NADPH oxidase (Nox-2)

generated ROS. ROS cause membrane damaging influencing the structural and functional alteration of inner proteins, DNA structural alteration and lipid denaturation [132]. DNA oxidation are very critical because it is responsible for alteration and mutation in gene expression. Mitochondrial DNA being deficient of repair enzymes is more susceptible to ROS generated mutations. Aggregation of insoluble protein due to their ROS induced oxidation provides the molecular basis of neurodegenerative disorders [137]. There is a strong evidence that large surface area of NMs plays a key role in generation of ROS which is contributor of diseases pathogenesis and cellular stress. Different types of NMs such metal oxides or CDs are responsible for overexpression of intracellular ROS [138].

Toxicological Study of Different Nanoparticles

The applications of NMs are increasing rapidly by its demand for nanotechnology, its toxicity is also escalating but if we know its lethal effects, we may able to control its amount and use. So that we can save our self and control the environmental destruction. In the next section of this chapter, we have summarized some of the recent literature reported regarding the toxicological study of nanomaterials like Ag NMs, Au NMs, carbon NMs, TiO_2 NMs, ZnO, silica, and Fe_2O_3 NMs.

Effect of Silver Nanomaterials

Due to different characteristics such as large surface area Raman disperse and antibacterial activity made Ag-NMs most popular public product used as medical related instruments, household utensil, nanodrugs and to clean environmental pollutants [139]. Bactria and fungi-free cloth are manufactured using Ag-NMs therefore extensively used in textile industries, it is also effective in coating of refrigerators and washing machine [140]. Ag-NMs have many applications and advantages but also show toxicity; that is why we need to find ways to minimize the harmful effects produced by these NMs [141].

1. Ag-NMs generate oxidative stress in cell by producing ROS and cause destruction of both DNA stands and denaturation of protein.
2. Ag can be de-attached from Ag NMs, and free in the cell. In this case, neutral silver atoms (of any form like Ag^{2+}, Ag_4^{2+}, Ag^{+}) released and leads toward non-oxidative stress mechanism and activate antibacterial property. Ag atom have ability to bind with having thiol group in enzyme or DNA because of phosphorous ultimately this Ag atom cause cell death by disturbing respiratory system and destroying DNA.
3. Ag-NMs also able to direct attach with plasma membrane and cause destruction of membrane.

Limited reports showing the toxicological effect of Ag-NMs are described below. Injections of synthetic Ag-NMs in rats, causing the detachment of Ag from nanomaterial and leads to neurotoxicity to cerebral astrocytes in rat [142, 143]. Cell death occur due to phosphorylation of c-Jun N-terminal kinases (JNK) from the generation of ROS. Ag-NMs are less toxic then Ag ions; that is why Ag ions directly cause cell necrosis and Ag NMs lead cells toward apoptosis. The toxic effect of three different synthetic Ag NMs coated with cetyl-trimethyl ammonium bromide (CTAB), citrate, and poly vinyl pyrrolidine (PVP) on *Allium cepa* roots were analyzed [144]. Ag-NMs-CTAB have most toxic effects due to oxidative stress. The Ag NMs coated with cationic surfactant CTAB have positive charged surface and small size causes better interaction with the root cell and cause cell destruction. While citrate-coated Ag-NMs have a negatively charged surface which caused a less toxic effect [59] have made Ag-NMs having two dissimilar size 20 nm and 100 nm, both have different coating on surface such as PVP and sodium citrate and find out its effect on various organ like intestines, muscles, and gills of zebra fish (*Danio rerio*) [59]. The results indicated that citrate coated particles have more toxicity and it vary organ to organ like it is more toxic in intestine then gills and very less in muscles. Ag NMs reveal its toxicity by changing in DNA sequence alter normal function of gene and misfolding of protein. Ag NMs also hazardous for aquatic life. Khosravi-Katuli et al. [91] have studied the effect of Ag NM toxicity on juvenile common carp. Ag ions collected in various organs like liver, intestines and gills of carps and caused poisonous effects. Ag-NMs also show effect on gene that regulate growth factor and ghrelin which regulate hunger. The study found that the genes are upregulated after exposure to Ag-NMs [91].

Effect of Gold Nanoparticles

Gold is normally not poisonous, dormant, also eco- and bio-friendly in nature when in bulk form but when we lower the dimension of the gold to nanometer level, its toxicity enhance, leads to harm effect on human health. Au-NMs have many applications in the biomedical field such as drug delivery, biosensing, bioaging, antimicrobial activity and also work very effectively as a probe for labeling of DNA [145]. Au NMs exist in various form such as nanobelts, nanoprisms, nanospheres, nanorods, nanocages. Au-NMs have different mode of incorporations into the body or cell mainly enters through skin, ingestion or breathing [146]. By passage of breathing Au NMs direct move into olfactory nerve of brain. Au-NMs also present in many cosmetics that leads to dermal contact of Au NMs [147]. Au-NMs can simply migrate to the various organ like kidney, liver or brain also in plasma of blood due to its nano or small size. Au-NMs can also enter the cell via phagocytosis (uptake of NMs through formation of small vesicles) or pinocytosis (Au-NMs suspended in an extracellular liquid engulfed by the cell) [16] Au-NMs are poisonous only due to the formation of ROS during oxidative stress and create imbalance in antioxidant concentration [57]. Plasma membrane is slightly permeable as it com-

posed of phospholipid. Au-NMs are positively charged particles have ability to cross plasma membrane by creating holes or thinning the membrane it leads to destruction of plasma membrane [148]. When Au-NMs enters in the cell after distortions of membrane it low the level of ATP also causes inflammation of cell and ultimately leads to cell necrosis. Mitochondria stops to work normally because of elevated levels of ROS due to low glutathione. Negatively charged Au-NMs attached with DNA grooves and change the DNA structure enhance show toxicity [149]. Au NMs also have ability to destroy endocrine gland resultant, hormonal imbalance. Some of the literature showing the toxicological study of Au NMs is discussed below. Nunes et al. (2019) studied effect of synthetic gold nanorods on cancerous cell's mitochondria in rat. Nanorods generate ROS and damage mitochondria by reducing phosphorylation rate and concentration of oxygen and by causing disturbance in the electron transport chain [150]. Teles et al. [151] determined the genotoxicity of Au-NM (40nm) in combination with human pharmaceutical gemfibrozil (GEM) (an environmental contaminant frequently present in aquatic system) having concentration of 4.80 μg/L and 1600 μg/L on gilthead seabream, a marine fish (as a model animal) for about 9h. GEM exposed to a level of 150 μg/L and to the mixture of Au NMs and GEM (80 + 150) μg/L. The results showed that Au-NMs are more poisonous and damaging to DNA [151, 152] investigated toxicity of various sizes of Au-NMs (30 nm, 50 nm, and 90 nm) in vitro by comet assay (on two cell lines; amidopyrimidine DNA glycosylase and endonuclease III) and in vivo by mutagenic activity (Drosophila). Results indicated that Au NMs those have 90 nm in size are more toxic then others and damage DNA via oxidative stress. [153] checked and standardized toxicity of Au NMs by changing their size, exposure time and concentration using Hela, Hep G2 through MTT [3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay, in vitro toxicity in various mammalian cells. Clearly, high oxidative stress due to production of ROS seems in the presence of small size Au NMs with high concentration. Depending on the size of Au NMs its accumulation vary among organs; NMs with a large size 42.5 nm to 61.2 nm assembled in liver and spleen cells, and NMs of 6.2 nm are mainly accumulated in other organs except spleen and liver and are also eliminated easily than large NMs [153].

Effect of TiO_2 Nanomaterials

TiO_2 nanomaterials are well-known, commercially most famous among other nanomaterials, so they have significant vulnerability to human being. Mainly it is used in manufacturing of battery, have greater importance in biomedical field. TiO_2 NMs are not expensive, also have compatible site and high chemical balance These are used as photocatalytic substance because of its antibacterial activity for the degradation of organic pollutant. TiO_2 NMs are also beneficial to produce cosmetics, food, drug and other personal care products. These can be revealed through breathing, cutaneous exposure and taken up in the form of nanodrugs or foods [154]. TiO_2 NMs exist in two different conformations, one is rutile and the other is anatase, each

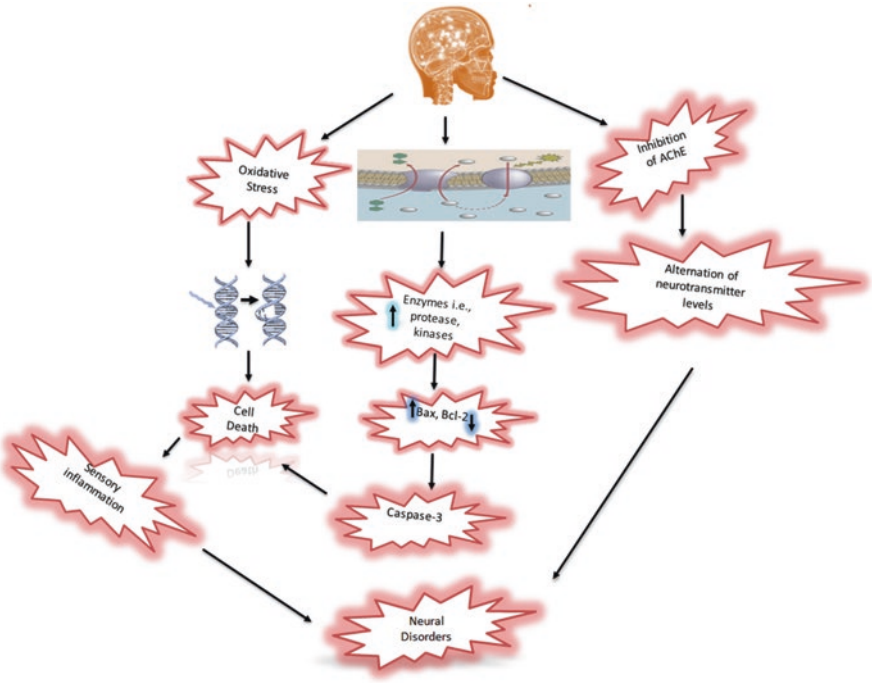

Fig. 16.8 Influence of NMs on CNS; Mechanism of action of NMs on the central nervous system

have dissimilar poisonous consequences (Fig. 16.8). In literature, rutile has less poisonous effect then anatase [87]. Later, depletion of TiO_2 NMs and pile-up in various organs such as brain, spleen, and kidney, lead to harmful consequences. In the kidney, it causes renal cysts and destroys renal cells, although it is present in little amounts [77]. The destructive nature of TiO_2 is to elevate the level of ROS by generating oxidative stress shown in Fig. 16.8, and also cause cell death by lowering the level of antioxidants. TiO_2 is responsible for the destruction of mitochondrial DNA, destroys bronchi, and causes imbalance in the systematic task of cell-like necrosis and the removal of methyl from DNA and leads to inflammatory disorder [155]. Laomettachit et al. [156] determined TiO_2 consequence on human liver on physiology based pharmacokinetic (PBPK) mode. The PBPK model scans the procedure of the accumulation in the cell of human liver. It was declared that accumulation at high level cause cell death, but it is just show poisoning effect and not cause death of cell because it split up through cell division [157]. Iswarya et al. [158] studied and observed the effect of tetracycline on the toxicity of TiO_2 nanoparticles in a fresh water algal species. They concluded that tetracycline causes more harmful impact than TiO_2 NMs [158] the TiO_2 uptake by algal bloom reduce in the existence of tetracycline which means TiO_2 is less toxic then antibiotic [110]. Karfa et al. studied influence of magnetic TiO_2 NMs on *Arabidopsis thaliana*. His group made

N-TiO_2/Fe_3O_4/SiO_2 (NTFS) which assembled in vascular and mesophyll tissues of plant. They concluded that the range of magnetic TiO_2 NMs is 0 to 1000 mg/L, NTFS is less poisonous for plant within this rang but this amount is carcinogenic for human if it enters in the body through food chain from plants [77]. Özgür et al. investigated the consequences of different concentrations and sizes of magnetic TiO_2 NMs on rainbow trout. Sperm cell impervious to antioxidant superoxide dismutase and glutathione within the concentration of 0.1 to 10 mg/L [159]. Sario et al. [160] performed experiments on *Drosophila melanogaster* to find the impact of magnetic TiO_2 NMs on neuroblasts cell by using comet prob., somatic transformation and recombination test. With the help of smart assay, it was shown that 8.0 μg/L of magnetic TiO_2 NMs alter the DNA neuroblasts cell [161]. The toxic effects of different metal oxide NMs are presented in Table 16.4.

Influence of Carbon-Based NMs

The unique properties such as thermal stability, high flexibility, large surface areas, high electrical conductivity, chemical stability of carbon-based nanomaterials revolutionized the field of nanotechnology by their wide scale aptness in tissues engineering, biomedicine, environmental remediation, tumor therapy, catalysis, power generation and bioimaging [162]. However, the wide scale medical as well as industrial applications of carbon based NMs have also initiated harmful effects on human health like other NMs [98]. Therefore, different types of engineered carbon based NMs especially carbon quantum dots (CDs or CQDs) and carbon nanotubes, which are further classified into (1) single-walled carbon nanotubes (SWCNT), (2) multi-walled carbon nanotubes (MWCNT), and (3) fullerenes, have extensively been studied with respect to their toxicity due to their large-scale application in different commercial products [163]. MWCNTs or SWCNTs are cylindrically arranged graphene sheets [164]. Due to inert nature CNTs, these are functionalized with -CHO, -OH or -COOH like functional groups for excel operations [165]. Toxicity of CNTs mainly depends on size, shape, geometry and functionalized surface. It has been reported that pristine CNTs are more toxic than functionalized CNTs. The possible mechanism of CNTs toxicity involves the liberation of time dependent reactive oxygen species leading to oxidation of cell constituents, disruption of cell membrane by penetration within it finally causing the growth inhibition. SWCNTs are reported to cause cell necrosis in human fibroblasts with highest toxicity and hydrophobicity than all other small size carbon based NMs [166]. Deng et al. [167] applied transcriptome sequencing (RNA-seq) technique to study the antagonistic toxic effect of pentachlorophenol and CNT on *E. coli*. Whereas results exhibited that 31.8% toxicity of CNTs is decreased by pentachlorophenol. Comparative analysis of hydroxylated and carboxylated MWCNT human endothelial stressed cells indicated functionalized CNTs have reduced ROS and cell viability resulting that CNTs toxicity could not be elevated by aggravation of stress inducer thapsigargin (TG: $C_{34}H_{50}O_{12}$) [168].

Table 16.4 Toxic effects of different metal oxide nanomaterials

Sr.#	Types of NPs	Types of toxicity	Types of experiments (in vivo/ex vivo)	Modes of research	References
1	Au, Ag, Fe_3O_4, CdSe/ZnS	Cytotoxicity	U937, HeLa MCF7, Caco-2, SH SY5Y, Huh-7	Cell membrane damage, vesicle lipid peroxidation, mitochondrial damage	[97, 221]
2	CeO_2, Ag, TiO_2	Genotoxicity	Human lymphocytes human epidermal cells, rats	Chromosomal fragmentation, DNA strand breakages, point mutations	[160, 222, 223]
3	Au/Ag/AgO nanocomposites, $CoOCeO_2/Fe_3O_4$, TiO_2/ZnONPs	Immunotoxicity	Fish, rat, monocytes, macrophages, nonprofessional defense cell	Allergic reactions, inflammation, bone marrow suppression	[139]
4	Ag, Cu, Al, TiO_2, MgO, ZnO	Neuro virulence	Rats, invertebrate animals	Distributing BBB membrane permeability, changing spatial learning and memory ability	[108, 224]
5	Au, Ag, Si	Hematotoxicity	Human or animal blood system	Coagulation, cardiovascular diseases	[149, 221]
6	SiO_2 NPs TiO_2, Ag	Hepatotoxicity	Kupffer cell BRL-3A cell mice or rats	Apoptosis, liver cell injury	[151]
7	Gold/Platinum/ copper ZnO/ Sn,Gadolinium powder	Nephrotoxicity	Rats	Acute renal failure, kidney function disruption	[146, 148]
8	Titanium Oxide	Cytotoxicity, genotoxicity	Human lung cell carcinoma	Oxidative stress, DNA adduct formation	[225]
9	Carbon fullerenes, carbon nanotubes	Oxidative stress	DNA mutation, protein dysfunction	Oxidative stress, inflammation, consequent damage to proteins, membranes, and DNA	[226]
10	Iron oxide	Cytotoxicity, genotoxicity	Rats mesenchymal stem cells	Decrease cell viability	[227]

(continued)

Table 16.4 (continued)

Sr.#	Types of NPs	Types of toxicity	Types of experiments (in vivo/ex vivo)	Modes of research	References
11	Silica	Carcinogenic	Hepatocellular carcinoma cells (HepG2)	ROS, mitochondrial damage, oxidative stress	[106]
12	Fullerenes	Oxidative stress	CHO, HELA, HEK293	DNA strand breakage, chromosomal damage	[228]
13	Aluminum oxide	Oxidative stress	HBMVECs	Decrease cell viability, decrease mitochondrial function, increase oxidative stress, alternation of proteins expression	[59]
14	Aluminum oxide	Cytotoxicity	MLCL	DNA damage	[229]
15	Titanium oxide	Genotoxicity	In vivo	DNA damage	[30]

Green Nanotechnology: A Proactive Approach to Minimize Nanotoxicity

Nanotechnology have various applications in the fields like solar energy conversion, catalysis, energy storage, water treatment, medicine, sensing, etc. For sustainable use (Fig. 16.9) of these nano-sized particles we must understand their associated hazards to human health and [169]. In green chemistry, we use sustainable techniques (Fig. 16.9) to reduce the potential of these hazards for the improvement of human health and environment [170]. The sustainable designing and manufacturing of these green nano-sized material must include elimination of toxic nanomaterials, choice of greener chemicals and alteration of physical and chemical properties to lower down their toxic effects [171]. Below some green chemistry principles have been described for safe designing of these high-performing nano-sized materials [59].

Designing Safer Nanomaterials

By lowering adverse biological interactions and through designing of safer nanomaterials, we can better understand the impact of physiochemical properties of these nanomaterials [172].

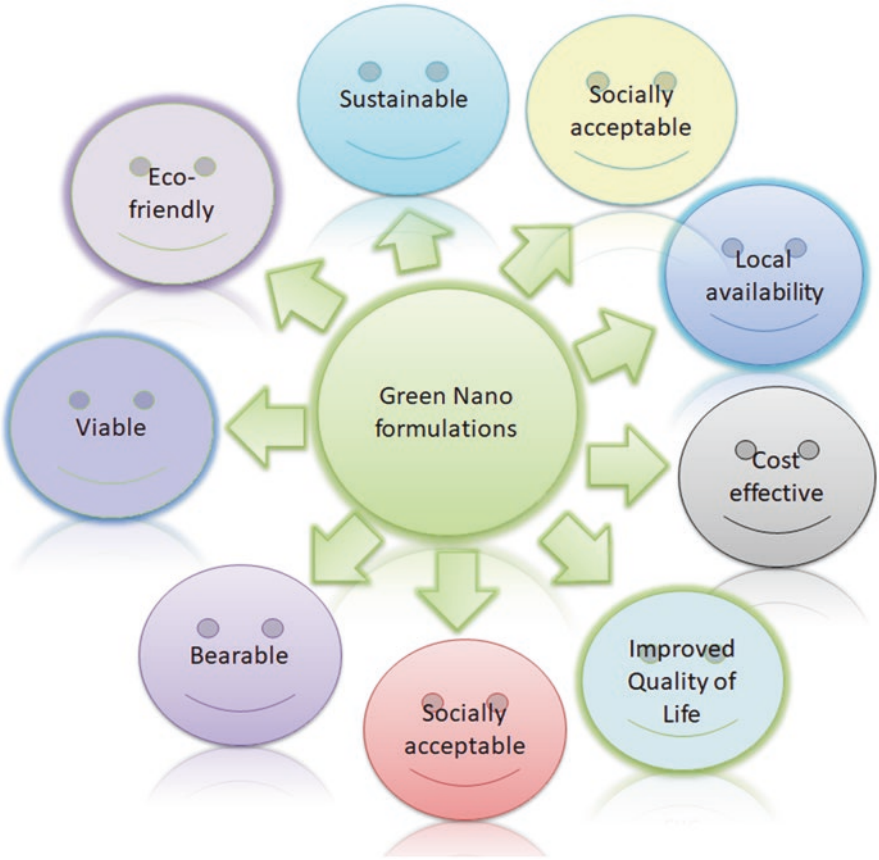

Fig. 16.9 Goals of sustainable approaches of nanotechnology

Process Safety

For safely processing, there is need to develop and design (Fig. 16.10) such advanced methodologies that can utilize natural materials to control the size and morphology of nano-sized materials to avoid the toxic [173].

Reduction of Environmental Impact

Before the chemical release into the environment, we have to better understand the safer biotransformation of these nanomaterials and their products in the environment to avoid from any harm [174].

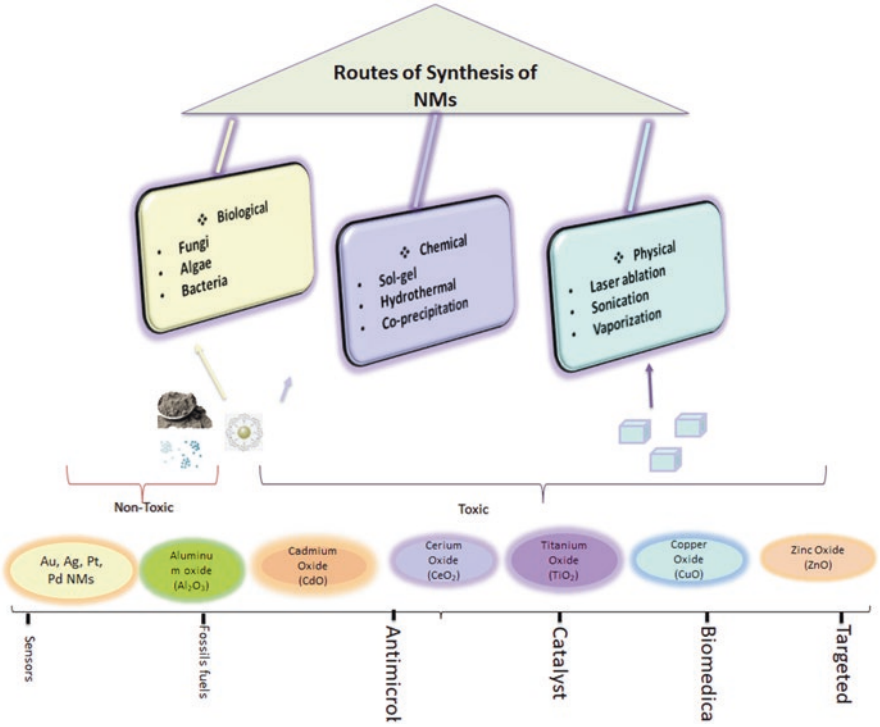

Fig. 16.10 Methods of synthesis of NMs; top-up and Top-Down approaches of NM fabrication with their applications

Nanomaterials Efficiency

To improve the purity and enhance the material efficiency of nanofabrication, there is need to design such strategies that promote selective nanosynthesis by minimizing intermediate steps with real time monitoring of process that control complex nanosynthesis [173].

Energy Efficiency

To design nanosynthetic methods that can enhance efficiency of nano processing by minimizing energy consumption methods enhance the as compare to traditional systems such as microwave irradiation, and ultrasonication.

Prevention of Waste

Design and develop such methods that can eliminate by-product (Fig. 16.10) formation with improved purification steps and require less utilization of stabilizing and capping agents [169]. Recent developments and utilization of green chemistry approaches to tackle nanotoxicity are discussed below.

Biosynthesis of Nanomaterials

Assembly of nanoforms with the help of utilization of biological system such as biomolecules is referred as green synthesis of nanomaterials. Nowadays great importance has been given to the biogenic synthesis of nanoparticles such as Au NMs, Ag NMs, ZnO NMs, SnO_2 NMs, CuO NMs, and Fe_3O_4 NMs [175]. For the growth and stabilization of nanomaterials, biogenic synthesis has rendered the utilization of different biometabolites and phytochemicals like flavonoids, proteins and amino acids, glycosides, polyphenolics, carbohydrates, and alkaloids for the growth and stabilization of nanoparticles [176]. Phytochemicals have a carbon backbone along with polar functional groups such as hydroxyl, aldehydes, ketones, esters, and amides, and also act as a capping and stabilizing agent by forming protective organic layers over the nanoparticles' surface [177]. When these nanoparticles are released into the environment this protective layer tries to minimize the aggregation and suspension of nanoparticles. It has been reported that the surface of nanoparticles such as Ag also have bifunctionalities properties that help to lower reactive oxygen species and nanotoxicity [30].

Surface Coating of Nanomaterials to Minimize Biological Interactions

Nanotoxicity of the nanomaterials can be reduced by coating the nanoparticles with different surfactants such as polymeric compounds and natural organic matters. CdO NM toxicity in contrast with zebrafish was examined by Mohanta and Ahmaruzzaman [178], in the presence and absence of Cd-citrate synchronization polymer coating. The external coating caused in lower toxicity as arbitrated by lesser oxidative stress level, which might be credited to the precise dissolution of Cd2+ ions due to carbon superficial coverage as linked to the pristine CdO NMs [178]. PVP surface coating of the Ag NMs against human HaCaT keratinocyte skin cells is reported to considerably lower the cytotoxicity of Ag NMs whereas in comparison with citrate coated Ag nano analogue toxicity extenuation is much higher. Sunlight exposure of the citrate coated Ag NMs may result in the chemical structure change of the nanoparticles due to which the extent of toxicity reduction is reduced. However PVP Ag NMs show comprehensive resistance against such exposure structural change but they might undergo some accumulation under sunlight irradia-

tion [179]. The toxicity is further reduced to a great extent by such accumulation and precipitation.

Sulfidation of Metal Nanomaterials

A safe chemical transformation of these nanomaterial aggregates can lower the hazards of nano toxicity. Sulfidation of metallic nanomaterial is an example of safe chemical transformation of silver nanoparticles into Ag_2S that can change chemical properties such as surface charge and dissolution of these nanoparticles and also can lower toxicity against *E. coli* [87] which in turn alleviate Ag nanoparticles toxicity as dissolute Ag^+ ions are known to be responsible for the toxicity of Ag nanoparticles [180].

Future Prospects

Large-scale production and applications of NMs boosted up with the increased demand. The commercial application of engineered nanoparticles has greatly increased the potential risk towards ecosystem. The toxicity of NMs has been explored in many studies yet there are certain limitations in the understanding of health hazards associated with nanoparticles that have great impact on human beings. The toxicity of nanoparticles depends on physiochemical properties of NMs including their composition, size and morphology. Thus, there is a need for extensive research to adjust the physiochemical properties of NMs according to requirements, which would lower their toxicity. Before their commercial use, safety guidelines must be adopted by professionals, such as the following.

- Implementation of potent measures to minimize hazards of NMs.
- Dose analysis of NMs, above or below which they cause health hazards.
- Understanding of NM toxicity and its prevention.
- Regulation of NM exposure.
- Enough health scanning of workers in NM fabrication cells.
- Adequate information, training, and supervision of the persons who are exposed to NMs while working.

In addition to that, a comprehensive understanding of their in vitro and in vivo mechanistic pathways is still limited. Consumers must be familiar with the exposure pathway of all engineered NMs, whether they are airborne or waterborne, to avoid health issues associated with interaction and consumption of these NMs. There is an increase in the toxicity of NMs as the consequence of increase in population and available varieties of engineered NMs, the demand for exposure biomarkers that can identify the toxicity levels of NMs has also increased. Therefore, extensive research is also needed in the field of biomarkers to enhance the future safety. Some studies reported that when toxic NMs are coated with functional groups after chemical treatments, modifications such as increase in bacterial property and hydrophobicity,

change in surface property, and decrease in solubility were observed. This kind of modification of NMs must be done to decrease their lethal effects on the ecosystem. Due to limited awareness and lack of study, these tools and measures have always been ignored. Thus, appropriate fortification from adverse effects of NMs, their meticulous applications, awareness of their toxicity, extrapolative manifestation of toxicity pathways, proper disposal protocols, and secure handling of engineered nanomaterials with suitable safety gears would ensure their safe large-scale utilization with significant benefits in the near future.

Conclusion

The increasing demand of nanomaterials in various commodities and their potential hazards towards public health and ambience conditions is of critical concern. Following the principles of green chemistry while using NMs is imperative for the continuity of nanotechnology in future. A proper knowledge of structure–property–hazard relationships is essential to address the toxicity of NMs. Various chemical and physical characteristics are pivotal to the toxicity of NMs. NM toxicity might be restricted to a great extent by manipulation of specific physicochemical characteristics. Adoption of proper disposal methods and biosynthetic routes may help to minimize the lethal effects of NMs. Furthermore, widespread practice of green chemistry principles will offer benign directions in nanotechnology, without imperiling human health and the environment. Every aspect of NM exposure is required to be monitored due to widespread applications of NMs. The present chapter has exhibited that in spite of vast studies and research on the risk assessment of NM exposure, comprehensive guidelines and protocols have not yet been made available for workers. Therefore, further indispensable attention is required to evaluate the workplaces where workers are exposed to nanomaterials and their health should be monitored regularly based on a comprehensive guideline.

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