Evidence based Assessment of Environmental Toxicity due to Pesticides & Nanomaterials Exposure

A thesis submitted

in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

By

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2022

Dedication

To my niece

Gianna K. Sangma

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Declaration

This is to declare that the content embodied in this thesis entitled "**Evidence based Assessment of Environmental Toxicity due to Pesticides & Nanomaterials Exposure"** is the result of investigation carried out by me under the supervision of Prof. Utpal Bora and Prof. Chandan Mahanta and is submitted to the Centre for the Environment, Indian Institute of Technology Guwahati, Kamrup 781039, Assam, India for the award of the degree of **Doctor of Philosophy**. This work has not been submitted elsewhere for any degree or diploma of any institute / university to the best of my knowledge and belief.

In keeping with the general practice of scientific investigation due acknowledgement has been made wherever the work of other investigators is referred.

Guwahati
18 August 2022

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Certificate

This is to certify that the content embodied in this thesis entitled "**Evidence based Assessment of Environmental Toxicity due to Pesticides & Nanomaterials Exposure"** is the result of investigation carried out by **Ponnala Vimal Mosahari (Roll No. – 146152001)** under our supervision at the Centre for the Environment, Indian Institute of Technology Guwahati, Kamrup 781039, Assam, India for the award of the degree of **Doctor of Philosophy**. This work has not been submitted elsewhere for any degree or diploma of any institute / university to the best of our knowledge and belief.

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- Vimal

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SYNOPSIS

Application of agrochemicals like pesticides, weedicides, fertilizers, food preservatives etc. are on the increase in leaps and bounds among the farmers. They are widely used for protection of crops against the pests, to help increase the yield and also for long term preservation. The application of agrochemicals is however not limited to food crops off late, fisheries are using different toxins illegally to prolong the preservation of fish and other aquatic food. Continuous exposure to agrochemicals results in toxicity which may pose significant risk to the taxa and ecological system (Relyea, 2005).

Decrease in land area for cultivation and pressure to increase output has resulted in increased use of pesticides. With the increased use, the production and dispersion to the environment has been increasing, which pollutes the environment. There is enough evidence to show that these chemicals are a potential risk to humans and other life forms and poses danger to the environment (Jeyaratnam 1985). The effect of pesticides effects directly either by exposure or indirectly by consumption of food products laced with pesticides residue (Keikotlhaile, 2010). About one million pesticide induced poisoning deaths and chronic illness are reported every year (Phugare, 2013). Only around 5% of the applied pesticides reach the target species, the remaining contaminate the soil and also percolates underground polluting the ground water (Kookana et al., 1998) and also spread over the non-targeted crops through drift effect (Damalas, 2011). Insecticides, may reach the soil by either missing the target or as a result of run-off from the leaves and stems (Omar, 1998).

The impact of pesticides and other related chemicals on animal and human health and the risk assessment processes are of great interest because anyone can be potentially exposed to these compounds, causing a variety of diseases, including metabolic syndrome, malnutrition, atherosclerosis, inflammation, pathogen invasion, nerve injury, and susceptibility to infectious diseases (Volodymyr I. Lushchak, 2018).

Continuous exposure to the pesticides may result in chronic illness with fatal results (Frazar, 2000). The solid organochloride accumulates in the adipose tissue and chlordane can be absorbed through skin (Reigart et al., 1999). Triazine is carcinogenic, stable in water and can easily spread out (Majewski et al., 2000) and organophosphates tends to be neurotoxic (Slotkin, 2004). Diethyltoluanide, an insect repellent is very harmful, nitrophenolic and nitrocresolic herbicides such as dinoseb is easily absorbed through derma (Reigart et al., 1999). Childhood leukemia was found to be associated with prenatal maternal occupational exposure (Wigle et al., 2009). Pregnant women employed in the farms were reported to have higher organophosphate insecticides metabolism levels (Bradman, et al., 2005).

The human nervous system coordinates the activity of the other organs and maintains the metabolic balance (Biology, 1989). The nervous system is quite sensitive and hence even the slight neurological damage manifests into significant phenotypic effects such as hearing loss, impaired motor function, loss of memory, etc. (Aarli, 2006). The sensitivity of the nervous system allows greater capability of adaptive mechanisms and quick response but also results in a higher prevalence of neurological disorders than other human diseases. Other unique features of the nervous system is its poor regenerative capacity, its multiple functions, unusual anatomy and dynamic presence throughout the body also makes it more susceptible to damage (Miller & Zachary, 2017). Besides physical injury, the nervous system is highly susceptible to disorders based on genetic factors and environmental factors. These factors also act synergistically causing nerve tissue damage and diseases (Neurological Diseases and Disorders - Climate and Human Health).

Neurotoxicity is of the major cause of neurodevelopmental and neurodegenerative disorders. Neurotoxicity may be triggered by acute or chronic exposure to contaminants like pesticides and nanomaterials among others. However, it is the magnitude of neural disorders due to chronic environmental exposure, that has yet to be extensively explored. Based on the target species neurotoxicity has been classified as environmental neurotoxicity and eco-neurotoxicity, where former neurotoxic impact on humans, and later being neurotoxic impact on other species other than humans.

With the advent of the identification of impact on varied biological properties of numerous neurotoxins, organizations have established many guidelines regarding the risk assessment of the neurotoxins. However, there is still a lack of evidence based assessment studies on humans due to chronic environmental exposure of such neurotoxins. The *in-vitro* and *in-vivo* studies do not provide an accurate analogy of the scale of neurotoxic effect as well the long term impact due to environmental exposure. There have been observational and longitudinal studies in this context, however since it is generally limited to certain geographical area or ethnicity, it does not give a holistic projection. Pesticides and nanomaterials owing to its broad range mechanism of action, and size and other features respectively, promptly react with the exposed sites. This has resulted in more reports of pesticides and nanomaterials neurotoxicity and its related neurological disorders.

Under these circumstances environmental impact and evidence based assessment of pesticide and nanomaterials induced toxicity and evidence synthesis for the same is very much needed. Owing to the rate of novel toxins being manufactured, a constant need to develop new toxicity assessment protocol is necessary. To assess the impact, it is necessary to synthesize the evidence derived from various longitudinal or observations studies, which are otherwise limited to various forms of geographical, ethnicity, physical and atmospheric constraints to obtain a comprehensive result. Combining evidences using evidence synthesis techniques such as systematic review or scoping review could provide a holistic approach for better understanding the toxicity of assessed chemicals/ particles. The present work explores the evidence synthesis techniques like Systematic Review and Scoping Review in organophosphate and nanomaterials induces environmental toxicity.

Chapter-wise summary is discussed below.

Chapter 1 introduces the thesis and the study it contains. It provides information on environmental toxicity due to pesticide exposure and nanomaterials exposure. The chapter also briefly introduces the evidence synthesis techniques like systematic review and scoping review.

Chapter 2 of the thesis is a general review of the literature available on pesticide and nanomaterials induced toxicity. It discusses the various routes of exposure, toxicity mechanism, risk assessment and evidence synthesis techniques. The chapter also sums up the existing systematic reviews on pesticide toxicity prior to the start of this work. The chapter is divided as follows

The following objectives were formulated to gain deeper understanding of evidence synthesis of pesticides and nanomaterials induced environmental toxicity.

a. Systematic Review of Organophosphate induced Environmental Toxicity.
b. Scoping Review of Engineered Nanomaterials induced Environmental Neurotoxicity.

Chapter 3 contains a systematic review of the organophosphate pesticides exposure and its association with various forms of toxicity impact. It provides an analysis of the evidences extracted to provide a synthesized evidence linking organophosphate with health impacts. Following standard systematic review methodology, after accessing and retrieving the articles in databases, 721 articles reporting OP toxicity, which included 429 studies on human and 292 being in-vivo studies, studies reported up to November 2021 were considered. The study revealed a positive association between environmental OP pesticide exposure and risk. It is further identified from this study that two exonic polymorphisms viz. PON1L55M and PON1Q192R SNPs of human PON1 alleles are responsible for susceptibility of these toxins. The mechanism of toxicity by OPs are attributed to inhibition of acetylcholinesterase (AchE).

OPs are also known to cause disruption of mitochondrial processes; however, it still requires further study.

The adverse effects of the pesticides on environment and human health is well documented. Neurological development disorder, neurodegenerative diseases, reproductive issues, cancer are said to have a link with various pesticides exposure. Although data were available scarcely indicating the link between pesticide exposure and development of neurological conditions, and other toxicity issues however each study performed and resulted in a discrete manner not able to establish the generalized notion. For which, a strategy to approach this problem by carrying out systematic review is adapted which brings out the meaningful comprehensive result from various similar studies. A comparison of the animal studies done to study the OP toxicity impact helps in establishing a more robust evidence. The systemic review has revealed that there is a strong positive association between environmental OP pesticide exposure and risk of various kinds of health impacts especially neurotoxicity and neurodevelopmental disorders. The mechanism of toxicity by OPs are attributed to inhibition of acetylcholinesterase (AChE). OPs are also may cause disruption of mitochondrial processes; however, it is still a subject for further studies.

Chapter 4 contains a scoping review of current research on NMs induced environmental neurotoxicity, the different neurodegenerative and neurodevelopmental disorders linked to it. The aim was to identify the studies and research works being carried out in the area and the knowledge gap that exists. The review found that there are very limited longitudinal studies done on environmental exposure assessment for NMs neurotoxicity. There are almost no observational studies to support the neurotoxicity due to chronic environmental exposure. The reviews also mostly cover the acute or occupational exposure of NMs and its impact. Most of the reviews considered for scoping review were based on in-vivo and in-vitro models, and few based on epidemiological studies. No observational studies for the pre-defined period were found. Most of the reviews emphasized on the neurotoxicity mechanisms and route of exposure.

The mechanism of NM nanotoxicity yet to be explored completely, hence is still an important area of research for the future. Most of the studies attribute NMs neurotoxicity to oxidative stress, however some NMs are antioxidants and free radical scavengers. Another issue with most of the *in-vivo* or *in-vitro* studies is the lack of standardized common terms, for experimentation repeatability in terms of exposure times, assays, cell lines etc. Many different types of NMs exist and all tend to have different responses, hence a common standard is the way forward. Also, during experimental studies, the NMs dose generally is not synchronous to exposure in real. Also, experimental studies on cells or animal models alone can never present the actual neurotoxic effect due to chronic environmental exposure. Therefore, observational studies are needed, and they should be supplemented with experimental studies.

Chapter 5 concluded the work with summary and future prospects.

In this chapter the methodology, results and discussion of a systematic review study carried out to get insight into the relationship between organophosphate pesticides and its toxic effects are discussed. The overall review of the articles established a strong positive link between environmental OP pesticide exposure and toxicity impact on human health, supported by *in-vivo* evidence. The study indicated that susceptibility to OP pesticide toxicity can be determine by two exonic polymorphisms viz. PON1L55M and PON1Q192R SNPs in human population. The mechanism of OP pesticide toxicity can be attributed to the inhibition of acetylcholinesterase (AChE). However, the association of OPs pesticides as cause of mitochondrial disruption is not conclusive as of now.

Scoping review done to investigate the possible link between engineered nanomaterials with neurotoxicity is discussed. The search words emphasizing on engineered nanomaterials and neurotoxicity or neurodegenerative diseases were designed to carry out literature retrieval from PubMed and Scopus databases. 12 studies were identified as relevant on the basis of inclusion criteria, which were found to be review articles. 3 out of 12 articles specifically focused on a single type of nano-materials, whereas 9 studies reviewed on neurotoxicity caused my nano-materials, without identifying any particular nano-material. The reviews are found to be based on *in-vivo* and *in-vitro* studies. The scoping review points out that adequate cohort or longitudinal studies have not been carried out to link AD or PD to NMs. It also concludes that there is a critical need for studies dealing with risk assessment of human health for a long term chronic exposure to NMs.

A better understanding of the underlying causal effect relationship of toxicant-induced toxicity will help to identify intervention strategies needed against environmental health impact. More observational, longitudinal and cohort studies in combination with supporting *in-vivo* studies are required to find the direct relationship between adverse effect of environmental toxicants and various forms of toxicity.

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LIST OF ABBREVIATIONS

ACh: Acetylcholine

AChE: Acetylcholinesterase

AD: Alzheimer's Disease

ADHD: Attention Deficit Hyperactivity Disorder

ADME: Absorption, distribution, metabolism and elimination

ALS: Amyotrophic lateral sclerosis

AOP: Adverse Outcome Pathway

ASD: Autism spectrum disorders

AVM: Avian Vacuolar Myelinopathy

Aβ: Amyloid-beta

BBB: Blood Brain Barrier

BHC: β-Hexachlorocyclohexane

CFDNP: Combustion and friction derived nanoparticles

CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas

CNS: Central Nervous System

CNT: Carbon Nanotubes

COPIND: Chronic Organophosphate-induced Neuropsychiatric Disorder

CPF: Chlorpyrifos

CS: choreoathetosis with salivation

CS: Cockayne Syndrome

CYPs: cytochrome P450 family

DDE: Dichlorodiphenyldichloroethylene

DDT: Dichlorodiphenyltrichloroethane

DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition

EBM: Evidence based medicine

EBPH: Evidence based Public Health

EFSA: European Food Safety Authority

ENM: Engineered Nanomaterial

EPA: Environmental Protection Agency

FAO: Food and Agriculture Organization

GFAP: Glial fibrillary acidic protein

GIS: Geographical Information System

GLP: Good Laboratory Practice

HEPO: heptachlor epoxide

hESC: Human embryonic stem cell

hGNs: glutamatergic neurons

MPTP:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NAPCCHH: National Action Plan for Climate Change and Human Health

NINDS: National Institute of Neurological Disorders and Stroke

NIOSH: National Institute of Occupational Safety and Health

NM: Nanomaterial

NOS: Nitric Oxide Synthase

NP: Nanoparticles

NTE: Neuropathic target esterase

OCPs: Organochlorine pesticides

OECD: Organisation for Economic Co-operation and Development

OP: Organophosphate

OPIDP: Organophosphate-induced Delayed Polyneuropathy

PD: Parkinson’s Disease

PM: Particulate matter

PNS: Peripheral nervous system

POD: Point of Departure

PPAR: Peroxisomal proliferators-activated receptors

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QSAR: Quantitative structure-activity relationship

QSPR: Quantitative structure property relationships

rBMEC: Rat brain microvessel endothelial cells

RCT: Randomized Controlled Trial

RfC: Reference Concentration

RfD: Reference Dose

ROS: Reactive Oxygen Species

SNP: Single Nucleotide Polymorphism

SNpc: Substantia nigra pars compacta

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

UAPP: unintentional, acute pesticide poisoning

VSSC: Voltage Sensitive Sodium Channels

WHO: World Health Organization

Chapter I

Introduction

Application of agrochemicals like pesticides, fertilizers, food preserving chemicals etc. are increasing in leaps and bounds among the farmers. They are widely used for protection of crops against the pests, to help increase the yield and also for long term preservation. The application of agrochemicals is however not limited to soil based agriculture, but off late, fisheries are using different toxins illegally to prolong the preservation duration of fish and other aquatic food. The main reason for such wide application of agrochemicals and toxins are generally in line to maintain the food security of the ever growing population, in-spite of adverse health effect on the humans. Continuous exposure to agrochemicals results in toxic effects which may pose significant risk to the taxa and ecological system (Relyea, 2005). Agricultural activities are generally concentrated around fresh water sources, exposing them to agro-chemicals contamination (Baker et al., 2013). Direct or indirect linkages exits for exposure of fresh waters such as intentional pest control, accidental overspray, runoff, sediment deposition etc. Agrochemicals exposure also affects the non-targeted insects or organism which may either have environmental or economic benefits.

Different types of pesticides are used to control the crop pests, so as minimize the output loss and also to prevent epidemics. With decreasing land area for cultivation and pressure to increase output has resulted in increased use of pesticides. High pesticide concentration in soil and food products affects humans and environment adversely. With the increased use, the production and dispersion to the environment has been increasing, which pollutes the environment. There is enough evidence to show that these chemicals are a potential risk to humans and other life forms and poses danger to the environment (Jeyaratnam 1985). The effect of pesticides effect directly either by exposure or indirectly by consumption of food products laced with pesticide residue (Keikotlhaile, 2010). In an ideal condition pesticide should be able to target only the predetermined species. The rampant use of pesticides has worsened the situation, about one million pesticide induced poisoning deaths and chronic illness are reported every year (Phugare, 2013). Only around 5% of the applied pesticides reach the target species, remaining pesticides contaminates the soil and also percolates underground contaminating the ground water (Kookana et al., 1998) and may also spread over the non-targeted crops through drift effect (Damalas, 2011). Insecticides may reach the soil by either missing the target or as a result of run-off from the leaves and stems (Omar, 1998).

The impact of pesticide and other related chemical on animal and human health risk assessment processes is of great interest because these compounds can potentially expose anyone to these compounds, which can cause a variety of diseases, including metabolic syndrome, malnutrition, atherosclerosis, inflammation, pathogen invasion, nerve injury, and susceptibility to infectious diseases (Volodymyr I. Lushchak, 2018). Future research should focus on the long-term consequences of low pesticide dosages, as well as how to reduce or eliminate pesticides' impact on non-target living organisms, develop more specialized pesticides, and use contemporary technology to reduce pesticide contamination of food and other items.

Continuous exposure to the pesticides may result in chronic illness with fatal results (Frazar, 2000). The solid organochloride accumulates in the adipose tissue and chlordane can be absorbed through skin (Reigart et al., 1999). Triazine is carcinogenic, stable in water and can easily spread out (Majewski et al., 2000) and organophosphates tends to be neurotoxic (Slotkin, 2004). Diethyltoluanide, an insect repellent is very harmful, nitrophenolic and nitrocresolic herbicides such as dinoseb is easily absorbed through derma (Reigart et al., 1999). Childhood leukemia was found to be associated with prenatal maternal occupational exposure (Wigle et al., 2009). Pregnant women employed in the farms were reported to have higher organophosphate insecticides metabolism levels (Bradman, et al., 2005).

The human nervous system is responsible for communication within the living body in response to external stimuli. It coordinates the activity of the other organs and maintains the metabolic balance (Biology, 1989). The nervous system is quite sensitive and hence even the slight neurological damage manifests into significant phenotypic effects such as hearing loss, impaired motor function, loss of memory, etc. (Aarli, 2006). The sensitivity of the nervous system allows greater capability of adaptive mechanisms and quick response but also results in a higher prevalence of neurological disorders than other human diseases. Other unique features of the nervous system is its poor regenerative capacity, its multiple functions, unusual anatomy and dynamic presence throughout the body also makes it more susceptible to damage (Miller & Zachary, 2017). Besides physical injury, the nervous system is highly susceptible to disorders based on genetic factors and environmental factors. These factors also act synergistically causing nerve tissue damage and diseases (Neurological Diseases and Disorders - Climate and Human Health).

Neurotoxicity is one of the major concern for neurodegenerative and neurodevelopmental disorders. It is the neurological damage resulting in various neurological disorders caused due to exposure to certain chemicals (mostly man-made) termed as neurotoxins. Depending on the chemical profile of these toxins, the mechanisms of action and the nervous system element they affect vary and include various symptoms (Risk, 1992). The scale of neuronal diseases and disorder that results due to environmental toxic chemicals are not completely known nor extensively explored.

Based on the huge impact of neurotoxins, inevitably neurotoxicity has been classified into environmental neurotoxicity and eco-neurotoxicity where the former implies neurological effects in humans due to the chemical exposures while the later describes neurotoxicity in species other than humans (Legradi et al., 2018). As per estimation for the period of 1972–1974 over a million or more Americans were exposed to about 197 chemicals in occupational setting, out of which a third of them had neuronal degenerative effects (NIOSH, 1977; Risk, 1992). Since then, numerous studies have been carried out and the magnitude of the effects of neurotoxicity have increased massively. Up to about 30% of all chemicals used commercially are potentially neurotoxic (Tilson et al., 1995).

Nanomaterials (NMs) are found everywhere in the present day environment. Ranging from 1 to 100 nanometer, these colloidal particles may be naturally occurring or synthetic and can be incidental or engineered. Due to multiple advantages such as enhanced mobility and chemical reactivity owing to their smaller size the rate of commercial production of engineered nanomaterials are rapidly increasing. These advantageous features, however, also contribute to rapid cytotoxicity arising from inflammation, oxidative stress, and subsequent damage to DNA, proteins and cell membranes. Cell death resulting from these damages lead to numerous diseases including neurotoxic diseases. Neurodegenerative or neurodevelopmental diseases occupy a critical prevalence since they are rapidly progressive and irreversible. Used for delaying the progression of neurodegenerative diseases and other diseases, NMs in the form of nano-medicines, with enhanced transportation ability to cross the blood brain barrier, have resulted in over accumulation, which in turn has rate of disease occurrence. Primary exposure in commercial production of engineered nanomaterials and environmental exposure has also increased the risk of neurotoxicity. The increased probability of exposure to NMs through various means is in sync with the increased occurrence of neuro degenerative diseases and neurodevelopmental disorder.

Naturally available nanometer sized particles are omnipresent in considerable amount in the environment and humans are continuously exposed to them. Due to their small size and physical resemblance to physiological molecules such as proteins, nanomaterials (NMs) possess the capacity to interfere with biological, physical and chemical processes at the molecular level. NMs, thus play a major role in photonics, magnetics, catalysis, and biotechnology including cosmetics and therapeutics. The size of NMs allow them to invade biological systems and also cross the blood brain barrier (BBB) of Central Nervous System (CNS) and interfere in their functioning. Smaller size of the NMs contribute to a greater reactive surface area, more chemical reactivity and production of greater number of free radicals like reactive oxygen species (Nel, Xia et al., 2006). Reactive oxygen species production is induced by a different types of nanomaterials like carbon nanotubes, carbon fullerenes and metal oxides (Oberdörster et al., 2005). This is one of the primary mechanisms of nanoparticle toxicity resulting in cell death via different ways, which includes oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA (Nel et al., 2006). The production and utilization of engineered nanomaterials (ENMs), mostly metal nanoparticles are continuously rising. Over 720 commercial products in the global market like electronic and sports equipment, sunscreens and other cosmetics, clothing with odorless and anti-wrinkle properties, long-lasting paints, fuel catalysts for better combustion, building equipment, medicines, and nutritive food products contain nanomaterials (Shand & Wetter, 2006).

Size, chemical composition, shape, surface charge, presence of functional groups of other chemicals as coatings, solubility etc. contribute to toxicity of a NMs (Nel et al., 2006). Mixture of these physiochemical properties are also responsible for determining the toxicity of a NM (Buzea et al., 2007). Nanomaterials has high functional potential due to their large surface area to mass ratio. This also results in higher levels of toxicity compared to the same material of larger size. The minute size of the NMs also lead to crossing of biological membranes including the blood brain barrier followed by neurotoxicity via mechanical injury or immunological reactions of the neural cells.

Uptake of nanoparticles by the cells are influenced by the charge on the particle due to the electrostatic interaction. Positively charged nanoparticles are more readily absorbed by the cells causing higher accumulation and hence increased chances of toxicity (Tarn et al., 2013). Negatively charged nanoparticles are also reported to have toxic effect when they interact with the membrane proteins, lipid raft structuring transmembrane proteins or channels (Lin et al., 2010). The functional groups present in the nanoparticles also determine the level of toxicity of the nanomaterial. Hydrophilicity is an important criterion for minimizing the toxicity level of the nanoparticle by reducing aggregation and hence enhanced dispersion, solubility and compatibility in the biological system (Zhang et al., 2011). Hydrophilic silver nanoparticles however, are suggested to be toxic due to the release of dissolved ions (Stensberg et al., 2011). Surface modification such as thiol capping may also alter the toxicity of nanomaterial (Templeton, Wuelfing, & Murray, 2000)

The use of solvents along with other chemicals involved in the synthesis of the NMs also determine its toxicity levels. Chemical synthesis of CNTs may use metal catalysts (such as iron or nickel) which can remain within CNTs as an impurity, and the residual catalyst can contribute to the toxicity (Shvedova et al., 2003; Shvedova et al., 2005).

Detailed information on the absorption, distribution, metabolism and elimination (ADME) of nanoparticles is essential (Hagens et al., 2007). They provide better insights in understanding their target sites and mechanisms of toxicity. These parameters are however, non-linear. Lower doese of certain nanoparticles such as PbS or Cu nanoparticle are also documented to be more toxic due to formation of aggregates, which is due its nonlinear surface function (Bell, Ives, & Jonas, 2014).

With the advent of the identification of the varied biological properties of numerous neurotoxins, numerous organizations have established many guidelines regarding the risk assessment of the neurotoxins. However, there is still a lack of adequate risk assessment studies based data and proper databases. One of the important databases providing comprehensive data regarding neurological disorders and information of the relevant chemicals is the NINDS (National Institute of Neurological Disorders and Stroke). Due to the massive amount of data, most other databases are rather targeting more specific information related to environmental toxicity (Judson et al., 2009).

It has been established that pesticides due to their broad range mechanism of action and nanomaterials due to their size and other features readily react with the target site (Costa et al., 2008; Teleanu et al., 2019). As most pesticides target the metabolic activities of the nervous system, not being particularly host specific, results in their interaction with the cells and metabolic processes of the human nervous system as well (Lushchak et al., 2018) . Owing to these reasons, reports of pesticide and nanomaterial toxicity are increasingly raising concern. Some of the pesticides e.g. 2,4-D, paraquat, β-Hexachlorocyclohexane [BHC] are all well known for their neurotoxic effects and are banned and/or restricted in most parts of the world including India. The effects of newly synthesized chemicals are unknown but have a potential of affecting the human nervous system as well (Jayaraj et al., 2016). Although the chemical nature of nanomaterials are well known and very specific, the rate and amount of their commercial production (specially heavy metal-oxide) has led to extensive exposure and due to their ability to move through small pores and high active sites they can pass cellular pores and cross the blood brain barrier, binding and reacting with the components of the nervous system causing interference in cellular processes and hence toxicity (Teleanu et al., 2019).

Hence, environmental impact and risk assessment of pesticide and nanomaterials induced toxicity is very much needed in the present scenario. The application of risk assessment principles for toxic chemicals require special consideration with respect to reversibility and redundancy of function in the nervous system (Neurotoxicity Risk Assessment for Human Health: Principles and Approaches) and other systems. Numerous documents including "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (EPA 1994), "A Review of the Reference Dose and Reference Concentration Processes" (EPA 2002) and "Benchmark Dose Technical Guidance" (EPA 2012) are issued by the environmental protection agency (EPA) based on which the assessments are carried out (Process et al., 2014). Due to the rate of new types of toxins produced the constant need to develop new protocols of toxicity assessment has become necessary. The methods need to be continually refined along with the availability of new data and technologies improving assessment (Krewski et al., 2010); Raies & Bajic, 2016). It has also become quite necessary to combine the various types of data available and is the key to providing appropriate risk assessments. As observed, numerous methodologies and data exist with their own advantages and restraints. Combining the information from the available studies using evidence synthesis techniques such as systematic review or Bayesian analysis could provide a holistic approach to better understanding the toxicity of assessed chemicals/ particles (Stroup et al., 2000; Sutton & Abrams, 2001). Several studies have been carried out to understand the potential of those techniques (Clarke, 2016).

Organizations such as EPA have used this technique in multiple studies (estimation of PODs, RfCs, RfDs or unit risks) and assessing the toxicity values combined and within the observed range (Process et al., 2014; Choi et al., 2012). Evidence synthesis techniques could also be used to study combined estimates from dose-response studies and multiple species thus establishing interspecies dose-response relationships.

Systematic review and scoping review synthesize the data from the existing primary research to give evidence based comprehensive overview. It is well conducted systematically done review which provides comprehensive data on any particular causal-effect research and also gives quantitative value to the research. Systematic review forms a potential tool to help the scientists trying to interpret and access evidence for further research or practice. It can be used to appraise, summarize, and communicate the results and implications of the otherwise unmanageable quantities of research based data (Green, 2005). Systematic reviews overcome the limitations in the narrative or traditional reviews like informal and subjective methods to collect and interpret data and selective citation of literature that supports preconceived beliefs (Pai et al., 2004). The traditional reviews generally do not describe the search techniques, selection and sorting of research and identify the quality of data. Systematic studies are exhaustive and focused study on primary research data, with set procedure for selection of research data, to appraise its quality, to synthesize the data without any preconceived results.

Systematic reviews however may or may not include statistical study i.e., meta-analysis, depending certain conditions that includes homogeneity. Systematic review and meta-analysis are two different components, where meta-analysis forms the optional subset of systematic review. Meta-analysis pools the data from the selected research to generated summary estimate of “effects”. The term “effect” is used for the measure of effect based on cause, of the comprehensive data subjected for study. If the data obtains high level of homogeneity of effect measures in the study, then data is combined using meta-analysis. In case of heterogeneity in effect measures, a meta-analysis may not be done, instead the study may be left at systematic review. Systematic reviews and meta-analysis happens to be the most statistically rigorous way of summarizing independent data from various sources (Bancroft et al., 2008). There are many ways to quantitatively combine environmental health data (Hasselblad, 1995) for meta-analysis.

Scoping review is a relatively novel approach to evidence based assessment and differs in aims and applications from systematic review (Munn et al., 2018) It involves aggregation of information from the available sources in a well-defined technique to interpret the data. Scoping review provides an overview of available research data, however it does not provide quantitative summary of the result of any research question (Arksey and O'Malley, 2005). Scoping reviews are useful in answering broad questions rather than specific causal effect relations, and can be used as a prior to systematic review.

Investigating the toxic effects of pesticides and nanomaterials by using systematic review and scoping review gives comprehensive picture of the scenario and may potentially contribute to conserve the natural biodiversity and also to identify human health effects. Scoping review of toxic effects helps in identifying the areas to be worked upon, may allow better management of the pesticides and nanomaterials application. Most studies focus on single chemicals or species, and quantify only the LC50 (lowest concentration needed to kill 50% of the test subjects) (Relyea, 2004), ignoring the other possible side effects on the environment. There are numerous pesticides and nanomaterials; a comprehensive and combined systematic review needs to be done of all the available primary research data to understand their toxic effects in general.

Chapter 2

Review of Literature

2.1 Environmental Toxicity due to Pesticides Exposure

Keeping up with the food requirements in the modern world, pesticides are widely used in agriculture to maintain a healthy crop yield avoiding the risk of any pest and pest-related disease outbreak along with increased amounts of agricultural products.

According to the Food and Agriculture Organization of the United Nations 80% of these increased requirements is estimated to come from increase in crop yield and not agricultural farm land (FAO, 2018). The extent of their use applied reaches every household and gardens. By 2020, the global pesticide usage has increased up to ~3.5 million tonnes, China being the major contributing country followed by the US and Argentina (Sharma et al., 2019).

Pesticides with similar chemical structures have similar properties and usually have a similar mode of action. Insecticides can be classified into the following chemical families: organochlorines, organophosphates, pyrethroids and carbamates (Jayaraj, Megha, & Sreedev, 2016; Martín Reina et al., 2017). Common classes of herbicides include phenoxy herbicides, urea based herbicides, triazines and benzoic acid herbicides (Sherwani et al., 2015). Biopesticides are a new emerging category of pesticides which can be a substitute highly toxic pesticides. Major classes of biopesticides are plant-incorporated-protectants (PIPs), microbial pesticides, biochemical pesticides (Chandler et al., 2011).

The ideal working mechanism of pesticides is to be highly specific for target species. However, majority of the pesticides are manufactured with very generic properties targeting a wide range of pests with the aim of being economically beneficial to the manufacturers (Kaur & Garg, 2014). This leads to toxicity towards many non-target species including humans.

Toxic effects of pesticides in humans vary, covering a variety of domains, from mild irritation in the skin, to affecting liver, lung or endocrine functions, to being carcinogenic (Jayaraj et al., 2016). Mode of action of a large number of pesticides is based on them disrupting the nervous system of the target species. These pesticides have neurotoxic effects in humans as well. Pesticide exposure also results in the development of neurodevelopmental (learning disabilities, attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, developmental delays) and neurodegenerative (Alzheimer's, Parkinson's) diseases and numerous other emotional and behavioural problems.

These neurological disorders are associated with genetic and social factors and the environmental factor also plays a major role in it. The statistics vary based on region and age. The contributions of the environmental factors also vary along with. Lead toxicity is calculated to have the highest impact among the other environmental factors (Lushchak, Matviishyn, Husak, Storey, & Storey, 2018). Furthermore, the data related to the effect based on levels of exposure are also not well known. Only ~5 of 201 reported toxic chemicals have been well documented as reasons of developmental neurotoxicity and 45% of the reported substances were pesticides (Bjørling-Poulsen, Andersen, & Grandjean, 2008). The cause of such a high rate is dependent both on the vulnerability of the developing brain and the wide range of chemicals which might lead to neurotoxicity even at very low doses (Grandjean & Landrigan, 2014).

2.1.1 Pesticides used in Agriculture

Agriculture is one of the important sectors majorly affected by pests and hence pest control is an important aspect of it. The largest user of pesticides is the agriculture industry. Using pesticides have been one of the important salvation of the agriculture industry owing to exponentially increasing demands of food supply.

Indian economy is largely based on the agriculture sector and hence the use and benefits of using pesticides are also very large. According to Indian Labour Statistics, 1994, food grain production increased from just 50 million tons in 1948 to 198 million tons in 1996 from around 169 million hectares of land and the use of agricultural chemicals played a large role (Aktar et al., 2009). Similar outputs were observed in the US corn yield and the UK wheat production yield. Weeds are reported to reduce crop yield by 37-79% (Singh, Das, Kaur, Raj, & Shekhawat, 2018). It is known that regular consumption of agricultural products like fruits and vegetables reduces the risk of many diseases including diabetes, heart diseases, high blood pressure, cancer, etc. Many research groups and organizations argue that the benefits of such diets outweigh the risk associated with the intake of low pesticide residues along with it (Anand et al., 2015).

However, with the massively increased usage of pesticides, the production and variability has increased to a great extent leading to previously unknown risks. Compounds of new chemical classes are constantly being produced. These risks have been exposed to the population both directly and indirectly. Pesticide poisoning has led to about 1 million deaths and chronic diseases worldwide ("Annual Review of Environment.," 1999). From production workers to formulators, sprayers, mixers, loaders and farmers, everyone working in the agricultural industry are at a high exposure risk. The hazardous nature of pesticides during manufacture and formulation are even higher as the raw materials include various toxic chemicals (Gupta et al., 2017).

2.1.2 Pesticides Induced Toxicity

Epidemiological data have established the clear relationship between increased use of pesticides and cases of neurodegenerative diseases (Kamel & Hoppin, 2004). Many studies have also suggested prenatal exposure to be responsible for numerous neurodevelopmental disorders (Herbstman et al., 2010). The mechanism of action varies with the active ingredient of the type of chemical compound used. Although there are numerous classes of compounds the most widely utilized are the organophosphates, carbamates, pyrethroids and the recently developed neonicotinoids (Martin Reina et al., 2017).

Apart from other diseases, organophosphates poisoning cause neurotoxic diseases such as cholinergic syndrome, organophosphate-induced delayed polyneuropathy (OPIDP), and chronic organophosphate-induced neuropsychiatric disorder (COPIND) with symptoms including excessive sweating, vomiting, slow heart rate, lacrimation, gastrointestinal troubles, etc. (Naughton & Terry, 2018). This class of pesticides work by inhibition of acetylcholinesterase (AChE) activity which causes acute cholinergic syndrome in humans. Cholinergic syndrome can be treated with drugs atropine sulphate combined with oxime, diazepam, etc. (Organophosphate Toxicity Medication: Anticholinergic agents, Antidotes, OP poisoning, Benzodiazepines," n.d.). However, diseases such as OPIDP and COPIND causing loss of peripheral nerves and ataxia are not treatable (Lotti & Moretto, 2005). Organophosphates such as chlorpyrifos (CPF) have been reported to be involved in developmental neurotoxicity leading to behavioral changes as well (Burke et al., 2017). Carbamates are divided into cholinesterase inhibiting and non-cholinesterase inhibiting, sulfur containing carbamates. While as defined, cholinesterase inhibiting carbamates are responsible for parasympathetic hyperactivity due to the accumulated acetylcholine (ACh) resulting from AChE inhibition (Chemicals & Chemicals, 1982; Colovic et al., 2013). The molecular mechanism of non-cholinesterase carbamates is not well established but are assumed to be related to their metal-chelating and enzyme-inhibiting properties. Pyrethroids work by disrupting the voltage sensitive sodium channels (VSSCs). They slow down the opening as well as the inactivation of the VSSCs leading to a more hyperpolarized action potential allowing more sodium ions to cross and inactivate the depolarize the neuronal membrane (Silver et al., 2014). Pyrethroid are largely responsible for neurodevelopmental disorders such as CS and T syndromes and many behavioural disorders (Chrustek et al., 2018). Neonicotinoids primarily act on the AChE system similar to that of OPs and carbamates. They also lead to NO production and oxidative stress. Besides these, several pesticides including phenylpyrazoles and chlorinated cyclodienes have been known to target the GABA receptors (Roberts & Karr, 2012). Well known herbicide paraquat related to the development of Parkinson's disease induces oxidative stress, mitochondrial dysfunction, α-synuclein fibrillation and neuronal cell loss (McCarthy, Somayajulu, Sikorska, Borowy-Borowski, & Pandey, 2004). Epidemiological studies relate pesticides with Alzheimer's disease also. The mechanism involved however, is not clear. Some of the proposed mechanisms include oxidative stress, AD-specific processes involving amyloid-beta (Aβ) and hyperphosphorylated tau (p-tau), microbiota dysbiosis, etc (Guo et al., 2020). The exposure to different types and amounts of pesticide cause crosstalks in complex ways, might be mutually enhancing and make it difficult to decipher simplistic causal relationships (Tang, 2020).

Alzheimer's disease is an irreversible brain disorder progressive with age. It is a condition caused based on factors including genetic(~70%), lifestyle and environmental conditions(~30%) ("Alzheimer's Disease Fact Sheet | National Institute on Aging," n.d.). Epidemiological associations between pesticides and the disease are however limited to in vitro studies (Yan, Zhang, Liu, & Yan, 2016). Organophosphates have mostly been associated with the developmental disease with concentration as low as ~0.2 ng/ml. Direct effects of organochlorines such as DDT and DDE have also recently been confirmed. Taking other factors such as age, sex, education, and genes into account, studies have found that people who worked with pesticides were 53% more likely to develop Alzheimer's disease (Yegambaram, Manivannan, Beach, & Halden, 2015)..

Long term pesticide exposure has been reported to aid to the early onset development of Parkinson's. Pesticides such as paraquat and rotenone have been mostly associated with Parkinson's disease (Brown et al., 2006). Case studies have shown that many of the subjects were not directly involved with the agricultural sector suggesting indirect exposure through household chemicals, through water supplies, etc. Besides genetic mutation, pathogenesis of Parkinson's involves several mechanisms including mitochondrial dysfunction and oxidative stress leading to dopaminergic neuron death in the substantia nigra pars compacta (McCarthy et al., 2004). The mode of action of Paraquat involves generation of Reactive Oxygen Species (ROS) causing oxidative stress of target species. Pesticides such as organochlorines have also been found to be linked with the development of Parkinson's via miRNA dysregulation. In-vitro studies have reported pesticides such as dieldrin, heptachlor, maneb and atrazine to be causative of Parkinson's via α-synuclein accumulation leading to cell degeneration and apoptosis (McCarthy et al., 2004). The combinatorial effects of these pesticides were larger compared to individual effects.

Autism spectrum disorders (ASD) including attention deficit disorder with and without hyperactivity (ADHD) are extensively studied neurocognitive disorders. They have mostly been associated with early developmental stages. Previously thought to be completely based on genetic factors, these diseases have received much need recognition in research during the past few decades, focused on potential environmental causes (Marks et al., 2010).

Most common pesticide linked with ADHD is pyrethroids, which was considered safer with respect to organophosphates. A study showed that for every 10-fold increase in 3-PBA, an indicator of pyrethroid in biological systems, increased risk of 50% for hyperactivity and impulsivity was reported (Bouchard, Bellinger, Wright, & Weisskopf, 2010).

According to several studies, male children were affected more compared to the female population. Although numerous other various studies have confirmed the link between pesticides and ADHD, the studies did not prove a cause-and-effect relationship. As ADHD is developed during early childhood, it is understood that prenatal exposure may be the cause (Gunier, Bradman, Harley, Kogut, & Eskenazi, 2017).

Along with common pesticides, many new insecticides such as Imidacloprid (neonicotinoid class), used in agriculture and domestic pet flea control were also associated with the disease (Hladik, Main, & Goulson, 2018). Studies with imidacloprid exposure to Drosophila showed abnormal flight speed, mobility and social interactions compared to control flies, similar to behavioral changes in children with ADHD. Imidaclopride act on nicotinic acetylcholinesterase receptors, a mechanism similar to Ops (Kim, Lee, & Park, 2017).

Elevated metabolites of chlorpyrifos, mancozeb and pyrethroids in cross-sectional studies involving urine collected from children living near farm areas were found to have weak working memory and poor visual motor coordination (Wang, Huang, Guo, & Lin, 2016). 24-month-old children exposed to OPs were associated with Pervasive Development Delays by the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) in California (Marks et al., 2010).

The rate of mental diseases has seen an increase of 37.6% in about two decades (1990–2010), making it a growing concern on the global scale. Long-term pesticide usage has mostly been associated to higher rates of depression and suicide. However, recent studies also show doubled risk of depression with heavy dose in a short amount of time (Khan, Kennedy, Cotton, & Brumby, 2019). Studies conducted in the Diagnostic Interview Schedule (using DSM-III diagnostic standards) concluded that farmers showed a higher rate of mental health issues compared with other professions. Direct occupational exposure was a major factor in case of depression and suicide caused by pesticides (Serrano-Medina et al., 2019).

Seminal studies involving organophosphates reported anxiety and mood disorders, depression and schizophrenia post-organophosphate poisoning. Compared with the control population, effects of OPs were observed even two years after poisoning (Balali-Mood & Saber, 2012). Various other epidemiological studies reported inconsistencies but a viable link was established. Environmental and/or occupational exposures disturb the neurochemistry causing psychological distress. However, studies on direct effects of OPs and other pesticides on suicidality is limited. Heightened suicide rates in farming populations indicate that it is a major concern to be studied extensively (Serrano-Medina et al., 2019).

According to a recent study, the mean suicide rate of farmers was 6.4 cases/100,000 per year (2006–2010), the male/female ratio being 4.2. Ecological analyses proved that the suicide rates were higher in micro-regions with a higher proportion being 35–64-year-old, female workers and on farms with better economic indicators (higher farming income, level of mechanization and farm area). Use of chlorpyrifos was related with increased suicide mortality (OR=2.37) in a study (Faria, Fassa, & Meucci, 2014; Beard et al., 2011).

The toxicity mechanism of carbamates and organophosphates is based on inhibiting AChE activity. Behaviors of anxiety and depression in mice, was linked to cholinesterase inhibition, some studies were also able to suggest such an association (Badr, 2020).

2.1.3 Organophosphates and Carbamates

Organophosphates and carbamates have a common target i.e. the enzyme acetylcholinesterase (AChE). The toxicological features however, vary. OPs were developed in the early 1940s and carbamates in the 1950s (Naughton & Terry, 2018). Organophosphates contains a phosphorus (P) atom that is bound to an oxygen (O) or sulfur (S) atom with double bond while it is bound to two alkoxy groups (OCH3 or OC2H5) and a "leaving group" of different chemical nature with single bond (Phang-Lyn & Llerena, 2020). The usually used insecticides contains OP which have phosphorus bound to sulfur. However, when it is metabolically bioctivated to the other form where it contains P = O (phosphorus bound to oxygen) moiety, it becomes toxic that effectively inhibits the enzyme AChE (Costa, 2018). Enzymes of the cytochrome P450 family (CYPs) triggers the bioactivation by oxidative desulfuration of sulfur atom to form an "oxon", or oxygen analog. Other biotransformation reaction that occurs are detoxication reaction that forms metabolites of lesser or no toxic effects. Some of these are mediated by CYPs while enzyme esterases (e.g. paraoxonase, carboxylesterase) also carry out formation of some of the metabolites (Islam & Malik, 2018).

2.1.4 Pyrethroids

A class of synthetic insecticides, apart from being used as agricultural pesticides are nowadays being widely used for pest control around households as common ingredients of household ectoparasite control products such as mosquitoes (Chrustek et al., 2018). Owing to increased usage, the abundance and variety of the chemical has increased. Recent studies have shown a greater risk potential of developmental neurotoxicity in pregnant women and kids (Roberts & Karr, 2012). Pyrethroids work by targeting and disrupting the voltage-sensitive sodium channels (VSCCs) and calcium channels in insects, the most important factors of neurotransmission. They slow the activation and inactivation of VSCCs resulting in a more hyperpolarized membrane potential at which the channels open and also are held open longer. This causes more sodium ions to pass through and cause depolarization of the neuronal membrane resulting in increasing the action potential followed by hyper excitability and depolarization-dependent block (Silver et al., 2014). The biophysical and pharmacological properties of the channel isoforms vary in mammals which results in differential sensitivity to pyrethroids (Bhardwaj, Sharma, Abraham, & Sharma, 2020). Some of the effects of pyrethroid toxicity were aggression and hypersensitivity followed by stimulus-induced bouts of tremor, convulsive twitching, sometimes coma and death. Also, salivation without lacrimation and followed by jerking of legs and progressive writhing convulsions (choreoathetosis) were observed (Chrustek et al., 2018).

The classification of pyrethroids is based on the different types of intoxication and their chemical structures. Type I compounds, eg. permethrin, resmethrin, and bifenthrin are based on the T (tremor) syndrome of intoxication while type II compounds are based on the CS (choreoathetosis with salivation) syndrome of intoxication and chemicals containing the α-cyano-3-phenoxybenzyl moiety, eg. deltamethrin, and fenvalerate, etc. The α-cyano substitutent in the phenoxybenzyl moiety was reported to have higher insecticidal potency. Many other structural modifications were introduced containing moieties with greater toxic properties and different mechanisms of action (Soderlund, 2012).

Pyrethroids were classified as EPA Category II, considered to be moderately toxic with LD50 values lying between 50 and 500 mg/kg due to which they were largely used to replace highly toxic organophosphates in the 1980s (Aggarwal & Diddee, 2009). However, recent studies have shown increased mortality rate from all causes especially cardiovascular diseases.

2.1.5 Organochlorine Compounds

Similar to pyrethroids, organochlorines such as dichlorodiphenyltrichloroethane (DDT) work by disrupting the voltage gated sodium ion channels of insects and non-target species. nerve cells leading to hyper excitability, the clinical signs being tremors (Silver et al., 2014). Most other organochlorines eg. dieldrin, endrin, heptachlor epoxide (HEPO) and endosulfan work by blocking the chloride channels of the GABA-A receptor via noncompetitive inhibition, causing seizures. OCPs are persistent pesticides and concentrated up in the food chain. They can be detected in the diet including drinking water (Arora, Batra, Sharma, Banerjee, & Gupta, 2013). Many OCPs induce nigrostriatal dopaminergic neurotoxicity through the generation of oxidative stress and mitochondrial dysfunction (Subramaniam & Chesselet, 2013). Compounds such as heptachlor were reported to play a role in idiopathic Parkinson's disease. In a recent study, no genetic linkage was found in many subjects which indicated the role of insecticides in the development of the disease to be greater than expected (Brown, Rumsby, Capleton, Rushton, & Levy, 2006).

2.1.6 Mechanism of Pesticides Induced Toxicity

Organophosphate pesticides (OPs) targets acetylcholinesterase (AChE), an enzyme that hydrolyzes acetylcholine and other choline esters functioning as neurotransmitters. This results in accumulation of acetylcholine at cholinergic synapses along with overstimulation of the muscarinic and nicotinic cholinergic receptors present in most parts of the body. This causes a cholinergic syndrome consisting of increased gastrointestinal motility, excessive sweating and salivation, bronchial secretion, muscular twitching and other CNS effects

(Roberts & Karr, 2012). Death is also observed due to inhibition of respiratory brain centres, bronchoconstriction and increased bronchial secretion and paralysis of respiratory muscles resulting from AChE inhibition (Kamel & Hoppin, 2004).

OPs with a P=O moiety, have less effect on the physiological state of the AChE substrates. The P=O moiety phosphorylates a hydroxyl group on serine in the active (esteratic) site of AChE which is hydrolyzed by water but at a very slow rate which can be facilitated by certain chemicals such as oximes. These chemicals are used for the treatment of OP poisoning. These chemicals are however ineffective at reactivating the phosphorylated enzyme once it has been completely hydrolyzed by the organophosphate pesticides (Soderlund et al., 2002).

Other methods for treating OP poisoning include usage of cholinergic muscarinic antagonist such as atropine which works by blocking the muscarinic receptors and preventing acetylcholine accumulation on these receptors. Some chemicals such as diazepam are reported to reduce the symptoms arising due to neurodegenerative diseases (Colovic et al., 2013).

2.1.7 Risk Assessment

Due to the increasing cases of toxicity cases associated with pesticides and their inherent toxic properties, market release and subsequent usage requires a comprehensive and highly regulated risk assessment, the responsibility being that of the pesticide producers. The rules are specific for different countries (Sharma et al., 2019).

The toxicological risk assessment starts with the laboratory production itself under Good Laboratory Practice (GLP) requirements with the aim of identifying and characterizing adverse/toxic effects of the pesticides produced. Certain test guidelines are established and the products are to be designed accordingly (Mie, Rudén, & Grandjean, 2018).

Major regulatory authorities such as the U.S. Environmental Protection Agency (EPA) and the European Food Safety Authority (EFSA) provide detailed evaluation reports on the chemicals followed by assessment. Some chemicals such as chlorpyrifos have been observed to have differences in safety assessment reports and hence comprehensive assessment is very necessary (Authority E.F.S., 2019).

2.1.8 Characterization

The qualitative characterization of toxic hazard can be based on either human or animal data. Such data can result from accidental, inappropriate, or controlled experimental exposures (Guidelines for Neurotoxicity Risk Assessment, 1998). Novel assessment systems are needed that can differentiate between species within the ecosystem. Real time biomonitoring systems may be used to monitor the behavioral patterns to detect neurotoxic effects and effect-directed analyses be used to identify the neurotoxins (Laboratory, N. R. C. (US), 2011). Additionally, toxic pressure calculations in integration with mixture modelling could use the data from environmental chemical monitoring to predict adverse effects of pollutants, and prioritize identified high risks hazards for laboratory testing (Mie et al., 2018). Toxicants can also be identified by applying cheminformatics tools based on computational toxicological data from in vitro and in vivo studies. Screening of compounds for toxicity can also be done by using an array of in vitro assays covering different modes of action. AOPs relevant for eco-neurotoxicity can be used to select in-vitro assays (Legradi et al., 2018).

2.1.9 *In vivo* studies

Evaluation of chemical mixtures with similar modes of action, without consideration of realistic exposure in the environment, might underestimate the toxicological risk associated with their exposure (“Toxicity and Assessment of Chemical Mixtures,” n.d.). *In vivo* studies are thus an important aspect to consider before releasing a pesticide for the population. Numerous in vivo studies have reportedly quantified the effects of pesticides on neurological disorders. Eg. the acute effects of sulfoxaflor on acetylcholinesterase (Piner Benli & Çelik, 2021). *In vivo* studies can be further used along with computational tools to evaluate and predict the effects of pesticides with similar structures on human beings.

2.1.10 *In vitro* studies

Rather than testing chemical mixture in animal models for hazard evaluation, it is convenient to perform it in *in vitro* cell lines. *In-vitro* testing offers advantages of performing a large number of experiment that are rapid and cost-effective. The experiments can be designed in different ways by grouping chemical based on their effects on key biological pathways and covering a large concentration range for all possible exposure scenarios (Aktar et al., 2009). The data from these evaluations can be considered for human population exposed to a chemical mixture of investigation as basis for an informed and focused approach for hazard assessment in risk-relevant manner. *In-vitro* experiments can be designed in such a way to represent a human population that will provide insight into intrinsic variability across different concentration in addition to hazard data. Regulatory bodies can rely on such data for making inform decision for protection of public health and especially the vulnerable sub-populations (Grandjean & Landrigan, 2014).

The methods of safety testing are not as standard or structured as it is for established individual pesticides. In vitro studies for risk assessment of neurotoxicity due pesticide exposure can be classified into two types based on the subject: Population-based in vitro models and studies involving variability in responses to toxicity among individuals. Population based in-vitro studies are used for toxicity evaluation with respect to comparative population genomics (Warheit, 2018).

2.1.11 Modelling & Simulation (QSAR)

With the development and accuracy of computational tools for prediction based on simulation and big data, the potential for risk assessment due to pesticide exposure has also increased. These non-animal test methods increase consumer safety along with the potential to perform better risk assessment analyses and are hence the preferred method for many present organizations (Villaverde, Sevilla-Morán, López-Goti, Alonso-Prados, & Sandín-España, 2020). Software tools based on quantitative structure relationship models, i.e. QSAR and QSPR have recently gained popularity among many others. QSARS are a tool to recognize the systematic relationships between the chemical behaviour and the biological and/or toxic activity of various chemicals. QSAR predicts data required for risk assessment that are not always available from field or laboratory studies. Various studies show that QSARs are more precise than individual tests as they combine large amounts of data with more specific chemical measurements and require a very short amount of time. QSARS are applied for toxicity assessment for either analysing the exposure or effects. Recent studies have shown improved potential with integrated analyses consisting of simulated exposure and effects predictions, statistical validation parameters and database information. QSAR models could quantify and analyze the mode of the toxic effects of as many as 200-300 pesticides collected from databases such as ECOTOX and OPP against various organisms such as rainbow trout fish, earthworm, honey bee, etc (Toropov et al., 2017; Ghosh et al., 2020; Yang et al., 2020). Hierarchical QSAR approach which consisted of chemical structures of various pesticides as input, executing a mechanistic estimation approach of the toxicological action in the case of avian pesticide toxicity, suggested that pesticides exert their toxic action through the interaction with some macromolecule, mostly protein of the biological system ("Evaluation of pesticide toxicity: a hierarchical QSAR approach to model the acute aquatic toxicity and avian oral toxicity of pesticides - Open Research Online," n.d.). Along with various ecotoxicology related databases and rapidly developing QSAR models, this aspect is a major breakthrough in pesticide toxicity assessment.

2.1.12 Evidence based Assessment

Risk assessment of pesticide impact is not an easy and accurate process. Many factors such as differences levels of exposure, duration of exposure, type of pesticides (regarding toxicity), mixtures used in the field, and the geographic, socio-economic and meteorological characteristics of the area where pesticides are applied are relevant for the studies. Hence, apart from the different methods used to study the risk assessment, summarized analyses based on toxicity evidence data is necessary. Systematic reviews and meta-analyses help with cumulative assessment based on previous evidence of toxicity of pesticides (Grandjean & Landrigan, 2014).

A meta-analysis on assessment of exposure to agricultural pesticides in residential areas helped assemble ~151 articles between 1988 and 2019 which established possible links between pesticide exposure and the onset of adverse health effects, principally cancers and reproductive outcomes (64.9%) (Grandjean & Landrigan, 2014). Another geography based systematic review covering 141 countries (58 based on 157 articles and 83 based on data by WHO Mortality Database) showed around 740,000 annual cases of unintentional, acute pesticide poisoning (UAPP) of which 7446 were fatal and 733,921 non-fatal cases. Based on these evidences, further analysis using model-based predictions resulted in an estimate of about 385 million cases of UAPP annually world-wide including around 11,000 fatalities, farmers being ~44% of that population. The greatest estimated number of UAPP cases were observed in southern and south-eastern Asia followed by east Africa (Boedeker, Watts, Clausing, & Marquez, 2020).

2.2 Environmental Neurotoxicity due to Nanomaterials Exposure

Nanomaterials (NMs) are found everywhere in the present day environment. Ranging from 1 to 100 nanometer, these colloidal particles may be naturally occurring or synthetic and can be incidental or engineered. Due to multiple advantages such as enhanced mobility and chemical reactivity owing to their smaller size the rate of commercial production of engineered nanomaterials are rapidly increasing. These advantageous features, however, also contribute to rapid cytotoxicity arising from inflammation, oxidative stress, and subsequent damage to DNA, proteins and cell membranes. Cell death resulting from these damages lead to numerous diseases including neurotoxic diseases. Neurodegenerative or neurodevelopmental diseases occupy a critical prevalence since they are rapidly progressive and irreversible. Used for delaying the progression of neurodegenerative diseases and other diseases, NMs in the form of nano-medicines, with enhanced transportation ability to cross the blood brain barrier, have resulted in over accumulation, which in turn has rate of disease occurrence. Primary exposure in commercial production of engineered nanomaterials and environmental exposure has also increased the risk of neurotoxicity. The increased probability of exposure to NMs through various means is in sync with the increased occurrence of neuro degenerative diseases and neurodevelopmental disorder.

Naturally available nanometer sized particles are omnipresent in considerable amount in the environment and humans are continuously exposed to them. Due to their small size and physical resemblance to physiological molecules such as proteins, nanomaterials (NMs) possess the capacity to interfere with biological, physical and chemical processes at the molecular level. NMs, thus play a major role in photonics, magnetics, catalysis, and biotechnology including cosmetics and therapeutics. The size of NMs allow them to invade biological systems and also cross the blood brain barrier (BBB) of Central Nervous System (CNS) and interfere in their functioning. Smaller size of the NMs contribute to a greater reactive surface area, more chemical reactivity and production of greater number of free radicals like reactive oxygen species (Nel, Xia et al., 2006). Reactive oxygen species production is induced by a different types of nanomaterials like carbon nanotubes, carbon fullerenes and metal oxides (Oberdörster et al., 2005). This is one of the primary mechanisms of nanoparticle toxicity resulting in cell death via different ways, which includes oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA (Nel et al., 2006). The production and utilization of engineered nanomaterials (ENMs), mostly metal nanoparticles are continuously rising. Over 720 commercial products in the global market like electronic and sports equipment, sunscreens and other cosmetics, clothing with odorless and anti-wrinkle properties, long-lasting paints, fuel catalysts for better combustion, building equipment, medicines, and nutritive food products contain nanomaterials (Shand & Wetter, 2006).

Size, chemical composition, shape, surface charge, presence of functional groups of other chemicals as coatings, solubility etc. contribute to toxicity of a NMs (Nel et al., 2006). Mixture of these physiochemical properties are also responsible for determining the toxicity of a NM (Buzea et al., 2007). Nanomaterials has high functional potential due to their large surface area to mass ratio. This also results in higher levels of toxicity compared to the same material of larger size. The minute size of the NMs also lead to crossing of biological membranes including the blood brain barrier followed by neurotoxicity via mechanical injury or immunological reactions of the neural cells.

Uptake of nanoparticles by the cells are influenced by the charge on the particle due to the electrostatic interaction. Positively charged nanoparticles are more readily absorbed by the cells causing higher accumulation and hence increased chances of toxicity (Tarn et al., 2013). Negatively charged nanoparticles are also reported to have toxic effect when they interact with the membrane proteins, lipid raft structuring transmembrane proteins or channels (Lin et al., 2010). The functional groups present in the nanoparticles also determine the level of toxicity of the nanomaterial. Hydrophilicity is an important criterion for minimizing the toxicity level of the nanoparticle by reducing aggregation and hence enhanced dispersion, solubility and compatibility in the biological system (Zhang et al., 2011). Hydrophilic silver nanoparticles however, are suggested to be toxic due to the release of dissolved ions (Stensberg et al., 2011). Surface modification such as thiol capping may also alter the toxicity of nanomaterial (Templeton, Wuelfing, & Murray, 2000)

The use of solvents along with other chemicals involved in the synthesis of the NMs also determine its toxicity levels. Chemical synthesis of CNTs may use metal catalysts (such as iron or nickel) which can remain within CNTs as an impurity, and the residual catalyst can contribute to the toxicity (Shvedova et al., 2003; Shvedova et al., 2005).

Detailed information on the absorption, distribution, metabolism and elimination (ADME) of nanoparticles is essential (Hagens et al., 2007). They provide better insights in understanding their target sites and mechanisms of toxicity. These parameters are however, non-linear. Lower doese of certain nanoparticles such as PbS or Cu nanoparticle are also documented to be more toxic due to formation of aggregates, which is due its nonlinear surface function (Bell, Ives, & Jonas, 2014).

2.2.1 Neurotoxicity Mechanism

NMs depending on the material are differentially eliminated by physiological clearance systems. Accumulation of these NMs within brain leads to further cytotoxicity. Various mechanical tissue injuries due to excess accumulations of NMs have been reported (Medina et al., 2007; Sharma & Sharma, 2007). The recovery from these injuries and other toxicological effects are dependent on the capacity of the CNS neurons to regenerate as therapeutic drugs are mostly impermeable to the Blood Brain Barrier (BBB). The self-regenerative ability of neurons, is however, reported to be limited (Steward, Sridhar, & Meyer, 2012)

NPs are easily translocated to the brain and CNS due to their extremely small size. One pathway for NPs to navigate to brain is via sensory nerve endings embedded in the respiratory epithelia or the olfactory bulbs, followed by axonal translocation to CNS structures (Gao, 2016; Medina et al., 2007; Oberdörster et al., 2005). Another pathway is through the BBB via systemic distribution. These pathways have been studied extensively for drug delivery, as a mechanism for delivering drugs to the brain (Kreuter, 2004). Physicochemical properties of the NPs at different stabilizers, surfactant concentrations, and amyloid-affinity agents were observed to evaluate the influence on transport mechanism (Roney et al., 2005). These properties were thus analyzed and further modified for improved translocation, for example, NPs coated with the polysorbate 80 (Tween 80) surfactants along with the drugs of interest have shown improved transportation of drugs through the BBB thus providing an important tool for diagnostic and therapeutic usage in neurological diseases and disorders (Chacko, 2018). These modifications also aid in the over accumulation of NPs in the CNS and brain region resulting in inflammatory diseases due to immunological reactivity, physical injury and other molecular changes of the neural cells (Chin-Chan et al.,2015).

Neurotoxic symptoms may appear immediately after exposure or it may be expressed in later phase of life. The magnitude of the toxicity depends on several factors like age (younger people are more vulnerable than adults), type of neurotoxic agents, extent of exposure (direct or indirect), environmental and genetic factors of a specific population etc. Several studies on

Indian population showed the disastrous health effect of popularly used insecticides causing severe neurological abnormality and death. Neurotoxic effects can be broadly categorized into four different groups based on general mechanism.

2.2.2 Neurotransmission Blockage

Neurotransmitters like acetylcholine (ACh), norepinephrine, dopamine, GABA etc. transmit chemical signals from pre-synaptic to post-synaptic neurons and plays a vital role in proper functioning of the nervous system. So, most of the widely used insecticides like organochlorine, organophosphate, carbamates etc. target neurotransmission in insects (Slotkin, 2004). The similarities between components of neurotransmission in insects and human nervous system makes humans vulnerable to the inhibitory effects of insecticides and in the recent years, several reports have been published which justify the fact (Bradbury & Coats, 1989).

The carbamate and organophosphorus (OP) pesticides are widely used to regulate a large variety of insects. These chemical compounds bind within the active site of acetylcholinesterase (AChE), blockage of enzyme AChE which inhibits the hydrolyzation of acetylcholine. As a result, the concentration of acetylcholine gradually builds up, accumulating at cholinergic synapses ultimately causing hyperexcitation. Blockage of AChE by OPs are long lasting, and reactivation of the enzymes takes from many hours to several days. Poisoning with organophosphorus (OP) compounds has been described as a global public health problem.

There have been reports on various carbamate-related neurotoxicity in human. Carabamate poisoning is characterized by acute cholinergic crisis, fasciculations as well as muscle weakness due to acetylcholinesterase (AChE) inhibition. High mammalian toxicity was common with organochlorines, a group of synthetic pesticides. Chlordecone whose use has been discontinued, was one of them and was believed to disrupt the movement of ions such as sodium, calcium, chloride and potassium into and out of nerve cells causing headache, tremors, and irritability. Organochlorines are extremely lipophilic and resistant to degradation, which allows them to accumulate and persist in the environment for several years. The premier target of endosulfan, a potent organochlorine is inhibition of the GABAA receptors, resulting in an alteration in GABAergic signaling in the central nervous system. As a consequence, these typical insecticides cause hyperexcitability and convulsions by blocking the inhibitory neurotransmitter, γ aminobutyric acid (GABA). Exposure to GABAA antagonists has also been reported to cause an alteration in neuronal outgrowth and disordered cortical architecture in human patients as well as autism spectrum disorder and alterations in multiple neurobehavioral disorders such as cognitive deficits and schizophrenia.

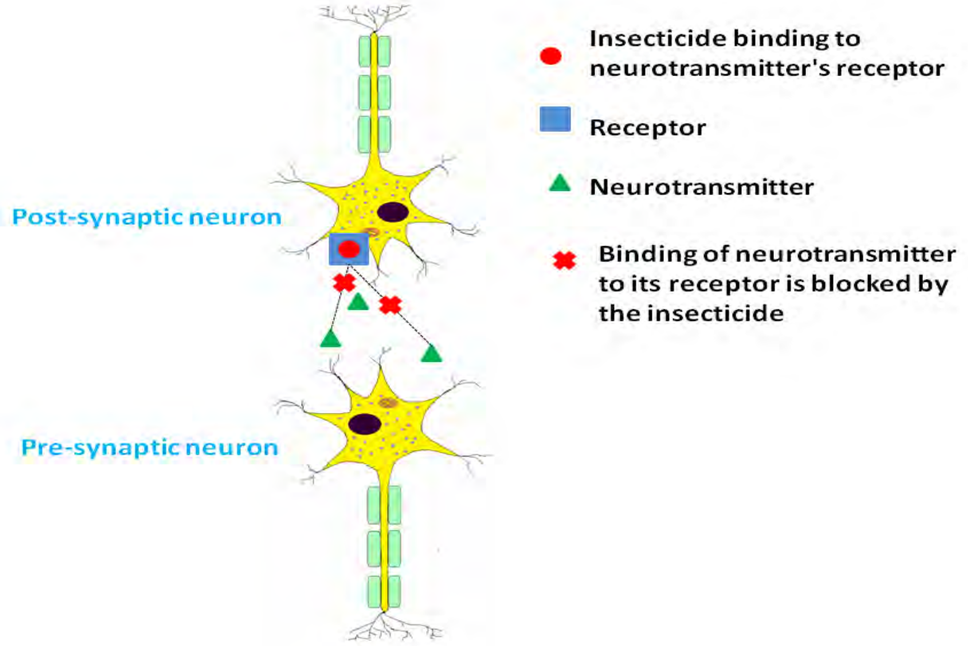

Figure 2.1: Neurotransmission Blockage

2.2.3 Axonopathy

Axonopathy mainly affects the peripheral nervous system (PNS), wherein axonal dysfunction leads to a spectrum of secondary pathological conditions such as weight loss, ataxia, etc. A large number of neurotoxic chemicals with broad agricultural and industrial application produce axonopathic syndrome in humans and experimental animals. Morphological studies have suggested that these functional effects are associated with degeneration of axon and myelin sheath in central as well as peripheral nervous system without affecting the cell body. The chemical compound causes "chemical transaction" of the axon at some point along its length, and the axons are that are lateral to that transaction gets separated from the cell body and degenerates.

Consumption of organophosphorus compounds leads to organophosphate induced delayed neuropathy (OPIDN) which is a type of distal axonapathy characterized by wrist and foot drop as well as loss of sensation. OPIDN is assumed to be caused by phosphorylation of the enzyme called neuropathic target esterase (NTE) leading to axon degeneration, myelin degradation and macrophage accumulation.

Acrylamides, hexanediones etc. are also considered to notorious among pesticides that produce distal axonopathy. Evidence suggest that 2,5-hexanedione targets cytoskeletal neurofilaments that housed throughout the entire length of the axon and function in axonal transport of proteins and other cellular components from cell body to axonal terminal. The good news is that if the condition is not severe, then there is a good probability of regeneration and recovery from weakness with the progression of time.

2.2.4 Myelinopathy

Myelinopathy, i.e., loss of myelin content occurs due to demyelination or blockage of myelin formation. This leads to functional alteration of the sensory and motor nerves of the central and peripheral nervous system.

A couple of chemical product are thought to target myelin, causing intramyelinic edema or demyelination. Organotin compounds are examples of well-known chemical insecticides that cause intramyelinic edema. Triethyl tin is typical organotin compound which causes severe headache, sickness and vomiting, psychological and visual disturbances, and sometimes loss of consciousness. Toxicity of triethyltin on the CNS of rodents was first elucidated by Stoner et al. in 1955. Further reports have shown that triethyltin may induced interstitial oedema of the white matter of the brain and spinal cord without obvious neuronal damage. There are also reports of severe myelinopathic effects from intoxication of Triethyl tin. A conclusion was drawn that the basic pathologic lesion by triethyltin was limited to myelin, however, few changes in the peripheral nervous system have also been observed.

Avian Vacuolar Myelinopathy (AVM) is separation of the myelin lamellae at the intraperiod line as a result of that extensive zygomorphic vacuolation of the white matter of the brain and spinal cord in herbivorous waterbirds and their avian predators, first reported in 1994. It is believed that a few unidentified neurotoxins are the most probable cause of AVM. Triethyltin, hexachlorophene (insecticide) and bromethalin (Rodenticide) known to create this type of lesions. Birds with AVM may exhibit few clinical signs, including problem in flying, difficulty to walk, inability to swim and general ataxia.

2.2.5 Neuronopathy

Neuronopathy may be defined as the loss of neurons or peripheral nervous system either by necrosis or by apoptosis due to toxic agents. Gliosis proliferation of astrocytes and microglial cells, is a common response to loss of neurons. With few exceptions, this type of injury is permanent. Neuronopathy is the part of polyneuropathy. Most common types of neuronopathies are-

a. Motor neuronopathy, where only collateral reinnervation occurs.
b. Sensory neuronopathy, which are usually sub-acute and induce clinical deficits that are more or less widespread to the whole body surface rather than distal.
c. Axonal neuronopathy, where terminal axonal reinnervation occurs, such as motor axon reflex.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a well-studied neurotoxicant that causes neuronopathy in human. It is reported to target dopaminergic receptors resulting in Parkinson's disease like symptoms. Trimethyltin and its analogue compounds are effective insecticides which leads to cognitive impairment by targeting hippocampal, amygdala and pyriform cortex neurons. Serial neuropsychological tests disclose that these may be the cause of persistent memory defects, cognitive dysfunction, and dysphoria in human after few years of exposure. However, proper physiological role of neuronopathy and the effects of nanomaterials on it is not properly understood.

2.2.6 Neuronal Degeneration and Diseases

Alzheimer disease (AD), the major causative of dementia, occurs due to neural inflammation because of plaques developing in the hippocampus. Inflammatory components related to AD neuro-inflammation consist of brain cells such as microglia and astrocytes activating the complement system, the pentraxin acute-phase proteins, neuronal-type nicotinic acetylcholine receptors (AChRs), peroxisomal proliferators-activated receptors (PPARs), cytokines and chemokines. Neurotoxic metals such as lead, mercury, aluminum and metallic nanoparticles have been involved in AD because of their ability to increase beta-amyloid peptide and the phosphorylation of Tau protein (P-Tau), resulting in amyloid plaques formation that are characteristic of AD (Hasegawa, 2016). Alzheimer's disease death risks have increased by 68% between 2000 and 2010. Drugs for AD are based on treatment of the cognitive impairments via neurotransmitter or enzyme modulation (Sood, Jain, & Gowthamarajan, 2014). Strategies for a successful treatment include enhanced drug delivery using NPs. However, recent studies involving TiO2-NPs (2.5–10 mg/Kg/90 days) and CuO-NPs (0.5 mg/Kg/day/14 days) reported neuronal death in the hippocampus and gliosis with augmented levels of ROS and reduced levels of antioxidants enzymes (Ze et al., 2014; An, Liu, Yang, & Zhang, 2012). Microarray analysis revealed a down regulation of genes associated with memory and cognition (Ze et al., 2014). Silica NPs (Si NPs) used in medicine were also found to increase P-Tau at Ser-262 and Ser-396, causing phosphorylation and hence formation of P-Tau (Yang et al., 2014).

Several other neurodegenerative diseases such as Parkinson Disease, characterized by the selective loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc); Huntington's disease, characterized by unstable CAG expansion causing dystonia; Amyotrophic lateral sclerosis (ALS) causing gradual deterioration of motor neurons; and Batten's disease, a neurodevelopmental disease causing blindness, dementia, and seizures which are mostly genetically inherited, are reported to be triggered by NM interference (Lane et al., 2002; Matés et al., 1999). These diseases involve cell apoptosis which are further mediated by excess NPs. Significant increase in risk of ALS has been observed due to exposure to environmental factors including metals, organic solvents, and pesticides (Sutedja et al., 2009).

These inhibitory effects are enlarged at industrial scale production area due to maximum unexamined exposure causing hazardous effects on the occupational as well as vicinity population. Epidemiological data comprising of the effects of NMs on these neurodegenerative data are not present. The studies at present are limited to small-scale diagnosis only (Devasena & Francis, 2015)

2.2.7 Risk Assessment

The techniques of risk assessment of chemicals cannot be applied for nanotoxicity risk assessment and hence appropriate techniques and protocols are needed. Thedata and databases on nanotoxicity studies and its effect on neuronal system are limited, unlike chemical toxicity databases. The nanotoxicity risk assessment techniques currently in application mostly do risk screening for research and are not suitable for regulatory assessment. One of the major hindrances for nanotoxicity risk assessment is lack of data.

Risk assessment is an amalgamation of scientific techniques with regulatory guidelines to describe the hazard and its intensity. The Organisation for Economic Co-operation and Development (OECD) defines risk assessment as the following:

"A process intended to calculate or estimate the risk to a given target organism, system or (sub) population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system." (OECD 1994)

The risk assessment method consists of four steps, (a) hazard identification, (b) hazard characterization, (c) exposure assessment, and (d) risk characterization. The basic idea of risk assessment is to measure or analyze the intensity of hazard on the identified organism or environment. Hazard identification is the first step in risk assessment and determines the qualitative nature of the effect of nanotoxic contaminants on the subject. This is on the basis of the results of the study in epidemiology, engineering or other concerned disciplines.

Nanomaterials can be categorized based on the location of the nanoscale structure in the system i.e. nanostructured in bulk processing, materials that have a nanostructure on the surface and materials that contain nanostructured particles. They are further subcategorized based on physical characteristics. This narrows down the task of hazard identification on physical and chemical properties (Oberdörster et al., 2005). Extensive literature review identifies the properties such as composition, shape, structure, size, solubility, surface area and adhesion as important parameters for hazard identification (Hansen et al., 2007).

Hazard characterization involves identifying the response generated based on the exposure intensity. This step involves experimental studies such as *in vivo* and *in vitro* experiments so as to substantiate the exposure response, as a need to extrapolate the findings. Sometimes, it becomes necessary to involve genetics to study the reason for higher hazard level for any particular set of population. Dose–response analysis is the general method to analyze the intensity–effect relationship; another method is to determine the highest level of concentration of the substance that does not cause any effect.

Exposure assessment is the stage where the level of exposure on the population, individuals or subjects are determined. There are various factors including climatic condition, air quality and location etc. that may influence the exposure dynamics. Various computing and statistical techniques may be used for the assessing the risks involved, including uncertainty analysis. Conventional risk characterization of substances which are genotoxic and carcinogenic is done by integrating the information from the hazard identification, dose–response and exposure assessments using a combination of qualitative and quantitative information and uncertainties. Shape of the material and its surface charge and coating play a very important role over conventional parameters such as dose response for nanotoxicity risk characterization (Tyshenko & Krewski, 2008). For new technologies with nanotechnology applications, two distinct approaches of risk management are adopted: (a) "precautionary approach" and (b) "risk-based approach." In the precautionary approach, if the safety of the product or technology is not established to a satisfactory level, it is not allowed to introduce into the market or for wide application. The risk-based approach allows the introduction of product or technology into the market but a constant monitoring is done for its regulation in case safety is compromised (Williams et al., 2010).

Nanotoxicity of composite materials and carbon-based nanoparticles presents a challenge to the current risk assessment methodologies (Institute of Medicine, 2005). The two important factors in risk assessment which plays a key role are the chance of the event to occur and its effect or intensity (Presidential and Congressional Commission on Risk Assessment and Risk Management, 1997). Most of the countries at present lack any proper evaluating and management technique (Tyshenko & Krewski, 2008). Various literature reviews and studies have shown the negative consequences of nanotoxicity in human and environmental health. Databases on nanotoxicity and its effect are discrete and mostly qualitative, and there is limited counter-control policy for nanotoxicity available (Emond & Britos, 2015). There is a lack of properly planned or designed counter management systems to deal with nanotoxicity. Risk assessment has to be coupled to risk management by reducing the risk to an acceptable level and continuous monitoring and control thereafter (Zimmerman, 1986)

2.3 Evidence based Assessment for Environmental Toxicity

Environmental toxicity is caused by various factors such as exposure to pesticides through air, water or food, or nanomaterials exposure due to high ambient concentration. These kind of exposure is causing a silent epidemic, which can be observed by the increase incidence in various forms of cancer, tumors or respiratory distress among others diseases. There is however, still very less evidence synthesis to study the impact of such environmental health factors.

Every year millions are exposed to pesticides used in agriculture including tea gardens, spice gardens, rice and wheat fields etc. (Muñoz-Quezada et al., 2016), with people living near such places being most vulnerable. Nanomaterials from automobile exhaust or industrial processes are also one of the identified health hazard (Yang et al., 2016). At this day and age, we are also facing micro-plastic pollution, effecting our entire food-chain and in turn human health. The residual soap-shampoo discharge from our households or industries, making its way into the rivers and oceans are also indirectly impacting the environmental health. Environmental pollutants exist in many forms and directly or indirectly impact the environment and human health. However, even after such known pollutants and hazards, there is a lack of discussion and acknowledgement of the pending doom.

As per the World Bank studies between 1995 and 2010, India was one of the major developing country which showed seriousness in tackling its environmental degradation (Chopra, 2016). As mentioned, environmental factors are one of the major contributors to chronic health issues and may impact livelihood and economy in the long run. India, since its independence while trying to pull out a vast majority of population out of poverty, ended up impacting the ecology and environment (Dubois, 2011). Unsustainable and unplanned consumption patterns of resources have resulted in serious level of air and water pollution, water scarcity, change in weather patterns as well as increased waste generation. Also, the huge population resulted in more mouths to feed, which paved way for increased consumption of fertilizers and pesticides. The increase in industrial and economic activities also released huge amount of engineered nanomaterials into the environment (Bundschuh et al., 2018). Untreated disposal of domestic and industrial waste and agricultural runoffs have increased water-borne diseases, whereas industrial activities mainly contributed to respiratory diseases, however both being responsible for neurotoxic diseases.

The Government of India in 2008 launched National Action Plan for Climate Change and Human Health (NAPCCHH) to monitor and assess the impact of climate and environmental change on public health. It also details out the preparedness and response needed at national, state and district level. India is a diverse country in terms of climate, population and geography etc. This diversity, may impact the morbidity, mortality and impact due to diseases in each region as per the population and geographic-climate conditions. Hence, the NAPCCHH identified that requires region specific planning to combat health impacts due to environmental causes and climate change (Government of India, 2018).

A preparedness and response at national level and local level needs additional measures, to combat environmental health impacts from known sources. A policy designed on the basis of evidence synthesis and systematic approach is required. All possible relevant available information needs to be the basis of policy for environmental health and intervention. Environmental health intervention has been defined as "… include those parts of the environment that can be modified by environmental management and environmental hazards against which people can be protected" (WHO, 2006). Such interventions may consist of varying ideas, including change in consumption and behavioral pattern or change in specific technology that may have direct or indirect impact (Rychetnik et al., 2004). Evaluation of multiple interventions forms a complex issue, and hence evidence of intervention and its impact needs to have defined techniques for its gathering, synthesizing and its application in decision making (Rychetnik et al., 2002; Craig et al., 2008; Thomson et al., 2004). Evidence Based Medicine (EBM) is well defined technique to evaluate the interventions either in the form of drugs or therapy systematically, collating and grading the evidence based on pre-defined set of rules and present the result for decision making. Systematic Review and Scoping Review are tools used in EBM that cumulates the data from the existing primary research to give meaningful comprehensive result for similar studies. Systematic review and meta-analysis is widely used for EBM approach for health care decision using the high quality research results (Sackett et al., 1996). Clinicians and medical practitioners use review articles as evidence for any clinical question. Environmental health evaluation based on various factor similar to EBM is a however novel concept, and comes under the purview of Evidence based Public Health (EBPH).

The EBPH is however dependent on EBM for its success directly and indirectly. The main idea of systematic review is to quantitatively summarize the research outcomes of certain question, it can also be used to evaluate the quality of primary studies, check for differences in the result outcomes and also determine the reason for such differences (Pai M., et al., 2003; Higgins et al., 2008). The comprehensive summary result of the systematic review can result in formulating new questions. Meta-analysis is a statistical tool, to pool the data of the studies to generate a summary effect (Higgins et al., 2008). A meta-analysis usually follows systematic review, only when the data generated from systematic review meets certain requirement; the meta-analysis is carried out (Pai M., et al., 2003).

Gene Glass coined the term meta-analysis for “the statistical analysis of a large collection of analysis results from individual studies for purposes of integrating the findings.” Thus the statistical tool is used to combine, synthesize and quantitatively summarize the data from different studies (Putzrath et al., 1991). Meta-analysis was first used in social sciences but was later introduced to the other fields which resulted in its extensive application in medical and environmental studies (Blair et al., 1995). Scoping review is a relatively novel approach to evidence based assessment and differs in aims and applications from systematic review (Munn et al., 2018). It involves aggregation of information from the available sources in a well-defined technique to interpret the data. Scoping review provides an overview of available research data, however it does not summarize the result of any research question (Arksey and O'Malley, 2005). Scoping reviews are useful in answering broad questions rather than specific causal effect relations, and can be used as a prior to systematic review.

The application of EBM into public health domain for evidence synthesis was not easy. Systematic reviews were mostly limited to randomized controlled trials (RCTs) and may discard certain outcome, which in other application may have been useful. Designing a better framework, to synthesize evidences for different types of research, which can be integrated to facilitate informed decision making (Petticrew, 2009).

Scientific evidence is the foundation for general acceptability for policy design and its efficiency. Globally, different non-government and quasi government bodies strive to facilitate the state towards evidence based informed policy design and decision. Evidence Synthesis is a technique of identification, selection and integrating the results from multiple different studies to give certain meaningful result. It combines the information together from various similar studies to provide an integrated result for any particular issue. Policy design and decisions are more successful when such policy or decision is supported by current and holistic evidence of an issue. An unbiased evidence synthesis is hence, the most valuable input for any policy design.

Environmental Health is an interdisciplinary field and takes input from a wide spectrum of evidence base, hence it needs approaches and techniques that can accept complex and dynamic evidence. To address the dynamics and complexity of the incoming information, requires tools and techniques that can result in a smooth system to generate evidence from complex and dynamic information input. Policy executioners definitely need to see the effectiveness of interventions, and the feedback be considered for dynamic interventions. Health system identifies certain functions and elements, building blocks, which are subject of policy implementation to evaluate health system performance (De Savigny & Adam, 2009). The different elements of the health system build a complex system, the elements are intertwined and understanding their relationship and causal-effect relationship is critical. Evidence synthesis needs to identify the study outcomes, to understand the health system outcomes (Oliver et al., 2015). Evidence synthesis can be used in mapping a complete picture of health system performance, how the interventions can shape or shaped by different elements in the health system (Travis et al., 2004). Different methods of evidence synthesis can be used to understand the efficiency of health systems interventions and feedback may be used for system strengthening (WHO, 2012). Policy makers and implementers tend to look for the effectiveness of any intervention, and on the same time the perception of the beneficiaries as well as other stake holders are important. Such, kind of evidence can be obtained by a combination of quantitative and qualitative synthesis.

Systematic Reviews are transparent and systematic in collection of data, and synthesize evidence based on the pre-existing scientific data to determine the efficacy of any intervention, which may act as an input for policy decisions. It is a time intensive process and takes months to years to complete.

Articles that dealt with public health policy and concerned with infectious disease or disease due to acute toxin exposures were found that used SR. There were few studies which were World Health Organization (WHO) guidelines highlighting environmental noise pollution and its associated diseases evaluated via systematic review. These were the only few papers which seemed closed to evidence synthesis in environmental health, however they were synthesis of evidence of diseases caused due to environmental exposure of noise. Nieuwenhuijsen et al., 2017, reviewed to gauge the evidence for the WHO guidelines, that linked aircraft and road traffic noise to birth outcomes like low birth weight, congenital malformation, preterm or small for gestational age. Similarly, other evidence synthesis done for WHO guidelines positively linked environmental noise especially aircraft, road traffic, turbines to annoyance, sleep disturbance, cardio-metabolic systems and cardiovascular diseases, cognitive impairment of children, tinnitus, permanent hearing loss, mental health and quality of life (Brown and Kamp, 2017; Guski et al., 2017; van Kempen et al., 2018; Śliwińska-Kowalska and Zaborowski, 2017; Clark and Paunovic, 2018). The above mentioned studies formed the basis of WHO Environmental Noise Guidelines for the European Region.

An integrated evidence synthesis for environmental health policy may consist of three basic iterative elements, (i) technique for evidence synthesis, (ii) a monitoring system to observe the implementation of intervention and its outcome and provide a continuous feedback and (iii) evidence based policy design. Systematic Review provides the evidence for an appropriate intervention based on data it synthesis from various data bases giving both qualitative and quantitative results. This provides us with historical context and the causal-effect of any particular intervention. This helps us in identifying potential failure of the intervention, the effect on the stake-holders, probable discourse in the long run, bottlenecks, other factors that may be as important as already considered may also be known.

Evidence synthesis by the application of Systematic Reviews are diligent in finding all the relevant studies, assesses them critically, in an unbiased manner it synthesizes the findings from each study, and present an unbiased summary of the findings. It duly considers any flaw in any study data while synthesizing the evidence. Systematic reviews can be very useful decision-making tools for policy makers and policy designers. They objectively summarize huge quantity of information, identify any possible gaps in the research, and identify the resultant effect of any intervention, which is can be useful for policy makers and designers. Any societal systems be in environmental health or overall public health, it is dynamic and complex and has multiple factors that influence any interventions.

The amount of articles regarding the application of evidence synthesis for environmental health shows that, there is still a lot to be done. Evidence synthesis can help us learn more about environmental health and interacting diseases, giving a real picture, a holistic epidemiology and policy interventions needed. The idea can be replicated with more specific health issues and its interventions.

Scoping review is a relatively novel approach to evidence based assessment and differs in aims and applications from systematic review (Munn et al., 2018) It involves aggregation of information from the available sources in a well-defined technique to interpret the data. Scoping review provides an overview of available research data, however it does not provide quantitative summary of the result of any research question (Arksey and O'Malley, 2005). Scoping reviews are useful in answering broad questions rather than specific causal effect relations, and can be used as a prior to systematic review.

Investigating the toxicity effects of pesticides and nanomaterials by using systematic review and scoping review will give a comprehensive picture of the scenario and may potentially contribute to conserve the natural biodiversity and also to identify human health effects. Scoping review of toxicity effects would help in identifying the areas to be worked upon also allow better management of the pesticides and nanomaterials application. Most studies focus on single chemicals or species, and quantify only the LC50 (lowest concentration needed to kill 50% of the test subjects) (Relyea, 2004), ignoring the other possible side effects on the environment. There are numerous pesticides and nanomaterials; a comprehensive and combined systematic review needs to be done of all the available primary research data to understand their toxicity effects in general.

Based on our literature review, the following objectives were formulated to gain deeper understanding of evidence synthesis of pesticides and nanomaterials induced environmental toxicity.

a. Systematic Review of Organophosphate induced Environmental Toxicity.
b. Scoping Review of Engineered Nanomaterials induced Environmental Neurotoxicity.

Chapter 3

Organophosphate induced Environmental Toxicity

Abstract

Background: There are numerous studies that have linked toxicity in humans to chronic exposure of pesticides and other agrochemicals like organophosphate. However, the amount of observational studies to support the study is very limited. There is a need to synthesize the evidences available to obtain a more comprehensive view of organophosphate induced toxicity.

Objective: The study undertakes a systematic review of the organophosphate pesticides exposure and the various diseases it causes. The aim is to carry out an analysis of the evidences extracted to provide a synthesized evidence linking organophosphate with various diseases and support the findings with the data on animal experimentation studies.

Design / Method: Online databases PubMed, Scopus, Web of Science, Ovid and BMJ Case Reports were used to identify papers published, the initial search of databases resulted in 12110 studies. After thorough review of titles and abstracts, 1841 full articles were sought for retrieval, 721 articles which fulfilled the eligibility criteria were used for the review. The retrieved studies consisted of 429 human studies that included and 292 animal studies.

3.1 Introduction

Application of agrochemicals like pesticides, weedicides, fertilizers, food preservatives etc. are on the increase. They are used to protect crops against pests, to help increase the yield and also for long term preservation. The application is however not limited to food crops, off late fisheries are using different chemicals to prolong the preservation of fish and other sea food. Continuous exposure to agrochemicals results in toxicity, which may pose significant risk to the ecological (Relyea, 2005). Agricultural activities are generally concentrated around fresh water sources, exposing them to agro-chemicals contamination (Baker et al., 2013). Intentional pest control activity, accidental overspray, runoff, sediment deposition etc. are some of the ways in which fresh water is contaminated. Agrochemical exposure also impacts the non-targeted insects or organism which have environmental or economic benefits.

There have been various studies on the negative effects of agro-chemicals on various non targeted organisms and insects of commercial value as well on human health. There is dearth of comprehensive review and those available however are bounded by the limitations in the methodology of the study. The reviews do not attempt to quantify the effects of the agrochemicals on the different target and non-target population. There is also no enough comprehensive data on the different health effects it causes.

Some of the major types of agrochemicals used in agriculture are pesticides, fertilizers, preservatives etc. Pesticides used in agriculture are used to protect crop against unwanted weeds, insects and fungus. Pesticides are made to control the pests, but they can also be poisonous to desirable plants, animals, organisms and humans. A small amount of some pesticides can irritate various sensory organs and may also kill a person. Most of the agrochemicals are toxic in nature and have been banned in the past when notified to bear potential hazards to human and nature, yet many continue to thrive on. The stable nature and extreme toxicity of the pesticide often results in severe pesticide poisoning.

The term pesticide is a group term for variety of different chemicals that include herbicides, insecticides, fungicides, rodenticides etc. (Soares, 2012; Frazer 2000). These classifications are based on the target species and mode of action. Herbicides are used to target weeds, fungicides to target fungi and insecticides to target insects. The major classification according to the chemical nature is organochlorine, organophosphorus, thiocarbamates, pyrethroids, and neonicotinoids (Otles, 2011).

Different types of pesticides are used to control the crop pests, so as minimize the output loss and also to prevent economic loss. With decreasing land area for cultivation and pressure to increase output has resulted in increased use of pesticides. With the increased use, the production and dispersion to the environment has been increasing, which pollutes the environment. There is enough evidence to show that these chemicals are a potential risk to humans and other life forms and poses danger to the environment (Jeyaratnam 1985; Igbedioh 1991; Forget 1993). The effect of pesticides effects directly either by exposure or indirectly by consumption of food products laced with pesticides residue (Keikotlhaile, 2010). In an ideal condition pesticide should be able to target only the predetermined species, which seldom happens. The rampant use of pesticides without any accountability has aggravated the situation. About one million pesticide induced poisoning deaths and chronic illness are reported every year (Phugare, 2013). Only around 5% of the applied pesticides reach the target species, the remaining contaminates the soil and also percolates underground polluting the ground water (Kookana et al., 1998) and also spread over the non-targeted crops through drift effect (Damalas, 2011). Insecticides, may reach the soil by either missing the target or as a result of run-off from the leaves and stems (Omar, 1998).

Continuous exposure to the pesticides may result in chronic illness with fatal results (Frazar, 2000). The solid organochloride accumulates in the adipose tissue and chlordane can be absorbed through skin (Reigart et al., 1999). Triazine is carcinogenic, stable in water and can easily spread out (Majewski et al., 2000) and organophosphates tends to be neurotoxic (Slotkin, 2006). Diethyltoluanide, an insect repellent is very harmful, nitrophenolic and nitrocresolic herbicides such as dinoseb is easily absorbed through derma (Reigart et al., 1999). Childhood leukemia was found to be associated with prenatal maternal occupational exposure (Wigle et al., 2009). Pregnant women employed in the farms were reported to have higher organophosphate insecticides metabolism levels (Bradman, et al., 2005). Pesticide exposure during the pre-conception period was found to possess risk of neural tube defects for the offspring in Mexican American women (Brender et al., 2010) and pesticides used in corns risk limb birth defect (Ochoa-Acuña et al., 2009). Use of herbicides cyanazine and dicamba in the preconception periods was found to cause significant birth defects among male offspring (Weselak et al., 2008)

Toxic effects of pesticides in humans vary, triggering a variety of manifestations, from mild irritation in the skin, to affecting liver, lung or endocrine functions, to being carcinogenic. Mode of action of a large number of pesticides is based on them disrupting the nervous system of the target species. These pesticides have similar neurotoxic effects in humans as well. Pesticide exposure also results in the development of neurodevelopmental (learning disabilities, attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, developmental delays) and neurodegenerative (Alzheimer's, Parkinson's) diseases and numerous other emotional and behavioral problems.

These neurological disorders are associated with genetic and social factors and the environmental factor also plays a major role in it. The statistics vary based on region and age. The contributions of the environmental factors also vary along with. Lead toxicity is calculated to have the highest impact among the other environmental factors. Furthermore, the data related to the effect based on levels of exposure are also not well known. Only ~5 of 201 reported toxic chemicals have been well documented as reasons of developmental neurotoxicity and 45% of the reported substances were pesticides. The cause of such a high rate is dependent both on the vulnerability of the developing brain and the wide range of chemicals which might lead to neurotoxicity even at very low doses.

The potential health effects of pesticides toxicity cannot be ignored and inconclusive evidences are available, but a comprehensive compilation of causal-effect is necessary in order to underline the gravity of the situation. Many pesticides have been banned in the past, but those get replaced with new ones and they are in some way equally harmful to the environment. Excessive use of some of the new replacements like neonicotinoids has become disastrous for economical insects like silkworm (Avramove et al., 2010) and honey bees (Mullin et al., 2010).

Uncontrolled use of pesticides has created a significant risk factor to the public health because of its long term and genotoxic effect. Pesticide exposure is not only a concern for those who are exposed occupationally but also to the public at large that exposed environmentally through various routes like air, water, food etc. in low and chronic dose. There has been an increase in number of people suffering from neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's etc., even among the young adult population. However, little evidence is available on the cause and the reason for increase in incidences of such neurodegenerative disorders. There have been however, many in-vitro studies on the role of pesticides in neurodegenerative diseases. The health risk due to exposure to toxic compounds are heavily based on genetics, as a result of variability of the genes metabolizing enzymes (Costa et al., 2003; Eaton et al., 1998; Furlong, 2007).

Systematic Review cumulates the data from the existing primary research to give meaningful comprehensive result for similar studies. Systematic review is widely used for evidence based medicine (EBM) approach for health care decision using the high quality research results (Sackett et al., 1996). Clinicians and medical practitioners use review articles as evidence for any clinical question. Narrative or general reviews tends to be of poor quality (McAlister et al., 1999), and are usually written by experts, it is qualitative in nature and tend to be a subjective interpretation based on preconceived ideas. Unlike narrative review, systematic review focuses on the methodology of searching, sorting and selecting the research as per the review objective, which is based on causal effect. It is feasible to develop a checklist to be used to assess the methodological study of non-randomized studies (Black et al., 1998). The main idea of systematic review is to quantitatively summarize the research outcomes of certain question, it can also be used to evaluate the quality of primary studies, check for differences in the result outcomes and also determine the reason for such differences (Pai M., et al., 2003; Higgins et al., 2008). The comprehensive summary result of the systematic review can result in formulating new questions.

Investigating the toxicity effects of pesticides and fertilizers by using systematic review and meta-analysis will give a comprehensive picture of the scenario and may potentially contribute to conserve the natural biodiversity and also to identify human health effects. Systematic review of toxicity effects would help in identifying the areas to be worked upon also allow better management of the pesticides application. Studies generally focus on single chemical or species and consider only the LC50, the lowest concentration required to kill 50% of the target species (Relyea, 2004), ignoring the other possible side effects on the environment. There are numerous pesticides and fertilizers; a comprehensive and combined systematic review needs to be done of all the available primary research data to understand their toxicity effects in general. The limited amount of studies available and the varying methodologies to study the exposure of organophosphate pesticides and its effects on human health make it difficult to collate or do any comparative analysis.

3.2 Method

3.2.1 Search Strategy

A systematic review of articles catering to certain predefined criteria were carried out in the databases such as PubMed, Scopus, Web of Science, Ovid and BMJ Case Reports using the predefined keywords, organophosphate AND (environmental OR ecology) AND (toxicity OR poisoning).

The initial search of databases resulted in 12110 studies, however 2256 duplicates were removed subsequently. After thorough review of titles and abstracts, 8017 were deemed ineligible, and 1841 full articles were sought for retrieval. The PRISMA flow diagram for literature selection is shown in Figure 1.

3.2.2 Inclusion and Exclusion Criteria

The articles shortlisted for review met the following inclusion criteria

(a) original articles

(b) articles published up to November 2021

(c) Written in English

(d) Evaluating Organophosphate Pesticides (OP) induced toxicity

(e) Full Free Text Available

We excluded reviews, editorials, studies that compared the mechanisms of toxicity of different pesticides, studies that observed the impact on biomarkers by pesticides without focusing on toxic health impacts, studies that dealt with ecological toxicity, studies that dealt with study design/ protocols for animal modelling, observational studies or other experimental studies. The review also does not include studies that dealt with acute toxicity, studies with objectives different than toxic impact on health, more than two types of pesticides in *in-vivo* studies and retracted studies. Those that failed to make the predefine criteria were excluded and a total of 721 publications were selected of which 429 were observational / cohort / longitudinal studies concerning human health and 292 were animal modelling or *in-vivo* studies corresponding various toxicity effects.

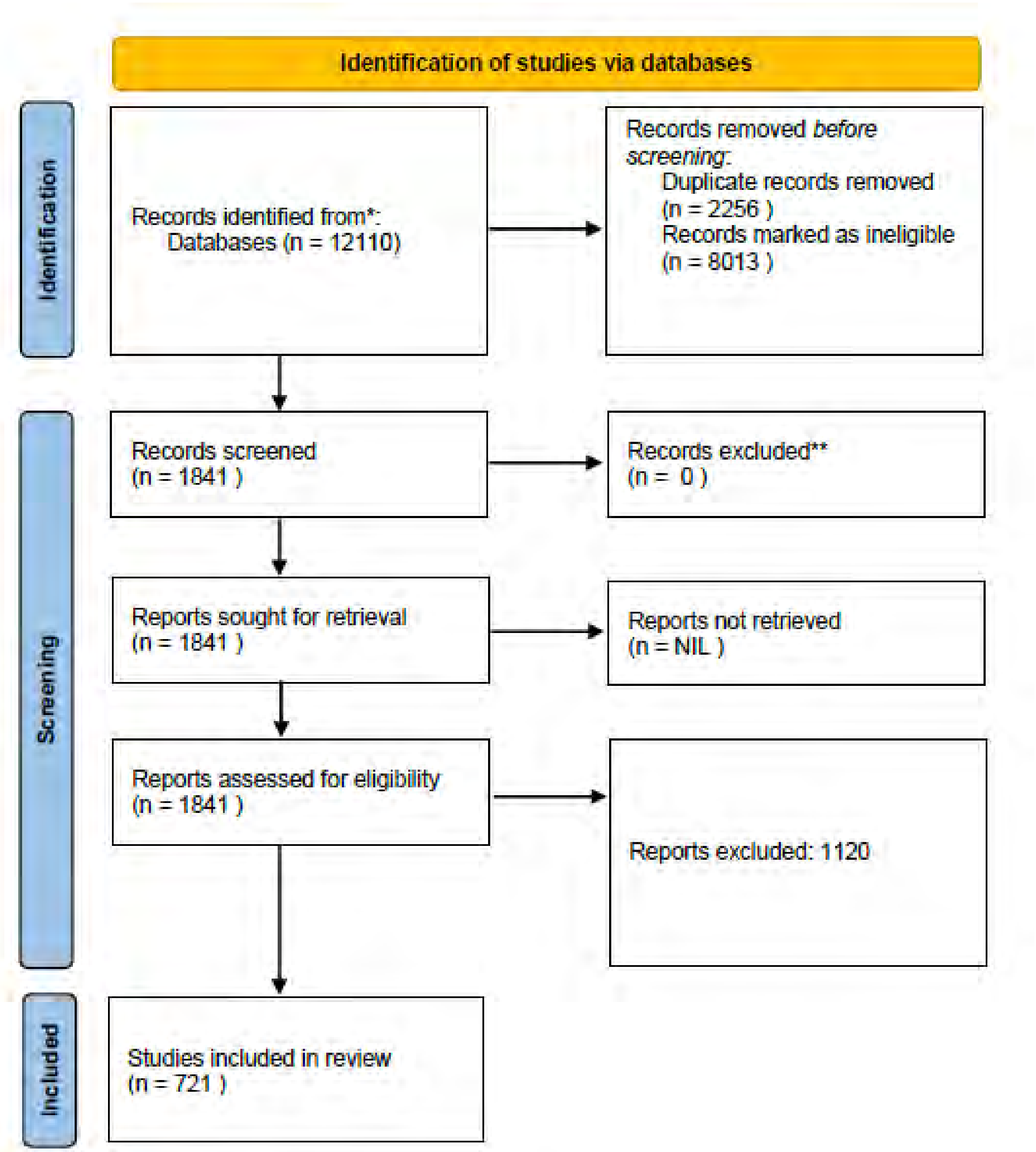

Figure 3.1: PRISMA Flow Diagram

3.2.3 Data Analysis

Studies that were included were scrutinized on the basis of different kinds of toxicity impact. The selected studies were compared under the following categories,

a. Study Design
b. Pesticide Species
c. Exposure assessment

3.2.4 Assessment of Methodological Quality of Articles

The quality of the articles in terms of methodology included for the review was determined using the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) - Statement' checklist (Tate and Douglas, 2011; Ramke et al., 2017). This statement based tool address multiple designs, three types of study designs addressed by STROBE are cohort studies, cross sectional research and case-control studies. The STROBE stamen consists 6 sections divided into 22 items of check list, addressing the title and abstract (1), introduction (2), methods (9), results (5), discussion (4), and (1) for additional information. The tool is however used in Systematic Review as well, apart from observational studies due to the lack of other tools (Rodríguez-Barranco et al., 2013, Olmos et al., 2008)

3.3 Result

1841 articles were identified and sought for retrieval using the search strategy as mentioned above. Manual scanning through those articles resulted in inclusion of 721 studies for the review. Rest of the studies were removed due to various reasons including articles not in English, irrelevant study as per the inclusion criteria. The objective was to look for environmental mode of exposure of OPs induced toxic effect in humans and in-vivo studies that supported such toxicity. Articles dealing with various kinds of toxicity including neurotoxicity, cytotoxicity, reproductive toxicity, genotoxicity, hepatotoxicity etc. were retrieved.

Representation of number of publications in three year brackets is given below for *in-vivo* studies (Figure 3.2) and human studies (Figure 3.3).

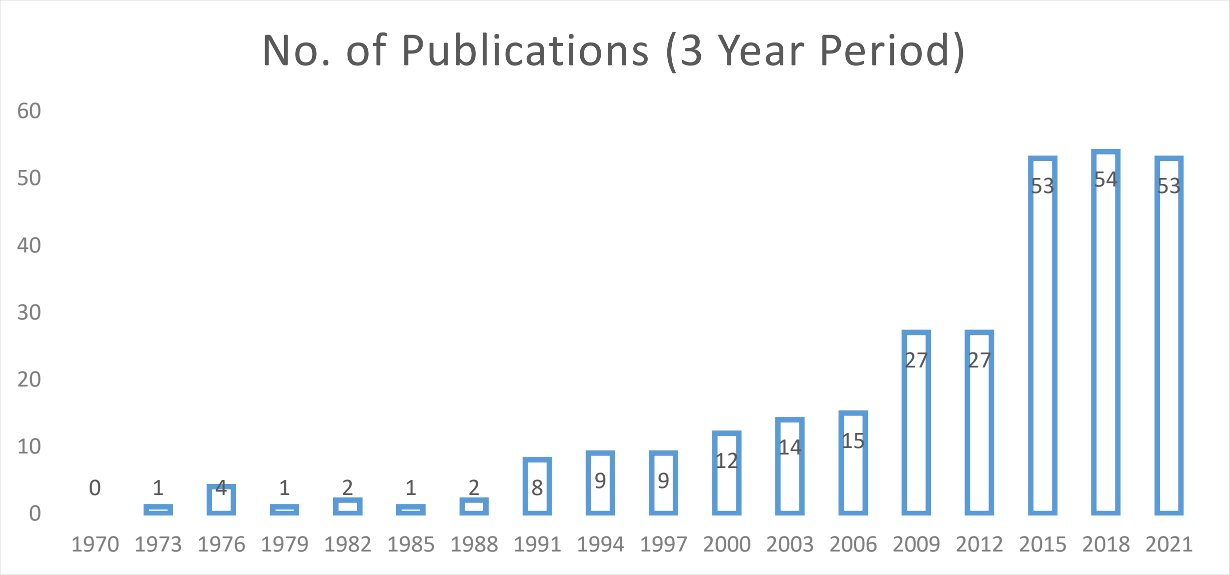

Figure 3.2: Number of publications of selected *in-vivo* studies over 3 year periods.

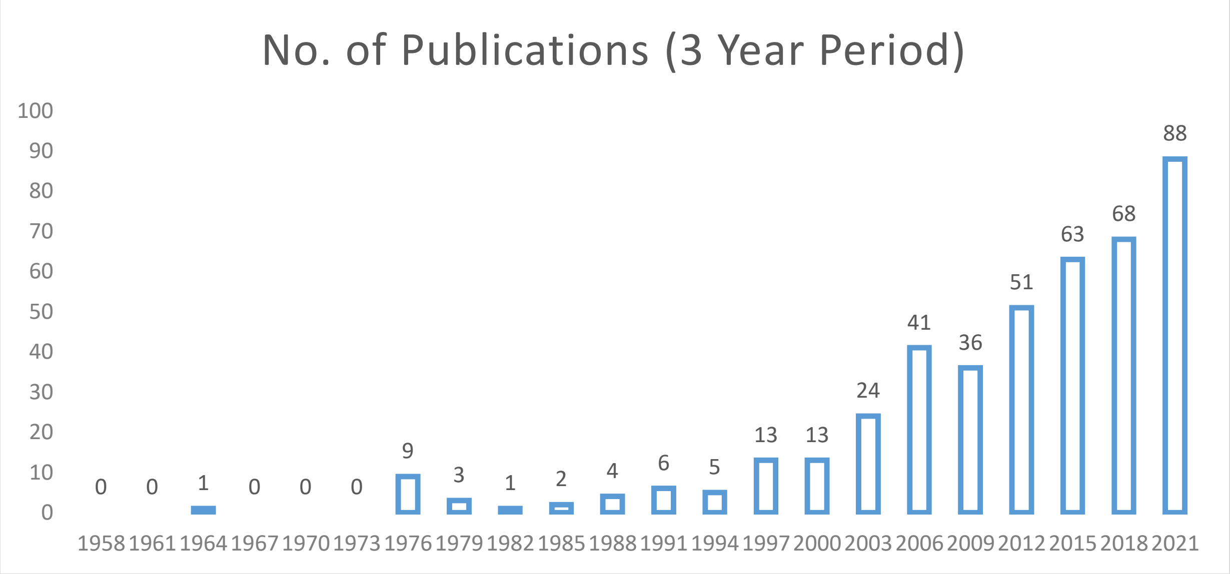

Figure 3.3: Number of publications of selected *human* studies over 3 year periods.

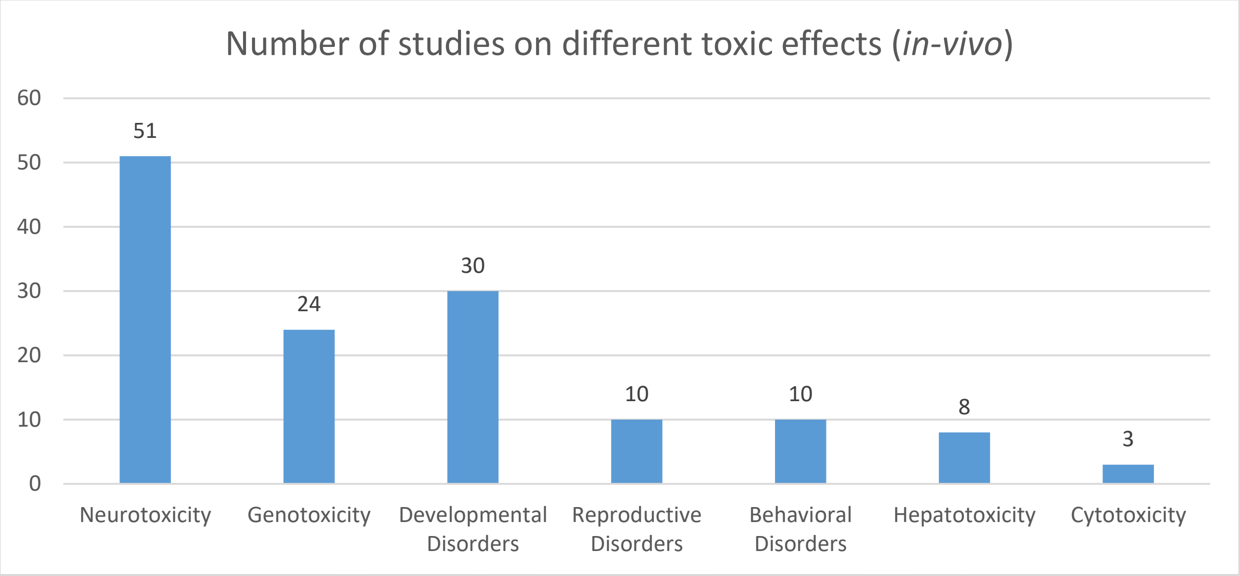

Figure 3.4: Number of *in-vivo* studies on different toxic effects.

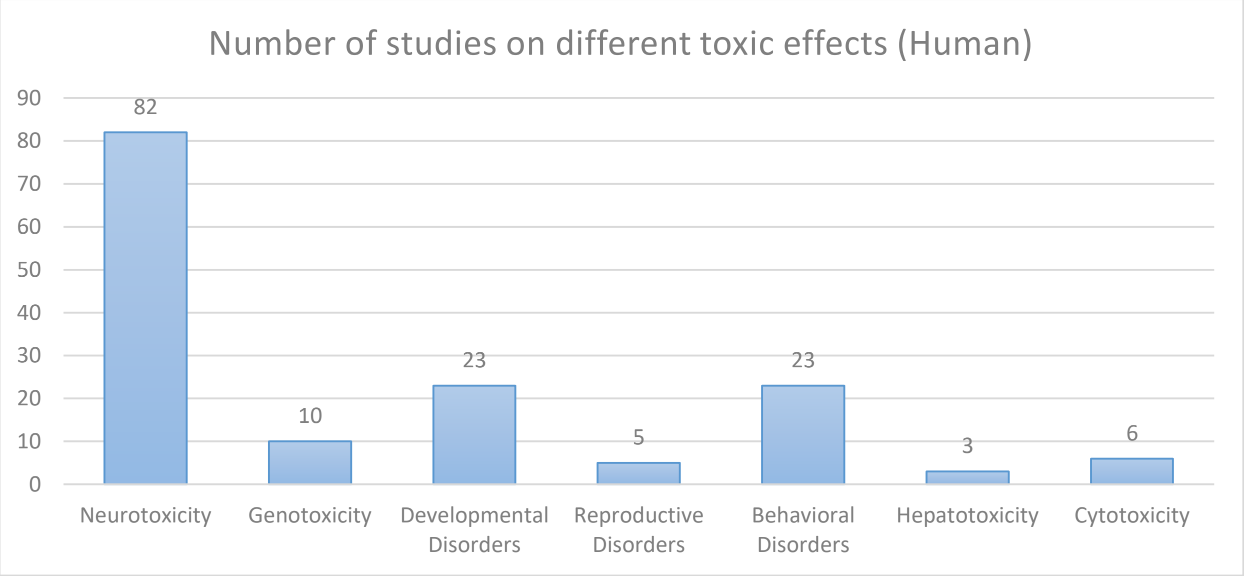

Figure 3.5: Number of *human* studies on different toxic effects.

On analyzing the shortlisted studies, it has been found that majority of the toxicity studies carried out in both in-vivo and on human dealt majorly with neurotoxicity. Although there were studies that mentioned various other forms of toxic effects of OP.

3.3.1 Exposure Assessment

Based on the methodology to assess exposure to OP pesticides, three types of studies were identified in case of human exposure assessment. The first kind was based on biological samples to analyze the exposure, i.e. using genotypic polymorphisms as determinant for OP toxicity. The study done by Paul et al. mentioned the investigation of eight Nitric Oxide Synthase (NOS) Single Nucleotide Polymorphism (SNP) and interaction with environmental, agricultural and household OP exposure analyzed with the help of Geographical Information System (GIS). In another study done by Lee et al., ambient exposure to parathion, diazinon and chlorpyrifos at work and residential areas were assesses using GIS, and three functional paraxonase (PON1) SNPs consisting of a promotor region variant (PON1C-108T) and two exonic polymorphisms (PON1L55M, PON1Q192R) were genotyped. The above two mentioned studies used both the GIS technology for exposure assessment as well as genotypic polymorphism as determinant for OP toxicity. In the study carried out by Narayan et al. for determining the relationship between household OP pesticide use and PD, the frequency of the household pesticide used. The effects of household pesticide exposure were estimated using logistic regression. The study carried out by Wang et al. to seek the association between ambient OP exposure and PD risk used GIS based tool to estimate ambient exposure to 36 commonly used OP.

In the *in-vivo* models studies dealt with subjecting the models to various pre-defined doses of pesticide species over pre-defined time frame. The analysis was done using histopathological methods, Gas Chromatography, NMR, behavioral studies etc.

Table 3.1: Few selected in-vivo studies of OP induced toxicity

Study	Title	Study Design	Pesticide Species	Toxicity assessment	Remarks
Yang et al., 2018	1 H-nuclear magnetic resonance metabolomics revealing the intrinsic relationships between neurochemical alterations and neurobehavioral and neuropathological abnormalities in rats exposed to tris(2-chloroethyl)phosphate	6-week-old female SD rats were administered 50, 100, or 250 mg/kg/d TCEP daily by oral gavage for 60 days. TCEP exposure produced neurotoxicity in the female SD rats.	tris(2-chloroethyl)phosphate	Neurotoxic Effects	TCEP exposure interfered with normal biological processes, including amino acid and neurotransmitter metabolism, energy metabolism, and cell membrane function integrity by changing the concentrations of glutamate, γ-aminobutyric acid, N-acetyl-d-aspartate, creatine, and lactic acid metabolites in the brain of treated rats.
de Blaquière et al., 1998	A comparison of the electrophysiological effects of two organophosphates, mipafox and ecothiopate, on mouse limb muscles	Adult male albino mice were subjected to single subcutaneous injections of either mipafox (110 mumol/kg) or ecothiopate (0.5 mumol/kg), two organophosphorus compounds (OPs).	mipafox and ecothiopate	Neurotoxic effect, Electrophysiological effect	Mipafox and ecothiopate both increased postjunctional (muscle action potential) jitter in the soleus and EDL at 7 days after dosing. Mipafox caused an increase in prejunctional (end-plate potential) jitter at 28 days after dosing in both muscles. A single dose of ecothiopate also caused an increase in

					prejunctional jitter at 28 days in the soleus. The OP-induced increase in jitter was different at different frequencies of stimulation.
Okamura 2005	A comprehensive evaluation of the testicular toxicity of dichlorvos in Wistar rats	Ten-week-old Wistar rats were divided into four groups (n=8 or 9) and were injected subcutaneously with DDVP (0, 1, 2 or 4 mg/kg) 6 days a week for 9 weeks	dichlorvos	Reproductive Toxicity	No significant difference was observed in the reproductive organ weights in any treated groups compared with the control group. Only the sperm motility deteriorated by DDVP exposure at doses inducing marked inhibition of cholinesterase activities in the rats, it was suggested that the risk of testicular dysfunction posed to occupationally exposed humans would be small in terms of the effect of DDVP exposure alone.
Tanvir et al., 2016	A model of chlorpyrifos distribution and its biochemical effects on the liver and kidneys of rats	Adult female Wistar rats (n = 12) were randomly assigned into two groups (one control and one test group; n = 6 each). The test group received CPF via oral gavage for 21 days at 5 mg/kg daily.	chlorpyrifos	General Toxicity	The detrimental effects of CPF on kidney function consisted of a significant increase in plasma urea and creatinine levels. Liver and kidney histology confirmed the observed biochemical changesCPF bioaccumulates over time and

					exerts toxic effects on animals.
Cabello et al., 2001	A rat mammary tumor model induced by the organophosphorous pesticides parathion and malathion, possibly through acetylcholinesterase inhibition.	Female Sprague-Dawley rats obtained from the Catholic University of Chile (Santiago, Chile) were used for the study.	Parathion and malathion	Carcinogenicity	These results indicate that OP pesticides induce changes in the epithelium of mammary gland influencing the process of carcinogenesis, and such alterations occur at the level of nervous system by increasing the cholinergic stimulation.
Yoshida et al., 1997	A safety study on rat's eye after 13-week oral administration with fenitrothion	Sprague-Dawley (Crj:CD) rats of both sexes received a diet containing the test compound at concentrations of 0, 2.5, 5, 10, or 30 ppm for 13 weeks.	fenitrothion	Ocular toxicity	Ophthalmological and histopathological examinations revealed that there was no evidence of ocular toxicity of fenitrothion for male and female rats at dose levels up to 30 ppm
Weis et al., 1976	Abnormal locomotion associated with skeletal malformations in the sheepshead minnow, Cyprinodon variegatus, exposed to malathion	Embryos of Cyprinodon variegatus were exposed to the organophosphate insecticide malathion at concentrations of 3 and 10 parts per million.	malathion	Developmental toxicity	Skeletal malformations developed. The severity of the abnormality was greater at the higher concentration of malathion.
Kim et al., 2005	Acetylcholinesterase and neuropathy target esterase activity in female and male rats exposed to pesticide terbufos	Sprague-Dawley rats, female rats received 0, 0.1, 0.4 and 0.8mg/kg TBF for 2 days and male rats 0, 0.1, 0.5 and 1.0mg/kg TBF for 3 days for	terbufos	sexual dimorphism	The study shows that female rats were more vulnerable to AChE inhibition than male rats after exposure to TBF.

		dose-dependent study. Age-matched female and male rats also received 0.5mg/kg TBF for 2 days and sacrificed 0, 6, 12, 24 and 72h after the last dose for time-dependent study. In the dose-dependent study, mortality was 25% in 1.0mg/kg TBF group of male and 50% in 0.4 and 0.8mg/kg TBF groups of female rats.			
Noyes et al., 2015	Advanced morphological - behavioral test platform reveals neurodevelopmental defects in embryonic zebrafish exposed to comprehensive suite of halogenated and organophosphate flame retardants	Zebrafish were exposed to flame retardants from 6 to 120 h post fertilization (hpf) across concentrations spanning 4 orders of magnitude (eg, 6.4 nM to 64 µM). Impact on survival and development were evaluated at 24 and 120 hpf.	Flame retardants	Neurodevelopmental toxicity	Zebrafish is highly sensitive to flame retardants and shows neurodevelopmental disorders. The study can be extrapolated to human impact.
Mansour et al., 2011	Adverse effects of exposure to low doses of chlorpyrifos in lactating rats	lactating rats were administered with CPF at 0.01 mg kg(-1) b.wt. (acceptable daily intake, ADI), 1.00 mg kg(-1) b.wt. (no observed adverse effects level, NOAEL)	chlorpyrifos		CPF caused dose-related histopathological changes in liver and kidney of the CPF-treated dams.

		and 1.35 mg kg(-1) b.wt. (1/100 LD(50)) from postnatal day 1 (PN1) until day 20 (PN20) after delivery.			
Mansour et al., 2010	Adverse effects of lactational exposure to chlorpyrifos in suckling rats	Doses equalled 0.01 mg kg(-1) body weight (b.wt.; acceptable daily intake, ADI), 1.00 mg kg(-1) b.wt. (no observed adverse effects level, NOAEL) and 1.35 mg kg(-1) b.wt. (1/100 lethal dose [LD(50)]) from postnatal day 1 until day 20 after delivery.	chlorpyrifos	oxidative damage, biochemical and histopathological alterations	CPF intoxication through the mother's milk resulted in oxidative stress and biochemical and histopathological alterations in the suckling pups.
Betancourt et al., 2007	Alteration of neurotrophins in the hippocampus and cerebral cortex of young rats exposed to chlorpyrifos and methyl parathion	Oral administration of CPS (4.0 or 6.0 mg/kg), MPS (0.6 or 0.9 mg/kg), or the safflower oil vehicle was performed daily from postnatal day 10 (PND10) through PND20	Chlorpyrifos, methyl parathion	Neurotoxicity	repeated developmental OP exposure during the postnatal period alters NGF and BDNF in the cortex and the hippocampus
Lari et al., 2014	Alteration of protein profile in rat liver of animals exposed to subacute diazinon: a proteomic approach	proteomics approach used to study the effects on the protein profile in the liver of rats of subacute oral exposures at 15 mg/kg of diazinon	diazinon	hepatotoxicity	diazinon induces hepatotoxicity through oxidative stress, apoptosis, and metabolic disorders
Bhatti et al., 2011	Alterations in Ca^{2+} homeostasis and oxidative damage induced by ethion	Adult male albino rats of Wistar strain were orally	ethion	homeostasis and oxidative damage	ethion exerts its toxic effect by increasing LPO (lipid

	in erythrocytes of Wistar rats: ameliorative effect of vitamin E	administered ethion and vitamin E daily for 28 days. Animals were randomly divided into four groups: control; ethion treated (2.7 mg/kgbw/day); vitamin E treated (50mg/kg of bw/day); ethion+vitamin E treated. The animals were sacrificed after 7, 14, 21 and 28 days.			pexoxidation), altering the activity of membrane bound enzymes and disturbing Ca(2+) homeostasis
Raines et al., 2001	Alterations in serotonin transporter expression in brain regions of rats exposed neonatally to chlorpyrifos	CPF were administered to neonatal rats on postnatal days (PN) 1-4 (1 mg/kg) or PN11-14 (5 mg/kg), treatments devoid of overt toxicity. At the end of the treatment period (PN5 and 15, respectively) and 5-7 days later, examined the effects on paroxetine (PXT) binding to the presynaptic 5HT high-affinity transporter, a marker for serotonin (5HT) projections.	Chlorpyrifos	Neurotoxicity	

3.3.2 Environmental Exposure of OP Pesticide

The study to determine if functional paraoxonase 1 variants modify the OP pesticide exposure risk of PD was done as a case-control study in central California, USA. It enrolled incident idiopathic PD patients from 2001 to 2007 and population based control from 2002 through 2011 from rural agricultural counties. Information from both cases and controls were collected by telephonic interview and the information collected included residential and workplace history, demographics and behavioral risk factors. The environmental exposure of OP pesticides like parathion, diazinon and chlorpyrifos were estimated for each subject via GIS based tool. The pesticide application report was combined with data collected by California Department of Pesticide Regulation, land use data by California Department of Water Resources. The GIS estimated the environmental pesticide exposure around home and workplace due to agricultural pesticide application. The genotyping for $PON1_{L55M}$(r854560) was done using buccal cells, saliva or blood samples provided by the participants. Genotyping call rates were 100%, 90% and 93% respectively for $PON1_{L55M}$, $PON1_{C\text{-}108T}$ and $PON1_{Q192R}$. A certain number of subject failed genotyping and did not contribute for $PON1_{C\text{-}108T}$ and $PON1_{Q192R}$ analysis. The findings indicate that subjects have been more exposed to environmental OP pesticide in workplace and residential settings. The study suggests that 55MM and 192QQ genotype variants add to PD risks in population exposed to OP pesticides like parathion, chlorpyrifos and diazinon. A strong association was found between participants carrying both $PON1_{55MM}$ and $PON1_{192QQ}$ genotypes exposed to OP pesticides and PD.

In the studies carried out to determine the contribution of NOS genes and OP pesticides and toxicity risk, controlling for PON1 status, subjects were enrolled along with control population from a region known for high pesticide. The self-reporting exposure assessment for risk factors were same as the mentioned above. The lifetime pesticide used at home was determined by calculating weighted average frequency of use. Environmental pesticide exposure due to commercial application was estimated through GIS. Blood and saliva samples were collected from saliva samples were collected from the participants for genetic analysis. The participants were most likely to have household pesticide application and also must have had high environmental OP pesticide exposure. The studies found a positive marginal association between different species of OP pesticides and various forms of toxicity majorly being neurotoxicity and developmental toxicity. In-vivo studies carried out also showed similar trends, and most of the model dealt with neurotoxicity and developmental toxicity to a long term exposure.

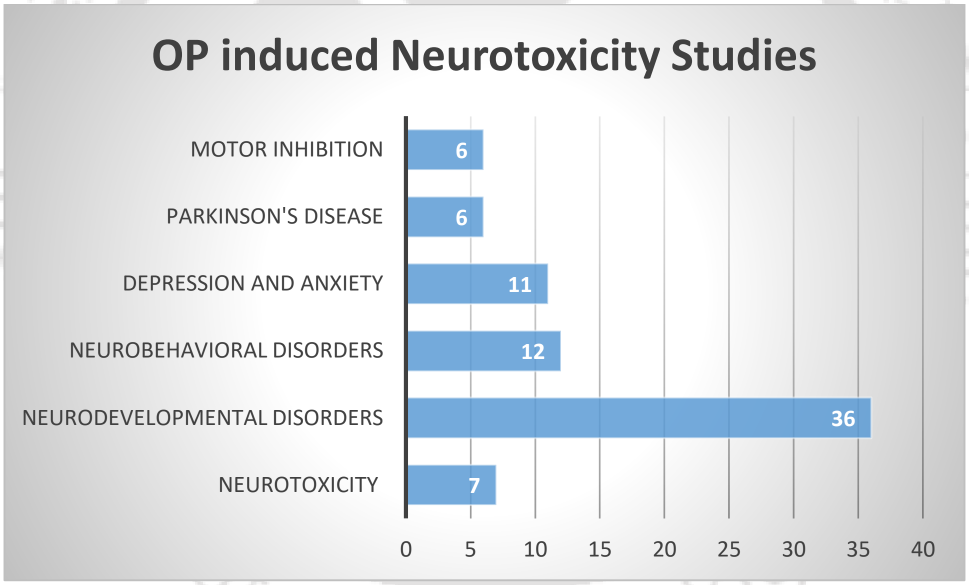

Figure 3.6: Types of OP induced Neurotoxicity Studies.

Most of the studies carried out for human exposure assessment dealt with AChE inhibition in general. There were few studies which focused on the role of OP poisoning and its different neurotoxic disorders. Majority of studies were related to neurodevelopmental disorders, due to exposure of either parents or childhood exposure of OP. There were few studies that associated

OP exposure to neurobehavioral disorders, depression and anxiety. OP was also found to cause motor inhibition as demonstrated in various studies.

3.4 Discussion

3.4.1 Effects Associated with Environmental Exposure of OP Pesticides

The studies show strong association between environmental OP pesticide exposure and risk of various forms of toxicity. The studies related to neurotoxic disease PD, concluded that neglecting polymorphism in the PON1 gene may be misleading, where the data comes from across ethnic groups where allele frequencies for these loci and protein functionality can vary a lot. Overall, the studies provide a positive link between OP pesticide and etiology of PD.

It is important to monitor and assess the OP pesticide exposures, not just in population with high probability or group who are occupationally exposed, but also among the general population. The populations living in the vicinity of agricultural farms especially the plantation crop farms are at a higher risk of pesticide exposure due to drift and hence more susceptible to various pesticide induced diseases. Most of the studies were carried out by recruitment of participants retrospectively, and data was collected by interview, also studies were complemented with GIS based tools to enhance data collection. Few studies collected blood, saliva or buccal cell samples The studies show strong linkage between OP toxicity among participants and with certain NOS1 genotype exposed to environmental OP pesticides, which was consistent with oxidative-stress inducing mechanism and enhance vulnerability due to low OP metabolizer capacity of PON1. The studies confirm the relationship between OP poisoning and various chronic diseases as well, including Alzheimer disease, reproductive disorders, cancer etc. OP is responsible for about 50% to 80% deaths due to pesticide poisoning (Zhang et al., 2014).

3.4.2 Toxicity Mechanism of OP Pesticide

The mechanism of OP pesticide toxicity can be attributed to the inhibition of acetylcholinesterase (AChE), which triggers AChE accumulation at cholinergic synapses, and overstimulates the nicotinic and muscarinic receptors (Ecobichon, 2001). AChE inhibition results in overstimulation of cholinergic system resulting in cell death (Karen et al., 2001). OPs are also known to cause the inhibition of mitochondrial processes (Terry Jr., 2012). The mechanism regarding mitochondrial inhibition has mostly been studied using large experimental doses of OP pesticides, which might have resulted in general toxicity effects. However, such experimentation does not represent the environmental exposure mechanism, of low dose chronic exposure.

3.5 Conclusion

The adverse effects of the pesticides on environment and human health is well documented. Neurological development disorder, neurodegenerative diseases, reproductive issues, cancer are said to have a link with various pesticides exposure. Although data were available scarcely indicating the link between pesticide exposure and development of neurological conditions, and other toxicity issues however each study performed and resulted in a discrete manner not able to establish the generalized notion. For which, a strategy to approach this problem by carrying out systematic review is adapted which brings out the meaningful comprehensive result from various similar studies. A comparison of the animal studies done to study the OP toxicity impact helps in establishing a more robust evidence. Accessing and retrieving the literature in various databases by following standard systematic review methodology, 721 articles reporting various forms of toxicity impact due to environmental OP exposure was identified reported up to November 2021. Out of these 429 were longitudinal / cohort / observation studies on human, and 292 being in-vivo studies establishing toxicity outcomes of various species of OP. The systemic review has revealed that there is a strong positive association between environmental OP pesticide exposure and risk of various kinds of health impacts especially neurotoxicity and neurodevelopmental disorders. The mechanism of toxicity by OPs are attributed to inhibition of acetylcholinesterase (AChE). OPs are also may cause disruption of mitochondrial processes; however, it is still a subject for further studies.

Chapter 4

Nanomaterials induced Environmental Neurotoxicity

Abstract

Background: There has been increased number of cases of people suffering from neurological degeneration or neuro development disorders. Research indicates that one of the major factor may be due to increased exposure to environmental exposure of nanomaterials (NMs).

Objective: The study undertakes a scoping review of current research on NMs induced environmental neurotoxicity, the different neurodegenerative and neurodevelopmental disorders linked to it. The aim is to identify the studies and research works being carried out in the area and the knowledge gap that exists.

Design/ Method: Online databases PubMed and Scopus were used to identify papers published between 2015 to 2019, from which 12 were selected which reported neurodegenerative disease or neurodevelopmental disorders as the primary outcome due to environmental exposure.

4.1 Introduction

Nanomaterials can enter into body through skin, nasal cavity, mouth and eyes. Their paths of translocation to reach organs distal site of uptake has been presented in Figure 3.1. Nano respiratory route is the most prominent route of exposure to airborne nanoparticles in work places. Very little or no transdermal absorption of nanomaterials from skin exposure has been detected. Oral exposure of nanomaterials occurs by intentional or unintentional ingestion of nanomaterials. Nanomaterials enter into GI tract via inhalation and also from ocular exposure. Uptake of nanomaterials directly from nasal cavity to brain via olfactory and trigeminal nerves are also reported. Other routes of uptake include absorption of nanomaterials from nasal cavity directly into systemic circulation, orotransmucosal involving buccal cavity and sublingual; and transdermal. Through these routes more nanomaterials reach organs and hence induce more adverse effects (Yokel and MacPhail, 2011).

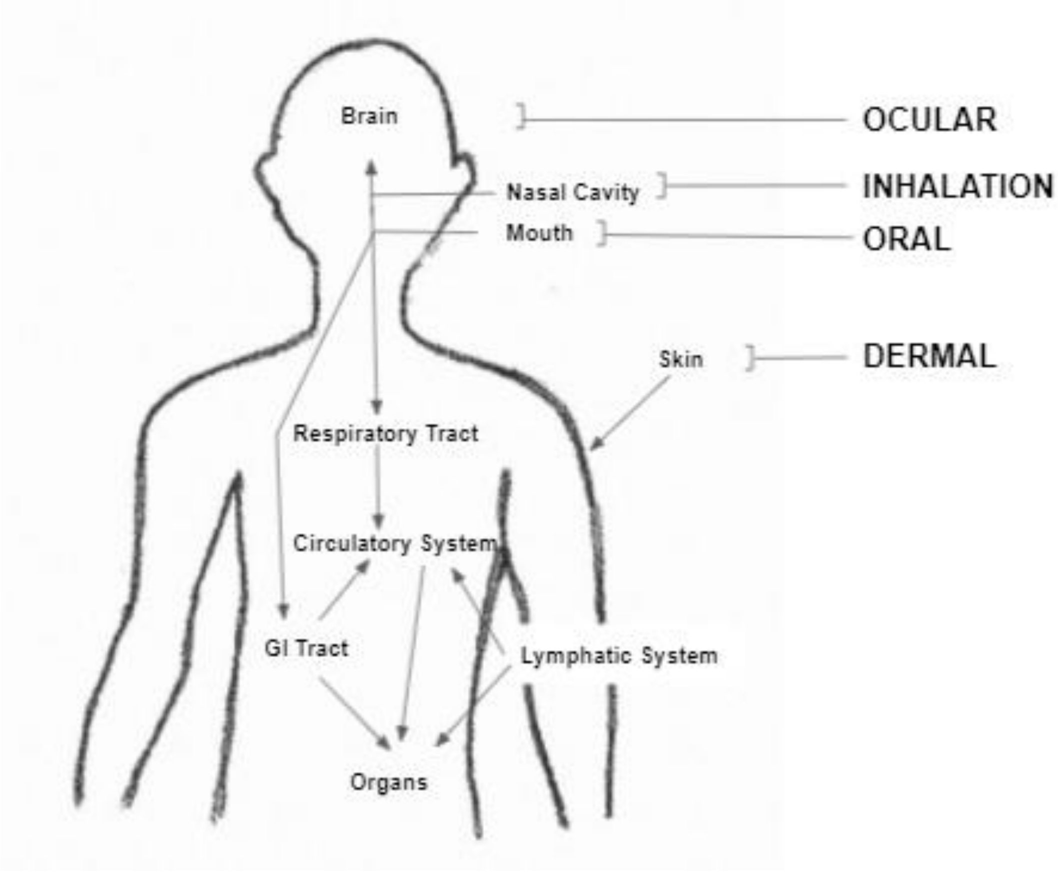

Figure 4.1: Route of Nanomaterials Exposure

Engineered nanomaterials toxicity depends on their size, shape, surface properties, solubility, surface reactivity, association with biological proteins, ability to bind with receptors, and their strong tendency to agglomerate. Smaller size nanomaterials are more biologically active and their uptake is more as compared to larger particles of same chemistry due to larger surface area (Gurr et al., 2005). Aspect ratio of nanomaterials is also an important factor. Nanomaterials with higher aspect ratio contained in inhaled asbestos were found to be more toxic than particles with less aspect ratio. This is because foreign particles with high aspect ratio are too large for macrophages and are not effectively cleared from lungs (World Health Organization, 1985). Studies suggest that nanomaterials with 10-30 nm diameter with spherical shape are more biologically active than either smaller or larger particles (Seipenbusch et al., 2008). Another important factor is their tendency to agglomerate. Nanomaterials agglomerate loosely by surface tension, electrostatic forces, van der Waal's force, and physical entanglement. The surface area of agglomerated particles sums up and hence results in larger surface area unlike aggregated particles where particles are tightly bound by covalent and metallic forces and hence smaller surface area. Nanomaterials with surface coat of biological components tend to agglomerate and therefore expected to affect their uptake (Yoker and MacPhail, 2011).

In the past few years, incidence of many brain diseases such as brain tumors, Alzheimer's disease, Parkinson's disease, etc. has increased at an alarming rate, the injury of which is generally irreversible (Farrer, 2001 and Oriinger et al., 2009). The use of chemotherapy limits its potentiality in the treatment of central nervous system (CNS) diseases. This is due to the existence of blood–brain barrier (BBB) which prevents the entry of many substances into the brain which in turn causes difficulty in drug delivery. As evident from numerous studies, nanocarriers emerged as promising brain-targeting drug and other molecule delivery strategy for diagnostic & therapeutic applications. There are several ways of administration of the NPs to human body like ingestion, inhalation, dermal route and injection, followed by their distribution to various tissues and organs via systemic circulation (Burch, 2002 and Takenaka et al., 2001).

Mostly affected human systems using NPs include circulatory, respiratory, gastrointestinal tract and CNS. Due to various properties like small size, large surface area and high biological surface reactivity, NPs can enter into the brain overcoming the BBB or through olfactory nerve pathway causing neurotoxicity. However, the full understanding on the potential neurotoxic effects and their precise mechanism within CNS is still limited (Karmakar et al., 2014; Khanna et al., 2015; Song et al., 2015; Song et al., 2016; Yarjanli et al., 2017). Thus, it is imperative to understand the neurotoxicity induced by NPs for designing safer therapeutics and reducing their toxicity in future (Hu & Gao, 2010).

Several studies have been conducted which demonstrate that NP exposure induces in vivo and in vitro neurotoxicity or progression of neurodegenerative diseases. The effect of NPs (neutral, anionic and cationic) on the integrity and permeability of BBB was evaluated by Lockman et al. (2004). The results showed that cationic NPs displayed an immediate toxic effect to BBB integrity. Similarly, changes in neurotransmitter levels and proinflammatory cytokine mRNA expressions were reported in the mice olfactory bulbs following intranasal instillation of 14-nm CB NPs in mice (Mitsushima et al., 2008). In a study, TiO_2 exposure was reported to change the levels of sodium, potassium, magnesium, calcium, iron, and zinc in the mice brain. TiO_2 NPs also led to impaired spatial recognition memory in mice brain suggesting that it could be associated with neurotoxicological effects (Hu et al., 2010). Another study demonstrated that AgNPs increased the permeability in primary rat brain microvessel endothelial cells (rBMEC) and induced the release of cytokines and inflammatory mediators (Trickler et al., 2010). The *in vitro* study performed on rat brain striatum and hippocampus using iron oxide nanoparticles (Fe_3O_4-NPs, 30 nm) also resulted in the accumulation and retention of NPs as well as oxidative stress in the rat brain striatum (Wu et al., 2013). Other *in vitro* studies also demonstrated highest toxicity of zinc oxide (ZnO) NPs on mice brain tumor cell lines (Neuro-2a) compared to Al_2O_3, TiO_2, Fe_3O_4 and CrO_3 NPs of similar size, induced DNA damage and cell apoptosis in mice neural stem cells and human SHSY5Y neuronal cells resulting in reduced activity (Jeng and Swanson, 2006; Deng et al., 2009; Valdiglesias et al., 2013). Yuan et al., 2015 reported the use of biodegradable nanoparticles (240 nm Tween 80-modified chitosan nanoparticles, TmCS-NPs) which are one of the most widely used brain targeting vehicles for neurotoxicity evaluation in rats. Seven-day exposure of TmCS-NPs was found to affect the body weight of the rats in dose dependent manner. Other changes observed in the rats include apoptosis, necrosis of neurons, slight inflammatory response in the frontal cortex and downregulation of Glial fibrillary acidic protein (GFAP) expression in the cerebellum. Begum et al., 2016 used human embryonic stem cell (hESC)- derived glutamatergic neurons (hGNs) as cellular model to evaluate neurotoxicity induced by 20 nm citrate-coated AgNPs (AgSCs) and Polyvinylpyrrolidone-coated AgNPs (AgSPs). AgSCs were found to cause significant damage to neuritic outgrowth, cell viability and increased phosphorylation of GSK-3b and Tau due to increased ROS production and Ca^{2+} influxes while AgSPs caused similar effects at high concentrations. A recent study also reported cytotoxicity in non-differentiated rat PC-12 cells when exposed to carbon black (CB, 10–100 μg/mL), single-walled nanotubes (SWNTs, 10–100 μg/mL), fullerene (C60, 100 μg/mL), cadmium selenide (CdSe, 10 μg/mL), CB (500 μg/mL), and dye-doped silicon nanospheres (NSs, 10 μg/mL). The results suggested increased formation of SBDP150/145 (spectrum breakdown products), contraction of cell membrane and formation of cytosolic vacuoles at higher concentrations of SWNTs, CB, and C60 (100 μg/mL) (Larner et al., 2017). Similar other studies conducted on potential toxicity of nanoparticles on the nervous system are listed in Table.

A recent study showed that AgNPs reduce brain inflammation and related neurotoxicity through induction of H_2S-synthesizing enzymes (Gonzalez-Carter et al 2017). Similarly, oral administration of Vitamin E was found to attenuate AgNP-induced effects on body weight and neurotoxicity in rats (Yin et al 2015). More relevant research is needed to characterize cellular uptake and transformation of NPs for better understanding of their bioreactivity to design safer NPs in future. In addition, more extensive *in vivo* experiments should be carried out in future for the assessment of NPs towards organ system, pharmacokinetic factors, neuro-development, cell-to-cell interactions which cannot be studied through *in vitro* methods.

The environmental neurotoxic effect of ENMs subjected to *in-vivo* or *in-vitro* study models, however it has its own limitations. A realistic picture of any ENMs induced environmental neurotoxicity effects on humans can only be deduced from the longitudinal studies. However, a single longitudinal or observational study does not provide enough weight to the findings, until it is amalgamated with other similar studies for evidence synthesis using methods like Systematic Review or Scoping Review.

Scoping review is one of the many approaches, that is used for evidence synthesis in research. Although completely different from Systematic Review in its aims and purpose (Munn et al., 2018), however it still goes through rigorous process and the method is transparent to ensure a trustworthy reproducible result. It involves aggregation of information from the available sources in a well-defined technique to interpret the data. Scoping review provides an overview of available research data, however it does not provide quantitative summary of the result (Arksey and O'Malley, 2005). Scoping reviews are useful in answering broad questions rather than specific causal effect relations, and can be used as a prior to systematic review.

4.2 Method

The present study was intended to take a comprehensive view of the cohort studies, longitudinal studies and reviews carried out linking engineered nanomaterials with neurotoxicity. A comprehensive literature review was done to identify the neurotoxic effects of engineered nano-materials, looking for neurotoxicity, neurodegenerative disorders, Alzheimer's disease and Parkinson's disease. The purpose of the scoping review consists of following objectives limited to the define timeline.

a. To examine the extent, range and nature of research activity.

b. To summarize and disseminate research findings.

c. To identify research gaps in the existing literature.

The intended study was carried out in databases such as PubMed and Scopus for aforementioned articles for the period between 2015 and 2019. The search terms included (engineered nanomaterials) AND (neurotoxicity), (engineered nanomaterials) AND (neurodegenerative), (engineered nanomaterials) AND (alzheimer) and (engineered nanomaterials) AND (parkinson).

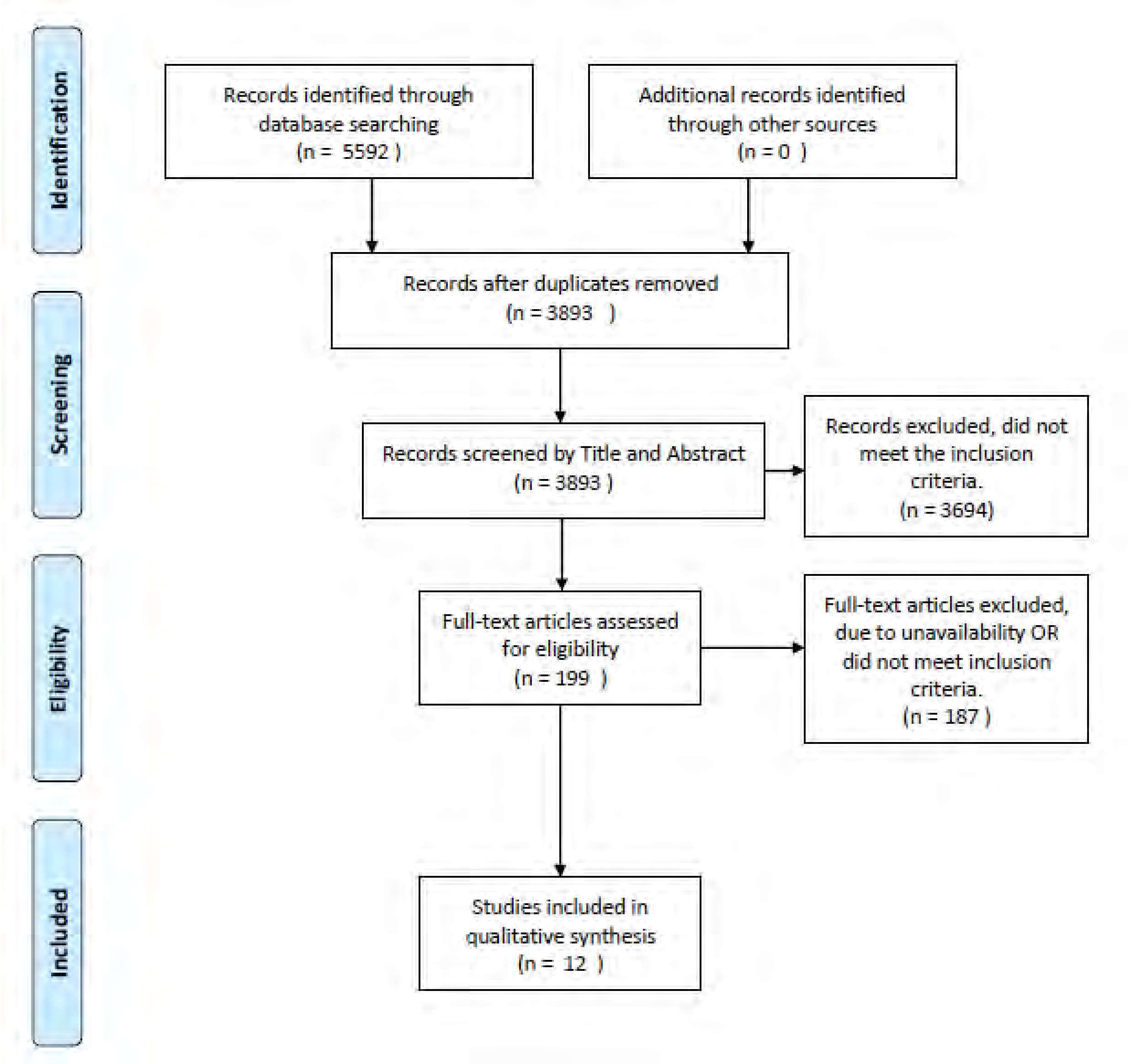

Figure 4.2: PRISMA Flow Diagram for Scoping Review

For inclusion, the study needed to be longitudinal studies or cohort studies on human environmental exposure or general reviews of engineered nanomaterials induced neurotoxicity, including *in-vivo* and *in-vitro* studies in context to public health. All titles and abstract were screened independently for inclusion. Parameters which were considered included author information, year of publication, types of neurotoxicity reviewed, mechanisms and routes and models of studies.

4.3 Results

The initial search using the above mentioned keywords and restrictions resulted in 5592 studies, after duplicate records were removed a total of 3893 study remained for screening on the basis of title and abstract. On screening of the articles, 3694 studies were excluded which did not meet the predefined inclusion criteria. Full text articles of 199 studies were retrieved and studied to screen the appropriate studies for scoping review. A total of 12 studies were finally shortlisted after being identified as relevant, rest were excluded for not fulfilling the pre-determined inclusion criteria or whose full texts were not available. All the studies identified turn out to be review articles and not a single longitudinal or cohort study was identified for said period. 3 out of 12 articles specifically focused on a single type of nano-materials, whereas 9 studies reviewed on neurotoxicity caused my nano-materials, without identifying any particular nano-material.

Table 4.1: Summary of studies, identified.

Authors	Year of Publication	Study Design / Type	Title / Journal	Types of NMs
Hougaard, K. S., Campagnolo, L., Chavatte-Palmer, P., Tarrade, A., Rousseau-Ralliard, D., Valentino, S., ... & Cassee, F. R.	2015	Review	A perspective on the developmental toxicity of inhaled nanoparticles. Reproductive Toxicology, 56, 118-140.	Non specific

Song, B., Liu, J., Feng, X., Wei, L., & Shao, L.	2015	Review	A review on potential neurotoxicity of titanium dioxide nanoparticles. Nanoscale research letters, 10(1), 1-17.	TiO_2
Facciolà, A., Visalli, G., La Maestra, S., Ceccarelli, M., D'Aleo, F., Nunnari, G., ... & Di Pietro, A.	2019	Review	Carbon nanotubes and central nervous system: environmental risks, toxicological aspects and future perspectives. Environmental toxicology and pharmacology, 65, 23-30.	CNTs
Feng, X., Chen, A., Zhang, Y., Wang, J., Shao, L., & Wei, L.	2015	Review	Central nervous system toxicity of metallic nanoparticles. International journal of nanomedicine, 10, 4321.	Non specific
Calderón-Garcidueñas, L., Reynoso-Robles, R., & González-Maciel, A.	2019	Review	Combustion and friction-derived nanoparticles and industrial-sourced nanoparticles: The culprit of Alzheimer and Parkinson's diseases. Environmental research, 176, 108574.	CFDNPs
Zhang, Y., Wu, J., Feng, X., Wang, R., Chen, A., & Shao, L.	2017	Review	Current understanding of the toxicological risk posed to the fetus following maternal exposure to nanoparticles. Expert opinion on	Non specific

			drug metabolism & toxicology, 13(12), 1251-1263.	
Chin-Chan, M., Navarro-Yepes, J., & Quintanilla-Vega, B.	2015	Review	Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in cellular neuroscience, 9, 124.	Non specific
Teleanu, D. M., Chircov, C., Grumezescu, A. M., Volceanov, A., & Teleanu, R. I.	2018	Review	Impact of nanoparticles on brain health: An up to date overview. Journal of clinical medicine, 7(12), 490.	Non specific
Carro, C. E., Pilozzi, A. R., & Huang, X.	2019	Review	Nanoneurotoxicity and potential nanotheranostics for Alzheimer's disease. EC pharmacology and toxicology, 7(12), 1.	Non specific
Heusinkveld, H. J., Wahle, T., Campbell, A., Westerink, R. H., Tran, L., Johnston, H., ... & Schins, R. P.	2016	Review	Neurodegenerative and neurological disorders by small inhaled particles. Neurotoxicology, 56, 94-106.	Non specific

Teleanu, D. M., Chircov, C., Grumezescu, A. M., & Teleanu, R. I.	2019	Review	Neurotoxicity of nanomaterials: An up-to-date overview. Nanomaterials, 9(1), 96.	Non specific
Ge, D., Du, Q., Ran, B., Liu, X., Wang, X., Ma, X., ... & Sun, B.	2019	Review	The neurotoxicity induced by engineered nanomaterials. International journal of nanomedicine, 14, 4167.	Non specific

Molecular and cellular mechanisms involved neurotoxicity induced by engineered nanomaterials were reviewed in 6 articles in length. Review on developmental toxicity due to inhaled nanoparticles, observed that multiples organs in the offspring may be susceptible to the prenatal exposure of particles (Hougaard et al., 2015). There are however, uncertainties on the impact on embryo-fetal development and possible long term effects. Although associations between ambient exposure to nanoparticles and adverse health effect on offspring has been shown by certain epidemiological studies, however they do not provide definitive statements for developmental toxicity of NPs (Hougaard et al., 2015). The study was a general review on developmental toxicity due to inhaled nanoparticles and did not specifically deal with neurotoxicity. However, it does discuss the developmental neurotoxicity, due to maternal airway exposure of NPs during pregnancy and reviews of 4 *in-vivo* mouse model based studies. It reviewed ROS and inflammation, effects on fetal development, indirect effects due to maternal inflammatory response and toxicity due to chemicals associated with NM as potential mechanisms of developmental toxicity. Review conducted by Song et al., 2015, tries to map out the interaction of TiO_2 NPs with the brain. It concluded that in all of the studies reviewed did not have standardized experimental perimeters, hence the studies were not comparable as well as conflicting in some cases. Neurotoxicity implications of TiO_2 NPs based on *in-vivo* or *in-vitro* models may not accurately represent the neurotoxic effects on humans as compared to human exposure studies or studies on human cells (Song et al., 2015). A review on dual impacts of metallic NPs on biomedical applications and neurotoxicity was carried out by Feng et al., 2015. The reviewed mostly focused on entry routes of NPs to CNS and mechanism of neurotoxicity. The study extensively reviewed the application in disease diagnostics and therapy, drug delivery system, nanoscaffolds for neurodegeneration, molecular imaging. It elaborated the possible mechanisms of NP neurotoxicity, which included oxidative stress, NP interaction with cytoplasmic enzymes, immune mechanism, apoptosis and autophagy dysfunction mechanism, activated cell signaling pathways among others. Another study reviewed the link between combustion and friction derived nanoparticles (CFDNPs) and Alzheimer's and Parkinson's disease. The review focused on the interaction of CFDNPs with biologicals systems and effect of entry routes, particle sizes, biodistribution, axonal transport etc. Heusinkveld et al., 2016 evaluated the relationship between exposure to inhaled ambient particles and neurodegeneration. The review based on *in-vitro* and *in-vivo* models, epidemiological, cohort and longitudinal studies explored the various neurotoxicity mechanism such as oxidative stress, metal homeostasis, protein homeostasis, neuroinflammation and disruption of the BBB. Review evidence suggested that inhalable PM plays are major role in pathophysiology of neurodegenerative diseases. However, due to the lack of measure of exposure levels, insufficient data on translocation kinetics for specific NPs and many other systemic effects, it is difficult to link any particular route to a main cause. Ge et al., 2019 reviewed the ENM induced neurotoxicity mechanisms such as oxidative stress, DNA damage, cell death, inflammation based on in-vivo and in-vitro studies. The mechanism may interact or may work independently.

Table 4.2: Reviews that discussed Mechanism of Neurotoxicity

Author	Neurotoxicity Type	Mechanisms / Routes	Types of studies reviewed
Hougaard et al., 2015	Developmental Neurotoxicity	ROS and inflammation, effects on fetal development, indirect effects due to maternal inflammatory response and toxicity due to chemicals associated with NM	Toxicokinetic pattern, In-vivo models, in-vitro models, human placental perfusion models
Song et al., 2015	Neurodegenerative Disorders	Translocation from blood to the brain, axonal translocation from blood to the brain, translocation into the brain of offspring through placental barrier	in-vitro models, in-vivo models
Feng et al., 2015	Neurotoxicity	oxidative stress, NP interaction with cytoplasmic enzymes, immune mechanism, apoptosis and autophagy dysfunction	In-vivo models, in-vitro models, computational models

		mechanism, activated cell signaling pathways	
Calderón-Garcidueñas et al., 2019	Alzheimer's and Parkinson's Disease, Neurodegenerative Diseases	Protein misfolding, aggregation and fibrillation, neuroinflammation, oxidative, endoplasmic reticulum (ER) and mitochondrial stress	In-vivo models, in-vitro models
Heusinkveld et al., 2016	Neurodegenerative and Neurological disorders	Oxidative stress, metal homeostasis, protein homeostasis, neuroinflammation, disruption of the BBB	In-vitro, in-vivo, epidemiological, cohort and longitudinal studies
Ge el al., 2019	Neurotoxicity	Oxidative stress, mitochondrial dysfunction, inflammation, DNA damage, differential cell death – apoptosis and necrosis, autophagy	In-vivo and in-vitro models

The remaining 6 studies explored various other domains of NM induced neurotoxicity. Facciola et al., in 2019 reviewed the environmental risks, toxicological aspects and perspective of the carbon nanotubes (CNTs) in context to central nervous system. The review explored the systemic, olfactory and trigeminal pathways of CNT toxicity. The review by Zhang et al., 2017, explored the transfer of NPs through placenta in the cases of materno-fetal transfers. The adverse effects such as malformations, neuro-developmental disorders, injury to organs in both prenatal and postnatal conditions were reviewed. The possibility of environmental pollutants including NPs as risk factors for neurodegenerative disorders like Alzheimer's and Parkinson's Disease were explored by Chin-Cha et al., 2015.

Table 4.3: Other relevant reviews on NMs induced Neurotoxicity

Author	Neurotoxicity Type	Relevant Salient Points	Types of studies reviewed
Facciola et al., 2019	Neurotoxicity	Review on carbon nanotubes neurotoxicity, CNT uptake in CNS – systemic pathway, olfactory pathway, trigeminal pathway	In-vivo and in-vitro models
Zhang et al., 2017	Developmental neurotoxicity	Review on fetal developmental neurotoxicity risk following maternal exposure to NPs, materno-fetal transfer of toxins,	In-vivo and in-vitro models.
Chin-Chan et al., 2015	Alzheimer's and Parkinson's Disease	Environmental pollutants including NPs as risk factors for Alzheimer's and Parkinson's Disease.	In-vivo and in-vitro models.
Teleanu et al., 2018	Neurodegenerative diseases	Impact on brain health due to NPs, explored both	In-vivo and in-vitro models.

		beneficial and negative brain impacts	
Carro et al., 2019	Alzheimer's Disease	Potential Nanotheranostics Application for AD and Neurotoxicity of NPs causing NPs	In-vivo and in-vitro models.
Teleanu et al., 2019	Neurotoxicity	The review is to emphasized neurotoxic effects induced by nanoparticles, liposomes, dendrimers, carbon nanotubes, and quantum dots. Reviewed the key neurotoxicology assays to evaluate them.	In-vivo and in-vitro models.

4.4 Discussion

Scoping Reviews are systematic way to map the research or studies being done in a particular area under a predetermined condition. They may be employed as a first step of systematic review to identify the researches being done and feasibility of carrying out systematic review or further meta-analysis. Scoping reviews are broad in its objective and do not look to establish any causal effect relationship. It's an important tool in identifying data gaps and future research prospects. It has off late been applied in environmental health applications as well (Bolden et al., 2017). Through this scoping review we tried to identify the cohort or longitudinal studies or reviews on environmental NMs or NPs induced neurotoxicity and more specifically neurodegenerative disorders for the period between 2015-19.

When reviewing the availability of environmental NMs induced neurotoxicity, there are sufficient literature on acute exposure, exposure in occupational settings, however environmental NMs neurotoxicity is far less in comparison. Also, in the predefined period, no cohort or longitudinal studies for NMs induced neurotoxicity due to chronic environmental exposure was found. All the studies short listed were reviews and most of them explored the mechanism diligently along with the routes of exposure and different neurotoxic disorders. However, all these reviews were also mostly based on *in-vivo* and *in-vitro* studies with only one study mentioning one cohort study. This clearly shows the lack of cohort or longitudinal studies for environmental exposure of NMs and its neurotoxicity effects.

Although, the long term exposure study on humans is lacking, there is an overwhelming *in-vivo* and *in-vitro* studies being done in this field. There was however, relatively fewer study found which directly links AD or PD to NMs, which shows that there is still lot to be explored in this area. In order to maintain a healthy environmental health and ecological balance, long term observational studies should be prioritized on NMs effect on human neuronal systems. There is a need for studies to be designed, relevant to risk assessment of human health for a long term chronic exposure. It is necessary to outline the present research and data gaps need to be identified.

4.5 Conclusion

The review found that there is huge gap in the study for environmental exposure assessment for NMs neurotoxicity. There are almost no observational studies to support the neurotoxicity due to chronic environmental exposure. The reviews also mostly cover the acute or occupational exposure of NMs and its impact. Most of the reviews considered for scoping review were based on *in-vivo* and *in-vitro* models, and few based on epidemiological studies. No observational studies for the pre-defined period were found. Most of the reviews emphasized on the neurotoxicity mechanisms and route of exposure.

However, the mechanism of NM nanotoxicity yet to be explored completely, hence is still an important area of research for the future. Most of the studies attribute NMs neurotoxicity to oxidative stress, however some NMs are antioxidants and free radical scavengers. Another issue with most of the *in-vivo* or *in-vitro* studies is the lack of standardized common terms, for experimentation repeatability in terms of exposure times, assays, cell lines etc. Many different types of NMs exist and all tend to have different responses, hence a common standard is the way forward. Also, during experimental studies, the NMs dose generally is not synchronous to exposure in real. Also, experimental studies on cells or animal models alone can never present the actual neurotoxic effect due to chronic environmental exposure, due to impossibility of replicating the environmental condition. Therefore, observational studies are needed, and they should be supplemented with experimental studies.

Chapter 5

Summary and Future Prospects

Evidence synthesis is one of the most primary and important step towards risk and impact assessment as well as policy design. In the present report we have explored evidence synthesis techniques like Systematic Review and Scoping Review in pesticides and nanomaterials induced environmental toxicity. In addition, we reviewed the application evidence synthesis for environmental health policy design. A chapter wise summary is provided below.

1. Organophosphate induced Environmental Toxicity

In this chapter we have described the methodology, results and discussion of a systematic review study carried out to get insight into the relationship between organophosphate pesticides and its toxicity effects. A search strategy was created by designing search words to retrieve literature emphasizing on environmental exposure of organophosphates causing various kinds of toxicity and also a search was made for *in-vivo* models that studied OP induced toxicity impacts. Inclusion and Exclusion Criteria was set to include original articles, published upto November 2021, written in English, availability of full free text. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach was selected for relevant literature selection. Assessment of quality of articles were done using 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) - Statement' checklist. Out of 1841 articles retrieved from PubMed, Scopus, Web of Science, Ovid and BMJ Case Studies, 721 articles were found to be fulfilled the search criteria. The overall review of the articles establishes a strong positive link between environmental OP pesticide exposure and toxicity impact on human health, supported by *in-vivo* evidence. Susceptibility to OP pesticide toxicity may determine by be two exonic polymorphisms viz. PON1L55M and PON1Q192R SNPs in human population. The mechanism of OP pesticide toxicity can be attributed to the inhibition of acetylcholinesterase (AChE). However, the association of OPs pesticides as cause of mitochondrial disruption is not conclusive as of now.

Future prospect:

- Inclusion of more studies retrieving from more number of databases in addition to the mentioned above.
- Utilization of grey literature such global or local governmental or other organizational report reports.
- Collaboration with other institutions across globe to get access to not-open source literature.
- More detailed side by side comparison between human studies and *in-vivo* studies.
- Development of a policy document for government to help in informed decision making.
- Development of a database on pesticide toxicity and neurotoxicity.

2. Nanomaterials induced Environmental Neurotoxicity

We have carried out a scoping review to investigate the possible link between engineered nanomaterials with neurotoxicity. The search words emphasizing on engineered nanomaterials and neurotoxicity or neurodegenerative diseases were designed to carry out literature retrieval from PubMed and Scopus databases. The duration of the study was selected between 2015 and 2019. The PRISMA Flow Diagram for Scoping Review was followed to select relevant literature.

The search was intended to retrieve articles that include either longitudinal studies or cohort studies or general reviews. Out of initial search results of 3893 unique articles, 199 full text articles were retrieved and studied. Only 12 studies were identified as relevant on the basis of inclusion criteria, which were found to be only review articles. 3 out of 12 articles specifically focused on a single type of nano-materials, whereas 9 studies reviewed on neurotoxicity caused my nano-materials, without identifying any particular nano-material. The reviews are found to be based on *in-vivo* and *in-vitro* studies. The scoping review points out that adequate cohort ot longitudinal studies have not been carried out to link AD or PD to NMs. It also reveals that there is a critical need for studies dealing with risk assessment of human health for a long term chronic exposure to NMs.

Future Prospect:

- To carry out a detailed scoping review followed by systematic review and meta-analysis on ENM and neurotoxicity.
- Design of systematic review studies categorically based on different nanoparticle and neurotoxicity.
- To carry out Systematic review on more granulation of study data such as geographical location, population genetics, nature and method of generation of engineering nanomaterials, etc.

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