

## **Environmental Neurotoxicology: A review**

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**Industry in the Kingdom of Saudi Arabia (KSA), making use of the amassed income from oil production, is showing phenomenal development and diversification in industrial products that have no match in the region. Chemical use in industry is on the rise worldwide and KSA is the main user and producer of chemicals (organic and inorganic compounds) in the Gulf region. A good number of chemicals, which may be the form of gas, liquid, or solid state, are neurotoxic causing poisoning, birth defects, severe illness, or even death.**

**Toxicity sometimes arises from the metabolite and not from the parent chemical. In this review, we have briefly discussed the symptoms, signs, diagnosis, management, and prevention of toxicity of various groups of neurotoxic chemicals which are most likely found in Saudi industry. The clinical features of neurotoxicity depend on several factors, such as the physical characteristics of the chemical, the route of entry, the dose and susceptibility of the exposed individual. Investigations depend on the type of the toxic agent. These range from measuring the toxic chemical or its metabolites in biological samples, electro-physiological and laboratory investigations or nerve biopsy. Management depends on the poisoning agent and the presenting symptoms and signs. Intensive care might be required for acutely intoxicated patients. Preventing occupational diseases, in general, requires joint efforts between governments, industry and employees. Elimination is the key to prevention with the use of personal protective clothing as the last resort.**

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Use of industrial toxic chemicals in the world is on the rise. In the United States, between 50,000 and 100,000 chemicals are in use in industry and more than a thousand new ones are sent yearly for evaluation<sup>1</sup>.

Some industrial chemicals such as polychlorinated biphenyls (PCBs), toluene, methyl mercury, lead, and arsenic are known neurotoxic chemicals. In addition, these substances can cause subclinical brain dysfunction and developmental disorders. Exposure during early fetal life can lead to brain damage at doses much lower than those affecting the mature adult brain<sup>2,3</sup>.

Gage found that some chemicals have various neurotoxic adverse effects; 1,1,1-trishydroxymethylpropane bicyclic phosphite (an organic phosphorus compound) was one of the most toxic compounds handled in that study<sup>4</sup>.

Saudi Arabia (KSA) is witnessing a rapid industrial growth that has no match in the Eastern Mediterranean Region following the amassed income from the oil production and exportation<sup>5</sup>. This industrial growth and diversification has entailed the production and use of different types of industrial chemicals some of which constitute a health hazard in the absence of preventive measures.

The aim of this review is to highlight the neurotoxicity of the different types and use of neurotoxic chemical groups, and discuss the modes of entry into the body, symptoms, signs, diagnosis, prognosis management and control.

### **What is a Toxic Substance?**

A toxic substance is any substance that causes poisoning, birth defects, severe illness, or death when it enters the body through ingestion, inhalation or dermal absorption. In other words, any naturally occurring or synthetic substance that negatively affects any of the structural or functional components of the nervous system is labeled as neurotoxic<sup>6</sup>.

These substances can also be carcinogenic, corrosives, mutagenic, teratogenic or reproductive hazards. The U.S. Department of Justice published a list of 98 toxic industrial chemicals (TICs) grouped by their hazard index. Twenty-one are considered highly hazardous, 38 medium, and the remaining 39 are listed under the low hazard index group. This classification was intended for the emergency first responders to select the appropriate equipment in case of an emergency<sup>7</sup>. Grandjean et al reported about 200 chemicals that are neurotoxic to adults<sup>2</sup>.

Industrial toxins come in the form of gas, liquid, or solid state. The severity of the adverse health hazards depends on the chemical structure of the agent, the total dose absorbed by the body, the route and the body's ability to detoxify or eliminate the substance<sup>8</sup>.

What makes the nervous system more vulnerable to toxic substances? The nervous system is a delicate organ and minor changes in its structure can have severe adverse effects. Not only toxic substances cause damage to the nervous system, but also aging causes progressive loss of neurons<sup>6</sup>.

### **Toxic Groups**

Three types of toxic entities were recognized; biological (bacteria and viruses), chemicals (organic and inorganic compounds), and physical (substances that can interfere with biological processes such as silica dust and asbestos). In this review, only chemical toxins at the occupational level will be discussed.

### **Routes of Entry of Toxic Chemicals**

Toxic chemicals might gain entry through inhalation, dermal, ingestion and injection; the chemicals might cross the blood-placental barrier passing from mother to the unborn baby.

Inhalation is the most important and common route of entry of toxic substances into the body. These toxic agents can be in the form of dusts, gases, fumes, mists, smoke, and vapors<sup>9</sup>.

The dermal route which include epidermal cells, hair follicles, and sebaceous glands, is an uncommon route. The skin permeability depends on the chemical and the skin<sup>10</sup>. Permeability differs between species. Humidity also might increase the rate of absorption<sup>11,12</sup>.

Aniline and nitrobenzene are two examples; once in contact with the skin the chemical may cause local irritation, necrosis, sensitization or may enter the blood circulation<sup>13</sup>. The skin sensitization may later trigger an allergic response both at the point of contact or in remote areas<sup>14</sup>.

The ingestion route is not as common as the inhalation route. Contaminated hands, drinking and swallowing contaminated mucus coughed up from the lungs are the possible modes of entry into the body. An ingested chemical after entering the body goes to the liver and may be immediately detoxified<sup>9</sup>.

Injection, as a route of introducing the toxic chemical directly into the blood stream, is an uncommon mode of intoxication in industrial settings. However, it might be due to accidental injuries by sharp instrument which is more common among healthcare workers where infectious agents rather than toxic chemicals are introduced in the body<sup>15,16</sup>.

### **Possible Chemicals in the Saudi Industry**

Several industrial establishments in the country either produce chemicals or manufacture products based on different types of chemicals. Examples of chemicals include, but are not limited to olefins (ethylene, propylene, butadiene, butene-1), methyl tertiary butyl ether (MTBE), methanol, industrial ethanol, styrene, benzene, paraxylene and purified terephthalic acid (PTA), ethylene dichloride (EDC), vinyl chloride monomer (VCM), and chlorine<sup>17</sup>. Other chemicals available include pesticides, lead, caustic soda, hydrochloric acid and sodium hypochlorite, to mention a few.

A number of these chemicals namely methanol, industrial ethanol, styrene, benzene, paraxylene, EDC, VCM, pesticides, lead, and sodium hypochlorite are known for their neurotoxicity.

### **Modes of Neurotoxicity**

According to Latov peripheral neuropathy and polyneuropathy are terms that describe syndromes resulting from diffuse lesions of peripheral nerves, usually manifested by weakness, sensory loss and autonomic dysfunction<sup>18</sup>.

Paracelsus considered “all substances as poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy”<sup>19</sup>.

Toxicity might arise from the metabolite and not from the parent chemical. This is true for the organophosphorus pesticide Malathion, which has to be converted to malaoxon to actively inhibit the enzyme acetylcholinesterase (AChE)<sup>20</sup>.

Fat soluble toxins have the ability to readily penetrate the blood-brain barrier and nerves. Many toxins do not affect the architecture of nerve cells, albeit they disrupt the chemical balance and function<sup>21</sup>.

A toxic chemical might affect the target organs at the molecular or cellular levels. At the molecular level, it might cause reduction of neurotransmitter; at the cellular level, the flow of ions across the cell membrane might be altered, thereby disturbing the transmission of signal between nerve cells<sup>22</sup>.

The effect might be confined to the central nervous system (encephalopathy) or the peripheral nervous system (polyneuropathy) or might involve both, which could be reversible or irreversible. Some neurotoxins could cause CNS nerve cells degeneration, such as mercury, or peripheral nerves, such as acrylamide monomer<sup>21</sup>. Some chemicals cause more than one illness following a single exposure. Ethanol causes CNS depression during the acute phase and liver cirrhosis as a sequel to chronic toxicity<sup>23</sup>.

Some chemicals have a predilection to specific organ or organs, while others are multi-organ poisons. Schaumburg et al think that the ideal classification of toxic chemicals “should link the vulnerable target of chemical attack to alterations in neural function”. However, this classification is faced with the fact that some chemicals might adversely affect different sites within the brain or the peripheral nervous system<sup>24</sup>.

### **Groups of Neurotoxic Agents**

Neurotoxic agents can be grouped into: gases, metals, monomers, organic solvents, pesticides, and a group that does not fit into any of these categories<sup>1</sup>.

Exposure to neurotoxic gases such as carbon dioxide (CO<sub>2</sub>), carbon monoxide (CO), hydrogen cyanide (HCN), hydrogen sulphide (H<sub>2</sub>S) and nitrous oxide (N<sub>2</sub>O) may be encountered in metal industry, mining and other industries.

The acute toxic effects that might arise following exposure to these gases range from headache and tremor to loss of consciousness or death; the chronic effects may be encephalopathy (HCN, H<sub>2</sub>S, N<sub>2</sub>O), or numbness of fingers and toes and reduced coordination following exposure to N<sub>2</sub>O<sup>1</sup>.

Ramazzini described the adverse effects of H<sub>2</sub>S; this gas, besides being neurotoxic, is known to cause olfactory fatigue at a concentration above 100 ppm so that the exposed worker smells this rotten gas once he enters the polluted area but soon the smell disappears and he continues to work in the area until he succumbs<sup>25</sup>.

Metals known to be neurotoxic include arsenic, cadmium, copper, lead, manganese, mercury, and zinc<sup>26</sup>. Others such as, selenium, tin, and aluminum have been reported to be neurotoxic as well<sup>27-29</sup>.

The exposure to these chemicals is likely to be in industrial settings, such as metal works, glass manufacturing, mining, aluminum smelting and lead-acid and nickel-cadmium batteries manufacturing. Some chemicals might have a synergistic effect causing neurological effects significantly greater than when either gain access alone. Examples are manganese chloride and lead acetate, and the anti-nerve gas drug pyridostigmine bromide, the insect repellent N, N-diethyl meta-toluamide (DEET), and the insecticide permethrin<sup>30,31</sup>.

Monomers include acrylamide, acrylonitrile, carbon disulphide and styrene. Acrylonitrile-butadiene-styrene (ABS) and acrylamide are used in industries such as water treatment, electronics and gold mining to mention a few. Acrylonitrile is used primarily to produce acrylamide, acrylic fibers, plastics, adiponitrile fibers and barrier resins<sup>32</sup>. Acrylonitrile besides its neurotoxicity is carcinogenic to mice and a possibly human (Group B1)<sup>33,34</sup>.

Carbon disulfide is mostly used for the production of viscose rayon and cellophane, among other uses<sup>35</sup>. It is known to cause severe neurotoxicity; motor and sensory nerve dysfunction, affective disorders and behavioral changes<sup>36</sup>.

Styrene, which is a monomer and a solvent, is used primarily to produce polystyrene, styrene homopolymers, copolymers and various other types of products<sup>37</sup>. Styrene has been reported to cause peripheral sensorimotor neuropathy and a “subclinical impairment of color vision”<sup>38,39</sup>. The International Agency for Research on Cancer (IARC) has categorized it as a possible human carcinogen (Group 2B)<sup>40</sup>.

Solvents are extensively used in the coatings industry because of their important role in the quality and durability of paints and varnishes. Shoe industry was found by De Rosa et al to have a high risk of neurotoxicity; the risk is lower in the printing industry and nearly absent during painting<sup>41</sup>.

According to Viaene, the reported acute symptoms following exposure to solvents included irritation of both the eyes and nose in addition to ataxia, dyspnea, headache, nausea, and a feeling of drunkenness. More severe symptoms include convulsions and coma<sup>42</sup>.

Chronic exposure may lead to narcosis, euphoria, agitation, discoordination, ataxia, dysarthria, dizziness, light-headedness that might progress to unconsciousness and death<sup>43,44</sup>. Methyl-n-butyl ketone (MBK or MnBK), n-hexane, and carbon disulfide are known for their neurotoxicity<sup>44</sup>.

Another form of CNS toxicity following long-term exposure to organic solvents is known as “painter’s syndrome”. This condition has multiple names and classifications. It is characterized by sensorimotor polyneuropathies and neuro-behavioral that persisted even after cessation of exposure to the offending solvent<sup>45,46</sup>.

Solvents toxicity is not limited to the nervous system but can affect the eyes, skin, liver, and kidneys, besides being cancer-risk. The visual defect arises after long term exposure. The color vision defect is loss of blue-yellow color discrimination or occasionally a combination of blue-yellow and red-green loss<sup>43,47</sup>.

Pesticide use is on the rise worldwide<sup>48</sup>. They come in the form of baits, chalk, gel, granules, liquid, paste, pellets, or powder. They are grouped as organo-phosphates, carbamates, organochlorines, and pyrethrins. Exposure can be at the production line, at home, in agriculture or during transport or municipal use.

The organophosphorous pesticides (OP) and the carbamates inhibit the activity of the enzyme acetylcholinesterase which leads to accumulation of acetylcholine at nerve endings and neuromuscular junctions. The acute symptoms include difficulty in breathing, neuromuscular paralysis, weakness, and convulsions<sup>49</sup>.

‘Ginger paralysis’ or ‘organophosphorus neurotoxicity’ is a delayed type of complication that occurs between 10 to 21 days post exposure<sup>50</sup>. Tri-p-ethylphenyl phosphate is an organophosphorus compound that produces neurotoxicity without inhibiting the enzyme cholinesterase<sup>51</sup>.

Some patients after apparent recovery from the acute cholinergic syndrome might develop a delayed respiratory muscle paralysis before the appearance of the delayed polyneuropathy. This condition is called the intermediate syndrome (IMS)<sup>52,53</sup>.

Herbicides, like paraquat and diquat and fungicides such as triadimefon, a triazole fungicide, have also been shown to possess neurotoxic properties in rats<sup>54,55</sup>. Other neurotoxic agrochemicals include organochlorine pesticides fungicides, pyrethroid insecticides, nicotine, rodenticides, fungicides, fumigants (sulfuryl fluoride; zinc, magnesium, and aluminum phosphides), chlorophenoxy herbicides, and warfarin<sup>56</sup>.

Organochlorine pesticides (OCP) have been linked with the development of Parkinson’s disease (PD)<sup>57</sup>. Chhillar et al conducted a case controlled study involving 70 PD patients and 75 age-matched healthy volunteers found strong association of dieldrin and  $\beta$ -hexachlorocyclohexane with the risk of PD<sup>58</sup>.

Vanadium pentoxide and tetraethyl lead (TEL) may adversely affect the nervous system. Vanadium-exposed workers were found to have intention tremor of the fingers and arms and reduced neurobehavioral abilities particularly the visuospatial abilities<sup>59,60</sup>. Lead comes in two forms: organic (tetraethyl and tetramethyl lead) and inorganic (or metallic lead); both forms are known to be neurotoxic agents<sup>61,62</sup>.

Tetraethyl lead was once an additive to gasoline to improve the octane level in diesel-powered cars. Many countries worldwide have banned its use and replaced it with methyl tertiary butyl ether (MTBE)<sup>63</sup>. However, it is still an additive to aviation fuel for piston-engine powered aircrafts.

## **Pathophysiology**

Axonal degeneration, segmental demyelination, and neuropathy are the three main pathological processes that affect the peripheral nervous system. Axonal degeneration is commonly seen in toxic conditions, besides nutritional, systemic, and metabolic disorders<sup>64</sup>.

Axonal degeneration is accompanied by the breakdown of the axon together with the myelin sheath, a condition known as “dying-back”. The axons gradually degenerate starting from the synaptic regions toward the cell body<sup>65,66</sup>.

The underlying pathology of segmental demyelination is destruction of the myelin sheath but sparing the axon, while neuropathy occurs at the level of the motor neuron or dorsal root ganglia. Recovery of neuropathy at this level is unlikely to be complete<sup>64,65</sup>.

## **Clinical Features of Neurotoxicity**

Neurotoxicity is characterized by a chain of symptoms. These depend on several factors, which include, but are not limited to the physical characteristics of the chemical, the route of entry, the body’s ability to metabolize and excrete the toxin, smoking habit and the dose and susceptibility of the exposed individual. Older subjects may be more vulnerable, and more so if they have another CNS disease<sup>66</sup>. The dose depends on the concentration in the workplace, the duration of exposure, and activity of the worker. Different concentrations of a specific chemical may cause different neurotoxic symptoms. These effects are usually reversible once exposure has ceased<sup>67</sup>.

The body reaction to the toxic substance might be motor, mood and personality effects, sensory, cognitive, behavioral disorders, and general, such as depression of neuronal activity, narcosis, stupor, fatigue, and nerve damage<sup>68,69</sup>.

The symptoms may immediately follow exposure or appear after a latent period. In the case of organophosphate pesticides, for example, the latency could vary between 2 to 6 weeks before the appearance of peripheral neuropathy<sup>70</sup>.

Inhaling a large dose of n-hexane, for example, may result in coma and death. Although, inhaling lower doses over several weeks may cause severe peripheral neuropathy with no CNS symptoms<sup>71</sup>.

The severity of the adverse effects is classified into several levels: level 1 (reversible, subjective symptoms) to level 6 (morphological changes; axonopathy and cell death, as well as subcellular morphological changes)<sup>1</sup>.

## **Diagnosis**

History of medical and occupational health is the key to exclude non-occupational causes of neuropathy<sup>72</sup>.

The symptoms and signs of polyneuropathy could be sensory loss, pain, thermal sensation, light touch, motor, autonomic (such as anhidrosis, dryness of the eyes and mouth, and orthostatic hypotension in advanced cases) or a combination of these<sup>73</sup>.

Greene J et al stated that the pathological processes that adversely affect the CN and the PNS are few<sup>74</sup>. They grouped these into inherited, developmental, acquired conditions, infectious diseases, inflammatory, ischemic, neoplastic, degenerative and toxic/metabolic disorders.

It is imperative that the treating physician ask the patient to describe in detail the current and previous jobs, exposures and whether personal protective equipment is provided and used. In the case of an acute exposure, the temporal onset of symptoms should be probed<sup>75</sup>.

The current clinical presentation might not be arising from workplace exposures. The home environment could be the source of the intoxication. This particularly applies to pesticides.

Sometimes, an accidental exposure to a neurotoxic chemical coincides with the appearance of a naturally occurring peripheral nerve disease or disorder leading to misdiagnosis; the condition was labeled pseudoneurotic disease by Albers and Berent<sup>76</sup>.

The patient may present with symptoms related only to the peripheral nerves, such as pain, tingling or numbness, or related to the central nervous system, such as hyperreflexia, Babinski reflex, sexual dysfunction, and tremor<sup>75</sup>. Autonomic, motor, sensory, or a combination may be damaged by neurotoxic substances<sup>77</sup>.

## **Physical Examination**

Peripheral nerve root lesions are usually asymmetric with a dermatomal pattern of sensory symptoms. Ataxia, speech difficulty, and double or color vision symptoms indicate involvement of the central nervous system; symptoms and signs of polyneuropathy could be sensory loss, pain, thermal sensation, light touch; motor, autonomic, such as anhidrosis, dryness of the eyes and mouth, and orthostatic hypotension in advanced cases or a combination of these<sup>78,73</sup>.

## **Differential Diagnosis**

Other causes of neuropathy that need to be excluded are the following: uremic neuropathy, diabetic neuropathy, polymyositis, amyotrophic lateral sclerosis (ALS), inclusion body myositis, neurosarcoidosis, syringomyelia (idiopathic and acquired), polyarteritis nodosa, vitamin deficiencies (E, B1, B6, and B12), past trauma, work-related musculoskeletal disorders (namely carpal tunnel syndrome), and alcohol.

Excessive alcohol is a risk factor for peripheral and autonomic neuropathy in addition to other CNS diseases such as cerebellar degeneration, cognitive deterioration, Wernicke's encephalopathy and Wernicke-Korsakoff syndrome (WKS)<sup>25,79</sup>.

HIV infection, varicella-zoster viruses, Epstein-Barr virus and herpes simplex, could damage the nervous system and should be excluded<sup>80</sup>.

Several types of antibiotics, anti-hypertensive, cardiovascular, anti-convulsants, and chemotherapy medications are known for their neurotoxicity<sup>81-86</sup>. Subjects with comorbidities such as a central nervous system or renal disease are more vulnerable to neurotoxicity.

## **Investigations**

The diagnosis of toxic neuropathy starts with basic investigations such as a complete blood count, erythrocyte sedimentation rate, fasting blood sugar, thyroid function test and vitamin B12.

CSF analysis might be required to diagnose chronic immune mediated axonal neuropathies or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)<sup>87</sup>. Non-occupational comorbidities need to be excluded, such as connective tissue disorders, inflammatory neuropathies, hereditary neuropathies, Krabbe's disease, diabetes, hypothyroidism, vitamins and iron deficiencies<sup>64</sup>. Measurement of blood and/or urinary levels of the suspected toxic chemical or its metabolite is necessary to confirm or repudiate the diagnosis. Some chemicals have specific metabolites which can be measured in biological samples as indicators of exposure to the toxic agent.

Electrodiagnostic evaluation may be required to check the integrity of the large myelinated nerve fibers and identify the predominant pathophysiology; it also helps determining the prognosis for some disorders<sup>88,89</sup>. Neuroimaging combined with neurophysiologic testing and neuropsychological evaluation will support the suspicion or the recognition of the toxic chemical. A repeat of the tests sometime after withdrawal from exposure is recommended whenever possible<sup>75</sup>.

Other investigations include sympathetic skin reflex, needle electromyography, somatosensory evoked potentials, and quantitative sensory testing (useful in detecting early sensory abnormalities in people exposed to occupational and environmental toxins). Nerve biopsies may be performed but only after adequate clinical, electrophysiological and laboratory investigations have been performed<sup>90,91</sup>.

## **Management**

### **Acute poisoning**

Immediate attention should be directed to adequacy of the airway and ventilation, cardiac function and skin decontamination to prevent further dermal absorption. The patient needs to be monitored and stabilized. Gastric lavage may be required in case of acute oral poisoning by substances other than corrosives and hydrocarbons. Otherwise, gastric emptying is recommended. A sample of the gastric content should be sent to the laboratory for analysis. Pharmacologic measures depend on the type of the toxic chemical. Specific antidotes should be used provided that there are no contraindications.

### **Chronic poisoning**

Once the diagnosis has been established and the causative neurotoxic agent has been identified, removal from further exposure is necessary in the management of occupation-related diseases, be it neurotoxic or otherwise, to prevent further deterioration of the condition. Some diseases might resolve or improve after cessation of exposure, such as type 1 solvent neurotoxicity, while others might not or even progress as in manganese-induced Parkinsonism<sup>44,92</sup>.

## **Prognosis**

Prognosis depends on the age of the exposed employee, the type of the neurotoxin, duration of exposure, presence of comorbidities and severity of the condition at the time of diagnosis. Early recognition and treatment will most likely lead to complete recovery or prevent possible complications. Protracted cases may take months or years before complete recovery, provided that no damage has occurred to the nervous system.

## **Control**

The National Institute for Occupational Safety and Health (NIOSH) in the United States of America has outlined actions to be taken to prevent work-related neurotoxic diseases. The International Labor Organization (ILO) has outlined the strategies for prevention of occupational diseases in a document prepared for the World Day for safety and health at work<sup>93,94</sup>. Preventing occupational diseases, in general, requires joint efforts between governments, industry and workers. ILO has recommended that countries develop “good national Occupational Safety and Health (OSH) system to strengthen the prevention of occupational diseases”. Both NIOSH and ILO have stressed the need for training and research to identify hazards control methods. Proper teaching and training of healthcare professionals, industrial hygienists, employees, and employers is a requirement for a successful OSH program.

### **The Hierarchy of Workplace Hazards Control<sup>95</sup>:**

- Elimination: remove the hazardous chemical or change work process that will keep the hazard away from the work site; This is the most effective means.
- Substitution: use a substance that is not toxic or less toxic.
- Engineering control: automation, guarding, isolation (to prevent the substance from reaching the exposed person) and local exhaust ventilation to remove the hazardous substance from the work site.
- Administrative control: involves proper training, education, work scheduling and supervision.
- Personal Protective Equipment (PPE): provide suitable PPE and educate workers of their proper use, storage, cleaning, and enforce their use; This is the least effective.

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