The Nervous System – Target Organ into the Twenty-First Century

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1. WHY NEURONS MAKE GOOD TARGETS FOR OCCUPATIONAL TOXICANTS

Neuroanatomical structures have large surface areas and receptor populations, e.g., the surface area of the brain’s 100 billion neurons totals hundreds of square metres.

Neurons have high rates of metabolism, e.g., the brain at 2% body mass consumes 20% of the whole body’s energy budget (Herculano-Houzel, 2011). 1 mol glucose $\rightarrow$ 38 mol ATP

High blood flow in the CNS enhances its exposure to circulatory toxicants, e.g., the brain receives 15% of cardiac output.

Neuronal tissues have high lipid content which facilitates lipophilic bioaccumulation.

The dense synaptic networks of neurons are susceptible to toxicants targeting their profuse receptor and neurotransmitter sites.

Neurons have limited regenerative capacity, e.g., CNS nerve axons do not regenerate.

Neurons are postmitotic and do not divide so neuronal loss is persistent throughout life.

The fetal nervous system is a susceptible target for adverse developmental effects, e.g., from methylmercury, lead, ethanol, etc. (Grandjean and Landrigan, 2006).

It is claimed that the high concentration of sulfur-containing amino acids, e.g., cysteine, in the brain makes it more susceptible to heavy metals, e.g., mercury binds to the sulfhydryl groups on cysteine (Shaw, 2010).

Finally, neuronal networks determine an infinite repertoire of behavioral and cognitive outcomes and toxic effects at cellular levels will have emergent properties at higher levels of neural organization (Kolodkin et al. 2012).

2. FROM CLASSICAL PLUMBISM TO BEHAVIORAL TOXICOLOGY

Hippocrates (c. 460-370 BC) has been cited as the first ancient author to describe a case of occupational neurotoxicity but this has been shown to be erroneous (Osler, 1907; Waldron, 1973, 1978; Skrabanek, 1986; Vance, 2007). The earliest report appears to be that of Nicander of Colophon (2nd cent. BC) who observed that in “psimuthion” i.e. white lead ($2\text{PbCO}_3\cdot\text{Pb(OH)}_2$) poisoning, the victim “grows chill, while sometimes his eyes behold strange illusions or else he drowses; nor can he bestir his limbs as heretofore, and he succumbs to the overmastering fatigue” (Gow and Scholfield, ed. and trans. 1953:99).

Due to their widespread usage since antiquity, there is a long history of recorded health effects from lead (Waldron, 1973; Nriagu, 1983a, 1983b; Wedeen, 1984; Green, 1985; Lessler, 1988; Hernberg, 2000; Tepper, 2007; Azizi and Azizi, 2010; Riva, 2012; Dissanayake and Erickson, 2012) and mercury (Goldwater, 1972; Wedeen, 1989) with notorious public exposures such as from methylmercury at Minamata Bay in the 1950s (Harada, 1995; Tsuda et al. 2009), tetraethyl lead in gasoline (Rosner and Markowitz, 1985) and leaded paints (Gibson 1904; Markowitz and Rosner, 2000; Warren 2000).
In two articles published in 1965 and in a posthumously published book in 1990, Gilfillan contended that lead contamination of water supplies and wine caused aristocratic infertility and sickness throughout the Roman Empire, leading to its collapse. Nriagu (1983c) and Woolley (1984) also promoted this theory. Besides the fact that the Eastern Roman Empire (“Byzantine Empire”) carried on well for a millennium and historians even debate “the fall of Rome,” Gilfillan’s work has been critiqued on toxicological and anthropological grounds (Scarborough, 1984; Needleman and Needleman, 1985; Retief and Cilliers, 2006; Reddy and Braun, 2010).

Ramazzini’s “Diseases of Workers” (1700) is considered to be an early description of occupational neurotoxicity but Ulrich Ellenbog had written about neurotoxicity among goldsmiths in 1473 (not published until 1524) saying that “this vapor of quicksilver, silver and lead is a cold poison, for it makes heavy and tight the chest, burdens the limbs and often makes them lame as one sees in foundries where men work with large masses” (Ashe, 1967:314).

In 1656 the German physician Samuel Stockhausen published his observations on chronic lead poisoning in miners exposed to “litharge” (PbO). In 1616 François Citois, Cardinal Richelieu’s physician, wrote about outbreaks of “colica Pictonum” in Poitou, France where “the movement of upper arm and hands, legs and feet perishes, feeling remains intact however, and... in many cases this paralysis is preceded by a number of epileptic convulsions” (Eisinger, 1982:301). The colic of Poitou was caused by lead-adulterated wines. Similar outbreaks known as “the Devonshire colic” in England (McConaghey, 1967; Waldron, 1970) were shown by George Baker (Baker, 1767, 1785), against general medical opinion, to be caused by lead leached from lead-lined cider presses.

In Scotland, the Lanarkshire lead smelters produced a condition known locally as “mill reek.” Dr. Wilson wrote an article about it in 1754 (Wilson, 1754) noting that “it mostly seizing, and violently affects the men whose daily business it is to melt down the lead... the legs become feeble, with a prickling numbness” (Meiklejohn, 1954:41).
Benjamin Franklin, the American printer and inventor, was well aware of neuropathy in lead typesetters (“the dangles”) and had met George Baker in 1757 (Finger, 2006). In 1767 Franklin visited La Charité hospital in Paris where he reviewed cases of lead poisoning and identified occupational exposures as a common cause (McCord, 1954). Franklin cited this research in his famous “lead letter” of 1786 in which he wrote that he had “found that all the patients were of trades, that, some way or other, use or work in lead” (Franklin, reprinted 1981).

By the 1800s occupational lead neuropathy was well recognized when Louis Tanquerel des Planches published his review of 1217 cases of lead poisoning (including 102 cases of neuropathy) from La Charité (Tanquerel des Planches, 1839). Similarly, Ramazzini (1700) and Kussmaul (1861) had reported palsies and a psychological disorder known as erethism in mirror makers using mercury. Mercurial tremors (“hatters’ shakes”) were reported in felt hat makers (Freeman, 1860; Dennis, 1879) but mercurialism is unlikely to be the basis of Lewis Carroll’s “mad hatter” character (Waldron, 1983; Davies, 2013).

The rise of scientific medicine and neurology (Finger, Boller and Tyler, eds., 2010), the growth of industry, and progress in toxicology itself (Stirling, 2006) developed the field of occupational neurotoxicology. Auguste-Louis Delpech had published his observations on the neurological and psychological effects of carbon disulfide in 1856 and 1863, introducing the modern era of behavioral neurotoxicology (O’Flynn and Waldron, 1990; Lucchini et al. 2012).

Dr. Karen Wetterhahn, an inorganic chemist at Dartmouth College, died in June 1997 after spilling a few drops of dimethyl mercury onto her latex gloved hand in August of 1996. By January 1997 she had ataxia, tremors, and slurred speech and in 3 weeks was in a coma. Her unfortunate clinical course was reported by Nierenberg et al., 1998.

3. TOXICOKINETICS, COMPARTMENTS, AND PBPK MODELS

Toxicokinetics is the study of the movement of an exogenous agent (element, mineral, or other chemical compound) into, through, and out of the body including its distribution, biotransformation, retention, and excretion.

Neurotoxicants are generally ingested or inhaled although some, as noted above, are readily absorbed through skin contact. The pathway from exposure to the neural target involves factors influencing absorption, e.g., concentration, duration of exposure, surface area, integrity and vascularity of the contact site, physicochemical properties of the neurotoxicant (lipid-water solubility, degree of ionization, molecular size, particle size, etc.), pulmonary ventilation rate, cardiac output, CYP450 induction, saturable kinetics.

Pre-systemic elimination may involve a first-pass elimination, e.g., manganese is taken up from the portal blood into the liver and excreted into the bile.
Neurotoxicants are distributed to organs either in solution in the blood or bound to circulating plasma proteins. The blood-brain barrier prevents access of hydrophilic chemicals to the brain except for those which are actively transported. However, lipophilic agents are able to pass through.

Toxication or metabolic activation may occur, e.g., parathion (a “pro-poison”) is biotransformed to the active cholinesterase inhibitor paraoxon. Detoxication involves enzyme-mediated phase I and phase II molecular transformations to enable excretion. Sometimes detoxication creates neurotoxic by products such as 2,5-hexanedione from n-hexane or methyl n-butyl ketone (see 4.1 below).

The nervous system presents a diverse array of cellular targets which may undergo chemical alterations or disruption by neurotoxicants, e.g.,

DNA
Protein synthesis
Enzymes, e.g. AChE, NTE
Energy metabolism
Membrane channels
   e.g., Sodium
   Potassium
   Chloride
   Calcium
Axonal transport
   OPs, Tl, As, n-hexane, CS₂, ricin
Neuroglia
   Pb, Hg, triethyltin,

Compartment models help to conceptualize the distribution of neurotoxicants throughout the body. The brain and spinal neurons are some of the most richly perfused tissues. The model below provides an example for a low molecular weight volatile organic chemical. Transport of such a chemical through body compartments is indicated by the arrows:

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PBPK Modeling

Physiologically based pharmacokinetic ("PBPK") models, sometimes referred to as physiological toxicokinetic ("PT") models, can show quantitative toxicant movements and distributions among body compartments and can enable calculations and predictions of tissue concentrations of xenobiotics.

The PBPK model is built up from data collected on physiological functions, e.g., blood flow rates in various organs and time-course chemical disposition, and then refined with mathematical modeling and laboratory testing. PBPK models, developed earlier for herbicides, solvents, industrial monomers, and hydrocarbons (Andersen, 2003), are now applied to risk assessment, toxicity testing, and are sometimes combined with micro cell culture analogs or "body-on-a-chip" devices.

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Types of Substrate</th>
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<tbody>
<tr>
<td>Phase I</td>
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<tr>
<td>Alcohol dehydrogenases</td>
<td>Ethanol</td>
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<tr>
<td>Aldehyde dehydrogenases</td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td>CYP1A1</td>
<td>Benzo(a)pyrene</td>
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<tr>
<td>CYP1A2</td>
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<td>Chlorzoxazone</td>
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<td>CYP3A4</td>
<td>Nefedipine</td>
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<td>Cholinesterases</td>
<td>Succinylcholine</td>
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<td>Arylesterases</td>
<td>Paraoxon</td>
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<tr>
<td>Epoxide hydrolases</td>
<td>Benzo(a)pyrene oxide</td>
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<td>Phase II</td>
<td>Paracetamol</td>
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<tr>
<td>UDP-glucuronosyl transferases</td>
<td>4-Nitrophenol</td>
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<td>Sulfo transferases</td>
<td>Sulfometazine</td>
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<td>N-acetyl transferases</td>
<td>Histamine</td>
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<td>N-methyl transferases</td>
<td>6-Mercaptopurine</td>
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<td>S-methyl transferases</td>
<td>Methyl chloride</td>
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<td>Glutathione-S-transferases T1</td>
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A schematic diagram of the various body compartments used in a PBPK model for lead with a more detailed schematic for lead in blood and extra vascular fluids (“EVF”) shown at the right.

Diffusible plasma is viewed as the central mobile compartment in this model (Leggett, 1993).
4. Toxicodynamics of the Nervous System

Toxicodynamics refers to the molecular, biochemical and pathophysiological effects of agents on the body.

Whereas Toxicokinetics can be thought of as:

“what the body does to the dose”

Toxicodynamics can be viewed as:

“what the dose does to the body”

Together they form a continuum from exposure to outcome as illustrated below. Toxicology simply describes this pathway.

TOXICOKINETICS

EXPOSURE
[conc.] of an agent in the environment
e.g., air-borne lead level

INTERNAL DOSE
[conc.] of an agent in a body tissue/fluid
e.g., blood lead level

BIOLOGICALLY EFFECTIVE DOSE
[conc.] of agent at a specific target site
e.g., bone marrow lead level

TOXICODYNAMICS

EARLY BIOLOGICAL EFFECT
(a subcellular/biochemical response)
e.g., inhibition of δALAD

ALTERED STRUCTURE/FUNCTION
(a preclinical change / dysfunction)
e.g., elevation of protoporphyrin

CLINICAL DISEASE
(overt disease/dysfunction)
e.g., lead anemia, neuropathy, etc.

4.1 Peripheral Neurons

Neurons are extraordinary cells that may extend for a metre, 200,000 times the length of other cells. The axonal volumes of peripheral nerves can be hundreds of times that of their cell bodies.
The neuron is a hub of metabolic activity and axonal transport – fast axonal transport along microtubules reaches 400 mm/day. If a neuron’s cell body (soma) is lethally damaged, the degenerative process is a “neuronopathy”. Mega doses of pyridoxine (vitamin B₆) produce sensory neuronopathy. Carbon monoxide causes neuronopathy, particularly in the basal ganglia, by anoxic anoxia. Cyanide causes neuronopathy by cytotoxic anoxia (irreversible inhibition of cytochrome oxidase).

When the site of injury is the axon, this form of damage is an “axonopathy” which has potential for regeneration. The Schwann cells in the PNS facilitate the regrowth of axons and recovery of their function if axonal contact is restored. Chemicals directly inducing distal axonopathies include:

- triorthocresyl phosphate (TOCP)
- acrylamide
- para-bromophenylacetylurea
- zinc pyridinethione
- isoniazid
- carbon disulfide
- disulfiram
- leptophos
- n-hexane
- methyl n-butyl ketone
- 2,5-hexanedione

We now know that the neurotoxicity of the hexacarbons requires a gamma-diketone structure i.e. the second ketone (the γ-position) is at the third carbon from the first ketone and 2,5-hexanedione is the active metabolite. Neither methyl ethyl ketone, methyl iso-butyl ketone or other alkane chains of less than 6 carbons can result in the γ-diketone form. The diketone hexacarbon binds to lysine in the neurofilaments of axons and disrupts axonal transport.

Axonopathies can also occur secondary to demyelination from other causes. Peripheral nerves are wrapped by Schwann cells which form multilamellar myelin sheaths around the larger diameter axons. A “myelinopathy” or myeloneuropathy can arise from exposure to hexachlorophene, lead, triethyl tin or tellurium. An unusual myeloneuropathy occurred in Cuba during 1992 and 1993 affecting 51,000 people who had a sensory peripheral neuropathy following an optic neuropathy. The cases almost all recovered and were eventually attributed to deficiency of thiamine (vitamin B₁) (Román, 1994).

Toxic neuropathies are usually of slow or delayed onset, are symmetrical, and present with distal sensory and motor symptoms. There may be reduced sensation, mild distal weakness and/or autonomic dysfunction. Laboratory findings may be unremarkable. Nerve conduction studies may show mild deficits and denervation on EMG. A careful history of workplace and non-occupational exposures is needed to focus on suspected agents. Historically these have included arsenic, lead, mercury, PCBs, thallium, methyl bromide, ethylene oxide, and organophosphates - one of the more infamous outbreaks from OPs involved thousands of Americans during the prohibition era who developed peripheral motor neuropathy after drinking “ginger Jake” a ginger extract contaminated with triorthocresyl phosphate (Morgan, 1982; Parascandola, 1994).
4.2 Synaptic Neurotransmission

The nervous system uses two main classes of neurotransmitters: various small-molecules (e.g. acetylcholine (ACh) and biogenic amines) and neuropeptides. Whereas small-molecule synaptic messengers act on adjacent receptors, neuropeptides act upon neuronal networks as hormonal-like cell signals. Acetylcholine synaptic transmission is a particular target of a large class of occupational neurotoxins known as the organophosphates and carbamates:

\[ \text{Organophosphate} \quad \text{Carbamate} \]

\[ R_L = \text{“the leaving group” i.e. the site of the binding to acetylcholinesterase} \]
\[ R_2 = \text{either methoxy, ethoxy, phenyl, amino, Alkylthio, or substituted amino groups} \]
\[ R_3 = \text{methyl or ethyl groups} \]

Some Carbamates

- aldicarb (Temik)
- bendiocarb (Ficam)
- bufencarb (Bux)
- carbaryl (Sevin)
- carbofuran (Furadan)
- formetanate (Carzol)
- methiocarb (Mesurol)
- methomyl (Lannate, Nudrin)
- oxamyl (Vydate)
- pinmicarb (Pirimor)
- propoxur (Baygon)

Some Organophosphates

- acephate (Orthene)
- azinphos-methyl (Guthion)
- carbofuran (Furadan, F formulation)
- carbophenothion (Trithion)
- chlorfenvinphos (Birlane)
- chlorpyrifos (Dursban, Lorsban)
- coumaphos (Co-Ral)
- crotamphos (Ciodrin, Ciovap)
- crufomate (Ruelene)
- demeton (Systox)
- diazinon (Spectracide)
- dichlorvos (DDVP, Vapona)
- dicrotophos (Bidrin)
- dimethoate (Cyon, De-Fend)
- dioxathion (Delnav)
- disulfoton (Di-Syston)
- ethoprop (Mocap)
- fenamiphos (Nemacur)
- fenitrothion (Sumithion)
- focophos (Dyfonate)
- isofenfos (Oftanol, Amaze)
- malathion (Cythion)
- methamidophos (Monitor)
- methidathion (Supracide)
- mevinphos (Phosdrin)
- naled (Dibrom)
- oxydemeton-methyl (Meta systox-R)
- parathion (Niran, Phoskil)
- phorate (Thimet)
- phosalone (Zolone)
- phosmet (Imidan, Prolate)
- phosphamidon (Dimecron)
- temephos (Abate)
- terbufos (Counter)
- tetrachlorvinphos (Rabon, Ravap)
- trichlorfon (Dylox, Neguvon)

Organophosphate Nerve Agents

- sarin, soman, VX
When an acetylcholine molecule attaches to the receptor on a post-synaptic neuron or a muscle cell, a cellular process is triggered which results in a nerve signal or a muscle fiber contraction. The receptor-bound acetylcholine is rapidly broken down by acetylcholinesterase (Silman and Sussman, 2008) which produces free choline that the pre-synaptic neuron can uptake and reuse for further pre-synaptic discharge. The receptor-bound acetylcholine only resides for a few milliseconds before being enzymatically broken down.

Certain sites on the acetylcholinesterase enzyme are attracted to the electropositive phosphorus group of organophosphate molecules and a stable bond creates a phosphorylated AChE which is biologically inactive. The organophosphates and carbamates (the latter are more reversible) inhibit AChE and produce a post-synaptic cholinergic “overdrive” due to the persisting ACh occupation of post-synaptic receptors. Instead of the usual microseconds of receptor activation, the blocked acetylcholinesterase enzyme now permits many minutes to hours of ACh activation with clinically-associated physiological effects (See 5.4 below).

4.3 Special Senses

Toxic optic neuropathy has resulted from methanol ingestion with permanent visual loss within hours to days. Methanol’s toxicity is due to its metabolite formic acid. Toluene can also produce optic neuropathy. Radiation induced optic neuropathy is a delayed toxic effect of radiation over weeks to months.

Olfactory dysfunction has been found with occupational exposures to cadmium even at relatively low concentrations (Doty and Hastings, 2001). Workers using solvents can develop “industrial anosmia” where extended exposures to strong odors results in a reduction in sensitivity confined to those odors. This effect is reversible after the worker is removed for a time from the exposure.

Olfactory deficits can occur after exposures to high concentrations of irritant gases due to damage to the olfactory epithelium. Neoplasms from exposures to nickel dust, wood dust, formaldehyde, or radiation can impair olfaction.

Styrene, ethylbenzene, and allylbenzene are potent ototoxins in lab animals (Gagnaire and Langlais, 2005)
A recent Swedish report (Johnson and Morata, 2010) states that:

“1) human data indicate auditory effects under or near existing OELs and robust animal data support an effect on hearing from exposure (styrene, toluene, carbon disulfide, lead, mercury, and carbon monoxide),

2) human data are lacking whereas animal data indicate auditory effects under or near existing OELs (p-xylene, ethylbenzene, and hydrogen cyanide),

3) human data are poor or lacking and animal data indicate an auditory effect well above the existing OELs (chlorobenzene, trichloroethylene, n-hexane, n-heptane, some solvent mixtures, trimethyltin, acrylonitrile, 3,3′-iminodipropionitrile, pesticides, and PCBs).”

4.4 Movement Disorders

The primary neurotoxic movement disorders include parkinsonism, tremor, and ataxia. The earliest descriptions of toxic movement disorders were from lead and mercury (Gillen, 1995). Manganese-induced ataxia was reported by Couper in 1837. Manganese, carbon monoxide, carbon disulfide, and hydrogen sulfide can produce parkinsonism.

Toluene, mercury, organophosphate organochlorine and pyrethroid pesticides can induce tremors. Toluene, organophosphates, thallium, and methyl mercury can produce ataxia.

Toxic effects on either the granular cells or the Purkinje cells of the cerebellum have been reported in lab animal exposures from 2-chloropropionic acid, methyl mercury, bilirubin, ionizing radiation and trichlorfon (Fonnum and Lock, 2000).

4.5 Neuroaffective and Neurocognitive Effects

The cerebral cortex is involved in many complex brain functions such as memory, attention, and thinking and the limbic system plays an important role in mood. Various occupational neurotoxicants have been shown to affect cognition and mood as shown below:

**Delirium**
- Carbon monoxide
- Lead
- Arsenic
- Manganese
- Solvents
- Organophosphate pesticides

**Dementia**
- Solvents
- Lead
- Manganese
- Arsenic

**Organic Delusional Disorder**
- Solvents
- Organophosphate pesticides

**Mood Disorder - Manic**
- Manganese
- Tetraethyllead

**Mixed Mood Disorders**
- Lead
- Organophosphate pesticides
- Carbon monoxide
- Solvents (e.g., carbon disulfide)
- Organotins
- Inorganic mercury

These neurotoxicants will be dealt with in more detail below. Some have complained that psychiatry has not been attentive enough to “psychotoxicology” (Dumont, 1989).
5. **Noteworthy Occupational Neurotoxicants**

5.1 “Heavy metals” (Pb, Hg, Tl) and other elements

**Lead (Pb)**

The extensive history of the occupational health effects of lead has been outlined above. Despite our longstanding awareness of lead’s neurotoxicity it remains a toxicant which must be kept “under watch.”

More than 30% of retained lead in the lungs enters the circulation where it is rapidly bound to red cell membranes (10%), red cell proteins, e.g., Hb (85%), and plasma proteins (Gonick, 2011). About 10% of ingested lead is absorbed, mostly in the upper small bowel by active transport (there is competitive kinetics with iron and calcium). Nonorganic lead is readily absorbed through the skin. In the bone marrow, lead is a potent non-competitive inhibitor of the sulphydryl-containing enzymes delta-ALA-synthetase, delta-ALA-dehydrogenase, CPG-oxidase, and Ferrochelatase, all necessary for heme synthesis. Elevated ALA is itself neurotoxic. Elevation of free erythrocyte protoporphyrin, “FEP”, is an early indicator of lead toxicity within 6-8 weeks of exposure (it is measured as zinc protoporphyrin, “ZPP”).

The half life of inorganic lead in blood is about 40 days so blood lead levels reflect recent exposures. This compartment is also chelatable with agents such as 3-dimercaptopropanesulfonic acid (DMPS) or the less toxic 2,3-dimercaptosuccinic acid (DMSA). Over 90% of the body burden of accumulated lead is stored in bone, particularly calcaneal (half-life of 16 years) and tibial (half-life of 27 years). X-ray fluorimetry (“XRF”) of cortical bone can provide a quantitative assessment of cumulative lead exposure.

There are questions as to whether or not adverse health effects can occur with high body burdens of lead even when blood lead levels remain normal. However, in its position statement, the American College of Medical Toxicology states that “post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning” (Charlton and Wallace, 2010; Jang and Hoffman, 2011; contra Crinnion 2009a, 2009b).

Overt lead neuropathy with chronic lead exposures usually onsets with motor deficits in forearm extensors (classical “wrist drop”), slowing of nerve conduction velocities, some thenar weakness, and, in more advanced cases, there may also be sensory involvement.

Sustained higher levels of lead can result in tremors, incoordination, ataxia, mood changes, various cognitive impairments, seizures, and even coma and death.

80% of absorbed lead is excreted in the urine with some in bile, GI secretions, and sweat. Lead reduces uric acid excretion and can cause so-called “saturnine gout”.

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**Diagram:**

LEAD INHIBITION OF HEME PATHWAYS (asterisks show the affected enzymes)
Mercury (Hg)

Elemental mercury (Hg\(^0\)) is a metallic liquid which is volatile at room temperature and its vapor is highly lipophilic. Elemental mercury is poorly absorbed orally but about 74% of Hg\(^0\) vapor is retained by inhalation (Syversen and Kaur, 2012). In both blood and brain, Hg\(^0\) is oxidized by catalases to Hg\(^{2+}\) which avidly binds to sulfhydryl groups. The half-life of Hg\(^0\) is about 60 days (Spaeth, Tsismenakis, and Kales, 2010) and excretion is mainly in the urine.

Inorganic mercury compounds i.e. mercury salts as “mercurous,” Hg\(^{2+}\), or “mercuric,” Hg\(^{2+}\) (the former are generally less soluble, e.g. calomel, Hg\(_2\)Cl\(_2\), once widely used as a cathartic) are up to 10% absorbed orally. Both Hg\(^{2+}\) and Hg\(^{2+}\) forms are protein-bound in plasma and do not readily cross the blood-brain barrier. Inorganic mercury can produce neurotoxicity as occurred in the felt hat industry from Hg(NO\(_3\))\(_2\) (see Section 2), e.g., sensory neuropathy and neurobehavioral changes may develop. The half-life of inorganic mercury is about 40 days with excretion in urine (20%) and feces (80%).

Organic mercury compounds have caused several large epidemic outbreaks, e.g., at Minamata Bay from industrial contamination and in Iraq in 1956, 1960, and 1972, from mercurial fungicide contaminated grains (Bakir et al., 1973). Minamata Disease has occurred at Niigata Japan in the 1960s (Maruyama, 2012) and in Canada at Grassy Narrows in the 1970s (Harada, 2005).

Ethyl- and methylmercury compounds have similar toxicology but the former is more rapidly degraded to Hg\(^{2+}\) and is less toxic. There is 80% GI and lung absorption and MeHg crosses cell membranes by passive diffusion and also by active transport, bound to cysteine. MeHg is mostly excreted in bile and feces bound to glutathione but some MeHg is metabolized to inorganic Hg and excreted in the urine. The half-life in blood is about 2 months but brain retention is much longer.

The clinical neurotoxicity of organic mercurials is usually delayed by 3 to 6 weeks from the onset of exposure. Early symptoms include distal and perioral paresthesiae, tremors, then ataxia, constriction of visual fields, central hearing loss, spasticity, cognitive deficits, and parkinsonism.

Significant 24-hour urine concentrations of mercury suggest elemental or possibly inorganic Hg exposure. Significant blood concentrations of Hg with low urine concentrations are suggestive of organic Hg exposure. Spot urine sampling can serve as a screening test for biomonitoring purposes. Although each cm of scalp hair can correlate with the mean blood Hg for a month, hair sampling is problematic because of improper specimen collection and handling as well as external contamination.

Was this man a “mad hatter”?

Thomas P. “Boston” Corbett worked as a hatter in Troy, N.Y. “for two decades or more” (Furgurson, 2009:51). In April of 1865 he shot and killed John Wilkes Booth, the assassin of President Lincoln. A judge later declared Corbett to be “hopelessly insane”.
**Thallium (Tl)**

Thallium salts are tasteless, odorless, and water soluble making them excellent poisons. Thallium is well absorbed orally or through the skin or lungs and is rapidly distributed. Like other heavy metals, Tl has an affinity for sulfhydryl groups and inhibits enzymes such as ATP-ase. Clinical features depend upon the dosage and duration of exposure.

Acute exposure produces gastrointestinal symptoms and neurological features including hyperesthesiae, hyperreflexia, ataxia, agitation, paresis, confusion, hallucinations, seizures, and coma. A rapidly progressive peripheral neuropathy is mostly sensory. If the victim survives, alopecia begins about a week or more after exposure. Ingestion of less than a gram of Tl can be lethal. Unlike many xenobiotics, thallium undergoes enterohepatic circulation with primary excretion in feces. The half-life of thallium is about 30 days.

Chronic thallium exposure results in insidious fatigue, insomnia, neurobehavioral disorders, peripheral neuropathy, and mood changes.

Diagnosis of thallium poisoning is by identification of elevated thallium in hair and 24-hour urine samples. Nerve conduction studies show axonal degeneration.

Prussian Blue (Fe$_4$[Fe(CN)$_6$]$_3$) is a specific antidote for thallium toxicity. Treatment with Prussian Blue in patients with thallotoxicosis can be life-saving but it does not improve all of the clinical signs, such as neurological signs or alopecia, particularly in late presenting patients. Prussian Blue exchanges potassium for thallium and the insoluble antidote is excreted as a fecal thallium-Prussian Blue complex. Prussian Blue also effectively absorbs caesium.

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**Manganese (Mn)**

Occupational exposures to manganese are mostly from mining, alloy production, and welding.

The early descriptions of “manganism” reported an extrapyramidal syndrome with personality changes, postural, gait, and speech abnormalities (Martin, 2006). Manganism victims continued to worsen for long periods after their exposure ceased. In the mid-twentieth century “manganese psychosis” was used to describe reversible behavioral changes with Mn exposure.

A Mn-induced parkinsonian syndrome was observed with tremor, gait disturbances, clumsiness, dystonia, and postural instability (Feldman and Ratner, 2001). Pathological studies showed consistent damage to the globus pallidus with sparing of the substantia nigra which contrasts with Parkinson Disease where the dopaminergic neurons in the substantia nigra degenerate and the neurons in the pallidum are preserved (Perl and Olanow, 2007). Moreover, those with manganism do not respond to levodopa treatment as do those with Parkinson Disease.
Manganese is a necessary trace element and is an enzyme cofactor, e.g., in superoxide dismutase which scavenges free radicals and glutamine synthetase in the GABA pathway.

Less than 5% of ingested Mn is absorbed. Once past the portal circulation, Mn is bound to plasm proteins and accumulates in many organs including the brain. Mn may also be taken up into the brain directly via olfactory pathways. Inhaled Mn is well absorbed.

Methylcyclopentadienyl manganese tricarbonyl (“MMT”) has been added to Canadian gasolines since 1976 as an anti-knock agent. This is now the major non-occupational source of Mn. In contrast to inorganic Mn compounds, MMT crosses the blood-brain barrier by passive diffusion and preferentially accumulates in the cerebellum.

The role of manganese in Parkinson Disease (“PD”) is under intense study. A recent review concludes that “while manganese exposure is widely studied in relation to PD, many believe that manganism is a separate entity as it predominantly involves the globus pallidus rather than the substantia nigra pars compacta, and the seemingly overlapping clinical signs may just be a result of the involvement of basal ganglia dysfunction and damage to common output pathways in both disorders” (Caudle et al., 2012:183).

Some studies of low level manganese exposure have found subclinical neurological deficits such as impaired coordination, postural instability and tremor.

Distinguishing manganism from PD can be challenging – dystonia is less prominent in PD and manganism has less resting tremor. Neither blood nor urine levels reflect well on acute, chronic, or toxic exposures and urine and blood levels correlate poorly with individual exposures.

**Arsenic (As)**

Arsenic has a “colorful” history, not only from its use as a yellow (As2S3) or red (As4S4) pigment, but from its use in medications, pesticides, and in homicides. Like thallium, arsenic is tasteless and odorless and so has been used for centuries as an ideal poison in the form of As2O3. Arsenic readily forms inorganic and organic compounds.

“Fowler’s solution,” a 1% solution of potassium arsenite, K2HAsO3, was a widely used tonic and skin home remedy well into the twentieth century. Arsenic-based pharmaceuticals were used to treat syphilis in the pre-penicillin era (Gibaud and Jaouen, 2010). Cacodylic acid (CH3)2AsO2H (“Agent Blue”) was used as a herbicide in the Vietnam War. Monosodium methyl arsenate (“MSMA”) is one of the remaining arsenic-based herbicides. Chromated copper arsenate (CrO3:CuO:As2O5 = 48:18:34) was used as a wood preservative for many years.

Occupational exposures to arsenic occur in mining, smelting, chemical production, and horticultural and agricultural applications.

Toxic levels of inorganic arsenic compounds can cause peripheral neuropathy and encephalopathy. Oral absorption varies with their solubility. Arsenic readily crosses the blood brain-barrier and preferentially accumulates in brain white matter and peripheral nerve myelin. As5+ (arsenate) is less toxic than its “detoxified” form As3+ (arsenite) which binds to sulfhydryl groups.

After biomethylation, monomethyl arsenic and dimethylarsenic are excreted in urine. As arsenic’s half-life is about one day, urine testing is unhelpful. Since hair binds inorganic As, it can indicate chronic exposure if external contamination is ruled out well.
Aluminum (Al)

Aluminum has been implicated in neurodegenerative diseases such as Alzheimer Disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson Disease (PD). The physical properties of aluminum and ferric iron ions are similar enough to suggest that aluminum uses mechanisms in place for iron transport to enter neurons involved in AD progression, accumulating in those neurons, and causing neurofibrillary damage (tangles).

Studies have found that cognitive functioning is affected at mean urinary Al concentrations between 30 and 61 micrograms/litre (Meyer-Baron et al, 2007). This is consistent with mild neurocognitive deficits and EEG abnormalities noted in dialysis patients at Al plasma levels of 50 micrograms/litre (Dobbs, 2009:285). Chronic occupational exposure to aluminum-containing welding fumes has resulted in delayed overall reaction times in some exposed workers.

In acute high exposures to aluminum, the outcomes reported in adults include agitation, confusion, myoclonic jerks, and coma. Up to 90% of aluminum in the plasma is in a complex with transferrin. The half-life in blood is about a week in acute exposures, much longer for chronic exposures.

The most frequently reported neurological symptoms in aluminum workers include (Feldman, 1999:133):

- Loss of Balance
- Memory Loss
- Dizziness
- Numbness and Paresthesiae
- Weakness
- Poor Concentration
- Tremor

As with manganism and PD, distinguishing Al toxicity and idiopathic AD is a challenge.

Tin (Sb)

Tin forms stannous (Sn^{2+}) and stannic (Sn^{4+}) inorganic compounds. Inorganic salts of tin are relatively insoluble and poorly absorbed. In contrast, the lipid-soluble organotins are well absorbed by all routes and cross the blood-brain barrier.

Triethyltin (TET) preferentially affects myelin and motor functions whereas trimethyltin (TMT) affects neurons more, causing neurobehavioral changes in mood, memory, cognitive performance. The primary target of TMT appears to be the hippocampus.

An accidental poisoning of 210 people in France in 1954 from a TET contaminated oral medication showed an LD50 of 50 mg. Initial symptoms included headaches, apathy, confusion, and later paresis, seizures and coma.

An occupational exposure to TMT among 22 workers in 1981 produced neurotoxic mayhem reported as “hearing loss, seizures, disorientation, confusion, confabulation, restlessness, aggressiveness, hyperphagia, disturbed sexual behavior, ataxia, neuropathy, blurred vision” (Feldman, 1999:151).

Tellurium (Te)

Tellurium is used in photovoltaic cells and gamma radiation sensors in the form of cadmium telluride. The preparation of CdTe crystals can expose workers to tellurium.

The neurotoxic effects of Te are due to damaged Schwann cells which result in segmental demyelination and motor neuropathy. Recovery of nerve function is possible with removal from exposure. The detoxication product of Te, dimethyl telluride, gives a garlic odor to the breath.
5.2 Organic Solvents

The common organic solvents include:

- Aliphatic hydrocarbons
- Cyclic hydrocarbons
- Aromatic hydrocarbons
- Halogenated hydrocarbons
- Ketones
- Amines
- Esters
- Alcohols
- Aldehydes
- Ethers

These solvents are lipophilic and readily cross membranes and the blood-brain barrier, hence the early use of organic solvents in inhalational anesthesia, e.g., ether \((\text{C}_2\text{H}_5)_2\text{O}\) and chloroform \(\text{CHCl}_3\).

There is a spectrum of neuropsychological effects from solvent exposures. Acute inhalational exposures can produce reversible euphoria, disinhibition, sedation, apathy, and confusion. With increased durations of exposures, neurobehavioral abnormalities may persist and intensify leading to deficits in memory, attention, mood, cognition, and personality changes. The World Health Organization criteria (1985) for chronic solvent-induced encephalopathy include 3 levels of CNS dysfunction:

1. **Organic Affective Syndrome**
   Reversible mood, motivation, memory, and concentration disorders without abnormal neurological findings or deficits on neuropsychological testing.

2. **Mild Chronic Toxic Encephalopathy**
   Ongoing features of OAS as above with persistent diminished memory, psychomotor functions, and other abnormalities of mood, personality, and behavior.

3. **Severe Chronic Toxic Encephalopathy**
   Loss of intellectual abilities of sufficient severity to interfere with social and/or occupational functioning; fixed impairment of abstract thinking and other cognitive functions, personality changes, some neuropsychiatric (e.g., by DSM-V criteria) and neuroradiological test abnormalities. Severe symptoms are usually irreversible.

There is a similar classification from the 1985 International Solvents Workshop in Raleigh NC which stratified the WHO “Type 2” into a primarily mood-personality disorder (“2A”) and a neurocognitive disorder (“2B”).

Volatile organic compounds (VOCs) are those which have boiling points between 50°C and 260°C. Organic solvents are widely used in many industrial, commercial, and domestic settings. Many commercial solvents contain mixtures of agents and workers often use multiple solvents in the course of their work. It is not always possible to attribute a clinical presentation to a specific solvent and most solvents have class effects from their shared physical-chemical properties.
Toluene,
\[ \text{C}_7\text{H}_8 \]
BP 111°C

Toluene is the most prevalent aromatic hydrocarbon in the atmosphere, and makes up 7% of gasoline by weight. Blood concentrations rapidly equilibrate with alveolar concentrations, it is carried unbound in the blood, passes readily through the blood-brain barrier, and higher concentrations of toluene are found in the brain’s white matter. Toluene’s effect on N-methyl-D-aspartate (NMDA) receptors in the hippocampus is thought to play a role in cognitive impairments.

Toluene has a typical profile of solvent neurobehavioral effects, e.g. at 150 ppm, there is a 7% decrease in performance on visual memory, verbal memory, visual pattern perception, and manual dexterity. Natural experiments in toluene toxicity by glue sniffers show prevalent cognitive deficits, cerebellar dysfunction (ataxia and postural tremor) and, in advanced cases, peripheral neuropathy and chronic encephalopathy with MRI changes.

Some toluene (15%) is eliminated unchanged by exhalation but the main pathway of detoxication is by transformation of the methyl group to conjugate with glucuronic acid (to form benzoyl glucuronide) and with glycine (to form hippuric acid, “HA”) so both can be excreted in the urine.

End of work shift urine hippuric acid levels correlate well with mean daily environmental concentrations and can serve as a marker of exposure. The half-life of toluene in blood is only a few hours.

Xylene,
\[ \text{C}_6\text{H}_4(\text{CH}_3)_2 \]
3 isomers
BP 139°C

Xylene is used as a thinner and solvent in paints, varnishes, adhesives, and inks and as a solvent in the leather, rubber, and printing industries. It is also used in histology labs.

The toxicokinetics of xylene are similar to toluene. Excretion is 5% unchanged in exhaled air and 95% by detoxication to methylhippuric acid.

Solvent-type neuropsychological effects have been noted at xylene levels of 90 to 200 ppm, e.g. impairments in reaction time and manual dexterity, and at 300 ppm subjects have experienced deficits in numerical ability and short-term memory. Xylene may disrupt fast axonal transport and a peripheral neuropathy from xylene has been (rarely) reported.

Styrene,
\[ \text{C}_8\text{H}_8 \]
BP 146°C

Styrene is a feedstock for polymers such as polystyrene, acrylonitrile-butadiene styrene (ABS) plastic, styrene-acrylonitrile (SAN) plastic, and styrene-butadiene rubber (SBR). It is also used in the manufacture of fibreglass reinforced plastic products (“fibrellass”).

Styrene is readily absorbed and crosses the blood-brain barrier where it accumulates in lipid rich brain tissue. The toxicity of styrene appears to be due to its biotransformation to styrene-7,8-oxide.

The neuropsychological effects of styrene appear to be less than toluene but decrements in neurobehavioral performance have been reported.
Subtle effects on central auditory pathways and vestibulomotor functions have been reported in styrene exposed subjects. There is some evidence for central styrene auditory toxicity (see 4.3 above).

Sensory neuropathy has been reported in workers exposed to over 100 ppm of styrene. Excretion is 3% unchanged in exhaled air and 95% by detoxication to mandelic acid (MA) and phenylglyoxylic acid (PGA) and a small proportion to hippuric acid. The sum of MA and PGA in the urine correlates well with recent exposure. Concurrent exposures to toluene or xylene can inhibit the metabolism and excretion of styrene.

**Trichloroethylene.**
\[ \text{C}_2\text{HCl}_3 \]
BP 87°C

Trichlorethylene was used in the past as an inhalational anesthetic and dry cleaning solvent. It is a metal degreasing solvent. It is classed as an IARC Group 1 carcinogen.

TCE is highly lipophilic and accumulates in the brain. Acute and chronic symptoms are typical of volatile organic solvents.

Trigeminal analgesia was a notable effect of TCE during its use as an inhalational anesthetic. Subsequently, trigeminal neuropathy has been reported with industrial TCE exposures. The mechanism is not known – some have suggested that TCE activates a latent herpes simplex virus in the nerve. The cranial nerve shows severe axonal degeneration and myelin breakdown.

Excretion is 10% unchanged in exhaled air and 90% by detoxication to trichloroethanol glucuronide and trichloroacetic acid (TCAA). TCAA is generally used as an end of shift biomarker of exposure.

**Tetrachloroethylene.**
\[ \text{C}_2\text{Cl}_4 \]
BP 121°C

Tetrachloroethylene or perchloroethylene (PERC) is a degreasing and dry cleaning solvent and a chemical feedstock. IARC has classified tetrachloroethylene as Group 2A, probably carcinogenic to humans.

The toxicokinetics of tetrachloroethylene are similar to trichloroethylene although a much higher proportion of PERC is excreted in exhaled air. Thus, the PERC concentration in alveolar air is the most accurate measure of exposure. Urinary PERC and its metabolites trichloroethanol and trichloracetic acid (TCAA) can be used as biomarkers of exposure but it should be noted that both TCE and PERC metabolize to the same excretory products. Moreover, concurrent exposure to TCE inhibits the metabolism of PERC.

Acute and chronic exposures to PERC produce symptoms similar to those with TCE.

**1,1,1-Trichloroethane.**
\[ \text{CH}_3\text{CCl}_3 \]
BP 74°C

Prior to the 1989 Montreal Protocol on chlorofluorocarbons, 1,1,1-Trichloroethane or methyl chloroform was used as a solvent and propellant. It is more stable than TCE and PERC with their reactive C=C double bond.

Acute and chronic exposures to trichloroethane produce symptoms similar to those with TCE and PERC. Trichloroethane can produce peripheral neuropathy in chronic exposures with evidence of axonopathy and secondary myelinopathy. Excretion is 90% unchanged in exhaled air and 90% by detoxication to trichloroethanol glucuronide and trichloroacetic acid (TCAA).
Carbon Disulfide
CS₂
BP 46°C

Auguste-Louis Delpech
(1818-1880)

In his time, CS₂ was just being used to cure rubber that was dipped in vats containing some sulfur chloride (SCl₂) dissolved in the CS₂. By the 1890s CS₂ was also being used in the production process for viscous rayon from cellulose (Blanc, 2009).

Delpech found that chronic exposures to CS₂ produced emotional lability, impulsiveness, disinhibition, memory loss, depression, insomnia, hallucinations, dizziness, loss of libido, distal numbness, weakness and paresthesiae (“carbon disulfide neurosis”).

At ambient CS₂ levels of between 20 to 40 ppm neuropsychological testing has shown deficits in intelligence, attention, memory, verbal skills, visuospatial ability, and changes in personality and affect. EEG abnormalities have been shown in 40% of workers at an ambient CS₂ of 40 ppm and 27% of workers at 22 ppm. Impairment of cognition, memory, intellect, concentration, and emotional lability have been reported in 27% of workers at 20 ppm (Krstev et al., 2003). It is reported that “carbon disulfide neuropathies have been extensively studied in animal models that accurately reproduce the clinical and pathological findings in humans” (Llorens, 2013). CS₂ forms dithiocarbamate and isothiocyanate adducts on proteins, which are able to generate dithiocarbamate ester and thiourea cross-links between proteins as shown below (R₁ and R₂ are proteins). This provides a mechanism for disruption of axonal transport quite similar to hexacarbon neurofilamentous axonopathy (see 4.1 above).
5.3 Gases

**Hydrogen Cyanide.**
HCN
BP 26°C

HCN avidly binds to iron e.g., in cytochrome oxidase in the electron transport cascade. Exposure to low concentrations may result in a range of non-specific symptoms including headache, dizziness, throat discomfort, chest tightness, skin and eye irritations, and hyperventilation. With more substantial exposures, features may include severe dizziness and pre-syncpe.

Clinical presentations from exposures to high concentrations of HCN include:
- Immediate hyperventilation
- Loss of consciousness
- Seizures
- Muscle rigidity
- Cherry red skin from elevated venous [O₂]
- Cessation of breathing
- Decerebrate posturing
- Dilated pupils
- Asystole

Time to death following hydrogen cyanide inhalation in humans is given below:

<table>
<thead>
<tr>
<th>Exposure to HCN</th>
<th>Time to Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/m³</td>
<td>ppm</td>
</tr>
<tr>
<td>150</td>
<td>135</td>
</tr>
<tr>
<td>200</td>
<td>180</td>
</tr>
<tr>
<td>300</td>
<td>270</td>
</tr>
</tbody>
</table>

Workers chronically exposed to 15 ppm hydrogen cyanide have reported fatigue, dizziness, headache, disturbed sleep, tinnitus, parathesiae, delayed memory, and visual impairment. Some neurological features have been reported to persist on cessation of chronic exposures. Long term effects are related to HCN neuronopathy and other effects of cytotoxic anoxia.

**Carbon Monoxide.**
CO
BP -192°C

Carbon monoxide is colorless and odorless and its toxicity depends on the intensity and duration of the exposure. CO rapidly binds to hemoglobin (Hb) to form carboxyhemoglobin (COHb) which markedly impairs tissue oxygenation leading to cellular hypoxia.

![Oxygen-Hemoglobin Dissociation Curve](image)

<table>
<thead>
<tr>
<th>Ambient CO concentration</th>
<th>% COHb in blood</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/m³</td>
<td>ppm</td>
<td>10</td>
</tr>
<tr>
<td>80</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>140</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>250</td>
<td>220</td>
<td>40-50</td>
</tr>
<tr>
<td>400-600</td>
<td>350-520</td>
<td></td>
</tr>
<tr>
<td>900-1400</td>
<td>900-1220</td>
<td>60-70</td>
</tr>
</tbody>
</table>

In up to 30% of CO poisoning survivors a delayed onset neuropsychiatric syndrome can occur with recovery in 50 to 75% of affected within one year (Ernst and Zibrak, 1998).
**Hydrogen Sulfide.**

H$_2$S

BP -60°C

H$_2$S is slightly heavier than air so “pockets” can occur in pits, silos, excavations, etc. It has a rotten egg odor but at levels over 100 ppm olfactory paralysis impairs detection. H$_2$S is second only to CO as a cause of fatal workplace gas inhalations (Guidotti, 2010).

Like hydrogen cyanide, H$_2$S binds with iron in mitochondrial cytochrome c oxidase and arrests aerobic metabolism. However, this may not be its only mechanism of toxicity.

<table>
<thead>
<tr>
<th>[H$_2$S] in ppm</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>Odor threshold</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Mild symptoms, headaches, teariness</td>
</tr>
<tr>
<td>&lt;100</td>
<td>Eye (“gas eye”) and airway irritation</td>
</tr>
<tr>
<td>100-200</td>
<td>Severe eye and airway irritation</td>
</tr>
<tr>
<td>200-400</td>
<td>Pulmonary edema if prolonged</td>
</tr>
<tr>
<td>500-800</td>
<td>“Knockdown” (unconsciousness), severe eye and lung effects, death within hours</td>
</tr>
<tr>
<td>800+</td>
<td>Immediate respiratory failure</td>
</tr>
</tbody>
</table>

In terms of lethality, concentration is more important than duration of exposure. Very brief “knockdown” exposures may have complete recovery but some chronic brain injury can occur (due to hypoxia?) including basal ganglia dysfunction and seizures. Peripheral neuropathy has not been well-documented to date in H$_2$S exposures.

The long term effects of acute H$_2$S exposure without knockdown have not been well investigated. Four such cases were reported (Hirsch, 2002) in which detailed standardized neurophysiological and psychometric tests were said to show “persistent sequelae of encephalopathy” in all subjects.

No effective antidote for H$_2$S poisoning is known. After removal from further exposure, some recommend immediate amyl nitrate and O$_2$ to be given and IV sodium nitrite as soon as possible to oxidize hemoglobin to methemoglobin which binds H$_2$S. Hyperbaric O$_2$ may be also be given if available.

**Ethylene Oxide.**

C$_2$H$_4$O

BP 11°C

Ethylene oxide (EtO) is used as a chemical feedstock for (poly) ethylene glycols and ethanolamines. It is also used in sterilization. It is reactive and flammable. It is an IARC Group I carcinogen.

EtO is very soluble in blood and passes throughout the body and across the blood-brain barrier.

Acute exposures have been associated with airway irritation, numbness, headaches, nausea, dizziness, and fatigue (Bryant, 1989). Some cases of delirium, ataxia and seizures have occurred.

Chronic exposures have produced impaired memory and concentration, insomnia, muscle hypertonicity, dysarthria, and parkinsonian features. Peripheral neuropathy has been reported.

One study (Patch and Hartlage, 2001) compared 64 traumatic brain injury (TBI) subjects with 22 cases of EtO toxicity. Both groups had similar MMPI scores and impairment of reaction time. On the Multiple Affect Adjective Checklist (MAACL) testing for anxiety, depression, and hostility, the EtO cases scored higher on all scales than the TBI group. Despite comparable educational levels, the EtO group scored “substantially lower” on IQ tests.

The exact mechanism of EtO neurotoxicity is not known but since it is electrophilic it is thought to interact with nucleophilic sites on DNA and RNA. EtO covalently binds to DNA at guanine and adenine and forms adducts which is evidence of its carcinogenicity.

The half-life of EtO is about one hour.
5.4 Pesticides

Symptoms of pesticide neurotoxicity depend on the intensity and duration of acute exposure, the specific agent(s), the relative contributions of muscarinic and nicotinic effects (see below), and individual variations in enzymatic breakdown (hydrolysis) of pesticides, e.g., by human serum paraoxonase (“PON1”) (Fukuto, 1990).

Organophosphates and Carbamates

In acute organophosphate exposures, even mild cases can have a reduction of 50% of normal AChE activity. Moderate exposures can reduce the enzyme activity to 20% of normal and severe poisonings can depress AChE to 10% or less. If treatment with atropine and oximes is delayed, the phosphorylated (inactivated) AChE can become “aged” and irreversibly inactive. Recovery is then dependent on replacement of AChE by metabolism which can take weeks.

Common acute neurotoxic effects of organophosphate exposures include:

- Agitation
- Confusion
- Loss of balance / gait
- Headache
- Hyporeflexia
- Respiratory depression
- Seizures
- Decreased consciousness
- Coma

The DUMBELS mnemonic:

- **D**iarrhea
- **U**rination
- **M**iosis
- **B**ronchospasm
- **E**mesis
- **L**acrimation
- **S**alivation

The Sympathetic and Parasympathetic Cholinergic Synapses

- “nic” = nicotinic receptors; “mus” = muscarinic receptors; “NA” = noradrenalin
Typical symptoms usually appear within 30 minutes of acute high exposures of organophosphates and almost always in less than 12 hours. Respiratory failure is the usual cause of death in severe acute exposures. With proper treatment, mortality rates from severe acute exposures are 10 to 20%. Those who survive organophosphate poisoning for 24 hours usually recover. There are two longer term conditions resulting from acute organophosphate poisoning that should be noted.

1 Intermediate Syndrome

A condition known as the “intermediate syndrome” occurs from 1 to 4 days after the acute phase and involves muscle weakness (mostly proximal) and cranial nerve palsies. An incidence rate of up to 65% has been reported for the intermediate syndrome. Recovery takes 1 to 2 weeks with cranial nerves regaining function first, then respiratory muscles and proximal limb motor function.

2 Organophosphate-Induced Delayed Polyneuropathy (OIDPN)

Since the organophosphates are esterase inhibitors they can affect more than just cholinesterase enzymes. There is a condition known as organophosphate-induced delayed polyneuropathy (“OIDPN” or “OPIDN”) which was first identified during the prohibition era in ginger extracts (“Ginger Jake”) contaminated by the organophosphate, tri-ortho-cresyl-phosphate. Symptoms of OIDPN appear 1 to 4 weeks after exposure but not all of the organophosphates cause OIDPN. Carbamates have been found to produce polyneuropathy (Lotti and Moretto, 2006). OICPN can occur after a single exposure to certain organophosphates, e.g. leptophos, dichlorvos, fenthion, isofenphos, trichloronate, trichlorfon, mephos, methamidophos, and chlorpyrifos (Jokanović et al., 2011). These organophosphates inhibit an enzyme known as neuropathy target esterase (“NTE”) which is involved in the metabolism of lysolecithin and membrane lipids. Symptoms include distal numbness and paresthesiae, muscle weakness, spasticity, and atrophy. Milder cases usually recover well but more severe initial deficits do poorly. Recovery time is from 6 to 12 months.

Biomonitoring for AChE inhibition

A baseline red cell cholinesterase level is determined prior to exposure (ideally an average of two tests, 3 to 14 days apart) and then periodic testing is done during employment when exposed (e.g., at the end of the spraying season). Incident testing is done if accidental exposure occurs or symptoms develop. If the cholinesterase level falls to less than 70% of baseline, the worker is removed from exposure and retested at biweekly intervals, returning to work when back to 80% of the baseline.

Organochlorines

The prototype organochlorine (OC) is DDT (dichlorodiphenyltrichloroethane). The OCs are lipophilic and readily absorbed by all routes. Because of their long half-lives in adipose tissue most OCs are now banned from use in the more developed countries.

Their mode of action is by blockade of neuronal sodium channels (DDT analogues) or by inhibition of GABA receptor synaptic transmission (cyclodienes and cyclohexanes). Acute effects include tremor, ataxia, hyperreflexia, paresthesiae, and convulsions. Seizures from acute OC exposure may be delayed as long as 6 to 8 months. Chronic effects include weakness, vision changes, cognitive deficits and other psychological changes, and weight loss.

![DDT](https://example.com/ddt.png)
**Pyrethroids**
Pyrethrins are naturally occurring in the seeds of the Chrysanthemum and have been used as insecticides for a century. Most of this botanical product now comes from East Africa. Synthetic pyrethroids have been developed to improve chemical stability. They are less neurotoxic than the OPs and OCs because mammalian enzymes provide rapid detoxication compared to insects.

Pyrethroids act similarly to DDT on sodium channels and can produce excitation, tremors, paresthesiae, fasciculations, and convulsions. There is little evidence to date regarding chronic neurotoxicity.

**Neonicotinoids**
This class of insecticides has been developed since the 1980s and are analogues of nicotine. Their mode of action differs from the OPs, OCs, and pyrethroids since they act specifically on the post-synaptic ligand-gated ion channels at nicotinic acetylcholine receptors (nAChRs). The neonicotinoids have lower binding affinities to nAChRs in humans than in insects. They also poorly cross the blood-brain barrier.

Neonicotinoids initially stimulate the nAChR receptors and interfere with the transmission of neuronal impulses by fatigue. Acute exposure produces dizziness, drowsiness, disorientation, nausea, diaphoresis, and coma with a mortality rate in one study (Phua et al., 2009) of 3% compared to 12% for OPs, 7% for carbamates, and 3% for pyrethroids. Neonicotinoids can produce clinical features similar to acute OP and carbamate poisonings such as miosis, bradycardia, increased salivation, and bronchorrhea.

Imidacloprid is the first commercialized neonicotinoid insecticide and is now the best-selling insecticide in the world. The other neonicotinoids that are currently in use are shown below:

![Imidacloprid](image)

**Imidacloprid**

![Acetamiprid](image)

**Acetamiprid**

![Clothianidin](image)

**Clothianidin**

![Thiacloprid](image)

**Thiacloprid**

![Dinotefuran](image)

**Dinotefuran**

![Nitenpyram](image)

**Nitenpyram**

![Thiamethoxam](image)

**Thiamethoxam**

**Structures of the Current Neonicotinoids (Lin et al., 2013)**
6. **CLINICAL NEUROTOXICOLOGY**

6.1 **Identification of Occupational Neurotoxic Disorders**

Foremost in the identification of an occupational neurotoxic disorder is the recognition of an adverse clinical health effect (which may be on a spectrum from early symptomatology to overt pathology). The necessary next step is the establishment of a causal linkage between this condition and the occupational exposure(s).

Ideally, we seek evidence of an exposure to a substance (or, often a mixture) which leads to an internal dose producing a specific biological effect. Most patients are seen long after their exposures have occurred so their occupational exposures are retrospective estimations usually based solely on the patient’s self-report. Quantitative measures of workplace exposures are rarely available. Careful inquiry is needed to determine the duration, intensity, and other characteristics of the exposure(s), e.g., review of MSDS information and actual work practices.

There is a growing body of literature accessible through the U.S. National Library of Medicine on-line (“PubMed”) and this can be readily searched for specific conditions and neurotoxicants. Where possible, we seek evidence from epidemiological studies and toxicological research which indicates that there is a possible or probable causal relationship between the condition in question and the putative exposure(s). There are, of course, varying levels of certainty regarding these associations and the quality of evidence must be weighed (Checkoway, Pearce and Kreibel, 2007). Expert reviews (e.g., ATSDR, IARC, Environmental Health Criteria, textbooks, monographs, etc.) and meta-analyses provide summaries and state of the art information that can be helpful in determining the likelihood of neurotoxicity.

Occupational neurotoxicants often produce effects which overlap with other medical conditions. Dobbs (2009:19) suggests the mnemonic “VITAMIN D&E” for differential diagnosis of possible neurotoxic disorders:

- **V** Vascular
- **I** Infectious
- **T** Toxic or Traumatic
- **A** Autoimmune or Amyloid
- **M** Metabolic
- **I** Inflammatory
- **N** Neoplastic
- **D** Degenerative
- **E** Epileptiform

Referrals to neurologists, psychiatrists, and neuropsychologists may be needed to confirm and refine diagnoses and to define specific neurocognitive deficits. There are, of course, many confounding issues including pre-morbid levels of health and functioning and non-occupational factors (e.g., substance abuse, prescription medications, hobby exposures, dietary habits, etc.) These all need to be carefully explored. It should also be noted that the prevalence of malingering in persons claiming exposures to occupational and environmental substances has been estimated to be up to 40% (Greve et al., 2006).

Detection of odors at work does not imply a medically significant exposure to a neurotoxicant (Greenberg, Curtis, and Vearrier, 2013). However, odors and their perceived health effects are themselves a significant health issue for many workers and a challenge for workplaces and occupational medicine (Dalton and Jaén, 2010).

> “Health professionals and other officials should consider toxicant exposure and adverse chemical accumulation as a potential determinant when individuals present with inexplicable mental health problems or disordered behavior.” (Genuis, 2009:476).
6.2 Biomarkers of Exposure and Effect

Although patients may present for assessment at some time after ceasing to be exposed to a neurotoxicant, it is often worthwhile to perform laboratory assessments for markers of exposure and/or effect and it is certainly worth assessing these markers if patients are still in contact with the agent(s) of concern. The relevant biomonitoring tests should be targeted from the conclusions regarding causative agent(s) as determined above.

Concentrations of substances in biological fluids are often compared with the ACGIH’s published TLVs and BEIs. These updated occupational exposure guidelines contain more than 50 Biological Exposure Indices that cover more than 80 chemical substances. The BEI indicates the concentration of a substance in a biological fluid, e.g., urine, that is likely to be found when the subject is exposed to the Threshold Limit Value (TLV) for that agent (Morgan 1997). It should be noted that the TLVs establish an exposure level above which adverse health effects are likely to occur but they do not set a level below which health effects will not occur. Detoxication enzyme polymorphism (see Section 3 above) may render some people more susceptible to toxic effects.

Sample collections should take note of the toxicokinetics of the substance of concern and proper collection technique is crucial to avoiding contamination. The lab providing the testing should have competence and quality control in analysing the substance. Laboratories provide differing reference values usually based on general population norms. These references will not match those of the ACGIH set for industrial settings. A further reference for some metals and organic chemicals is now available through the Canadian Health Measures Survey (CHMS).

Statistics Canada began conducting the CHMS in 2007. Ongoing data collection continues in two year cycles. The survey directly collects physical measures of Canadians’ health including blood and urine samples for laboratory testing. For each two-year collection period, about 5,500 participants are sampled among the ages of 3 to 79. The U.S. National Health and Nutrition Examination Survey has recently published the “Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, September 2013” (CDC).

Reference ranges for blood and urine levels intended for the general population cannot be meaningfully applied to people undergoing chelation challenge tests (provocation chelation) used to diagnose metal toxicity (Brodkin et al., 2007). There has been concern expressed that “the use of chelation (a) for diagnostic purposes, (b) for asymptomatic patients with urine or blood mercury levels approximating normal / background population values, or (c) following the removal of dental amalgam fillings is considered to be unnecessary and to place the patient at some additional risk” (Risher and Amler, 2005, 697).

Comparison of BEIs and NHNES data shows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>BEI</th>
<th>NHNES adult 95th %-iles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pb</td>
<td>30 μg/dL</td>
<td>1.71 μg/dL</td>
</tr>
<tr>
<td>Blood inorganic Hg</td>
<td>15 μg/L</td>
<td>0.54 μg/L</td>
</tr>
<tr>
<td>Blood C₂Cl₄</td>
<td>1 mg/L</td>
<td>0.13 μg/L</td>
</tr>
<tr>
<td>Blood Cd</td>
<td>5 μg/L</td>
<td>1.55 μg/L</td>
</tr>
<tr>
<td>Blood toluene</td>
<td>1 mg/L</td>
<td>0.9 μg/L</td>
</tr>
<tr>
<td>Blood Styrene</td>
<td>20 μg/L</td>
<td>0.15 μg/L</td>
</tr>
</tbody>
</table>

A study of 14 healthy individual volunteers given 30 mg/kg oral DMSA (see Section 5.1) showed an average increase in their urinary mercury of 7 times the pre-provocation levels (Archbold, McGuckin and Campbell, 2004).
6.3 Clinical Investigations of Neurotoxicity

Various neurophysiological, imaging, and neuropsychological tests are available to help to define specific deficits from neurotoxicants. These tests require specialized expertise and specific test equipment or psychometric tools. Clinical investigations are directed toward the particular neurotoxic condition of concern. For example, the neuropsychological assessment of chronic solvent-induced encephalopathy (CSE) requires the evaluation of the following cognitive domains (van Valen et al., 2012):

**Attention**
- Processing speed
- Complex attention

**Memory**
- Immediate recall
- Delayed recall
- Recognition

**Fine motor performance**
- Motor speed
- Dexterity

**Concept formation and reasoning**
- Verbal
- Non-verbal

**Construction**

The complex functions of sensory organs, nerve conduction, neuronal networks/centres, and higher cerebral integration are evaluated using various tests as shown below.

**Nerve Functions and Their Related Tests**

<table>
<thead>
<tr>
<th>Cognitive – verbal</th>
<th>Vocabulary WAIS-R</th>
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<tbody>
<tr>
<td></td>
<td>Adult reading test revised</td>
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</table>

<table>
<thead>
<tr>
<th>Cognitive – spatial</th>
<th>Block design WAIS-R</th>
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<tbody>
<tr>
<td></td>
<td>Raven’s progressive matrices</td>
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<thead>
<tr>
<th>Concentration / Attention</th>
<th>Reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroop color-words test</td>
</tr>
<tr>
<td></td>
<td>Continuous performance test</td>
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<tr>
<td></td>
<td>Trail-making test</td>
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<tr>
<th>Motor skills</th>
<th>Purdue pegboard test</th>
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<tbody>
<tr>
<td></td>
<td>Lafayette dexterity test</td>
</tr>
<tr>
<td></td>
<td>Finger tapping</td>
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<td></td>
<td>Hand and pinch dynamometry</td>
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| Gait | Video motion analysis |

<table>
<thead>
<tr>
<th>Visuomotor coordination</th>
<th>NES hand-eye test</th>
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<tbody>
<tr>
<td></td>
<td>Digit symbol WAIS-R</td>
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<tr>
<td></td>
<td>Boston quantitative battery</td>
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<thead>
<tr>
<th>Memory – verbal</th>
<th>Logical memory WMS-R</th>
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<tr>
<td></td>
<td>California verbal learning test</td>
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<td></td>
<td>Digit span WAIS-R</td>
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<tr>
<th>Memory – visual</th>
<th>Visual reproduction WMS-R</th>
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<tbody>
<tr>
<td></td>
<td>Complex figure test</td>
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<td></td>
<td>Paired associates WMS-R</td>
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<tr>
<th>Sensory tests</th>
<th>Auditory</th>
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<tr>
<td></td>
<td>Sound booth audiometry</td>
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<tr>
<td></td>
<td>Brain stem evoked potentials</td>
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<table>
<thead>
<tr>
<th></th>
<th>Visual</th>
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<tbody>
<tr>
<td></td>
<td>Snellen, other optometrics</td>
</tr>
<tr>
<td></td>
<td>Ishihara plates, Farnsworth</td>
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</tbody>
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|                   | Olfactory |
|                   | U. Penn. smell ID test |

|                   | Vibratory |
|                   | Optacon tactile tester |

|                   | Equilibrium |
|                   | Dynamic posturography |

|                   | Tactile |
|                   | 2-point discrimination |

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<thead>
<tr>
<th>Affect/Potentiality</th>
<th>Profile of mood states</th>
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<tbody>
<tr>
<td></td>
<td>Beck depression inventory</td>
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<td></td>
<td>MMPI</td>
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<thead>
<tr>
<th>Peripheral nerves</th>
<th>Nerve conduction studies</th>
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<tr>
<td></td>
<td>Conduction velocity</td>
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<td></td>
<td>Amplitude</td>
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<td>Electromyography</td>
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<th>Trigeminal nerves</th>
<th>Blink reflex</th>
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<th>Sleep</th>
<th>Polysomnography</th>
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<tr>
<th>Synchronous cerebral activity</th>
<th>EEG</th>
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<tr>
<th>Brain neuro-pathological changes</th>
<th>MRI scanning</th>
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</table>

**Abbreviations**

NES = Neurobehavioral Evaluation System
WAIS-R = Weschler Adult Intelligence Scale-Revised
WMS-R = Weschler Memory Scale-Revised
MMPI = Minnesota Multiphasic Personality Inventory

(adapted from Fiedler, 1996)
DEDICATION

Dedicated to Dr. James O. Emmett
Who introduced me to Occupational Medicine