Occupational NeuroToxicology

CBOM-U of A Part C Pathway for Advanced Accreditation of Family Physicians in Occupational Medicine

The Nervous System as a Target Organ in Occupational Exposures

R. Douglas Hamm MD, CCFP, FRCPC (Occ Med), FCBOM

CONTENTS

*for access to the references cited in Parts 4 & 5 see 'CCBOM Pathway Resources' at *cbom.ca*

1.0 Why Do Neurons Make Such Good Targets for Occupational Toxicants?

Neuroanatomical structures have large surface areas and dense receptor populations, e.g., the surface area of the brain's 100 billion neurons (Lent et al., 2012) totals many square metres.

Neurons have high metabolic rates, e.g., the brain at 2% of body mass consumes 20% of its glucose (Herculano-Houzel, 2011). In theory, 1 mol glucose → 38 mol ATP but, in vivo it is more likely ~32 ATP. High CNS blood flow enhances its exposure to circulating toxicants – the brain receives 15% of cardiac output. Neuronal O_2 consumption is ~10 times that in neuroglial cells (Dorman, 2000; Dienel, 2019).

Neuronal tissues have high lipid content which facilitates toxic **lipophilic bioaccumulation**. The dense synaptic networks of neurons are susceptible to toxicants targeting their profuse receptor and neurotransmitter sites. 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 such as mercury which binds to the sulfhydryl groups on cysteine (Shaw, 2010).

Neurons have limited regenerative capacity, e.g., CNS nerve axons do not regenerate, and there may be no alternate neuronal pathway for loss of specific tracts (Norton, 1988). Neurons are postmitotic and do not divide so neuronal loss is persistent throughout life although PNS axons can recover (Maurer and Philbert, 2015).

The fetal nervous system is a susceptible target for **developmental neurotoxicity** (DNT), e.g., from methylmercury, CO, lead, ethanol, etc. (Grandjean and Landrigan, 2006). Neuronal networks enable an unlimited repertoire of cognitive / behavioral outcomes. Neurotoxic effects at cellular levels can have amplified emergent properties at higher levels of neuro-cognitive performance (Kolodkin et al., 2012).

2.0 From Classical Plumbism to Behavioral Toxicology

Hippocrates (c. 460-370 BC) is still cited as the first ancient author to describe a case of occupational neurotoxicity but this has been shown to be erroneous (Osler and McCrae, 1907:84; Waldron, 1973a,b, 1978; Skrabanek, 1986; Vance, 2007). The earliest such report appears to be in **Nikander** of Kolophon's *Alexipharmaka* (2nd cent. BC) where it is observed that in "*psimuthion*" poisoning, i.e. from white lead ($2PbCO_3$-$Pb(OH)_2$), 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, eds. and translators, 1953:99).

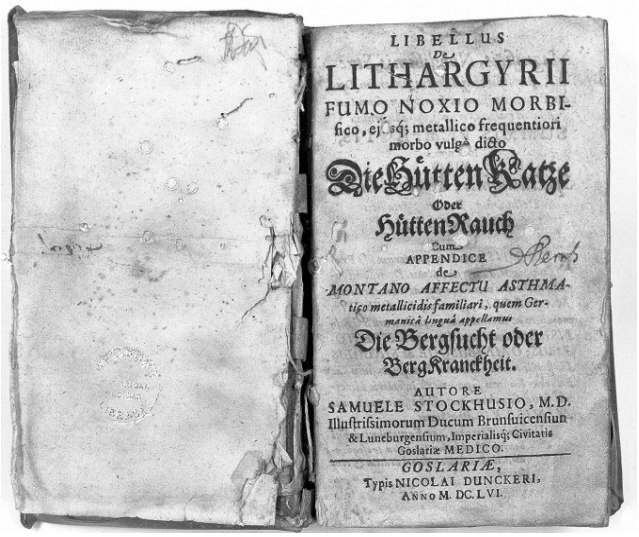
Due to the widespread use of lead since antiquity, there is a long history of its recorded adverse health effects (Major, 1931; McCord 1953-1954; Waldron and Wells, 1979; Morris, 1980; Nriagu, 1983a,b; Wedeen, 1984; Woolley, 1984; Curran, 1984; Green, 1985; Lessler, 1988; Hernberg, 2000; Tepper, 2007; Azizi and Azizi, 2010; Riva et al., 2012; Dissanayake and Erickson, 2012, etc.) with public exposures in modern times from **tetraethyl lead** gasoline additive (Rosner and Markowitz, 1985) and from **lead-based paints** (Gibson 1904; Markowitz and Rosner, 2000; Warren 2000; O'Grady and Perron, 2011).

In three articles published in 1965 and 1967 and in a posthumously published book in 1990, S.C. Gilfillan (1889-1987) contended that lead contamination of water supplies and wine caused aristocratic infertility and sickness throughout the Roman Empire, leading to its collapse. Besides the fact that the Eastern Roman Empire (the "*Byzantine Empire*") carried on for a millennium and historians even debate "the fall of Rome," Gilfillan and his fellow proponent Nriagu (1983) have been convincingly critiqued (Scarborough, 1984; Phillips, 1984; Needleman and Needleman, 1985; Retief and Cilliers, 2006, 2014; Reddy and Braun, 2010; Delile et al., 2014).

Ramazzini's "Diseases of Workers" (1700) has some description of occupational neurotoxicity but the physician Ulrich Ellenbog had written about neurotoxicity among goldsmiths in 1473 (but not published until 1524) commenting 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, cf. 1996). The **colic of Poitou** was caused by lead-adulterated wines and similar outbreaks of **Devonshire colic** in England (McConaghey, 1967; Waldron, 1970) were shown by Dr. George Baker (Baker, 1767, 1768) to be due to lead leached from lead-lined cider presses. Baker had discussions about these lead effects with Benjamin Franklin (Hamm, 2018).

Feldkirch, Austria, birthplace of Ulrich Ellenbog, as it appeared in the fifteenth century


LIBELLUS
De
LITHARGYRII
FUMO NOXIO MORBIfico, ejúsq; metallico frequentiori morbo vulgò dicto
Die Hütten Katze
Oder
Hütten Rauch
Cum
APPENDICE
de
MONTANO AFFECTU ASTHMAtico metallicidis familiari, quem Germanicè lingua appellamus
Die Bergsucht oder Berg Kranckheit.
AUTORE
SAMUELE STOCKHUSIO, M.D.
Illustrissimorum Ducum Brunsuicensium & Luneburgensium, Imperialisq; Civitatis Goslariæ MEDICO.
GOSLARIÆ,
Typis NICOLAI DUNCKERI,
ANNO M. DC. LVI.

Title page of Samuel Stockhausen's 1656 book
digitale-sammlungen.de/en/search?query=all%3A%28Samuele+Stockhusio+1656%29

In Scotland the Lanarkshire lead smelters produced a condition known locally as "***mill reek***." Dr. James Wilson wrote an article about it in 1754 (Wilson, 1754) noting that "*it mostly seizes, 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; Risse, 2005)

"*The lead, Sir. Sure 'tis the lead-mills, where the women gets took on at eighteen-pence a day, Sir, when they makes application early enough and is lucky and wanted, and 'tis lead poisoned she is, Sir, and some of them gets lead-poisoned soon and some of them gets lead-poisoned later, and some but not many never, and 'tis all according to the constitution, Sir, and some constitutions is strong and some is weak…"* — Charles Dickens, "A Small Star in the East," published in his weekly journal *All The Year Round* on December 19, 1868 (Slater and Drew, 2000:355)

Benjamin Franklin, American printer and inventor, was well aware of **lead neuropathy** in typesetters ("*the dangles*") and had met Dr. George Baker in London (Finger, 2006:181-196). In 1767 Franklin visited La Charité hospital in Paris where he reviewed many cases of lead poisoning and identified occupational exposures as a common cause. 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, 1786, reprinted in Wright, 1939; Nichols 1965; Felton, 1967).

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, 1839; cf. Walusinski, 2021). Ramazzini (1700) and Kussmaul (1861) had similarly reported palsies and a psychological disorder ("***erethism***") in mirror makers using mercury. Mercurial tremors ("*hatters' shakes*") were reported in felt hat makers (Freeman, 1860; Dennis, 1879) but mercurialism is unlikely the basis of Lewis Carroll's "*mad hatter*" figure (Waldron, 1983; Wedeen, 1989; Davies, 2013)

The rise of scientific medicine and neurology (Finger, Boller and Tyler, eds., 2010; Lazar, 2010), the growth of industry, and progress in toxicology (Stirling, 2006) served to advance occupational neurotoxicology. 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** on 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.

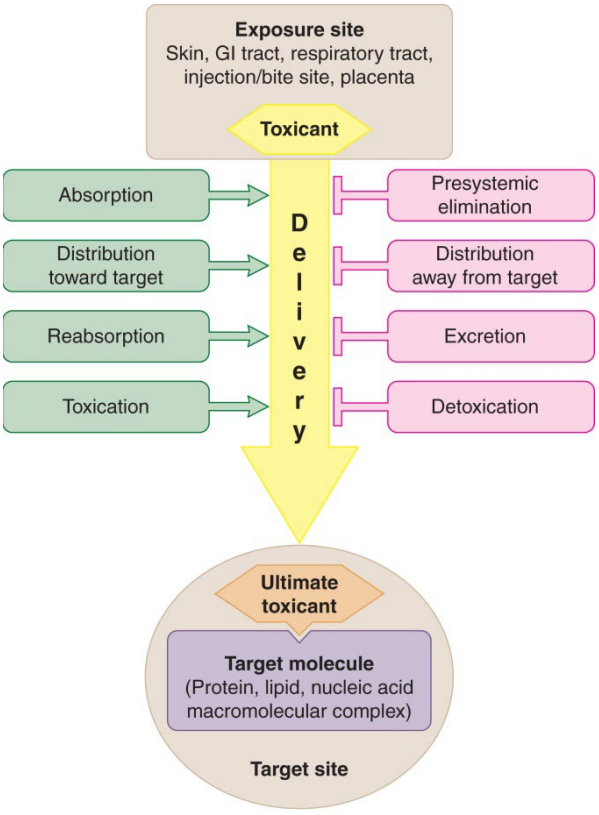
3.0 Toxicokinetics, PBPK Models and Body Compartments

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 portal blood into the liver and then excreted into the bile (Aschner and Aschner, 1991).

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.

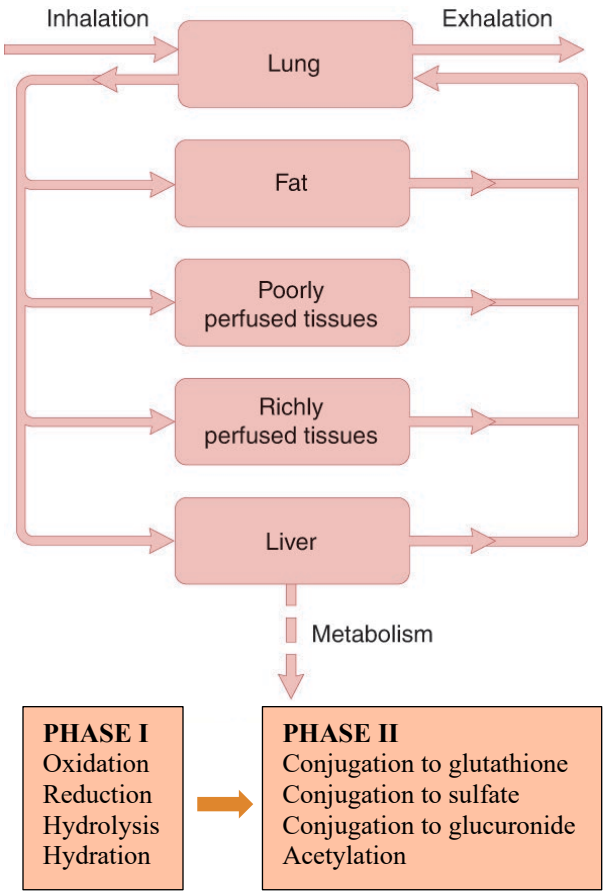
Toxication or metabolic activation may occur, e.g., parathion (a "pro-poison") is biotransformed to the active cholinesterase inhibitor paraoxon. Detoxication involves enzyme-mediated phase I and phase II molecular transformations to enable excretion. Sometimes detoxication creates neurotoxic by products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



The nervous system presents a diverse array of **cellular targets** which may undergo chemical alterations or disruption by neurotoxicants as illustrated in the following list:

DNA	mycotoxins, radiation, trichlorfon, ethylnitrosourea
Protein synthesis	methylmercury
Enzymes	organophosphates (OPs),
e.g., AChE, NTE	carbamates
Energy metabolism	CO, Cyanide, As, Tl,
Membrane channels	
e.g., Sodium	organochlorines, pyrethroids
Potassium	Ba, Cs, bee venoms
Chloride	avermectin parasiticides
Calcium	maitotoxin LD50=50 ng/kg
Axonal transport	OPs, Tl, As, n-hexane, CS_2, 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:



Metabolic transformation can vary due to enzyme polymorphisms, e.g.,

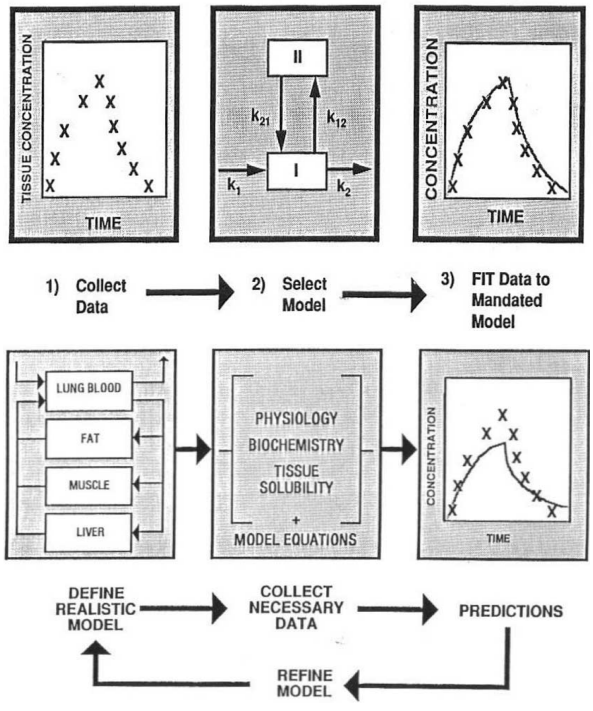
Xenobiotic-Transforming Enzymes with Known Polymorphism in Humans (from Löf and Johanson, 1998:613)

	Enzymes	**Types of Substrate**
Phase I	Alcohol dehydrogenases	Ethanol
	Aldehyde dehydrogenases	Acetaldehyde
	CYP1A1	Benzo(a)pyrene
	CYP1A2	Caffeine
	CYPA6	Coumarin
	CYP2C19	Mephenytoin
	CYP2D6	Debrisoquine
	CYP2E1	Chlorzoxazone
	CYP3A4	Nefedipine
	Cholinesterases	Succinylcholine
	Arylesterases	Paraoxon
	Epoxide hydrolases	Benzo(a)pyrene oxide
Phase II	UDP-glucuronosyl transferases	Paracetamol
	Sulfo transferases	4-Nitrophenol
	N-acetyl transferases	Sulfometazine
	N-methyl transferases	Histamine
	S-methyl transferases	6-Mercaptopurine
	Glutathione-S-transferases	Methyl chloride

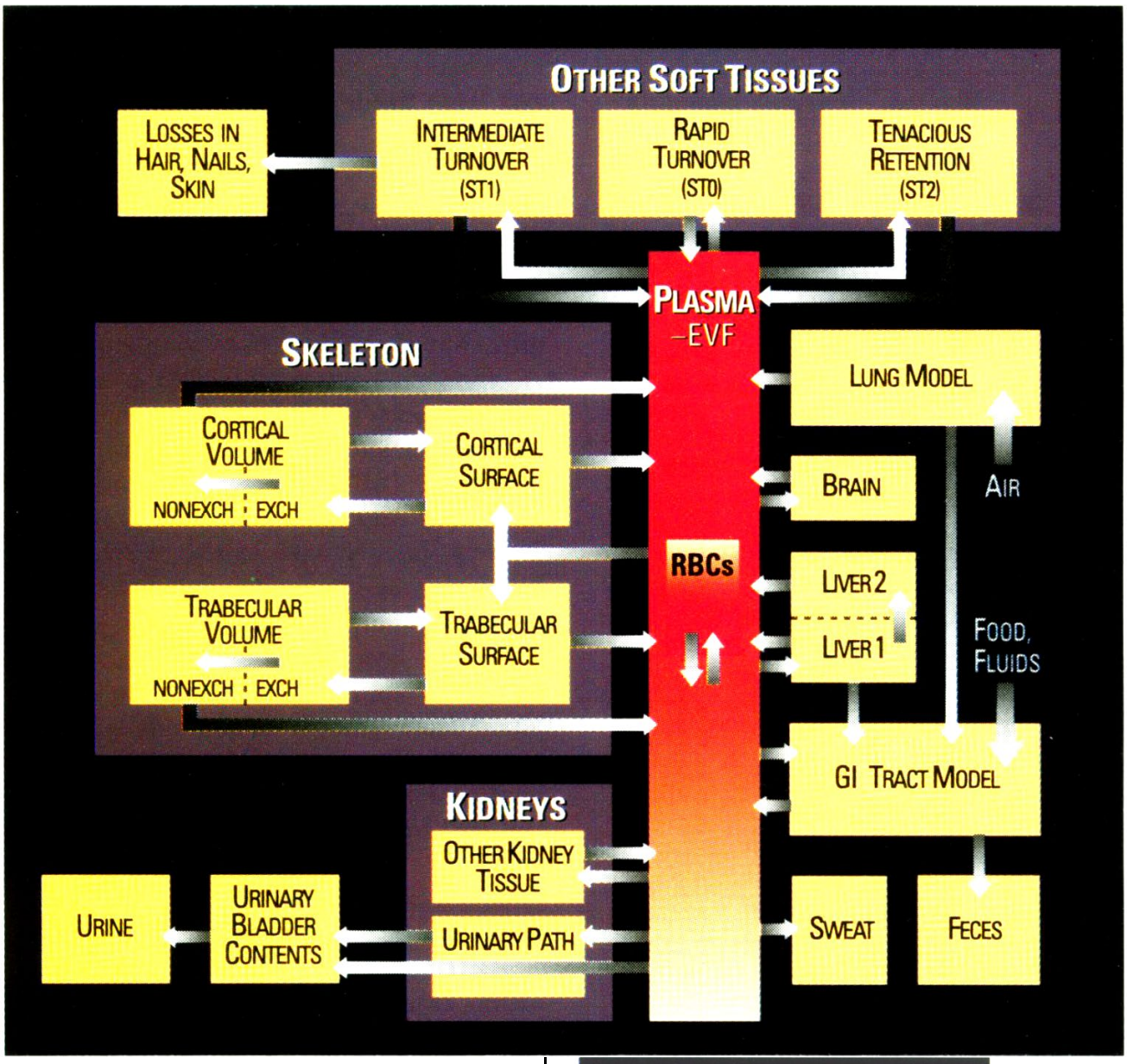
PBPK Modeling

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** (Upton et al., 2016).

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.



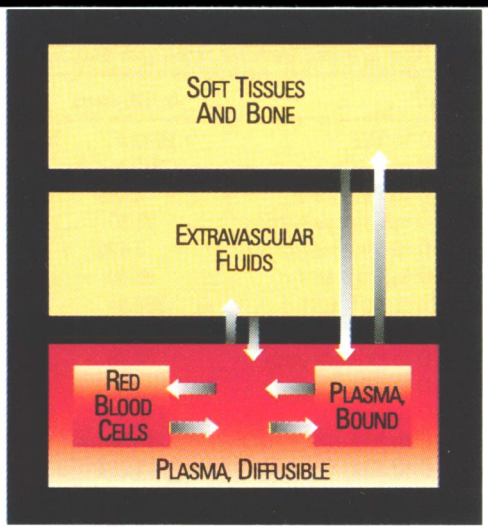
(from Andersen, 2003:10,11)



This is a schematic diagram (Leggett, 1993:599) 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..

Diffusable plasma (highlighted in red) is viewed as the central mobile compartment in the lead PBPK model by Leggett (1993:599).

Many other agents have been studied with PBPK modeling as a tool in health risk assessment (Cohen Hubal et al., 2019).



4.0 Diverse 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

↓

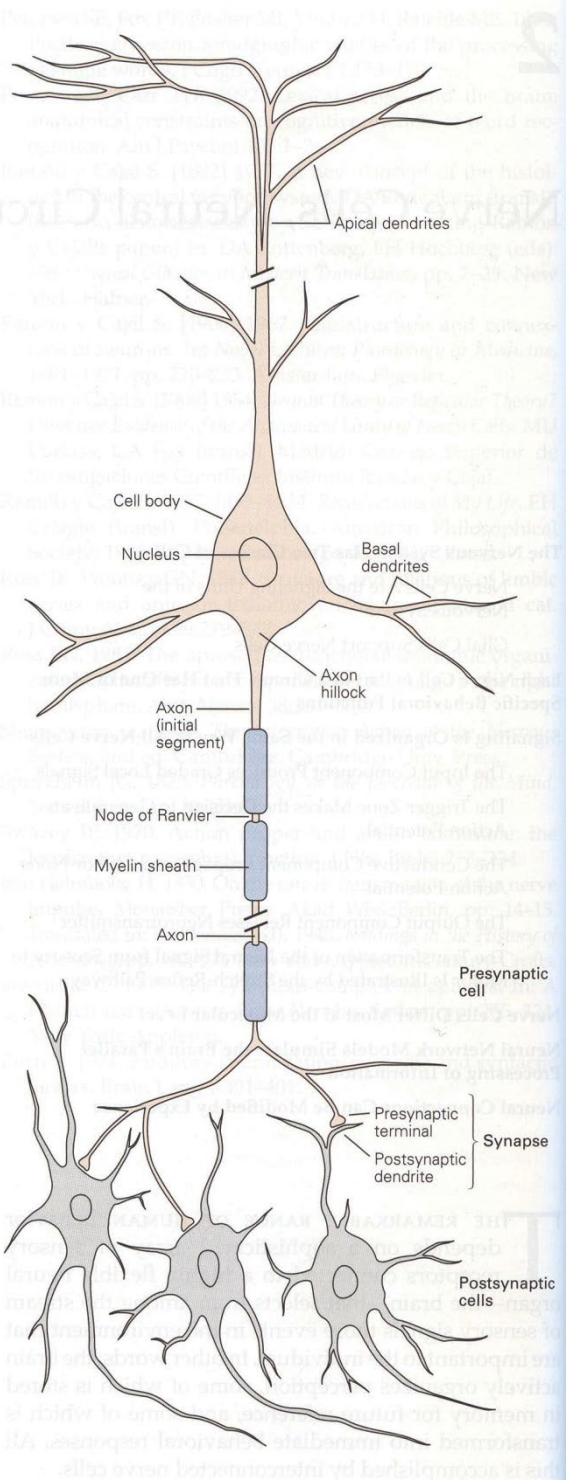
ALTERED STRUCTURE/FUNCTION
(a preclinical change / dysfunction)
e.g., elevation of protoporphyrin

↓

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.

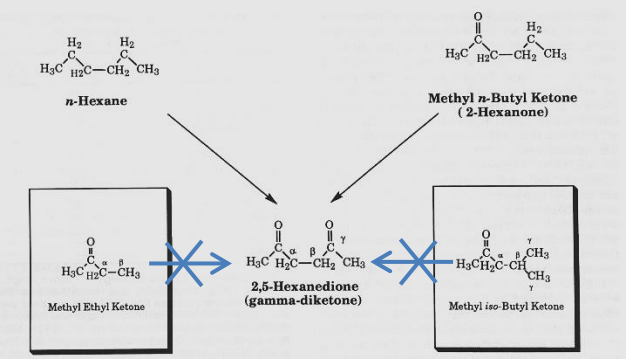


The neuron is a hub of metabolic activity and axonal transport – fast axonal transport along microtubules reaches 400 mm/day. If a neuron's cell body (soma) is lethally damaged, the degenerative process is a "***neuronopathy***". Mega doses of pyridoxine (vitamin B6) can produce a neurotoxic sensory neuronopathy (Kulkantrakorn, 2014). Carbon monoxide can cause a neuronopathy, particularly in the basal ganglia, by anoxic anoxia. Hydrogen cyanide neuronopathy results from cytotoxic anoxia by irreversible inhibition of cytochrome oxidase.

When the site of injury is the axon, this form of damage is an "***axonopathy***" which has potential for PNS 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 the following (Toledano, 2020):

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

} see below:



The neurotoxic gamma-diketone structure of hexacarbons (Spencer, 2020)

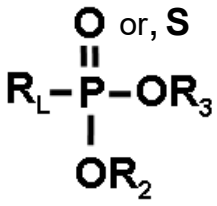
We now know that the neurotoxicity of the hexacarbons requires a gamma-diketone structure i.e. the second ketone (the γ-position) is at the third carbon from the first ketone and 2,5-hexanedione is the active metabolite. Neither methyl ethyl ketone, methyl iso-butyl ketone or other alkane chains of less 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. Secondary demyelination can occur.

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 a deficiency of thiamine (vitamin B_1) (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, n-hexane, ethylene oxide, and organophosphates (OPs) - one of the more infamous outbreaks from OPs involved many 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).

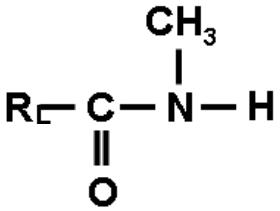
4.2 Synaptic Neurotransmission

The nervous system uses two main classes of neurotransmitters: 1) small-molecules such as **acetylcholine** (ACh) and biogenic amines, and 2) neuropeptides. Whereas small-molecule synaptic messengers act upon adjacent receptors, neuropeptides act upon neuronal networks as hormonal-like cell signals. ACh synaptic transmission is a particular target of the occupational neurotoxins known as the organophosphates (OPs) and carbamates (CBs) (Fukuto, 1990; Lionetto et al., 2013). They also appear to have mitochondrial toxicity (Leung and Meyer, 2019).



Organophosphate

"insecticide"



Carbamate

"insecticide"

R_L = "the leaving group" i.e. the site of the OP or CB binding to acetylcholinesterase

R_2 = either methoxy, ethoxy, phenyl, amino, alkylthio, or substituted amino groups

R_3 = methyl or ethyl groups

Some Carbamates (CBs):

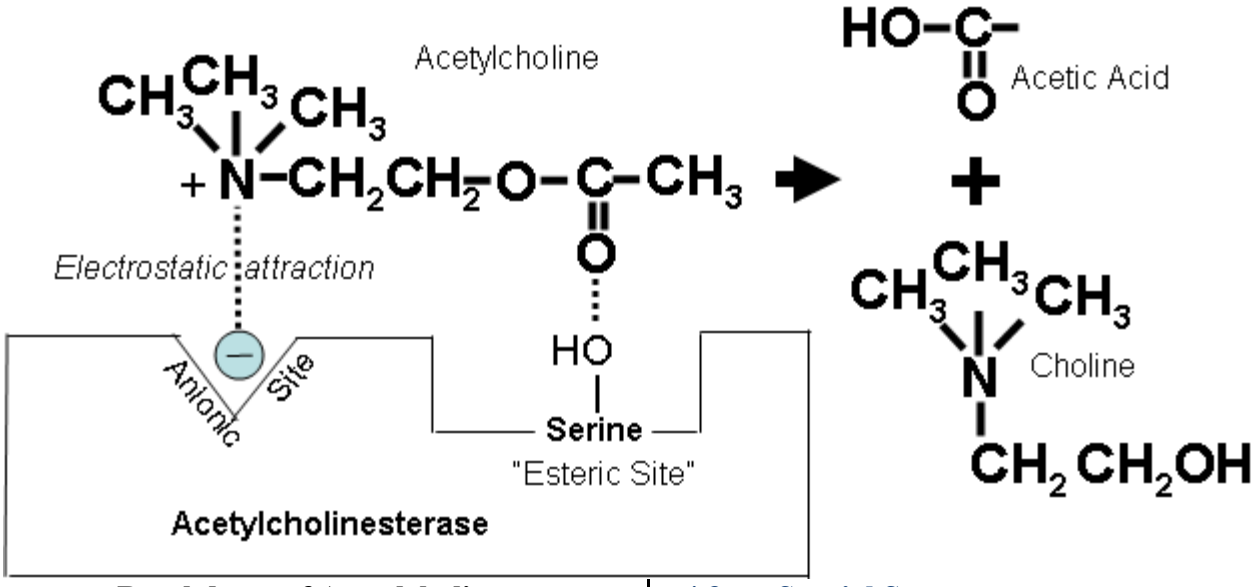
- aldicarb (Temik)
- bendiocarb (Ficam)
- bufencarb (Bux)
- carbaryl (Sevin)
- carbofuran(Furadan)
- formetanate (Carzol)
- methiocarb (Mesurol)
- methomyl (Lannate, Nudrin)
- oxamyl (Vydate)
- pinmicarb (Pirimor)
- propoxur (Baygon)

Some Organophosphates (OPs):

- acephate (Orthene)
- azinphos-methyl (Guthion)
- carbofuran (Furadan, F formulation)
- carbophenothion (Trithion)
- chlorfenvinphos (Birlane)
- chlorpyrifos (Dursban, Lorsban)
- coumaphos (Co-Ral)
- crotoxyphos (Ciodrin, Ciovap)
- crufomate (Ruelene)
- demeton (Systox)
- diazinon (Spectracide)
- dichlorvos (DDVP, Vapona)
- dicrotophos (Bidrin)
- dimethoate (Cygon, De-Fend)
- dioxathion (Delnav)
- disulfoton (Di-Syston)
- ethoprop (Mocap)
- fenamiphos (Nemacur)
- fenitrothion (Sumithion)
- fonofos (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 (Zolonc)
- phosmet (Irnidan, Prolate)
- phosphamidon (Dimecron)
- temephos (Abate)
- terbufos (Counter)
- tetrachlorvinphos (Rabon, Ravap)
- trichlorfon (Dylox, Neguvon)
  (spontaneously converts to dichlorvos)

Some Organophosphate Nerve Agents:

sarin, soman, VX



Breakdown of Acetylcholine

When an acetylcholine (ACh) molecule attaches to a post-synaptic receptor or a muscle cell receptor, a cellular cascade is triggered which results in a nerve signal or a muscle fiber contraction. The receptor-bound ACh is rapidly broken down by **acetylcholinesterase** (Silman and Sussman, 2008) which produces free choline that the pre-synaptic neuron can uptake and reuse as Ach for further pre-synaptic discharge. Receptor-bound ACh only resides for a few milliseconds before being enzymatically broken down and released (Jett, 2011; Mackenzie Ross et al., 2013).

Certain sites on the acetylcholinesterase enzyme (AChE) are attracted to the electropositive phosphorus group of organophosphate molecules and a stable bond creates a ***phosphorylated* AChE** which is biologically inactive. The OPs and CBs (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 minutes to hours of receptor-bound ACh activation with associated physiological effects (See **Part 5.4**).

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 and nickel even at relatively low concentrations (Doty, 2015:306). 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). Noise is a well known potent **cochlear ototoxic agent** (Le et al., 2017).

A recent Swedish report (Johnson and Morata, 2009) 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; Ganguly et al., 2021). Manganese-induced ataxia was reported by Couper in 1837 (Blanc, 2018). Manganese, carbon monoxide, carbon disulfide, TCE, PERC, 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 (Caudle et al., 2012).

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:

<u>Delirium</u>
- Carbon monoxide
- Lead
- Arsenic
- Manganese
- Solvents
- Organophosphate pesticides

<u>Dementia</u>
- Solvents
- Lead
- Manganese
- Arsenic

<u>Organic Delusional Disorder</u>
- Solvents
- Organophosphate pesticides

<u>Mood Disorder - Manic</u>
- Manganese
- Tetraethyllead

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

These neurotoxicants will be dealt with in more detail below in **PART 5**. Some have complained that psychiatry has not been attentive enough to "*psychotoxicology*" (Dumont, 1989; cf. Stollery, 1996; Singer, 2011).

5.0 NOTEWORTHY OCCUPATIONAL NEUROTOXICANTS

5.1 The "Heavy metals" (Pb, Hg, Tl) and other elements

Lead (Pb) inorganic

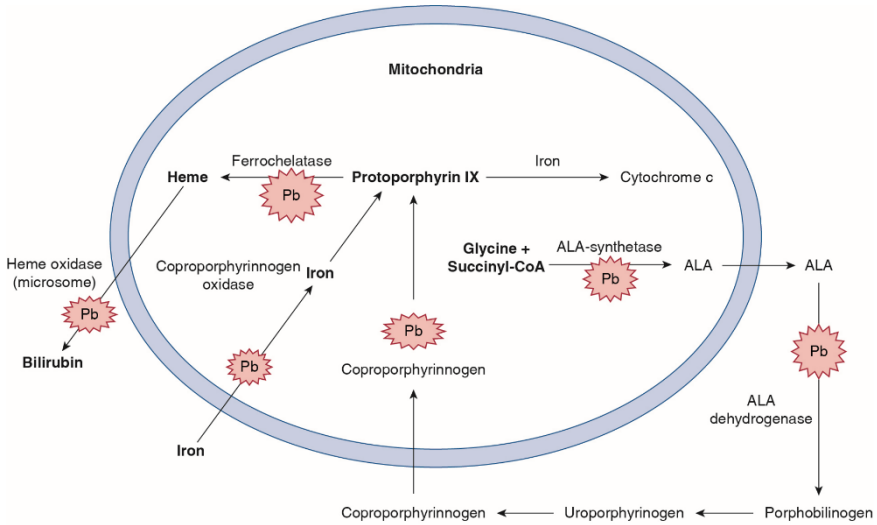
See the extensive history of the health effects of lead in **Part 2.0**. There are now a number of biomarkers of exposure (Barbosa et al., 2005).

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 enzyme inhibitor** of sulfhydryl-containing δ-aminolevulinic acid dehydrogenase (ALAD), ferrochelatase, and to a slightly lesser degree, Pb blocks coproporphyrinogen oxidase and δ-aminolevulinic acid synthetase, all necessary for heme synthesis (see the diagram below). Elevated ALA is itself neurotoxic. Elevation of free erythrocyte protoporphyrin, "*FEP*", is an early indicator of lead toxicity, e.g., within 6-8 weeks of exposure, and is measured as **zinc protoporphyrin**, "*ZPP*" (Karacić et al., 1980).

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). (See the lead PBPK compartment model in **Part 3.0**) 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 fluorescence ("*XRF*") of cortical bone can provide a quantitative assessment of cumulative lead exposure.

There are questions about health effects from high body burdens of lead even while blood lead levels remain normal. However, in its position statements, 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; ACMT, 2017; cf. 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 distal sensory deficits.

Sustained higher levels of lead can result in tremors, incoordination, ataxia, mood changes, various cognitive impairments, seizures, and even coma and death (Eiró et al, 2021; Castellino, Castellino, and Sannolo, eds. 1995; Skerfving and Bergdahl, 2007; ATSDR, 2020). 80% of absorbed lead is excreted in the urine with some in bile, GI secretions, and sweat. Lead impairs uric acid excretion and can cause so-called "*saturnine gout*" (In alchemy, metallic lead was associated with Saturn, hence the terms "*saturnine*" and "*saturnism*").



LEAD INHIBITION OF HEME PATHWAYS (zig zag circles show the Pb-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, Kalos, 2010) and excretion is mainly in the urine.

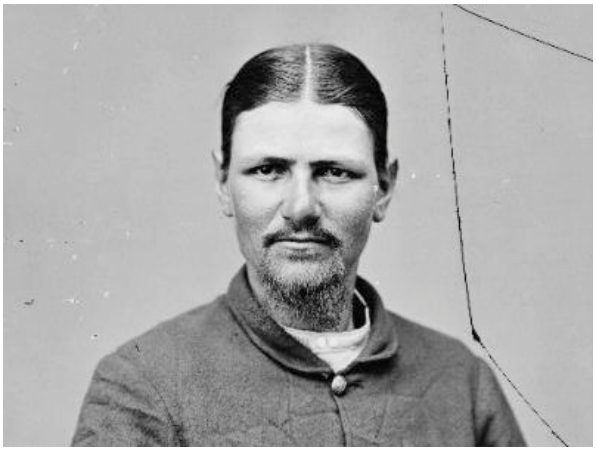
Inorganic mercury compounds are mercury salts as Hg_2^{2+} "*mercurous*" or Hg^{2+} "*mercuric*" (the former are generally less soluble, e.g. calomel, Hg_2Cl_2, once used as a cathartic) and are up to 10% absorbed orally. Both Hg_2^{2+} and Hg^{2+} forms are protein-bound in plasma and do not readily cross the blood-brain barrier. Inorganic mercury can produce neurotoxicity as occurred in the felt hat industry ("*erethism*") from $Hg(NO_3)_2$ e.g., sensory neuropathy and neurobehavioral changes may develop (Ross et al., 1977). The half-life of inorganic mercury is about 40 days with excretion in the urine (20%) and feces (80%) (Berlin et al., 2007).

Organic mercury compounds have caused several large epidemic outbreaks, e.g., at Minamata Bay from industrial contamination (Harada, 1995; Hachiya, 2006; Tsuda et al., 2009) and in Iraq in 1956, 1960, and 1972, from mercurial fungicide contaminated grains (Bakir et al., 1973). Organic mercury disease has occurred in Canada at Grassy Narrows (Harada et al., 2005; Mosa and Duffin, 2017).

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 (Ceccatelli and Aschner, eds. 2012).

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 over 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 Abraham 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 (Osorio-Rico et al, 2017).

Diagnosis of thallium poisoning is by identification of elevated thallium in blood, hair and 24-hour urine samples (Liu and Liao, 2021). Nerve conduction studies show axonal degeneration.

Prussian Blue ($Fe_4[Fe(CN)_6]_3$) is a specific antidote for thallium toxicity (Hoffman, 2003). 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 cesium.

Tianle Li, a New Jersey pharmaceutical company research chemist, was convicted in July 2013 of murdering her estranged husband with thallium she obtained through her work.

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 but inhaled Mn is well 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 (Tjälve and Henriksson, 1999).

Methylcyclopentadienyl manganese tri-carbonyl ("*MMT*") was added to Canadian gasolines from 1976 to 2004 as an anti-knock agent and was a major non-occupational source of Mn (Minjares and Walsh, 2009). In contrast to inorganic Mn compounds, MMT crosses the blood-brain barrier by passive diffusion and 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 (Olanow, 2004). Neither blood nor urine levels reflect well on acute, chronic, or toxic exposures and urine and blood levels correlate poorly with individual exposures (Kim et al., 2015; Ward et al., 2018; Gurol et al., 2021).

Arsenic (As)

Arsenic has a "colorful" history, not only from its use as a yellow (As_2S_3) or red (As_4S_4) 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 As_2O_3. Elemental arsenic As^0 readily forms inorganic and organic compounds.

"*Fowler's solution*," a 1% solution of potassium arsenite, K_2HAsO_3, was a widely used tonic and skin home remedy well into the twentieth century. Arsenic-based medications were used to treat syphilis in the pre-penicillin era (Gibaud and Jaouen, 2010). Cacodylic acid $(CH_3)_2AsO_2H$ ("Agent Blue") was used as a herbicide in the Vietnam War. **Chromated copper arsenate** (CrO_3:CuO:As_2O_5 48:18:34) was used as a wood preservative for many years. **Monosodium methyl arsonate** "MSMA" was one of the last arsenic-based herbicides.

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. As^{5+} (arsenate) is less toxic than its "detoxified" form As^{3+} (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, this can indicate chronic exposure if external contamination has been ruled out.

Aluminum (Al)

Aluminum has been implicated in neuro-degenerative 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 baresthesiae
- Weakness
- Poor concentration
- Tremor

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

Tin (Sn)

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 $(C_2H_5)_2O$ and chloroform $CHCl_3$ (Evans and Balster, 1991) .

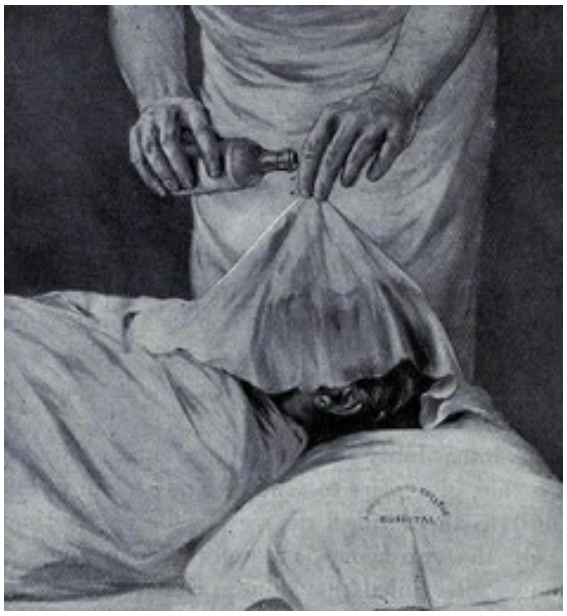
There is a spectrum of neuropsychological effects from solvent exposures. Acute inhalational exposures can produce reversible euphoria, disinhibition, sedation, apathy, and confusion. With increased durations of exposures, neurobehavioral abnormalities may persist and intensify leading to deficits in memory, attention, mood, cognition, and personality changes. The World Health Org. criteria (1985) for **chronic solvent-induced encephalopathy** include 3 levels of CNS dysfunction (van Valen et al., 2012, 2018):

1. **Organic Affective Syndrome (OAS)**

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.



Early organic solvent anesthesia

3. **Severe Chronic Toxic Encephalopathy**

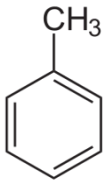
Loss of intellectual abilities of sufficient severity to interfere with social and/or occupational functioning; fixed impairment of abstract thinking and other cognitive functions, personality changes, some neuropsychiatric (e.g., by DSM-5 criteria) and neuroradiological test abnormalities. Severe symptoms 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 250°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 physico-chemical properties.

Toluene

C_7H_8
BP 111°C

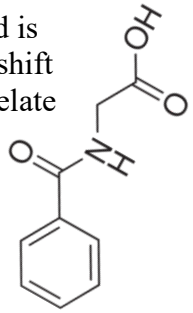


Toluene is the most prevalent aromatic hydrocarbon in the atmosphere, and makes up 7% of gasoline by weight. Blood concentrations rapidly equilibrate with alveolar concentrations, it is carried unbound in the blood, passes readily through the blood-brain barrier, and higher concentrations of toluene 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 .

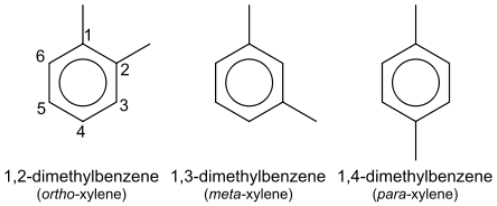
The half-life of toluene in blood is only a few hours. End of work shift urine **hippuric acid** levels correlate well with mean daily environmental concentrations and can serve as a marker of toluene exposure (Angerer and Krämer, 1997)



Hippuric acid

Xylene

$C_6H_4(CH_3)_2$
3 isomers →
BP 139°C

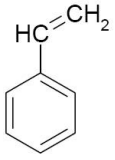


Xylene is used as a thinner and solvent in paints, varnishes, adhesives, and inks and as a solvent in the leather, rubber, and printing industries. It is also used in histology labs. Solvent-type neuropsychological effects have been noted at xylene levels of 90 to 200 ppm, e.g. impairments in reaction 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 (Rajan and Malathi, 2014).

The toxicokinetics of xylene are similar to toluene. Excretion is 5% unchanged in exhaled air and 95% by detoxication, mostly to **methylhippuric acid** (Kawai et al., 1991).

Styrene

C8H8
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 ("fibreglass").

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** (Guillemin and Berode, 1988; Linhart, 2001). The neuropsychological effects of styrene appear to be less than toluene but notable decrements in neurobehavioral performance have been reported. Styrene is classified by IARC as Group 2A "*probably carcinogenic to humans*."

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 **Part 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 (TCE)

C_2HCl_3
BP 87°C

Trichlorethylene (TCE) 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 (Chiu et al, 2006).

Tetrachloroethylene (PERC)

C_2Cl_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

CH_3CCl_3
BP 74°C

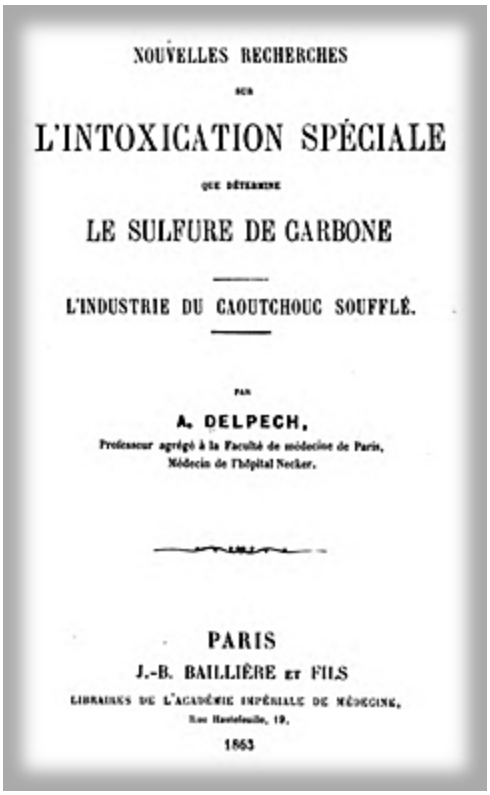
Prior to the 1989 Montreal Protocol on chlorofluorocarbons, 1,1,1-Trichloroethane or methyl chloroform was used as a solvent and propellant. It is more stable than TCE and PERC with their reactive C=C double bond.

Acute exposures to trichloroethane (TCA) produce symptoms similar to those with TCE and PERC. TCA can produce peripheral neuropathy in chronic exposures with evidence of axonopathy and secondary myelinopathy. Excretion is 90% unchanged in exhaled air and most of the remainder by detoxication to **trichloroethanol** and **trichloroacetic acid** (TCAA) conjugated as glucuronides. TCEtOH and TCAA are generally used as end of shift biomarkers of exposure.

Carbon Disulfide

CS_2
BP 46°C

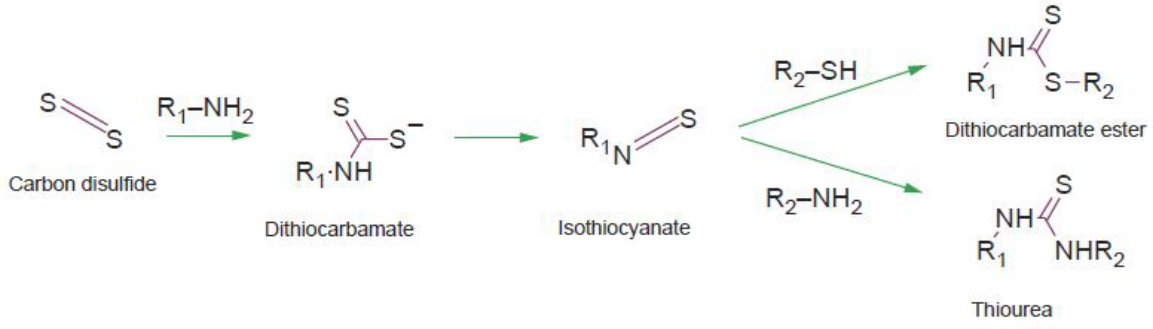
Auguste-Louis Delpech (1818-1880)


NOUVELLES RECHERCHES
SUR
L'INTOXICATION SPÉCIALE
QUE DÉTERMINE
LE SULFURE DE CARBONE
L'INDUSTRIE DU CAOUTCHOUC SOUFFLÉ.
PAR
A. DELPECH,
Professeur agrégé à la Faculté de médecine de Paris,
Médecin de l'hôpital Necker.
PARIS
J.-B. BAILLIÈRE ET FILS
LIBRAIRES DE L'ACADÉMIE IMPÉRIALE DE MÉDECINE,
1863

In his time, CS_2 was just being used to cure rubber that was dipped in vats containing sulfur chloride (SCl_2) that was dissolved in the CS_2. By the 1890s CS_2 was also being used to make viscose rayon from cellulose (Blanc, 2016).

Delpech found that chronic exposures to CS_2 produced emotional lability, impulsiveness, disinhibition, memory loss, depression, insomnia, hallucinations, dizziness, loss of libido, distal numbness, weakness and paresthesiae ("carbon disulfide neurosis").

At ambient CS_2 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 CS_2 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, 2013:481). CS_2 forms dithiocarbamate and isothiocyanate adducts on proteins, which are able to generate dithiocarbamate ester and thiourea cross-links between proteins as shown below (R_1 and R_2 are proteins). This provides a mechanism for disruption of axonal transport which is quite similar to **hexacarbon neurofilamentous** axonopathy (see **Part 4.1**).



5.3 Gases

Hydrogen Cyanide

HCN
BP 26°C

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

Clinical presentations from exposures to higher concentrations of HCN include:

- Immediate hyperventilation
- Loss of consciousness
- Seizures
- Muscle rigidity
- Cherry red skin from elevated venous [O_2]
- Cessation of breathing
- Decerebrate posturing
- Dilated pupils
- Asystole

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

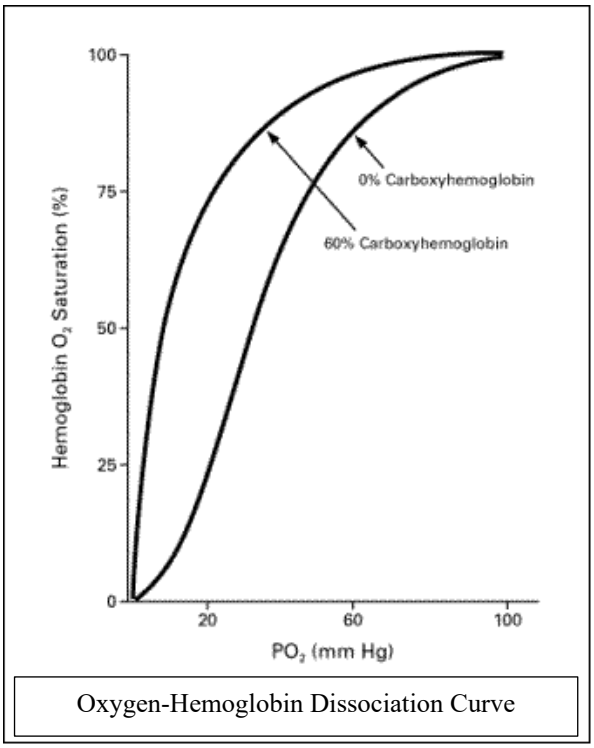
Exposure to HCN		Time to Death
mg/m^3	ppm	
150	135	30 minutes
200	180	10 minutes
300	270	immediate

Workers chronically exposed to 15 ppm hydrogen cyanide have reported fatigue, dizziness, headache, disturbed sleep, tinnitus, parethesiae, 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** (Cooper and Brown, 2008).

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. (Ernst and Zibrak, 1998; Weaver, 2009).



Oxygen-Hemoglobin Dissociation Curve

Ambient CO concentration			% COHb blood	Health Effects
mg/m^3	%	ppm		
80	0.007	70	10	Mild symptoms
140	0.012	120	20	SOB, headaches
250	0.022	220	30	Irritability, fatigue, dizziness, visual change
400-600	0.035-0.052	350-520	40-50	Confusion, weakness, ataxia, collapse
900-1400	0.090-0.120	900-1220	60-70	Unconsciousness, seizures, resp. failure leading to death

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 (Watt et al., 2018).

Hydrogen Sulfide

H_2S
BP -60°C

H_2S is slightly heavier than air so "pockets" can occur in pits, silos, excavations, etc. It has a rotten egg odor ("sour gas") but, at [H_2S] over 100 ppm, olfactory paralysis impairs detection. H_2S is second only to CO as a cause of fatal workplace inhalations (Guidotti, 2010).

Like hydrogen cyanide, H_2S binds with iron in mitochondrial cytochrome oxidase complexes and arrests aerobic metabolism. However, this may not be its only mechanism of toxicity.

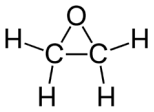
[H_2S] in ppm	Effects
< 1	Odor threshold
<20	Mild symptoms, headaches, teariness
<100	Eye ("gas eye") and airway irritation
100-200	Severe eye and airway irritation
200-400	Pulmonary edema if prolonged
500-800	"Knockdown" (unconsciousness), severe eye and lung effects, death within hours
800+	Immediate respiratory failure

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_2S exposures.

The long term effects of acute H_2S 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_2S 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 in order to oxidize hemoglobin to methemoglobin which binds H_2S. Hyperbaric O_2 may be also be given if available.

Ethylene Oxide



C_2H_4O
BP 11°C

Ethylene oxide (EtO) is used as a chemical feedstock for (poly) ethylene glycols and ethanolamines. It is also used as a sterilant for medical equipment and food products. It is reactive and flammable. It is classified as an IARC Group 1 **carcinogen** (but see Vincent et al., 2019; Lynch et al., 2022).

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 et al., 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 and serves as a biomarker of exposure (Kirman et al., 2021). 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; Bosak et al., 2020).

Organophosphates and Carbamates

(see a list of some OPs & CBs in **PART 4.2**)

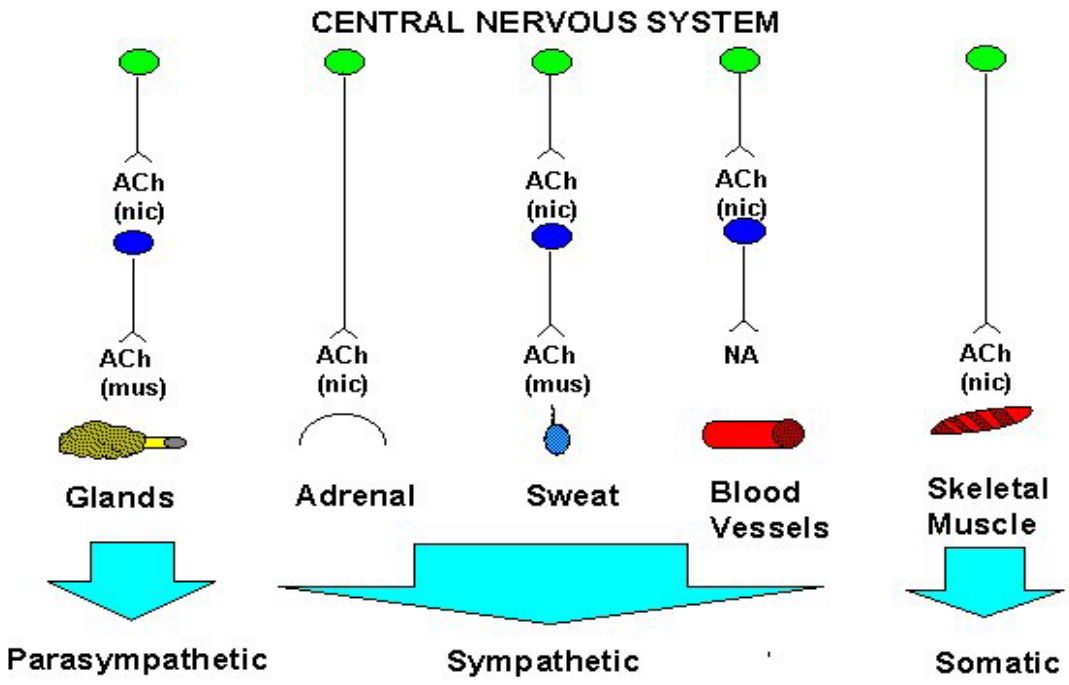
In acute organophosphate exposures, even mild cases can have a reduction of 50% of normal AChE activity. Moderate exposures can reduce the enzyme activity to 20% of normal and severe poisonings can depress AChE to 10% or less. If treatment with atropine and oximes is delayed, the phosphorylated (inactivated) 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:

- Muscle fasciculations / paralysis
- Agitation
- Confusion
- Loss of balance / gait
- Headache
- Hyporeflexia
- Respiratory depression / arrest
- 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, e.g., pralidoxime (2-PAM) 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

This condition occurs from 1 to 4 days after the acute toxic 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. (De Bleecker et al., 1992).

2 Organophosphate-Induced Delayed Polyneuropathy (OIDPN or OPIDP)

Since the organophosphates are *esterase* inhibitors they can affect more than just cholin*esterase* 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, **triorthocresyl 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). OIDPN can occur after a single exposure to certain organophosphates, e.g. leptophos, dichlorvos, fenthion, isofenphos, trichloronate, trichlorfon, merphos, 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 parethesiae, 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.

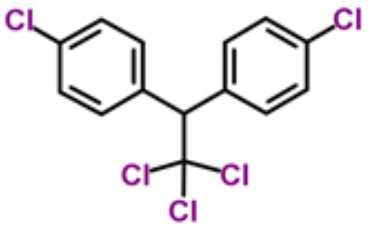
Biomonitoring for AChE inhibition

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 (Lessenger and Reese, 1999).

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 many 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

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.

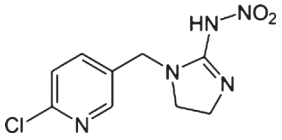
Pyrethroids act similarly to DDT on sodium channels and can produce excitation, tremors, paresthesiae, fasciculations, and convulsions. There is little evidence to date regarding chronic neurotoxicity (Chrustek et al., 2018).

Neonicotinoids

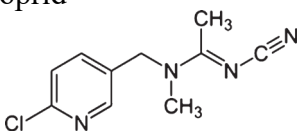
This class of insecticides has been developed since the 1980s and are analogues of nicotine. Their mode of action differs from the OPs, OCs, and pyrethroids since they act specifically on the post-synaptic ligand-gated ion channels at **nicotinic acetylcholine receptors** (nAChRs) (Costas-Ferreira and Faro, 2021). The neonics' binding affinities to nAChRs are lower in humans than in insects and they cross the blood-brain barrier poorly.

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. Neonics can produce clinical features that are similar to acute OP and carbamate poisonings such as miosis, bradycardia, bronchorrhea, salivation, etc.

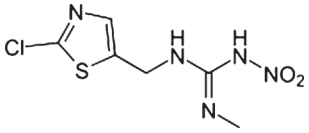
Imidacloprid is the first commercialized neonicotinoid insecticide and is now one of the best-selling insecticides in the world. Some currently used neonicotinoids are shown here:



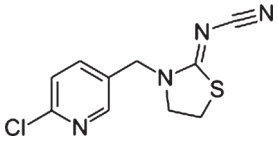
Imidacloprid



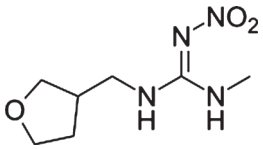
Acetamiprid



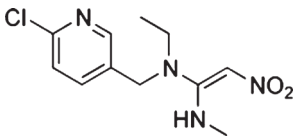
Clothianidin



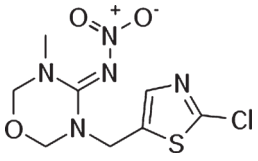
Thiacloprid



Dinotefuran



Nitenpyram



Thiamethoxam

Structures of Some 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 necessarily imply a medically significant exposure to a neurotoxicant (Greenberg, Curtis, 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 annually updated 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 **PART 3.0** above) may render some people more susceptible to toxic effects.

Sample collecting 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 many metals and organic chemicals is available through the **Canadian Health Measures Survey** (CHMS). Statistics Canada began conducting the CHMS in 2007. The survey directly obtains physical measures of Canadians' health including blood and urine samples for laboratory testing. Ongoing data collection continues in two year cycles with 6 detailed reports (Health Canada, 2010-2021). Cycle 7 from January 2022 to December 2023 is now underway. The U.S. **National Health and Nutrition Examination Survey** (NHANES) has published their "*Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2021*" (CDC, 2021).

Reference ranges for blood and urine levels intended for the general population cannot be meaningfully applied to people who are 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 BEI and NHANES data shows:

	ACGIH BEI	**NHANES** adult 95th %-iles
Blood Pb	30 µg/dL	1.71 µg/dL
Blood inorganic Hg	15 µg/L	0.54 µg/L
Blood C_2Cl_4	1 mg/L	0.13 µg/L
Blood Cd	5 µg/L	1.55 µg/L
Blood toluene	1 mg/L	0.9 µg/L
Blood styrene	20 µg/L	0.15 µg/L

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

RECOMMENDED ACTIONS FOR OCCUPATIONAL BLOOD LEAD LEVELS (Ontario Min. Labour, 2020)

Blood Lead Level Inorganic Pb µmol/L	Test-Retest Recommendation	Recommended Action
Most Canadians are < 0.15 µmol/L **0.15**	Baseline test at the employment onset	ROUTINE personal health care and diligence in workplace health and safety measures
If < 0.25 µmol/L (< 5 µg/dL) **0.25**	Test every 4 months for the first year at work	NO SPECIFIC ACTIONS if blood lead levels are below 0.25 µmol/L
If 0.24-0.48 µmol/L (5-10 µg/dL) **0.5**	Test every 6 months while less than 0.5 µmol/L	**REVIEW** sources of exposure, control measures, work practices, and optimize personal protective measures IF >0.25 µmol/L increase from baseline test at onset of their job Or >0.25 µmol/L and worker is pregnant or of child-bearing potential Or worker has kidney disease, neurological disease or high blood pressure conditions
ACGIH BEI women = 10 µg/dL (0.5 µmol/L) **If 0.48-0.96 µmol/L** (10-20 µg/dL) ACGIH BEI men = 20 µg/dL (1 umol/L) **1.0**	Test every 3 months while between 0.5-1.0 µmol/L (10-20 µg/dL)	**GENERAL REVIEW** If >0.5 µmol/L, review sources of exposure, control measures, work practices, and optimize personal protective measures **REMOVE** women from potential lead exposure who are pregnant or child-bearing potential if > 0.5 µmol/L (>10 µg/dL) 1. **ACCOMMODATE** in work with no potential lead exposure until <0.25 µmol/L 2. **RETURN TO PREVIOUS DUTIES** when both of the following apply: • The blood lead level is <0.25 µmol/L (<5 µg/dL) • Exposure is minimized by implementing optimal control measures, work practices, and personal protective measures
If 0.97-1.45 µmol /L (20-30 µg/dL) **1.5**	Test monthly until less than 1 µmol/L (20 µg/dL)	**REMOVAL FROM POTENTIAL LEAD EXPOSURE** 1. **ACCOMMODATE** in work with no potential lead exposure 2. **RETURN TO PREVIOUS DUTIES** when both of the following apply: • The blood lead level is <0.7 µmol/L (<14.5 µg/dL) • Exposure is minimized by implementing optimal control measures, work practices, and personal protective measures
If > 1.45 µmol/L (> 30 µg/dL)		**REMOVAL FROM POTENTIAL LEAD EXPOSURE** 1. Remove from further lead exposure if a single test is > 1.4 µmol/L 2. Accommodate all affected workers so no potential lead exposure until <0.7 µmol/L 3. Also pregnant or child-bearing potential until <0.25

A Sample Lead Exposure Questionnaire

Name: _____ Gender: ☐ M ☐ F Date of Birth: _____

Lead Exposure

1. What type of work have you done in the past which may have exposed you to lead?

Type of Work	# of Year in this Role	Lead Exposure Source

2. What workplace exposure to lead do you have now? _____

3. Do you use a private water supply? ..... ☐ No ☐ Yes
4. Do you live in a building constructed before 1950? ..... ☐ No ☐ Yes
5. Do you live in a building which may contain lead-based paint? ..... ☐ No ☐ Yes
6. Do you live in a building which may contain lead plumbing or lead-based solders on pipes? ..... ☐ No ☐ Yes
7. Do you live on or near land which was used for mining or metal smelting, metal or batter salvaging/recycling, radiator repair, or hazardous waste treatment? .... ☐ No ☐ Yes
8. Do you have work or hobbies involving lead-containing ammunition, inks, scrap metals, fishing tackle, jewelry making, pewter, batteries, pottery, ceramic glazing, stained glass, glass blowing, enameling, or soldering? ..... ☐ No ☐ Yes
9. Do you eat wild animals or birds harvested with lead shot or bullets? ..... ☐ No ☐ Yes
10. Do you use Ayurvedic, folk medications, or herbal remedies which may contain lead? ..... ☐ No ☐ Yes
11. Do you use imported lead-glazed or lead-lined cookware or containers? ..... ☐ No ☐ Yes
12. Do you consume an food or beverages that have been prepared or stored in containers made with lead allow or fittings? ..... ☐ No ☐ Yes
13. Do you use imported spices? ..... ☐ No ☐ Yes
14. Do you use any lead-containing cosmetics, or do you wear lead containing jewelry? ..... ☐ No ☐ Yes

A Sample Lead Exposure Questionnaire cont.

15. Do you smoke tobacco? ☐ No ☐ Yes

16. Are you exposed to second-hand smoke from others? ☐ No ☐ Yes

Lead Symptoms

Do you have any of the following conditions?

1. Cognitive difficulties ☐ No ☐ Yes
2. Unusual taste in your mouth ☐ No ☐ Yes
3. Sleep disturbance ☐ No ☐ Yes
4. Numbness or tingling ☐ No ☐ Yes
5. Difficulty in coordination ☐ No ☐ Yes
6. Loss of touch or temperature sensation ☐ No ☐ Yes
7. Specific muscular weakness or tremor ☐ No ☐ Yes
8. Difficulty in balance ☐ No ☐ Yes
9. Difficulty in fine motor function / hand dexterity ☐ No ☐ Yes
10. Joint or muscle pain ☐ No ☐ Yes
11. Abdominal pain ☐ No ☐ Yes
12. Constipation ☐ No ☐ Yes
13. Anemia ☐ No ☐ Yes
14. Problems with your mood (e.g. anxiety or depression) ☐ No ☐ Yes
15. If you are female, spontaneous miscarriage(s) or premature births ☐ N/A ☐ No ☐ Yes
16. If you are female, difficulty becoming pregnant ☐ N/A ☐ No ☐ Yes
17. If you are male, difficulty in your partner becoming pregnant ☐ N/A ☐ No ☐ Yes
18. Problems with kidney function ☐ No ☐ Yes
19. High blood pressure ☐ No ☐ Yes
20. Headaches ☐ No ☐ Yes
21. Fatigue ☐ No ☐ Yes

Have you had any past blood lead testing? No Yes If yes, when? _____

6.3 Clinical Investigations of Neurotoxicity

Based on awareness of agents and effects from the foregoing sections, assessment of individual cases of occupational neurotoxicity requires astute clinical observations and specialized tests (Lotti and Aminoff, 2015). Various neurophysiological, imaging, and neuropsychological tests are available to help to define specific deficits related to neurotoxicant exposures. These tests require specialized expertise and specific test equipment or psychometric tools. Clinical investigations are directed toward the particular neurotoxic condition(s) of concern. For example, the neuropsychological assessment of **chronic solvent-induced encephalopathy** (CSE) requires the evaluation of the following cognitive domains (Sainio, 2015; van Valen et al., 2018):

1. Attention
   - Processing speed
   - Complex attention
2. Memory
   - Immediate recall
   - Delayed recall
   - Recognition
3. Fine motor performance
   - Motor speed
   - Dexterity
4. Concept formation and reasoning
   - Verbal
   - Non-verbal
5. 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

(adapted from Fiedler et al., 1996)

Cognitive – verbal	Vocabulary WAIS-R Adult reading test - revised
Cognitive – spatial	Block design WAIS-R Raven's matrices
Motor skills	Purdue pegboard test Lafayette dexterity test Finger tapping ? Hand / pinch dynamometry
Concentration / Attention	Reaction time Stroop color-words test Continuous perform. test Trail-making test, PVT
Gait/Balance	Video motion analysis, VORs
Visuomotor coordination	NES hand-eye test Digit symbol WAIS-R Boston quantitative battery
Memory – verbal	Logical memory WMS-R California verbal learning test Digit span WAIS-R
Memory – visual	Visual reproduction WMS-R Complex figure test Paired associates WMS-R
Sensory tests	
Auditory	Sound booth audiometry Brain stem evoked potentials
Visual	Snellen, other optometrics Ishihara plates, Farnsworth
Olfactory	U. Penn. smell ID test
Vibratory	Optacon tactile tester
Equilibrium	Dynamic posturography, ENG
Tactile	2-point discrimination
Affect/Personality	Profile of mood states Beck inventory, MMPI, etc.
Peripheral nerves	Nerve conduction studies Conduction velocity Amplitude Electromyography
Trigeminal nerves	Blink reflex
Sleep	Polysomnography
Synchronous cerebral activity	EEG
Brain neuro-pathological changes	MRI/CT/SPECT scanning

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

PART 1.0 WHY DO NEURONS MAKE SUCH GOOD TARGETS FOR OCCUPATIONAL TOXICANTS?

Lent R, Azevedo FAC, Andrade-Moraes CH, Pinto AVO. "How many neurons do you have? Some dogmas of quantitative neuroscience under revision." *European Journal of Neuroscience* 35.1 (January 2012): 1-9.

Herculano-Houzel S. "Scaling of brain metabolism with a fixed energy budget per neuron: Implications for neuronal activity, plasticity and evolution." *PLoS ONE* 6.3 (March 2011): 1-9.

Dorman DC. "An integrative approach to neurotoxicology." *Toxicologic Pathology* 28.1 (January-February 2000): 37-42.

Dienel GA. "Brain glucose metabolism: Integration of energetics with function." *Physiological Reviews* 99.1 (January 2019): 949-1045.

Shaw W. "The unique vulnerability of the human brain to toxic chemical exposure and the importance of toxic chemical evaluation and treatment in orthomolecular psychiatry." *Journal of Orthomolecular Medicine* 25.3 (July-September 2010): 125-134.

Norton S. "The nervous system as a target for toxic agents." pages 3-21 in C.L. Galli, L. Manzo, PS Spencer, eds. *Recent Advances in Nervous System Toxicology*. (NATO Advanced Science Institutes, Series A – Life Sciences, Volume 100) New York: Plenum Press, 1988.

Maurer LL, Philbert MA. "The mechanisms of neurotoxicity and the selective vulnerability of nervous system sites." pages 61-70 in M. Lotti and M.L. Bleecker, eds. *Handbook of Clinical Neurology* 131 (Occupational Neurology). Edinburgh/New York: Elsevier, 2015.

Grandjean P, Landrigan PJ. "Developmental neurotoxicity of industrial chemicals." *Lancet* 368.9553 (December 16, 2006): 2167-2178.

Kolodkin A, Simeonidis E, Balling R, Westerhoff HV. "Understanding complexity in neurodegenerative diseases: *In silico* reconstruction of emergence." *Frontiers in Physiology* 3 Article 291 (July 2012): 1-11.

PART 2.0 NEUROTOXICITY FROM CLASSICAL "PLUMBISM" TO BEHAVIORAL TOXICOLOGY

Osler W and McCrae T. *A System of Medicine: By Eminent Authorities in Great Britain, the United States and the Continent*. London: Henry Frowde/Hodder & Stoughton, 1907.

Waldron HA. "Hippocrates and lead." *Lancet* 302.7829 (September 15, 1973): 626.

Waldron HA. "Lead poisoning in the ancient world." *Medical History* 17.4 (October 1973): 391-399.

Waldron HA. "Did Hippocrates describe lead poisoning?" *Lancet* 312.8103 (December 16, 1978): 1315.

Skrabanek P. "The case of a missing reference: Is Hippocrates guilty?" *Irish Journal of Medical Science* 155.11 (November 1986): 407.

Vance MA. “Hippocrates and lead poisoning.” *American Journal of Health-System Pharmacy* 64.15 (August 2007): 1584.

Gow ASF and Schofield AF. eds. and trans. *Nicander. The Poems and Poetical Fragments*. Cambridge: Cambridge University Press, 1953.

Major, RR. “Some landmarks in the history of lead poisoning.” *Annals of Medical History* new series (1929-1938), 3.2 (1931): 218-227.

McCord CP. “Lead and lead poisoning in early America: Benjamin Franklin and lead poisoning.” *Industrial Medicine and Surgery* 22.9 (September 1953): 393-399.

McCord CP. “Lead and lead poisoning in Early America: Lead mines and lead poisoning.” *Industrial Medicine and Surgery* 22.11 (November 1953): 534-539.

McCord CP. “Lead and lead poisoning in early America: The pewter era.” *Industrial Medicine and Surgery* 22.12 (December 1953): 573-577.

McCord CP. “Lead and lead poisoning in early America: The lead pipe period.” *Industrial Medicine and Surgery* 23.1 (January 1954): 27-31.

McCord CP. “Lead and lead poisoning in early America: Lead compounds.” *Industrial Medicine and Surgery* 23.2 (February 1954): 75-80.

McCord CP. “Lead and lead poisoning in early America: Clinical lead poisoning in the colonies.” *Industrial Medicine and Surgery* 23.2 (March 1954): 120-5.

McCord CP. “Lead and lead poisoning in early America: Shot towers.” *Industrial Medicine and Surgery* 23.4 (April 1954): 169-72.

Waldron T, Wells C. “Exposure to lead in ancient populations.” *Transactions and Studies of the College of Physicians of Philadelphia* series 5, 1.2 (June 1979): 102-115.

Morris E. “Lead poisoning: An historic view.” *Occupational Health* 32.9 (September 1980): 449-459.

Nriagu JO. *Lead and Lead Poisoning in Antiquity*. New York: John Wiley & Sons, 1983.

Nriagu JO. “Occupational exposure to lead in ancient times.” *The Science of the Total Environment* 31.2 (November 1983): 105-116.

Wedeen RP. *Poison in the Pot: The Legacy of Lead*. Carbondale and Edwardsville IL: Southern Illinois University Press, 1984.

Woolley DE. “A perspective of lead poisoning in antiquity and the present.” *Neurotoxicology* 5.3 (1984): 353-362.

Curran AS. “Lead poisoning: A historical perspective.” *New York State Journal of Medicine* 84.9 (September 1984): 437-438.

Green DW. “The saturnine curse: A history of lead poisoning.” *Southern Medical Journal* 78.1 (January 1985): 48-51.

Lessler MA. “Lead and lead poisoning from antiquity to modern times.” *Ohio Journal of Science* 88.3 (June 1988): 78-84.

Hernberg S. “Lead poisoning in a historical perspective.” *American Journal of Industrial Medicine* 38.3 (September 2000): 244-254.

Tepper LB. “Industrial plumbism: Antiquity to modern times.” *The Journal of the Society for Industrial Archeology* 33.2 (January 2007): 53-66.

Azizi MH, Azizi F. “Lead poisoning in the world and Iran.” *The International Journal of Occupational and Environmental Medicine* 1.2 (April 2010): 81-87.

Riva MA, Lafranconi A, D’Orso MI, Cesana G. “Lead poisoning: Historical aspects of a paradigmatic ‘Occupational and Environmental Disease’.” *Safety and Health at Work* 3.1 (March 2012): 11-16.

Dissanayake V, Erickson TB. “Ball and chain: The global burden of lead poisoning.” *Clinical Toxicology* 50.6 (June 2012): 528-531.

Gibson JL. “A plea for painted railings and painted walls of rooms as the source of lead poisoning amongst Queensland children.” *Australasian Medical Gazette* 23 (April 20, 1904): 149-153. Reprinted in “Special report on lead poisoning in children.” *Public Health Reports* 120 (May-June 2005): 301-304.

Markowitz G, Rosner D. “‘Cater to the children’: The role of the lead industry in a public health tragedy, 1900-1955.” *American Journal of Public Health* 90.1 (January 2000): 36-46.

Warren C. *Brush with Death: A Social History of Lead Poisoning*. Baltimore: Johns Hopkins Press, 2000.

O’Grady K, Perron A. “Reformulating lead-based paint as a problem in Canada.” *American Journal of Public Health* 101.S1 (September 2011): S176-S187.

Gilfillan, SC. “Roman culture and dysgenic lead poisoning.” *The Mankind Quarterly* 5.3 (January-March 1965): 131-148.

Gilfillan, SC. “Lead poisoning and the fall of Rome.” *Journal of Occupational Medicine* 7.2 (February 1965): 53-60.

Gilfillan, SC. “Dysgenic lead poisoning as the principal destroyer of ancient genius and culture.” *Journal of Applied Nutrition* 19 (1967): 95-99.

Gilfillan, SC. *Rome’s Ruin by Lead Poison*. Long Beach CA: Wenzel Press, 1990.
Nriagu JO. “Saturnine gout among Roman aristocrats: Did lead poisoning contribute to the fall of the empire?” *New England Journal of Medicine* 308.11 (March 17, 1983): 660-663.

Scarborough, J. “The myth of lead poisoning among the Romans: An essay review of Jerome O. Nriagu, Lead and Lead Poisoning in Antiquity.” *Journal of the History of Medicine and Allied Sciences* 39.4 (October 1984): 469-475.

Needleman L, Needleman D. “Lead poisoning and the decline of the Roman aristocracy.” *Echos du Monde Classique*/*Classical Views* 29 new series 4.1 (1985): 63-94.

Retief FP, Cilliers LP. “Lead poisoning in ancient Rome.” *Acta Theologica* 26.2 Supplementum 7 (2006): 147-164. Reprinted as “Lead Poisoning and the downfall of Rome: Reality or myth?” pages 118-126 in *History of Toxicology and Environmental Health - Toxicology in Antiquity*. Volume 1. Philip Wexler, ed. Amsterdam: Elsevier 2014.

Phillips, CR. “Old wine in old lead bottles: Nriagu on the fall of Rome.” *The Classical World* 78.1 (September-October 1984): 29-33.

Reddy A, Braun CL. “Lead and the Romans.” *Journal of Chemical Education* 87.10 (October 2010): 1052-1055.

Delile H, Blichert-Toft J, Goiran J-P, Keay S, Albarède F. “Lead in ancient Rome’s city waters.” *Proceedings of the National Academy of Sciences* 111.18 (May 6, 2014): 6594-6599.

Ashe WF. “One of Ramazzini’s predecessors.” *Journal of Occupational Medicine* 9.6 (June 1967): 311-314.

Eisinger J. “Lead and wine: Eberhard Gockel and the *Colica Pictonum*.” *Medical History* 26.3 (July 1982): 279-302.

Eisinger J. “Sweet poison.” *Natural History* 105.7 (July 1996): 48-53.

McConaghey RMS. “Sir George Baker and the Devonshire Colic.” *Medical History* 11.4 (October 1967): 345-360.

Waldron HA. “The Devonshire Colic.” *Journal of the History of Medicine and Allied Sciences* 25.4 (October 1970): 283-413.

Baker G. *An Essay Concerning the Cause of the Endemial Colic of Devonshire*. London: J. Hughs 1767. Reprinted by the Delta Omega Society in 1958 and available online at https://s3.amazonaws.com/aspphwebassets/delta-omega/archives/devon.pdf. See also George Baker, "An inquiry concerning the cause of the endemial colic of Devonshire." *Medical Transactions of the College of Physicians in London* 1 (1768): 175-256 with "An Appendix," pages 460-468. Available online at https://archive.org/details/s14id11855510/page/n3/mode/2up

Hamm RD. "Ben Franklin's adventures in occupational and environmental toxicology." *BC Toxicology News Monthly Bulletin* 3.11 (November 2018): 382-404.

Wilson J. "An account of the disease called mill reek." *The Scots Magazine* 16 (June 1754): 287-288.

Meiklejohn A. "The mill reek and the Devonshire colic." *British Journal of Industrial Medicine* 11.1 (January 1954): 40-44.

Risse GB. "'Mill reek' in Scotland: Construction and management of lead poisoning." pages 199-228 in *New Medical Challenges During the Scottish Enlightenment*. Clio Medica 78 (The Wellcome Series in the History of Medicine). Amsterdam: Rodopi, 2005.

Slater M, Drew J. eds. "*The Uncommercial Traveller" and Other Papers 1859-70.* The Dent Uniform Edition of Dickens' Journalism, Volume 4. London: J.M. Dent, 2000. Dickens' article is also available online at https://archive.org/details/allyearround01charrich/page/62/mode/2up

Finger S. *Doctor Franklin's Medicine*. Philadelphia: University of Pennsylvania Press, 2006.

Franklin, B. Letter written to his friend Benjamin Vaughan on July 31, 1786. A letter press copy of Franklin's original handwritten letter to Vaughan is viewable at the *Library of Congress* website at https://www.loc.gov/item/mss21451025/ "Benjamin Franklin Papers: Series II, 1726-1818; 1785, May 26-1786, Dec. 10 (vol. 23)" where the 4-page original letter is found at *Images 185-188*. The text of Franklin's "lead letter" is found at the *Online Library of Liberty* website at http://oll.libertyfund.org/titles/franklin-the-works-of-benjamin-franklin-in-12-vols under "The Works of Benjamin Franklin, Vol. XI Letters and Misc. Writings 1784-1788" (go down that section's *Table of Contents* to the entry titled *"To Benjamin Vaughan1" and scroll to "31 July, 1786"*).

Wright RD. "'Dr.' Franklin." *The Health Officer* 3.10 (February 1939). Reprinted in *Public Health Reports* 91.2 (March-April 1976): 178-183.

Nichols RF. "Franklin on Bifocals and Lead Poisoning, 1785-86." *Medical Affairs* (September, 1965): 24-27.

Felton, JS. "Man, Medicine, and Work in America: A Historical Series. III. Benjamin Franklin and His Awareness of Lead Poisoning." *Journal of Occupational Medicine* 9.11 (November, 1967): 543-554.

Tanquerel des Planches L. *Traité des Maladies de Plomb ou Saturnines*. Paris: Ferra, 1839. Online at https://archive.org/details/traitdesmaladies02tanq English translation by Samuel L. Dana. *Lead Diseases: A Treatise from the French of L. Tanquerel des Planches*. Boston: Tappan, Whittemore & Mason, 1850. Online at https://archive.org/details/leaddiseasestrea00tanq

Walusinski O. "Louis Tanquerel des Planches (1810-1862) and the history of discovering lead poisoning in the nervous system." *Revue Neurologique* (2021): 11 pages. Pre-publication online at https://doi.org/10.1016/j.neurol.2021.08.009

Ramazzini B. *De Morbis Artificum Diatriba*. Modena: Antionio Capponi, 1700. 1703 edition at https://archive.org/details/bernramazzinide00porzgoog/page/n2/mode/2up?view=theater

Kussmaul A. *Untersuchungen über den constitutionellen Mercurialismus und sein Verhältniss zur constitutionellen Syphilis*. (Studies on constitutional mercurialism and its relation to constitutional syphilis) Wurzburg: Druck und Verlag, 1861. Available online at https://iiif.wellcomecollection.org/pdf/b28100864

Freeman JA. "Mercurial poisoning among hatters." *Transactions of the Medical Society of New Jersey* (1860): 61-64.

Dennis L. "Hatting as affecting the health of operatives." *Report of the New Jersey State Board of Health* 2 (1878): 67-85. Reprinted in *The Sanitarian* 7.77 (August 1879): 362-374.

Waldron HA. "Did the Mad Hatter have mercury poisoning?" *British Medical Journal* 287.6409 (December 24-31, 1983): 1961. Comments by Price TML; Lightwood R; Goodacre SH; *BMJ* 288.6413 (January 28, 1984): 324-325.

Wedeen RP. "Were the hatters of New Jersey "mad"?" *American Journal of Industrial Medicine* 16.2 (1989): 225-233.

Davies M. "Hatter matter." *The Times Literary Supplement* No. 5746 (May 17, 2013): 14-15.

Finger S, Boller F, Tyler KL. eds. *Handbook of Clinical Neurology* 3rd Series Vol. 95 (History of Neurology). Edinburgh/New York: Elsevier, 2010.

Lazar, JW. "Acceptance of the neuron theory by clinical neurologists of the late-Nineteenth Century." *Journal of the History of the Neurosciences: Basic and Clinical Perspectives* 19.4 (October 2010): 349-364.

Stirling DA. "History of toxicology and allied sciences: A bibliographic review and guide to suggested readings." *International Journal of Toxicology* 25.4 (July-August 2006): 261-268.

O'Flynn RR, Waldron HA. "Delpech and the origins of occupational psychiatry." *British Journal of Industrial Medicine* 47.3 (March 1990): 189-198.

Lucchini RG, Riva MA, Sironi VA, Porro A. "*Torvis oculis*: Occupational roots of behavioral neurotoxicology in the last two centuries and beyond." *NeuroToxicology* 33.4 (August 2012): 652-659.

Nierenberg DW, Nordgren RE, Chang MB, Siegler RW, Blayney MB, Hochberg F, Toribara TY, Cernichiari E, Clarkson T. "Delayed cerebellar disease and death after accidental exposure to dimethylmercury." *New England Journal of Medicine* 338.23 (June 4, 1998): 1672-1676. Comments by Byard RW, Couper R; Lockwood AH, Landrigan PJ; Hanlon DP; and authors' reply; *NEJM* 338.17 (October 22, 1998): 1243-1244.

PART 3.0 TOXICOKINETICS, COMPARTMENTS, AND PBPK MODELS

Aschner M, Aschner JL. "Manganese neurotoxicity: Cellular effects and blood-brain barrier transport." *Neuroscience and Biobehavioral Reviews* 15.3 (Autumn 1991): 333-340.

Löf A, Johanson G. "Toxicokinetics of organic solvents: A review of modifying factors." *Critical Reviews in Toxicology* 28.6 (1998): 571-650.

Upton RN, Foster DJR, Abuhelwa AY. "An introduction to physiologically-based pharmacokinetic models." *Pediatric Anesthesia* 26.11 (November 2016): 1036-1046.

Andersen ME. "Toxicokinetic modeling and its applications in chemical risk assessment." *Toxicology Letters* 138.1-2 (February 2003): 9-27.

Leggett RW. "An age-specific kinetic model of lead metabolism in humans." *Environmental Health Perspectives* 101.7 (December 1993): 598-616.

Cohen Hubal EA, Wetmore BA, Wambaugh JF, El-Masri H. Sobus JR, Bahadori T. "Advancing internal exposure and physiologically-based toxicokinetic modeling for 21st-century risk assessments." *Journal of Exposure Science and Environmental Epidemiology* 29.1 (January 2019): 11-20.

PART 4.0 THE DIVERSE TOXICODYNAMICS OF THE NERVOUS SYSTEM

4.1 Peripheral Neurons (neuronopathy, axonopathy, myelinopathy)

Kulkantrakorn K. "Pyridoxine-induced sensory ataxic neuronopathy and neuropathy: Revisited." *Neurological Sciences* 35.11 (November 2014): 1827-1830.

Toledano M. "Toxin-induced Neuropathies." *Neurologic Clinics* 38.4 (November 2020): 749-763.

Spencer PS. "Neuroprotein targets of γ-diketone metabolites of aliphatic and aromatic solvents that induce central-peripheral axonopathy." *Toxicologic Pathology* 48.3 (April 2020): 411-421.

Román GC. "An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy." *Journal of the Neurological Sciences* 127.1 (December 1994): 11-28.

Morgan JP. “The Jamaica ginger paralysis.” *Journal of the American Medical Association* 248.15 (October 15, 1982): 1864-1867.

Parascandola J. “Pharmacology and public health: The Jamaica ginger paralysis episode of the 1930s.” *Pharmacy in History* 36.3 (1994): 123-131.

4.2 Synaptic Neurotransmission (cholinergic pathways)

Fukuto TR. “Mechanism of action of organophosphorus and carbamate insecticides.” *Environmental Health Perspectives* 87 (July 1990): 245-254.

Lionetto MG, Caricato R, Calisi A, Giordano ME, Schettino T. “Acetylcholinesterase as a biomarker in environmental and occupational medicine: New insights and future perspectives.” *BioMed Research International* 2013:321213. doi: 10.1155/2013/321213

Leung MCK, Meyer JN. “Mitochondria as a target of organophosphate and carbamate pesticides: Revisiting common mechanisms of action with new approach methodologies.” *Reproductive Toxicology* 89 (October 2019): 83-92. doi: 10.1016/j.reprotox.2019.07.007.

Silman I, Sussman JL. “Acetylcholinesterase: How is structure related to function?” *Chemico-Biological Interactions* 175.1-3 (September 2008): 3-10.

Jett DA. “Neurotoxic pesticides and neurologic effects.” *Neurologic Clinics* 29.3 (August 2011): 667-677.

Mackenzie Ross S, McManus IC, Harrison V, Mason O. “Neurobehavioral problems following low-level exposure to organophosphate pesticides: A systematic and meta-analytic review.” *Critical Reviews in Toxicology* 43.1 (January 2013): 21-44.

4.3 Special Senses (visual, auditory, olfactory)

Doty RL. “Neurotoxic exposure and impairment of the chemical senses of taste and smell.” pages 299-324 in M. Lotti and M.L. Bleecker, eds. *Handbook of Clinical Neurology* 131 (Occupational Neurology). Edinburgh/New York: Elsevier, 2015.

Gagnaire F, Langlais C. “Relative ototoxicity of 21 aromatic solvents.” *Archives of Toxicology* 79.6 (June 2005): 346-354.

Le TN, Straatman LV, Lea J, Westerberg B. “Current insights in noise-induced hearing loss: A literature review of the underlying mechanism, pathophysiology, asymmetry, and management options.” *Journal of Otolaryngology – Head and Neck Surgery* 46.41 (May 2017): 1-15.

Johnson A-C, Morata TC. *Occupational Exposure to Chemicals and Hearing Impairment*. 142. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals NR 2010;44(4) University of Gothenburg: Geson Hylte Tryck, 2009.
https://www.norskoljeoggass.no/globalassets/dokumenter/drift/arbeidsmiljo/kjemisk-

arbeidsmiljo/fagtema/horselsskadelige-kjemikalier/occupational-exposure-to-chemicals-and-hearing-impairment.pdf

4.4 Movement Disorders (parkinsonism, ataxia, tremor)

Gillen HW. "Occupational neurotoxicology and movement disorders: A historical perspective." *Journal of the History of the Neurosciences* 4.1 (March 1995): 63-66.

Ganguly J, Kulshreshtha D, Jog M. "Mercury and movement disorders: The toxic legacy continues." *Canadian Journal of Neurological Sciences* 2021 published online June 24, 2021:1-9. doi: 10.1017/cjn.2021.146

Blanc PD. "The early history of manganese and the recognition of its neurotoxicity, 1837-1936." *NeuroToxicology* 64 (January 2018): 5-11.

Caudle WM, Guillot TS, Lazo CR, Miller GW. "Industrial toxicants and Parkinson's disease." *NeuroToxicology* 33.2 (March 2012): 178-188.

Fonnum F, Lock EA. "Cerebellum as a target for toxic substances." *Toxicology Letters* 112-113 (March 2000): 9-16.

4.5 Neuroaffective and Neurocognitive Effects

Dumont MP. "Psychotoxicology: The return of the mad hatter." *Social Science and Medicine* 29.9 (September 1989): 1077-1082.

Stollery BT. "Cognitive neurotoxicology: A luxury or necessity?" *Neurotoxicology and Teratology* 18.4 (July-August 1996): 359-364.

Singer R. "Neurotoxicity in neuropsychology." Pages 813-838 in M.R. Schoenberg and J.G. Scott, eds. *The Little Black Book of Neuropsychology*. New York: Springer, 2011.

PART 5.0 SOME NOTEWORTHY OCCUPATIONAL NEUROTOXICANTS

5.1 The "Heavy metals" (Pb, Hg, Tl) and other elements (Mn, As, Al, Sn, Te)

Barbosa F, Tanus-Santos J, Gerlach RF, Parsons PJ. "A critical review of biomarkers used for monitoring human exposure to lead: Advantages, limitations, and future needs." *Environmental Health Perspectives* 113.12 (December 2005): 1669-1664.

Gonick HC. "Lead-binding proteins: A review." *Journal of Toxicology* 2011.686050 (2011):1-10.

Karacić V, Prpić-Majić D, Telisman S. "The relationship between zinc protoporphyrin (ZPP) and 'free' erythrocyte protoporphyrin (FEP) in lead-exposed individuals." *International Archives of Occupational and Environmental Health* 47.2 (January 1980): 165-177.

Charlton N, Wallace KL. “American College of Medical Toxicology position statement on post-chelator challenge urinary metal testing.” *Journal of Medical Toxicology* 6.1 (March 2010): 74-75.

American College of Medical Toxicology. “ACMT recommends against use of post-chelator challenge urinary metal testing.” *Journal of Medical Toxicology* 13.4 (December 2017): 352-354.

Jang DH, Hoffman RS. “Heavy metal chelation in neurotoxic exposures.” *Neurologic Clinics* 29.3 (August 2011): 607-622.

Crinnion WJ. “The benefits of pre- and post-challenge urine heavy metal testing: Part 1.” *Alternative Medicine Review* 14.1 (March 2009): 3-8.

Crinnion WJ. “The benefits of pre- and post-challenge urine heavy metal testing: Part 2.” *Alternative Medicine Review* 14.2 (June 2009): 103-108.

Eiró LG, Ferreira MKM, Frazão DR, Aragão WAB, Souza-Rodrigues RD, Fagundes NCF, Maia LC, Lima RR. “Lead exposure and its association with neurological damage: Systematic review and meta-analysis.” *Environmental Science and Pollution Research* 28 (July 2021): 37001–37015.

Castellino N, Castellino P, and Sannolo N. eds. *Inorganic Lead Exposure – Metabolism and Intoxication*. Boca Raton: Lewis, 1995.

Skerfving S, Bergdahl IA. “Lead.” pages 599-643 in GF Nordberg, BA Fowler, M Nordberg, LT Friberg, eds. *Handbook on the Toxicology of Metals*. 3rd ed. Amsterdam/New York: Elsevier, 2007.

Agency for Toxic Substance and Disease Registry. *Toxicological Profile for Lead*. Atlanta: Centers for Disease Control and Prevention, August, 2020. https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf

Syversen T, Kaur P. “The toxicology of mercury and its compounds.” *Journal of Trace Elements in Medicine and Biology* 26.4 (October 2012): 215-226.

Spaeth KR, Tsismenakis AJ, Kales S.N. *Heavy Metals: A Rapid Clinical Guide to Neurotoxicity and Other Common Concerns*. New York: Nova Science Publishers, 2010.

Ross WD, Gechman AS, Sholiton MC, Paul HS. “Need for alertness to neuropsychiatric manifestations of inorganic mercury poisoning.” *Comprehensive Psychiatry* 18.6 (November-December 1977): 595-598.

Berlin M, Zalups RK, Fowler BA. “Mercury.” pages 675-729 in GF Nordberg, BA Fowler, M Nordberg, LT Friberg, eds. *Handbook on the Toxicology of Metals*. 3rd ed. Amsterdam/New York: Elsevier, 2007.

Harada M. “Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution.” *Critical Reviews in Toxicology* 25.1 (1995): 1-24.

Hachiya N. “The history and the present of Minamata Disease – Entering the second half a century.” *Japan Medical Association Journal* 49.3 (March 2006): 112-118.

Tsuda T, Yorifuji T, Takao S, Miyai M, Babazono A. “Minamata disease: Catastrophic poisoning due to a failed public health response.” *Journal of Public Health Policy* 30.1 (April 2009): 54-67.

Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, Al-Raawi NY, Tikriti S, Dhahir HI, Clarkson TW, Smith JC, Doherty RA. “Methylmercury poisoning in Iraq.” *Science* 181.4096 (July 20, 1973): 181-242.

Harada M, Fujino T, Oorui T, Nakachi S, Nou T, Kizaki T, Hitomi Y, Nakano N, Ohno H. “Followup study of mercury pollution in indigenous tribe reservations in the Province of Ontario, Canada, 1975-2002.” *Bulletin of Environmental Contamination and Toxicology* 74.4 (April 2005): 689-697.

Mosa A, Duffin J. “The interwoven history of mercury poisoning in Ontario and Japan.” *Canadian Medical Association Journal* 189.5 (February 6, 2017): E213-E215.

Ceccatelli S. Aschner M. eds. *Methylmercury and Neurotoxicity*. New York: Springer, 2012.

Fergurson EB. “The man who shot the man who shot Lincoln.” *American Scholar* 78.2 (Spring 2009): 42-51.

Osorio-Rico L, Santamaria A, Galván-Arzate S. “Thallium toxicity: General issues, neurological symptoms, and neurotoxic mechanisms.” pages 345-353 in M. Aschner and L.G. Costa, *Neurotoxicity of Metals* (Advances in Neurobiology 18). New York: Springer, 2017.

Liu H, Liao G. “Long-term misdiagnosis and neurologic outcomes of thallium poisoning: A case report and literature review.” *Brain and Behavior* 11.3 (March 2021): e02032. doi: 10.1002/brb3.2032

Hoffman RS. “Thallium toxicity and the role of Prussian blue in therapy.” *Toxicological Reviews* 22.1 (March 2003): 29-40.

Tjälve H, Henriksson J. “Uptake of metals in the brain via olfactory pathways.” *NeuroToxicology* 20.2-3 (April-June 1999): 181-195.

Minjares RJ, Walsh M. *Methylcyclopentadienyl Manganese Tricarbonyl (MMT): A Science and Policy Review*. ICCT (International Council on Clean Transportation): January 2009. Online at https://theicct.org/wp-content/uploads/2021/06/MMT_dec08.pdf

Olanow CW. “Manganese-induced parkinsonism and Parkinson’s disease.” *Annals of the New York Academy of Sciences* 1012.1 (March 2004): 209-223.

Kim G, Lee H-S, Bang JS, Kim B, Ko D, Yang M. “A current review for biological monitoring of manganese with exposure, susceptibility, and response biomarkers.” *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis and Ecotoxicology Reviews* 33.2 (2015): 229-254.

Ward EJ, Edmondson DA, Nour M, Snyder S, Rosenthal FS, Dydak U. “Toenail manganese: A sensitive and specific biomarker of exposure to manganese in career welders.” *Annals of Work Exposures and Health* 62.1 (January 2018): 101-111.

Gurol KC, Aschner M, Smith DR, Mukhopadhayay S. “Role of excretion in manganese homeostasis and neurotoxicity: A historical perspective.” *American Journal of Physiology. Gastrointestinal and Liver Physiology* 322.1 (January 2022): G79-G92.

5.2 Organic Solvents (toluene, xylene, styrene, C_2HCl_3, C_2Cl_4, CH_3CCl_3, CS_2)

Evans EB, Balster RL. “CNS depressant effects of volatile organic solvents.” *Neuroscience and Biobehavioral Reviews* 15.2 (Summer 1991): 233-241.

van Valen E, van Thriel C, Akila R, Nilson LN, Bast-Pettersen R, Sainio M, van Dijk F, van der Laan G, Verberk M, Wekking E. “Chronic solvent-induced encephalopathy: European consensus of neuropsychological characteristics, assessment, and guidelines for diagnostics.” *NeuroToxicology* 33.4 (August 2012): 710-726.

van Valen E, Wekking E, van Hout M, van der Laan G, Hageman G, van Dijk F, de Boer A, Sprangers M. “Chronic solvent-induced encephalopathy: Course and prognosis factors of neuropsychological functioning.” *International Archives of Occupational and Environmental Health* 91.7 (October 2018): 843-858.

Guillemin MP, Berode M. “Biological monitoring of styrene: A review.” *American Industrial Hygiene Association Journal* 49.10 (October 1988): 497-505.

Linhart I. “Stereochemistry of styrene biotransformation.” *Drug Metabolism Reviews* 33.3-4 (August-November 2001): 353-367.

Chiu WA, Okino MS, Lipscomb JC, Evans MV. “Issues in the pharmacokinetics of trichloroethylene and its metabolites.” *Environmental Health Perspectives* 114.9 (September 2006): 1450-1456.

Angerer J, Krämer, A. “Occupational chronic exposure to organic solvents. XVI. Ambient and biological monitoring of workers exposed to toluene.” *International Archives of Occupational and Environmental Health* 69.2 (December 1996): 91-96.

Rajan ST, Malathi N. “Health hazards of xylene: A literature review.” *Journal of Clinical and Diagnostic Research* 82.2 (February 2014): 271-274.

Kawai T, Mizunuma K, Yasugi T, Horiguchi S, Uchida Y, Iwami O, Iguchi H, Masayuki I. "Urinary methylhippuric acid isomer levels after occupational exposure to a xylene mixture." *International Archives of Occupational Environmental Health* 63.1 (May 1991): 69-75.

Blanc PD. *Fake Silk: The Lethal History of Viscose Rayon*. New Haven/London: Yale University Press, 2016.

Krstev S, Peruničić B, Farkić B, Banićević R. "Neuropsychiatric effects in workers with occupational exposure to carbon disulfide." *Journal of Occupational Health* 45.2 (March 2003): 81-87.

Llorens J. "Toxic neurofilamentous axonopathies: Accumulation of neurofilaments and axonal degeneration." *Journal of Internal Medicine* 273.5 (May 2013): 478-489.

5.3 Gases (HCN, CO, H_2S, ethylene oxide)

Cooper CE, Brown GC. "The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: Chemical mechanism and physiological significance." *Journal of Bioenergetics and Biomembranes* 40.5 (October 2008): 533-539.

Ernst A, Zibrak JD. "Carbon monoxide poisoning." *New England Journal of Medicine* 339.22 (November 26, 1998): 1603-1608.

Weaver LK. "Carbon monoxide poisoning." *New England Journal of Medicine* 360.12 (March 19, 2009): 1217-1225.

Watt S, Prado CE, Crowe SF. "Immediate and delayed neuropsychological effects of carbon monoxide poisoning: A meta-analysis." *Journal of the International Neuropsychological Society* 24.4 (April 2018): 405-415.

Guidotti TL. "Hydrogen sulfide: Advances in understanding human toxicity." *International Journal of Toxicology* 29.6 (December 2010): 569-581.

Hirsch AR. "Hydrogen sulfide exposure without loss of consciousness: Chronic effects in four cases." *Toxicology and Industrial Health* 18.2 (March 2002): 51-65.

Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, Best EA, Mundt KA. "Ethylene oxide: Cancer evidence integration and dose-response implications." *Dose-Response* 17.4 (December 2019): 1559325819888317.

Lynch HN, Kozal JS, Russell AJ, Thompson WJ, Divis HR, Freid RD, Calabrese EJ, Mundt KA. "Systematic review of the scientific evidence on ethylene oxide as a human carcinogen." *Chemico-Biological Interactions* 364 (September 2022): 110031.

Bryant HE, Visser ND, Yoshida K. "Ethylene oxide sterilizer use and short-term symptoms amongst workers." *Journal of the Society of Occupational Medicine* 39.3 (Autumn 1989): 101-106.

Patch PC, Hartlage LC. “Neurological and emotional sequelae of exposure to ethylene oxide.” *International Journal of Neuroscience* 106.1-2 (January 2001): 101-107.

Kirman CR, Li AA, Sheehan PJ, Bus JS, Lewis RC, Hays SM. “Ethylene oxide review: Characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management.” *Journal of Toxicology and Environmental Health, Part B. Critical Reviews*. 24.1 (2021): 1-29.

5.4 Pesticides (organophosphates, carbamates, organochlorines, pyrethroids, neonicotinoids)

Bosak A, Bavec A, Konte T, Šinko G, Kovarik Z, Goličnik M. “Interactions of Paraoxonase-1 with pharmacologically relevant carbamates.” *Molecules* 25.1 (January 2020): 211. doi: 10.3390/molecules25010211.

De Bleecker J, Van Den Neucker K, Willems J. “The intermediate syndrome in organophosphate poisoning: Presentation of a case and review of the literature.” *Journal of Toxicology. Clinical Toxicology* 30.3 (1992): 321-329; editorial comment by LM Haddad, 331-332.

Lotti M, Moretto A. “Do carbamates cause polyneuropathy?” *Muscle and Nerve* 34.4 (October 2006): 499-502.

Jokanović M, Kosanović M, Brkić D, Vukomanović P. “Organophosphate induced delayed polyneuropathy in man: An overview.” *Clinical Neurology and Neurosurgery* 113.1 (January 2011): 7-10.

Lessenger JE, Reese BE. “Rational use of cholinesterase activity testing in pesticide poisoning.” *Journal of the American Board of Family Practice* 12.4 (July-August 1999): 307-314.

Chrustek A, Hołyńska-Iwan I, Dziembowska I, Bogusiewica J, Wróblewski M, Cwynar A, Olszewska-Słonina. “Current research on the safety of pyrethroids used as insecticides.” *Medicina (Kaunas)* 54.4 (August 2018): 61 doi: 10.3390/medicina54040061.

Costas-Ferreira C, Faro, LRF. “Neurotoxic effects of neonicotinoids on mammals: What is there beyond the activation of nicotinic acetylcholine receptors? A systematic review.” *International Journal of Molecular Sciences* 22.16 (August 2021): 8413. doi: 10.3390/ijms22168413.

Phua DH, Lin C, Wu M-L, Deng J-F, Yang C-C. “Neonicotinoid insecticides: An emerging cause of acute pesticide poisoning.” *Clinical Toxicology* 47.4 (April 2009): 336-341.

Lin P-C, Lin H-J, Liao Y-Y, G H-R, Chen K-T. “Acute poisoning with neonicotinoid insecticides: A case report and literature review.” *Basic and Clinical Pharmacology and Toxicology* 112.4 (April 2013): 282-286.

PART 6.0 CLINICAL NEUROTOXICOLOGY

6.1 Identification of Occupational Neurotoxic Disorders

Checkoway H, Pearce N, Kriebel D. "Selecting appropriate study designs to address specific research questions in occupational epidemiology." *Occupational and Environmental Medicine* 64.9 (September 2007): 633-638.

Dobbs MR. "Approach to the outpatient with suspected neurotoxic exposure." pages 17-29 in Michael R. Dobbs, ed. *Clinical Neurotoxicology*. Philadelphia: Saunders/Elsevier, 2009.

Greve KW, Bianchini KJ, Black FW, Heinly MT, Love JM, Swift DA, Ciota M. "The prevalence of cognitive malingering in persons reporting exposure to occupational and environmental substances." *NeuroToxicology* 27.6 (December 2006): 940-950.

Greenberg MI, Curtis JA, Vearrier D. "The perception of odor is not a surrogate marker for chemical exposure: A review of factors influencing human odor perception." *Clinical Toxicology* 51.2 (February 2013): 70-76.

Dalton PH, Jaén C. "Responses to odors in occupational environments." *Current Opinion in Allergy and Clinical Immunology* 10.2 (April 2010): 127-132.

Genuis SJ. "Toxicant exposure and mental health – Individual, social, and public health considerations." *Journal of Forensic Sciences* 54.2 (March 2009): 474-477.

6.2 Biomarkers of Exposure and Effect

Morgan MS. "The Biological Exposure Indices: A key component in protecting workers from toxic chemicals." *Environmental Health Perspectives* 105.Suppl 1 (February 1997): 105-115.

Health Canada. *The Canadian Health Measures Survey. Biomonitoring Content*. Online at https://www.canada.ca/en/health-canada/services/environmental-workplace-health/environmental-contaminants/human-biomonitoring-environmental-chemicals/canadian-health-measures-survey.html

Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 1 (2007–2009). Health Canada. Ottawa: August 2010.

Second Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 2 (2009–2011). Health Canada. Ottawa: April 2013.

Third Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 3 (2012–2013). Health Canada. Ottawa: July 2015.

Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 4 (2014–2015). Health Canada. Ottawa: August 2017.

Fifth Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 5 (2016–2017). Health Canada. Ottawa: November 2019.

Sixth Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 6 (2018–2019). Health Canada. Ottawa: December 2021.

Centers for Disease Control and Prevention. *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2021*. Atlanta: 2021. Online at https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2021-508.pdf

Brodkin E, Copes R, Mattman A, Kennedy J, Kling R, Yassi A. "Lead and mercury exposures: Interpretation and action." *Canadian Medical Association Journal* 176.1 (January 2, 2007): 59-63.

Risher JF, Amler SN. "Mercury exposure: Evaluation and intervention. The Inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning." *NeuroToxicology* 26.4 (August 2005): 691-699.

Archbold GP, McGuckin RM, Campbell NA. "Dimercaptosuccinic acid loading test for assessing mercury burden in healthy individuals." *Annals of Clinical Biochemistry* 41.Pt 3 (May 2004): 233-236. Comments by Miller NJ, Howard MA; Hibberd AR; and authors' reply; *Ann Clin Biochem* 41.Pt 5 (September 2004): 421-423.

Ontario Ministry of Labour. Designated Substances Regulation 490/09 (2019). *Code for Medical Surveillance for Designated Substances (amended January 1, 2020).* https://www.ontario.ca/document/code-medical-surveillance-designated-substances/part-ii-medical-surveillance-program-requirements-individual-designated-substances#section-4

6.3 Clinical Investigations of Neurotoxicity

Sainio MA. "Neurotoxicity of solvents." pages 93-110 in in M. Lotti and M.L. Bleecker, eds. *Handbook of Clinical Neurology* 131 (Occupational Neurology). Edinburgh/New York: Elsevier, 2015.

Van Valen E, Wekking E, van Hout M, van der Laan G, Hagemen G, van Dijk F, de Boer A, Sprangers M. "Chronic solvent-induced encephalopathy: Courses and prognostic factors of neuropsychological functioning." *International Archives of Occupational and Environmental Health* 91.7 (October 2018): 843-858.

Fiedler N, Feldman RG, Jacobson J, Rahill A, Wetherell A. "The assessment of neurobehavioral toxicity: SGOMSEC joint report." *Environmental Health Perspectives* 104.Suppl 2 (April 1996): 179-191.

Lotti M, Aminoff MJ. "Evaluating suspected work-related neurologic disorders (clinical diagnosis)." pages 9-21 in in M. Lotti and M.L. Bleecker, eds. *Handbook of Clinical Neurology* 131 (Occupational Neurology). Edinburgh/New York: Elsevier, 2015.