Environmental Neurotoxicants and Endocrine Disruptors

A SUN-DARKENED, WIZENED-LOOKING OLD MAN, supported by a distraught young man, erratically walked and stumbled into the emergency room (ER) of a small, semi-rural hospital. The old man's clothes and heavy boots were well worn and covered in dirt. As he got closer to the desk, the admitting clerk could see his drowsy eyes staring off into the distance. The young man nervously explained that he had found his grandfather wandering around in the hills after he did not come home as expected. The grandson said that his grandfather was not speaking coherently, and he did not seem to know where he was. Upon further questioning, it was determined that the high price of gold had prompted the old man to start reworking his gold mining claim about 6 months ago, after years of inactivity.

When the doctor examined the man, he saw an intention tremor, an inability to perform rapid alternating movements (adiadochokinesis, a clinical manifestation of cerebellar dysfunction), and mild rigidity. Hypertension and tachycardia also were present. The old man could not contribute to his medical history, but his grandson said that his grandfather had shaking hands for several months and recently had complained of headaches, fatigue, and a "pins and needles" feeling in his arms and legs.

When asked to explain what his grandfather did at the mine and if he had been exposed to anything, the young man said that his grandfather first mined the rock containing gold and then ground it up and mixed it with a silvery liquid until it formed a small ball (**Figure 1**). Then he heated the ball in a pan over a camp stove until just the gold was left. When asked where and how often this process was performed, the young man replied that when the weather was warm, the task was done outside almost every day, but since the weather was cold, his grandfather had moved the operation into the old mine shack.

Figure 1 Amalgamation Often the gold is so small that it is not easily seen or removed by panning methods—a lot can just float away. Mercury captures the gold in an amalgam. Gold miners crush rock that contains gold; extract as much rock by washing it away, or if the gold is in mud, just wash away the mud and let the gold settle out or float in the water; combine the remains (gold dust or bits) with mercury to form a ball (combined mercury and gold), as shown in the figure; and then burn off the mercury leaving the gold behind.

The ER doctor ordered standard blood and urine tests and urinary heavy metals. The urine sample revealed 748 µg mercury/l (normal range, 1 to 8 µg/l). The patient was given chelation therapy[1] with dimercaprol and gradually recovered from most effects over the next 6 months.

This chapter will explore the neurotoxic aspects of selected environmental toxicants and endocrine disruptors, including persistent and semi-persistent organic pollutants, insecticides, and toxic metals.

Neurotoxicity

Neurotoxicity is the adverse change in the structure or function of the central or peripheral nervous system. A **neurotoxicant**[2] is an element or compound that elicits this adverse effect by direct or indirect action on one or more components of the adult nervous system or the developing nervous system in utero or during childhood. Indirect actions include effects mediated via other systems that are necessary for the development or maintenance of nervous system function.

Neurotoxic effects may be transient or permanent and may manifest either immediately following exposure or at some later time, even years after exposure. Individual neurotoxicants are found in many different chemical and product classes.

The mechanisms of neurotoxicity are far ranging but can be generalized into several broad classes: oxidative stress, cell death (necrosis or apoptosis; see Chapter 8), disruption of signaling pathways, disruption of homeostatic mechanisms, interference in neurotransmission, interference with synthesis or metabolism of key cellular components and macromolecules, and disruption of the endocrine system. Additionally, for the developing nervous system, mechanisms may include disruption of morphogenic signals (i.e., signals that regulate the structural development of the brain); interference with the morphogenic roles of hormones, neurotransmitters, and their receptors; and inappropriate stimulation of neuronal differentiation or apoptosis by various mechanisms. A diagram of brain development and the vulnerability of developmental processes is shown in **Figure 2**.

Exposures to environmental neurotoxicants and endocrine disruptors occur via air, water, soil, and food. Although these agents may exert toxicity in other organ systems, the nervous system is different because it is incompletely developed in children and neurogenesis is lacking in adults except for a few restricted brain areas; that is, in adults, destroyed neurons are not replaced, and their absence potentially affects multiple functions and numerous interconnections between cells of the nervous system and those of other organs.

The risk for neurotoxicity, as for any form of toxicity, is related to the intensity, frequency, and duration of exposure to the neurotoxic agent. Risk is also influenced by the physical and chemical (**physicochemical**) properties of the agent, the route of exposure,

[1]Chelation therapy is the administration of chelating agents. In the case of metals, it is the use of specific agents that will bind the metal at two or more sites (chelate) so that the metal will no longer react with biological molecules and will be eliminated from the body.

[2]The term *neurotoxin* is sometimes used in place of neurotoxicant; however, *neurotoxin* is generally reserved for those toxic substances produced by a living organism, such as botulinum toxin (botulism).

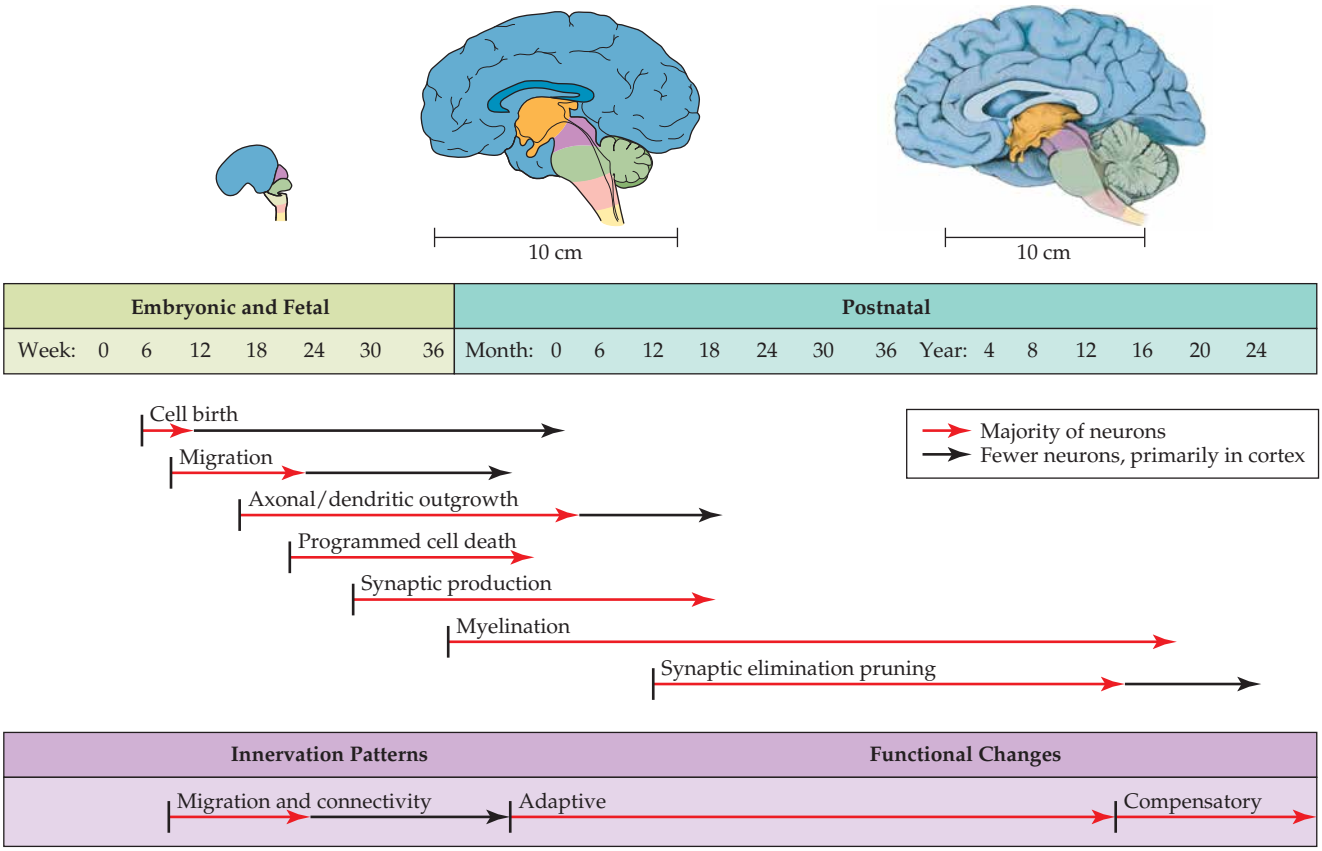


Figure 2 **The development of the brain** is shown from the embryonic and fetal stages on the left, progressing to 24 years of age on the right. The developmental processes and their duration are depicted in the center. Each process has its unique vulnerabilities to environmental insult. The bottom panel indicates that early alterations in normal processes can have lasting effects on neural connectivity and patterning, but later insults may be more adaptive or compensatory in nature. (After Andersen, 2003.)

the concentration achieved at the target site, and the inherent toxicity of the agent itself.

The young and the elderly are two potentially vulnerable populations with respect to the effects of neurotoxicants. For the young, the central nervous system (CNS) develops over an extended period postnatally, and any neurotoxic insult can induce morphological, functional, and behavioral changes that may persist throughout life. For the elderly, the natural aging process results in loss of nervous system plasticity and compensatory capacity.

Assessment of neurotoxicity in humans is based on clinical observations following exposure and the results of epidemiological studies specifically designed to investigate the association of exposure and neurotoxicity endpoints. Neuropsychological and behavioral testing performed in humans includes cognitive testing batteries, psychiatric and symptom questionnaires, behavioral and neurophysiological tests, and neuroimaging (e.g., magnetic resonance imaging [MRI], positron emission tomography [PET], and single-photon emission computed tomography [SPECT]; see Chapter 4). Additionally, blood and urine can be evaluated for neurochemicals, hormones, metabolites, and other biomarkers of interest.

Animal studies can raise questions of risk, help identify mechanisms of action, and explore the relationship of defined exposures (i.e., dose, route, and duration) to neurological endpoints. Several agencies throughout the world have developed guidelines for evaluating the potential neurotoxicity of agents in animal studies. The guidelines by the U.S. Environmental Protection Agency (EPA, 1998), as an example, give five categories of neurotoxicity evaluation:

1. Structural or neuropathological (e.g., morphological endpoints, **neurite** outgrowth, myelination of peripheral and central nerves, integrity of the blood–brain barrier)
2. Neurophysiological (e.g., axonal transport, electrophysiological indices, calcium homeostasis, hormone concentrations)
3. Neurochemical
4. Behavioral/neurological[3]
5. Developmental

Any identified adverse changes could then be investigated by appropriate means.

[3]The functional observational battery (FOB) is the primary means of screening and comprises a number of aspects of behavior and neurological functions to identify specific deficits in sensory and motor function.

Endocrine Disruptors

Endocrine disruption is just one of many mechanisms of action that can result in neurotoxicity. **Endocrine disruptors** (**EDs**), as the name implies, interfere with the endocrine system and may cause adverse effects in development or in the reproductive, nervous, or immune system. An ED is a natural or synthetic substance that directly or indirectly interrupts the action of the endocrine system by altering the synthesis, metabolism, regulation, or transport of one or more hormones; altering the release of hormone from an endocrine gland; or altering the normal hormonal response at the level of the hormone receptor.

The first evidence for the adverse effects of what would later be described as an ED was published in 1971, when Herbst et al. (1971) reported that daughters born to women treated with diethylstilbestrol (DES) during pregnancy were diagnosed with uncommon vaginal adenocarcinomas during their teens and early 20s. DES is a synthetic nonsteroid with potent estrogenic properties that was administered during pregnancy to reduce the risk of complications and miscarriages. The effects and mechanisms of DES-induced endocrine disruption subsequently were investigated and confirmed in animal models. Since that time, there has been a growing awareness of the potential endocrine disrupting effects of environmental agents at low levels of exposure. In 2001, an expert panel for the U.S. National Toxicology Program (NTP) reported that there was sufficient evidence to support the endocrine disruption effects of DES, genistein (an isoflavone derived from soy inhibits thyroid hormone metabolism), methoxychlor (an insecticide that has estrogenic activity), and nonylphenol (an industrial chemical identified in drinking water supplies that has estrogenic activity) at low dose exposures (NTP, 2001). None of the recognized effects was directly related to the nervous system, and the only potential indirect effect was on brain sexual dimorphism by genistein and nonylphenol.

Endocrine disruptors can interfere at any level of the endocrine system, causing perturbations in normal function and homeostasis. For instance, EDs may mimic a natural hormone and bind to cellular receptors in the membrane, cytosol, or nucleus (see Chapter 3). As a mimic (or agonist), the ED can elicit the same response as the natural hormone, although the response may be different in magnitude. EDs can also act as antagonists and bind to a receptor without eliciting a response and prevent the binding of the endogenous hormone. Alternatively, EDs can bind and elicit a nontypical response. EDs also can have effects that are not dependent on hormone receptor binding. EDs can directly or indirectly interfere with normal hormone synthesis, metabolism, uptake, or release, thus affecting the availability of hormone.

The effects of hormones and EDs are dose dependent, and physiological concentrations can produce different effects than are produced by high or systemically toxic concentrations. Examples of dose-specific effects include signaling via a single steroid receptor at low doses versus signaling via multiple receptors due to nonselectivity at high doses, up-regulation at low doses versus receptor down-regulation at high doses, and high-dose cytotoxicity (toxicity to cells). The sensitivity of different organ systems to ED effects also can be related to differences in tissue receptor distribution and tissue specificity of endocrine-transcriptional elements.

As awareness of the effects of endocrine disruption grew, it was evident that endocrine disruption could also be responsible for perturbations in the nervous system resulting in neurological and neurobehavioral deficits. This chapter will focus on ED effects that potentially impact the nervous system.

The connection between the nervous and endocrine systems is complex and manifold. The nervous system is intimately involved in the actions of the endocrine system and vice versa, so much so that the term *neuroendocrine system* has been assigned to the interactions of the nervous and endocrine systems. As was previously mentioned in Chapter 3, the endocrine system consists of the following glands: pineal, hypothalamus, pituitary, thyroid, parathyroids, thymus, adrenals, pancreas, and ovaries in females, and testes in males. All endocrine glands act by secretion of a hormone into the bloodstream. That hormone then regulates some body system, which may be close in proximity or at some distance from the secreting gland.

One often thinks of hormones as steroids, but hormones also include amines (amino acid derivatives), polypeptides, and glycoproteins (proteins that contain one or more sugar molecules as part of their structure). Neurons can synthesize and release polypeptides that act as hormones and affect release of other hormones or hormone actions at target organs. An example is gonadotropin-releasing hormone (GnRH) a decapeptide from the basal hypothalamus that stimulates gonadotropin release from the anterior pituitary gland. If the synthesis or release of this hormone is altered, then downstream effects related to ovarian and testicular steroidogenesis (steroid hormone synthesis) and gametogenesis (formation of the gametes, namely, eggs and sperm) are also affected. Just as important as the hormones are the receptors for those hormones found throughout the body, including the CNS, where neurons of the noradrenergic, serotonergic, and dopaminergic systems express steroid hormone receptors.

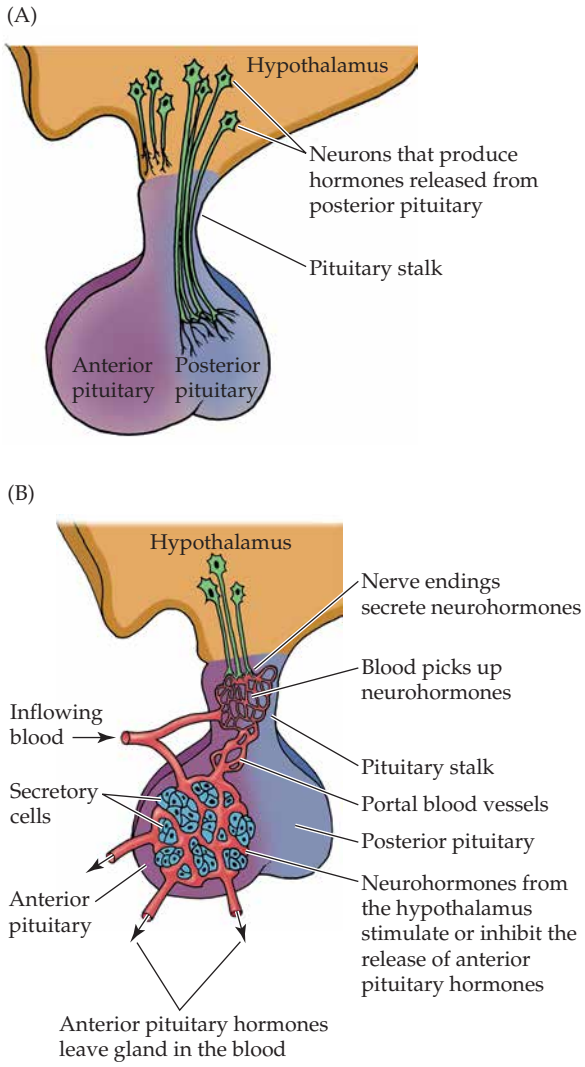


Figure 3 Neuroendocrine interactions at the hypothalamus and posterior and anterior pituitary (A) Neurons in the hypothalamus produce oxytocin and vasopressin. Action potentials travel down the axons to the axon terminals in the posterior pituitary where the hormones are released. (B) Neurohormones, known as releasing factors or hormones, are produced by and released from the hypothalamus. Hypothalamic hormones such as thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), and corticotrophin-releasing hormone (CRH), cause their corresponding hormones that are produced in the anterior lobe of the pituitary (throid-stimulating hormone [TSH], follicle-stimulating hormone [FSH], lutenizing hormone [LH], prolactin [PRL], growth hormone [GH], and adrenocorticotropic hormone [ACTH]) to be released into the circulation. (From Purves et al., 1998.)

The central neuroendocrine system is primarily responsible for the neural modulation of endocrine function near the brain, and it consists of interaction of the nervous and endocrine systems at the level of the hypothalamus and the posterior and anterior pituitary, as shown in **Figure 3**. Neural–endocrine interactions outside the area of the brain are often referred to as the diffuse neuroendocrine system. The central and diffuse neuroendocrine systems control diverse functions such as reproduction, metabolic energy balance, osmoregulation, and other homeostatic processes.

The neuroendocrine actions of EDs also may occur via non-hormonally mediated mechanisms. Numerous neurotransmitter systems such as dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate, and others are sensitive to endocrine disruption via many mechanisms. The effects in these systems help to explain how EDs can negatively influence cognition, learning, memory, and other nonreproductive behaviors.

A majority of studies published on potential EDs are related to the hypothalamic–pituitary–gonadal (HPG) axis and the hypothalamic–pituitary–thyroid (HPT) axis. The brief discussion here is limited to these two systems, but the principles of interaction apply for other components of the neuroendocrine system.

Hypothalamic–Pituitary–Gonadal (HPG) System

The hypothalamus controls reproductive function through complex interactions with the anterior pituitary. Endocrine disruptors can interfere with function in the adult and alter normal reproductive function. EDs can also have long-lasting effects on the developing organism. The regions of the hypothalamus that control the reproductive neuroendocrine systems undergo development during specific periods. That development is controlled in large part through exposure to endogenous estrogen and androgen hormones. Exogenous hormones may perturb steroidal actions by binding to steroid receptors, changing steroid metabolism, or altering normal sexual dimorphism. Disruption of normal brain sexual differentiation may affect both reproductive physiology and behavior later in life. For example, developmental exposures have been shown to affect mate preference behavior in rats that is passed on to subsequent generations through epigenetic modification of specific genes (Crews et al., 2007).

Hypothalamic–Pituitary–Thyroid (HPT) System

As mentioned previously, hormones released from the hypothalamus interact with the anterior pituitary. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and interacts in the anterior pituitary, where it causes release of thyrotropin, also known as thyroid-stimulating hormone (TSH). TSH,

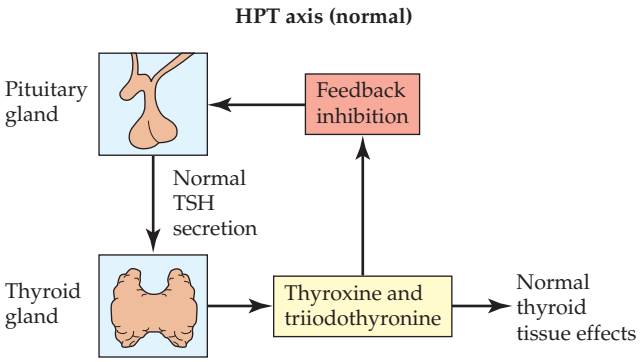


Figure 4 The normal release of TSH from the anterior pituitary and subsequent release of TH and its negative feedback. (After Baxter and Webb, 2009.)

as shown in Figure 4, stimulates the release of thyroid hormones (TH) (thyroxine [T4] and triiodothyronine [T3]). Under normal circumstances, the accumulation of TH will trigger a negative feedback response at the level of the anterior pituitary and inhibit TRH release and thus the downstream release of TH.

A complex neural circuitry in the hypothalamus regulates energy and metabolic homeostasis. Changes in thyroid gland function or interference with TH distribution or action may produce effects on development, metabolism, or adult physiology. The function of the thyroid can be impacted directly or indirectly at different points of TH synthesis, release, transport, metabolism, and clearance. In addition, alterations in uptake of iodide (I^-) and disruption of the sodium/iodide co-transporter (NIS)[4] can affect thyroid hormone levels. Figure 5 gives one an idea of the complexity of the HPT system and the multiple points at which an environmental neurotoxicant may interfere with normal TH synthesis.

[4]This cotransporter is also known as the Na^+/I^- symporter (NIS). NIS is a transmembranal protein that transports I^- along with Na^+ into follicular cells of the thyroid gland. I^- uptake is the first step in TH synthesis (Dohan et al., 2003).

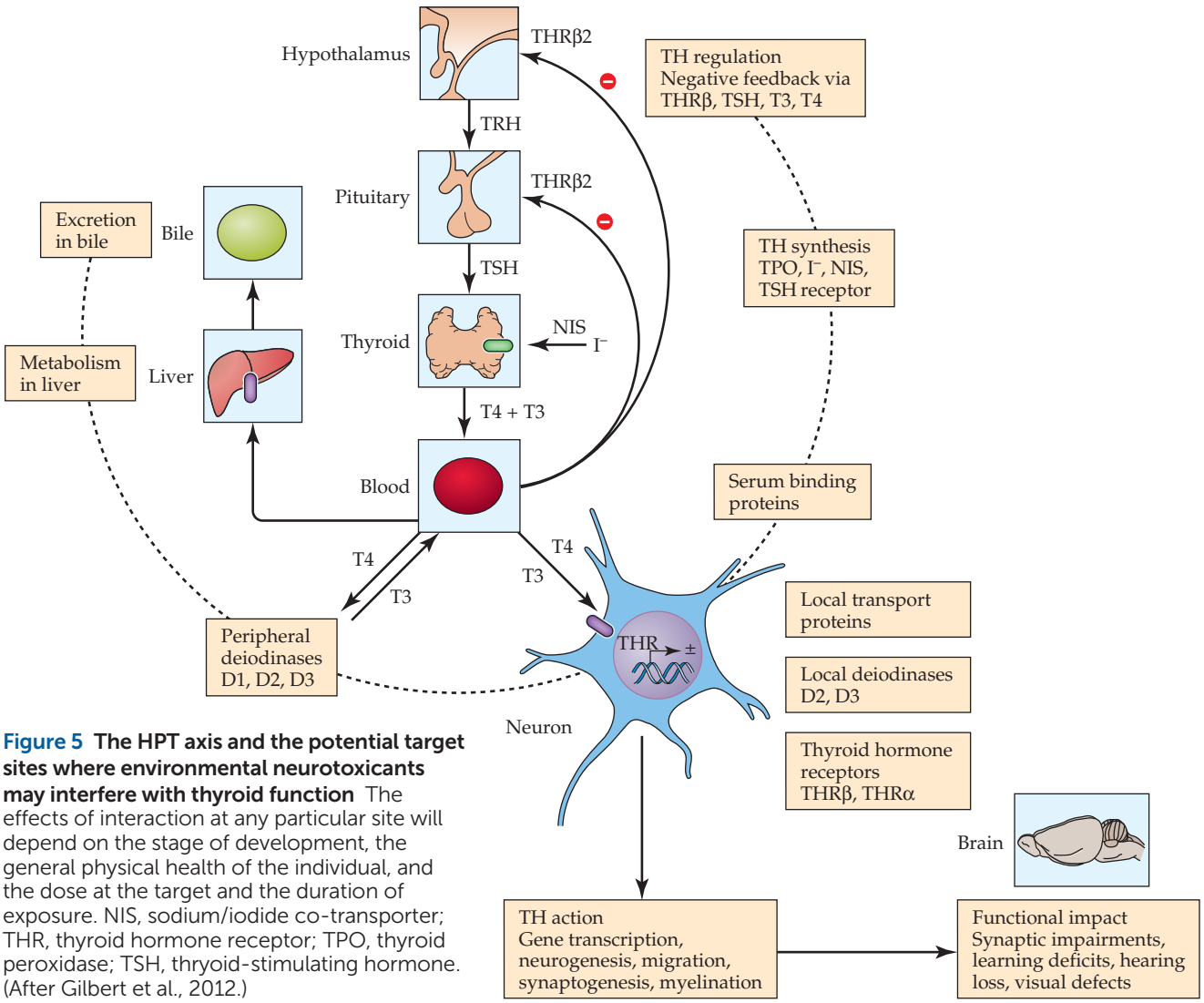


Figure 5 The HPT axis and the potential target sites where environmental neurotoxicants may interfere with thyroid function The effects of interaction at any particular site will depend on the stage of development, the general physical health of the individual, and the dose at the target and the duration of exposure. NIS, sodium/iodide co-transporter; THR, thyroid hormone receptor; TPO, thyroid peroxidase; TSH, thryoid-stimulating hormone. (After Gilbert et al., 2012.)

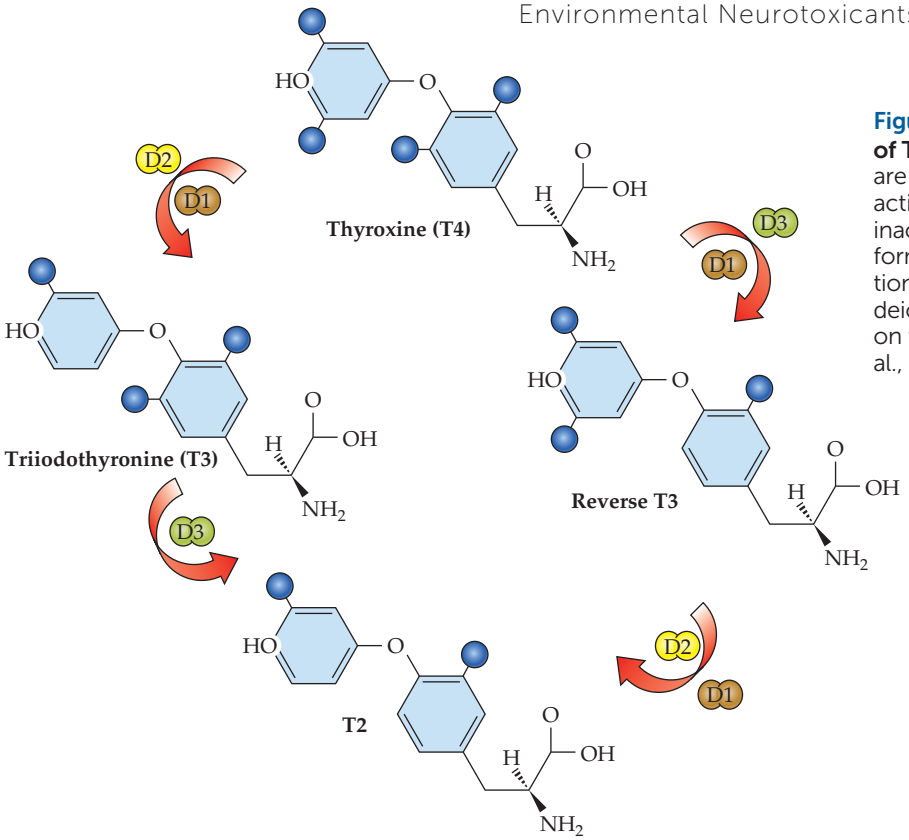


Figure 6 Deiodinases in the metabolism of TH (T4 and T3) The major deiodinases are not only involved in the synthesis of active TH, they are also involved in their inactivation. Reverse T3 is the inactive form of T3. The activation or inactivation is determined by the order in which deiodinases (shown as double ovals) act on the major iodothyronines (Gereben et al., 2008).

Once TH is secreted into the blood, its availability to cells can be affected by accessibility of specific carriers or binding proteins in the blood and by cell-specific transporters that control TH uptake into various tissues and cells. Inside the cell, T4 is converted to T3 by **deiodinases** (enzymes that remove iodine), which is an important step in TH action. There are several deiodinases present in tissues as shown in Figure 6. A number of environmental chemicals are known to affect deiodinase activity and produce symptoms and hormone levels that are not entirely consistent with hypothyroidism. In these cases, mechanistic studies are required to identify the etiology.

TH is known to play an essential role in normal brain development, and experimental hypothyroidism is associated with numerous neuroanatomical and behavioral effects, including deficits in learning and habituation, changes in anxiety, and hyperactivity in rats (Negishi et al., 2005; Zoeller and Crofton, 2005).

Figure 7 shows how TH mimetics might induce hyperthyroidism in some tissues while inducing hypothyroidism in others. The results are dependent on the distribution of tissues that can and cannot efficiently take up the TH mimetic.

The interested reader is invited to examine *The Endocrine Society's Scientific Statement*, which reviews studies of EDs and their mechanisms of action (Diamanti-Kandarakis et al., 2009) and two recent reviews published by Parent et al. (2011) and Vandenberg et al. (2012).

Section Summary

- Neurotoxicity is the adverse change in the structure or function of the nervous system.
- A neurotoxicant is an element or compound (agent) that elicits neurotoxicity via direct or indirect actions on the mature or developing nervous system.

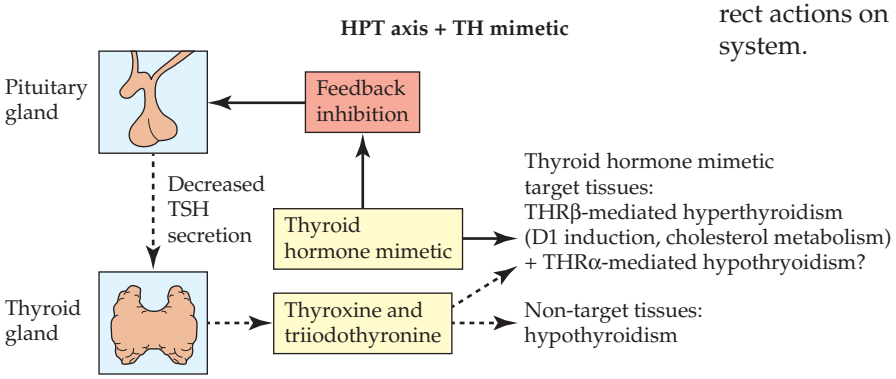


Figure 7 The influence of thyroid hormone (TH) mimetics on normal TH function potentially results in hyperthyroid-like effects in some tissues (target tissues) while producing hypothyroid-like effects in other tissues (non-target tissues). D1, deiodinase 1; THR, thyroid hormone receptor; TSH, thyroid-stimulating hormone. (After Baxter and Webb, 2009.)

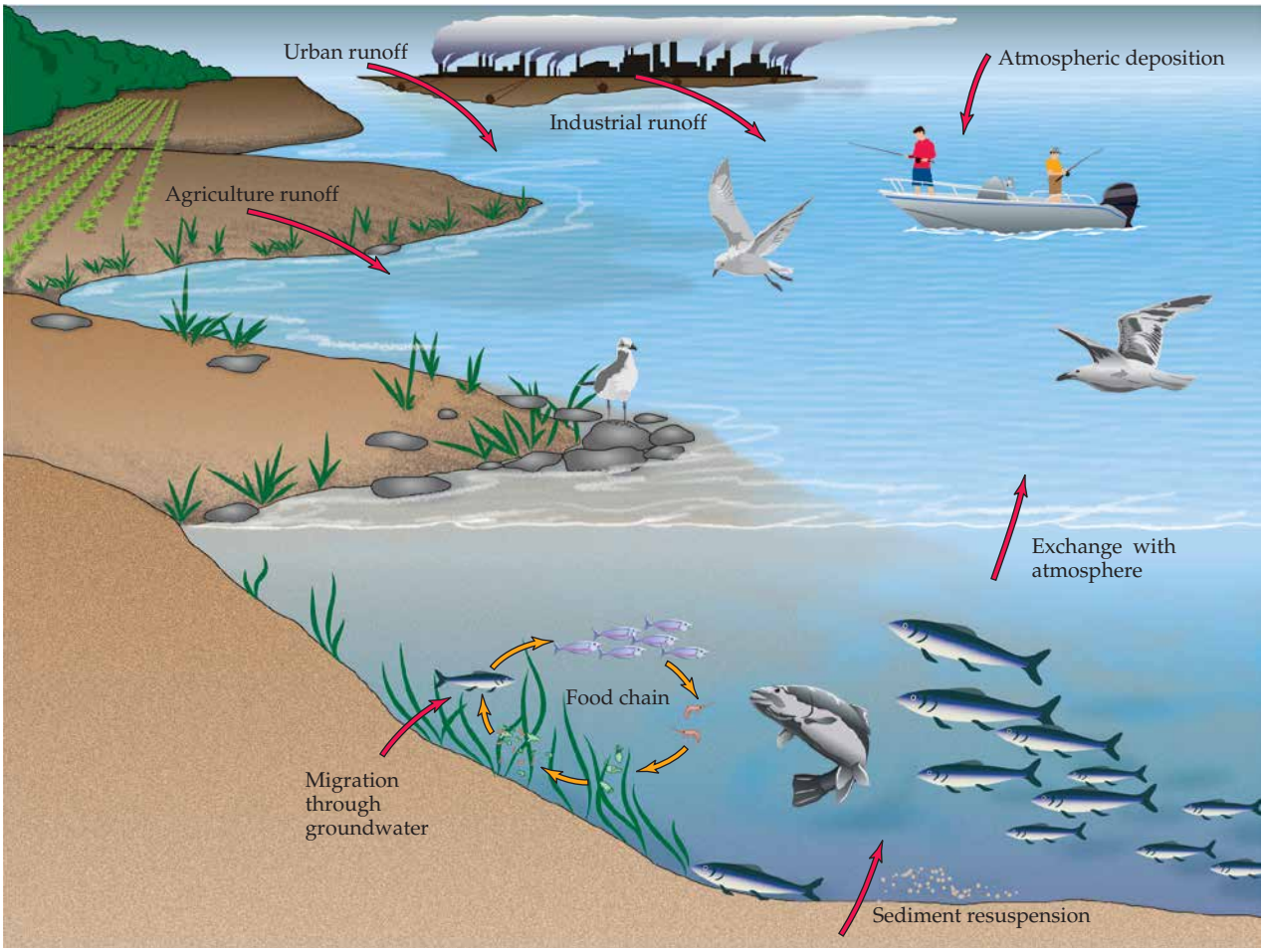


Figure 8 The distribution and accumulation of POPs in the environment and the food chain POPs enter the environment through atmospheric deposition and various types of runoff. Additionally, POPs deposited on land can reach surface waters by migrating through groundwater. Once in surface waters, the chemicals move up the food chain and become more concentrated by accumulating in the tissue of living organisms.

- Neurotoxicity is dependent on the agent, the exposure (dose, frequency, and duration), the route of exposure, the concentration at the target site, and the status of the nervous system (e.g., developing, mature, senescent).
- The mechanisms of neurotoxicity are numerous, including cell death, disruption of signaling pathways, and endocrine disruption, to name a few.

Persistent and Semi-Persistent Organic Pollutants

Persistent organic pollutants (**POPs**) are synthetic organic compounds that are resistant to environmental degradation through chemical, biological, and photolytic processes. The POPs are ubiquitous and persistent because of their physicochemical properties, which include low water solubility, high lipid solubility, semi-volatility, and relatively high molecular masses. POPs with molecular masses lower than 236 g/mole are less persistent in the environment (Ritter et al., 1995). These pollutants are of concern because their persistence and lipid solubility result in **bioaccumulation** in fatty tissues and **bioconcentration** up the food chain. Figure 8 depicts how POPs move in the environment, bioconcentrate in the aquatic food chain, and ultimately end up being consumed by humans and animals that eat fish or the animals that feed on fish. In addition to the aquatic cycles, animals bioaccumulate POPs by feeding on contaminated plants.

In May 1995, the United Nations Environment Programme Governing Council began investigating 12 priority POPs known as the "dirty dozen": aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-ρ-dioxins (PCDDs),

polychlorinated dibenzofurans (PCDFs), and toxaphene (WHO, 2010). The list has been informally enlarged to include other organic pollutants, sometimes referred to as **semi-persistent organic pollutants** (**semi-POPs**), such as bisphenol A (BPA), polycyclic aromatic hydrocarbons (PAHs), phthalates, and polybrominated diphenyl ethers (PBDEs), to name a few.

In the following sections, PCBs are discussed as an example of POPs, and PBDEs and BPA as examples of semi-POPs.

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (**PCBs**) are synthetic chlorinated aromatic compounds that were used in industrial and consumer products such as dielectrical fluids in capacitors and transformers, hydraulic fluids, and lubricating oils, and in plasticizers. Although PCB production was banned in the late 1970s, they persist as environmental contaminants worldwide. There are 209 PCB **congeners** (chemicals synthesized by the same synthetic chemical reactions and procedures) containing from 1 to 10 chlorines (although technically not polychlorinated, the monochlorinated compounds are usually included in the discussion of PCBs) with corresponding molecular weights of 188.7 to 498.7 g/mole. The general structure of PCBs is shown in **Figure 9**.

The general population is exposed to PCBs primarily through ingestion of contaminated foods (e.g., fish, meat, dairy products). The fetus is exposed via placental transfer, and the infant via breast milk. Measurable levels of PCBs are found in the serum of a majority of the U.S. population (CDC, 2009, 2012a). Although individual congeners are present at low concentrations in human tissue, it is not unusual to be exposed simultaneously to a number of congeners with similar physicochemical properties because they migrate and bioaccumulate in similar manners. The longest half-lives for PCBs in humans are estimated to be 10 to 15 years (Ritter et al., 2011). Reports of longer half-lives have been attributed to ongoing exposure and weight gain (increased adipose tissue stores) with age.

There are two distinct categories of PCBs, referred to as *coplanar* and *non-coplanar* congeners. Coplanar molecules have a fairly rigid structure that potentially allows them to bind at the aryl hydrocarbon receptor (AhR)[5] and gives them a different toxicity profile than the non-coplanar congeners that do not bind at the AhR. As could be expected, classes of congeners with a similar mechanism of action are likely to act additively to produce effects. Although some studies have addressed specific PCB congeners, as opposed to mixtures, understanding the neurotoxicity of PCBs is hampered by the fact that many congeners have not been studied, and their potency as neurotoxicants is unknown. Overall, evidence for neurotoxicity of the PCBs is growing. No regulatory guidance for PCBs based on neurotoxicity, however, has been established by the EPA. Goodman et al. (2011) suggest that insufficient evidence from epidemiological studies, due to a lack of comparability across studies, make it impossible to establish a strong assessment based on a weight of evidence approach.

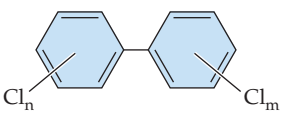


Figure 9 General structure of PCBs The subscripts "m" and "n" refer to the number of chlorines attached to the phenyl rings.

Neurotoxicity in adults

No reports of acute poisoning solely with PCBs have been identified. A variety of symptoms such as chloracne (an acne-like condition produced by some halogenated compounds), hyperkeratosis (abnormal thickening of the skin), goiter, pigmentation, abnormal nails, hearing loss, eye disorders, and jaundice are attributed to chronic PCB poisoning; however, there are no reports of PCB poisoning in the absence of other potential contaminants. In 1968 and 1979, there were mass poisonings via PCB-contaminated rice oil in Japan and Taiwan, respectively (Guo et al., 1999; Masuda, 2003). Clinical signs of toxicity were observed in thousands of people. Neurological studies performed in a subset of the Taiwan victims revealed electrophysiological sensory and motor neuropathies at 2 and 4 years post-exposure (Chia and Chu, 1985). In both the Japan and Taiwan incidents, the PCBs were co-contaminated with PCDDs and PCDFs, so it is impossible to know the contributions of these toxic compounds to the observed effects (WHO, 2010).

A more recent study of adults exposed chronically to PCBs via consumption of fish from the Great Lakes showed impaired memory and learning, but no effects on executive functioning (e.g., cognitive flexibility [or set shifting], response inhibition, working memory, attention, planning) and visuospatial function (Schantz et al., 2001). Other contaminants identified

[5]The AhR is a member of a family of transcription factors. The endogenous biomolecule that binds to this receptor is unknown. The receptor, however, is known to bind a variety of cyclical (ring-containing) exogenous molecules, some of which are naturally occurring, and others of which are generated by human activity (e.g., synthetic compounds like PCBs or compounds produced by combustion of fossil fuels).

from blood samples (i.e., lead, mercury, and dichlorodiphenyldichloroethylene [DDE]) were not associated with impairments. The authors were careful to state that their "study suggests … that PCB exposure during adulthood may be associated with impairments in certain aspects of memory and learning," and "it would be prudent to interpret the findings with caution until they have been replicated in an independent exposure cohort."

Neurotoxicity in children and the developing nervous system

The poisonings in Japan and Taiwan also raised awareness about the developmental toxicity of PCBs because the individuals most affected were children who had been exposed in utero. These children exhibited delayed cognitive development and behavioral problems, in addition to growth retardation (Guo et al., 2004). Further attention was drawn to this issue by studies of Jacobson and colleagues in the 1980s and 1990s that examined children from infancy to late childhood who had been exposed prenatally to PCBs through maternal fish consumption. They reported associations between higher PCB exposures and decrements in behavioral endpoints, such as decreased activity and hypotonic motor reflexes, and IQ. Voluminous research has been performed on PCB exposures and neurobehavioral endpoints; however, the findings have not been as consistent as one would hope. Several reviews have been written on one or more aspects of neuropsychological function following prenatal PCB exposure, and the interested reader is referred to those articles for additional information (Boucher et al., 2009; Schantz et al., 2003; Stewart et al., 2012). The following discussion gives a summary of the overall findings and controversies.

In an effort to identify a profile of cognitive effects from prenatal PCB exposure, Boucher et al. (2009) reviewed studies of nine prospective longitudinal birth cohorts from Canada, the Faroe Islands, Germany, Japan, the Netherlands, and the United States that examined prenatal PCB exposure and aspects of cognition in children. They identified the most consistently reported effect as impaired executive functioning. The authors also identified negative effects on processing speed, verbal abilities, and visual recognition memory in most of the studies. These effects appeared to be independent of sensory and motor functions.

Inconsistent results among epidemiological studies of PCBs and IQ have been interpreted by some as suggesting that, at most, a case could be made for subtle effects at low-level exposure. Stewart et al. (2012) hypothesized that confounding due to the presence of non-PCB organochlorines such as DDE, hexachlorobenzene (HCB), and Mirex;[6] differences in maternal age, environmental factors, and parental IQ (leading to type I statistical error); and the presence of potential suppressor variables (leading to type II errors) could explain the lack of association between PCB exposure and IQ decrements in some studies. Their examination of the effects of confounding supported their hypothesis that IQ decreased but had been obscured. Additional studies with appropriate controls will be needed to lay the question to rest.

Studies of PCBs also are complicated by contaminants such as PCDDs and PCDFs. Measurement of PCDDs and PCDFs in epidemiologic studies has been rare because of analytical difficulties. In the Dutch PCB/PCDD study, however, lactational exposure to dioxin (a PCDD) was not associated with child cognitive abilities at 42 months of age (Patandin et al., 1999), suggesting that any observed effects were attributable to PCBs. Similarly, a German birth cohort study of PCDDs and PCDFs did not find an association with mental and psychomotor developmental indexes at 12 and 24 months of age (Wilhelm et al., 2008).

Developmental animal studies are supportive of the neurotoxic effects of PCBs. These studies have shown behavioral deficits across many different tests of executive function, including cognitive flexibility, working memory, and inhibitory control (Sable and Schantz, 2006). Animal PCB studies also have shown that altered motor behavior was associated with changes in cerebellar function and anatomy.

More recently, the question has been raised as to whether PCB exposure could be linked to the increased prevalence of attention deficit hyperactivity disorder (ADHD) (Eubig et al., 2010), although no human studies have directly assessed the association of ADHD with PCB exposure. Aspects of both executive functioning and attention are impaired in ADHD and with PCB exposure, which suggests a possible association. ADHD is a highly heritable disorder, however, and until human studies appropriately examine this confounder, the causal association of PCB exposure and ADHD is only speculation (Brondum, 2011).

Mechanisms of action

The mechanisms for the neurotoxic effects of PCBs are neither well known nor uniform across the 209 congeners. From the animal studies that have been conducted on individual congeners and congener mixes, the effects observed point to mechanisms related to

[6]Cohorts from the Great Lakes (Michigan and New York) showed the association of IQ with quartiles of PCBs and quartiles of HCB, both of which were similar in predicting IQ.

ED for some and to direct toxic action for others, while still other congeners and mixtures point to both mechanisms of action. Effects are seen with direct estrogenic or antiandrogenic activity, interaction at the AhR, interference with one or more aspects of thyroid function, and interference with neurotransmitter effects.

In rats, PCB congeners can affect the HPT axis in several ways, including causing a reduction in circulating levels of T4 or inhibiting the TSH response to thyrotropin-releasing hormone. From the available evidence, it appears that PCBs may exert different actions on thyroid function, depending on many factors.

PCBs also cause cell death, although mechanisms vary between congeners. Coplanar PCBs act through the AhR to induce cell death, while non-coplanar PCBs act through alteration of intracellular secondary messengers, alteration of cell membranes, or inhibition of DA synthesis.

Other potential mechanisms of action are interference in calcium homeostasis (affecting many calcium-dependent systems, including neurotransmitter release); inhibition of the DA transporter (responsible for reuptake of DA into the neuron) and the vesicular monoamine transporter (VMAT2) (responsible for packaging cytosolic DA into vesicles for later release); oxidative stress and production of reactive oxygen species (ROS); and alteration in long-term potentiation (LTP) (controlled by intracellular second messengers).

Polybrominated Diphenyl Ethers (PBDEs)

Polybrominated diphenyl ethers (**PBDEs**) are organobromine compounds that are used as flame retardants in products such as plastics, polyurethane foams, and electronics. PBDEs resemble PCBs in molecular structure and also have 209 possible congeners, containing from 1 to 10 bromines (although technically not polybrominated, the monobrominated compounds are usually included in the discussion on PBDEs) with corresponding molecular weights of 249.1 to 959.2 g/mole. See the structure of PBDEs in **Figure 10** and note the similarity to the PCBs.

PBDEs were commercially marketed as one of three mixtures: pentabrominated BDE (pentaBDE), octabrominated BDE (octaBDE), and decabrominated BDE (decaBDE) (ATDSR, 2004). PentaBDE, which was primarily used in North America, and octaBDE have been banned in the European Union (EU) and in several states in the United States. In 2004, the production of pentaBDE and octaBDE in the United States ceased voluntarily. Globally, decaBDE is the most widely used PBDE and is still produced in the United States and Europe. It must be remembered that all PBDE products are mixtures of congeners, not just a single congener.

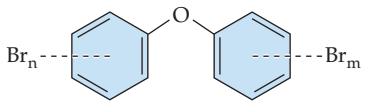


Figure 10 General structure of PBDEs The subscripts "m" and "n" refer to the number of bromines attached to the phenyl rings.

Similar to PCBs, the PDBEs are lipophilic and bioaccumulate in the food chain (ATDSR, 2004). PBDEs have been detected in the air, sediments, soil, house dust, some foods, and many animal species. The general population is exposed to PBDEs primarily through diet and house dust. PBDEs have been detected in human tissues, blood, and breast milk. Five congeners of the tetra-, penta-, and hexaBDEs (congeners BDE-47, -99, -100, -153, -154) usually account for 90% of the total body burden (ATDSR, 2004; McDonald, 2005). Concentrations of PBDEs (primarily lower brominated congeners) are particularly high in breast milk (ATSDR, 2004). Estimated exposure of an infant through breast milk is about 0.3 µg/kg-day, with a range up to 4.1 µg/kg-day (Jones-Otazo et al., 2005). These levels are within the current **reference doses** (**RfDs**; estimates of the daily oral exposure of humans, including sensitive subgroups, which are not likely to cause harmful effects over a lifetime of exposure) of most PBDEs as set by the EPA (2008a-d).

Extremely high PBDE levels in humans also have been reported: maternal and fetal blood plasma concentrations as high as 580 and 460 ηg/g lipid, respectively (ATDSR, 2004), and a toddler with plasma levels of 418 ηg/g lipid (651 ηg/g if including BDE-209) (Costa and Giordano, 2007). These levels are nearly ten-fold that reported for the general U.S. population (Sjodin et al., 2008).

In rodents, the total body half-lives of all PBDEs are in the order of several days to several months; decaBDE is cleared most rapidly, with a half-life of less than 24 hours (ATDSR, 2004). The half-lives in humans are estimated to be several years for the lower brominated congeners, and days to months for the octa- to decaBDEs.

Neurotoxicity in adults

No reports were identified regarding PBDE neurotoxicity in adults. In contrast to the large database on PBDE body burden, there is almost no information on possible adverse health effects in humans from PBDE exposure. In rodents, PBDEs have low acute toxicity with oral LD_{50}s (lethal dose in 50% of animals) in animals greater than 5 g/kg (ATSDR, 2004). With

chronic exposure, the target organs are liver, kidney, and thyroid gland. Toxicological profiles appear to be similar among congeners. The lesser potency of decaBDE compared with the lower brominated congeners appears to be related to differences in lipophilicity and bioaccumulation.

Neurotoxicity in children and the developing nervous system

Similar to adults, there is essentially no information on the neurotoxic effects of PBDEs in infants or children with acute or chronic exposure. There has been concern, however, regarding potential developmental neurotoxicity of PBDEs in humans (Costa and Giodano, 2007; McDonald, 2005). This concern arises from the following:

- PBDEs are known to cross the placenta and have been detected in fetal blood and liver.
- Developmental neurotoxicity has been reported following prenatal and early postnatal exposure of rodents to one or more PDBE congeners.
- Neurochemical changes are observed following developmental exposure of rodents to PBDEs.
- PBDEs affect TH homeostasis.
- PBDEs are excreted in milk.
- Infants and toddlers have the highest body burden of PBDEs because of exposure via maternal milk and house dust.
- Levels of PBDEs causing developmental neurotoxicity in animals are similar to those found in highly exposed infants and toddlers.
- Young animals have higher tissue concentrations than adults and may have a reduced ability to excrete PBDEs.

The daily intake of PBDEs for breast-fed infants, estimated at 20.6 ηg/kg-day in Taiwan, was correlated with lower birth weight and length, lower head and chest circumference, and decreased body mass index (Chao et al., 2007). Much higher infant PBDE exposure levels, however, have been estimated for Canada and the United States at 280 ηg/kg-day and 306 ηg/kg-day, respectively (Jones-Otazo et al., 2005; Schecter et al., 2006), which raises the question as to possibly greater effects in these populations.

Two epidemiological studies have shown significant effects following PDBE prenatal exposure. A longitudinal cohort study in New York of prenatal exposure to several PBDE congeners assessed neurodevelopmental effects at 12 to 48 months of age (Herbstman et al., 2010). Children with the highest exposure levels of three congeners (BDE-47, -99, and -100) scored lower on mental and physical developmental tests. Some associations were statistically significant for 12-month Psychomotor Development Index (PDI) (BDE-47), 24-month Mental Development Index (MDI) (BDE-47, -99, and -100), 36-month MDI (BDE-100), 48-month full-scale and verbal IQ (BDE-47, -99, and -100), 36-month MDI (BDE-100), and 72-month performance IQ (BDE-100). A prospective cohort study in the Netherlands examined the association between neuropsychological functioning at 5 to 6 years and maternal blood organohalogens measured at 35 weeks of pregnancy (Roze et al., 2009). In this study, PBDEs correlated with worse fine manipulative abilities and attention, but with better visual perception and behavior.

TABLE 1 EPA-Derived Chronic Oral RfDs for Single PBDE Congeners[a]

Congener	Number of chlorines	RfD[b]
BDE-47	4	100
BDE-99	5	100
BDE-153	6	200
BDE-10	10	7000

Source: EPA, 2008a–d.

[a]Based on developmental neurotoxicity in animals.

[b]Expressed in ηg/kg-day.

Both short-term exposure of animals during the perinatal period and exposures throughout gestation to weaning commonly have resulted in alterations in motor activity and impaired learning and memory, with hyperactivity being most consistent (Driscoll et al., 2012). There is a question, however, of whether hyperactivity is permanent or only transient. One study suggests that BDE-209 reduces LTP and affects synaptic plasticity (Xing et al., 2009).

Table 1 shows the EPA RfDs for four BDE congeners. Note that the RfD for BDE-209 (the chlorine-saturated congener) is the greatest, which reflects its relatively lower toxicity. Confidence in the RfDs for all of these congeners, however, was listed as "low," reflecting the lack of human data and an inconsistency in animal data. To put these RfDs in perspective, the PBDE **no observed effect levels** (**NOELs**), determined in animal studies that examined either developmental neurotoxicity or TH changes, range from 140 to 1000 µg/kg-day (McDonald, 2005).

Mechanisms of action

Various animal studies of adult or prenatal and postnatal PBDE exposures have shown perturbation of the thyroid system and TH disruption, mostly reduced circulating levels of T4 or T3 (Costa and Giodano,

2007). The mechanism for this effect has not been elucidated. In a study of adult rats, a decrease in circulating T4 was found at 421 µg BDE-47/g lipid (Darnerud et al., 2007), which is about three orders of magnitude higher than levels measured in highly exposed humans. Although it has been proposed that PBDEs bind to the TH receptor (THR) because of their structural similarity to T4, in vitro studies have not revealed high affinity of PBDEs for the THR.

Human studies are still needed to confirm the potential effects on the TH system because rats and mice appear particularly sensitive (Herbstman et al., 2008). A recent epidemiologic study of PBDEs suggested a slight decrease of TSH in exposed pregnant women (Chevrier et al., 2010), but another study of electronic-waste recycling workers revealed higher TSH levels than in controls (Yuan et al., 2008). A study comparing maternal and fetal blood PBDE levels found no correlation with serum T4 concentrations (Mazdai et al., 2003). Clearly, well-designed studies investigating the relationship between body burden of PBDEs and child development are needed to validate the animal findings.

Additional mechanisms for PBDE-induced neurotoxicity are alterations in signal transduction pathways; induction of oxidative stress; interactions as antagonists or agonists at androgen, progesterone, and estrogen receptors;[7] induction of mixed-function monoxygenases (a family of enzymes that participate in many biochemical reactions); and inhibition of cytochrome P450 17 (CYP17), a key enzyme in the synthesis of testosterone (Canton et al., 2006).

Bisphenol A (BPA)

Bisphenyl A (**BPA**; 4,4-isopropylidenediphenol) is a synthetic monomer that is one of the highest production synthetic compounds worldwide. It is a semi-persistent organic pollutant (molecular weight, 228.3 g/mole) that is used primarily in the production of plastics, including polycarbonate plastics and epoxy resins. These materials are found in toys, compact disks, paints, food and beverage containers, dental sealants, and flooring (NTP, 2008). The chemical structure of BPA is shown in **Figure 11**.

The primary source of exposure for the general population is through food and water. It has been estimated that human consumption of BPA from epoxy-lined food cans alone is over 6 µg/person-day (Chapin et al., 2008). The neonate is exposed to BPA through infant formula, maternal milk, or canned food. Concentrations in the range of 1 to 10 ηg/ml have been reported in the serum of pregnant women, fetal amniotic fluid, and cord serum collected at birth (Diamanti-Kandarakis et al., 2009).

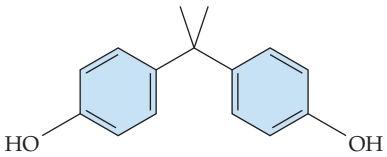


Figure 11 **Chemical structure of BPA**

BPA is quickly absorbed from the gastrointestinal (GI) tract following oral exposure. Little free BPA, the biologically active form, remains following metabolism in the liver to BPA-glucuronide, the primary metabolite of BPA (NTP, 2008). The half-life of the glucuronide, which is excreted in the urine, is less than 6 hours.

Data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) database for the U.S. population reported the daily intake of BPA at the 95th percentile to be 195.8 ηg/kg for women and 237.9 ηg/kg for men (LaKind and Naimon, 2011), which corresponds to 11.7 µg/day for a 60-kg (132 pound) woman and 16.7 µg/day for a 70-kg (154 pound) man. The Centers for Disease Control and Prevention (CDC) reported that of 2517 Americans aged 6 years and older surveyed in 2003–2004, 92.6% had detectable BPA (including metabolites) in their urine (Calafat et al., 2008). Similarly, a Canadian study found that 91% of people 6 to 70 years of age had detectable levels of BPA (Bushnik et al., 2010). There were no reports of acute or chronic toxicity identified in human adults.

Neurotoxicity in children and the developing nervous system

The effect of BPA in humans with regard to developmental neurotoxicity is an area of intense debate because of the inconsistencies in published findings (Braun et al., 2009). One U.S. prospective birth cohort study of infants assessed at 5 weeks of age did not identify any significant associations between neurobehavior and maternal urinary BPA measured at about 16 and 26 weeks of gestation (Yolton et al., 2011). However, investigators did report a trend toward hypotonia (decreased muscle tone) associated with BPA exposure at 16 weeks of gestation. In another study of prenatal BPA exposure in which maternal urinary BPA also was measured at about 16 to 26 weeks of pregnancy and at birth, the BPA levels were

[7]Most PBDEs have antiandrogenic activity; tetra- to hexaBDEs have potent estrogenic activity in vitro; heptaBDE and 6-OH-BDE-47, a metabolite of BDE-47, have antiestrogenic activity (Hamers et al., 2006; Meerts et al., 2001).

associated with externalizing behaviors (e.g., hyperactivity and aggression) that were stronger for females than males at 2 years of age (Braun et al., 2009). At the 95th percentile, the mean maternal urinary BPA values across the sampling period were 7.8 and 8.0 µg BPA/g creatinine for male and female offspring, respectively. A case report arising from the same study population noted a woman with a urinary BPA concentration of 583 µg/g creatinine at 27 weeks of pregnancy (cohort mean was 2.0 µg/g) and 1.9 µg/g at parturition (Sathyanarayana et al., 2011). Her infant male was normal at birth but presented with neurobehavioral abnormalities at 1 month. The etiology is unclear because the child was normal at birth and at annual evaluations performed from 1 to 5 years of age.

Animal studies have shown an association between prenatal and early postnatal exposure to very low BPA doses (10 to 100 µg/kg-day) and neurobehavioral effects such as increased anxiety, cognitive deficits, altered sexually dimorphic behaviors, and changes in dopaminergic and NMDAergic systems (Palanza et al., 2008; Poimenova et al., 2010; Tian et al., 2010). Other studies have showed no effects on reproduction, development, or sexual differentiation at similarly low doses (2 to 200 µg/kg-day) (Ryan et al., 2010).

The National Toxicology Program reported "some concern" for BPA's effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current exposure levels (NTP, 2008). "Some concern" represents the midpoint level of concern used by the NTP where there are insufficient data from human studies but there is limited evidence of developmental changes in some animal studies at doses potentially relevant to humans. In January 2010, the U.S. Food and Drug Administration (FDA) announced that it agreed there is reason for some concern about the potential effects of BPA (FDA, 2010). The interested reader is invited to read an Expert Panel Report by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)[8] on the reproductive and developmental toxicity of BPA (Chapin et al., 2008).

Mechanisms of action

The primary mechanism of action for BPA is endocrine disruption related to its weak estrogenic properties and interaction on the nuclear estrogen receptor (ER) and the membrane ER. BPA is known to cross the placenta readily and to bind to □-fetoprotein, the estrogen-binding protein that normally prevents maternal estrogen from entering the fetal circulation. By binding to □-fetoprotein, BPA could potentially decrease □-fetoprotein binding of endogenous estrogen and thus increase estrogen bioavailability to the fetus (Diamanti-Kandarakis et al., 2009).

BPA also has been shown to bind to the thyroid hormone receptor (THR) and to antagonize its activation by T3. As little as 1 µM BPA significantly inhibits THR-mediated gene activation (Diamanti-Kandarakis et al., 2009). Developmental exposure of rats to BPA produces normal TSH levels but elevated T4 levels, which is consistent with BPA inhibition of THR-mediated negative feedback.

Seiwa et al. (2004) showed that developmental exposure to BPA blocks T3-induced oligodendrocyte development from precursor cells. In addition, it has been proposed that there may be an association between thyroid resistance syndrome and ADHD in humans and rats. Well-designed human studies are needed to test this hypothesis.

Section Summary

- POPs, including semi-POPs, are ubiquitous contaminants that bioconcentrate in the food chain and are found in human blood and tissues.
- Mechanisms of toxicity for POPs include both direct action on nervous system components and indirect action through endocrine disruption.
- Acute high-level exposure to PCPs is associated with toxicity in adults; however, co-contamination with other halogenated hydrocarbons makes it impossible to isolate the effects inherent to PCPs.
- Chronic exposure of the developing human nervous system to PCBs is a concern, although results of epidemiological studies have been inconsistent. Animal studies have shown altered motor behavior and deficits in cognitive flexibility, working memory, and inhibitory control.
- Neurotoxicity resulting from exposure to PBDEs has little supporting evidence in the human literature; evidence is based on animal studies.
- BPA has no acute or chronic studies showing human toxicity. The only mechanism for neurotoxicity thus far identified from animal studies is endocrine disruption.

Insecticides

Insecticides encompass a variety of chemical classes and products. They are used both outdoors and indoors, and the majority of the U.S. population has

[8]The tasks carried out by CERHR (1998–2010) are now carried out by the NTP Office of Health Assessment and Translation (OHAT) (http://ntp.niehs.nih.gov/pubhealth/hat).

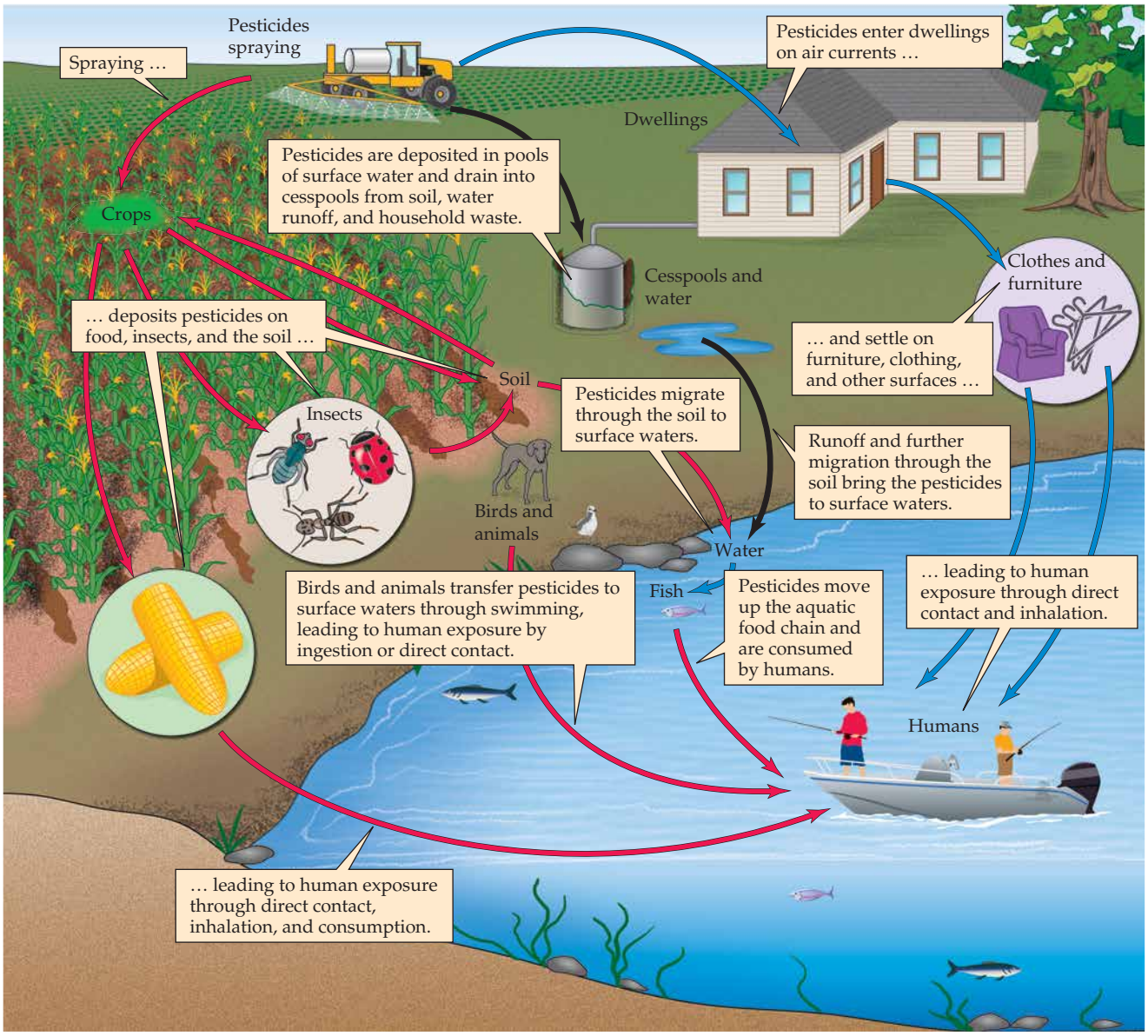


Figure 12 The pathways for human exposure to insecticides and other pesticides (After Sarkar, 2003.)

detectable concentrations of several insecticides and their metabolites in the urine (CDC, 2009, 2012a). Exposure of the general population to insecticides is primarily through contaminated food and water and home and garden products, as depicted in **Figure 12**. Other sources of exposure are also represented. Occupational exposures can be significant, especially for pest applicators, agricultural workers, ranchers, and farmers.

Two classes of insecticides—organophosphates and pyrethrins/pyrethroids—are discussed here. The interested reader is invited to read reviews of these and other pesticide health effects (Bjorling-Poulson et al., 2008; OCFP, 2012).

Organophosphate Insecticides

The organophosphate insecticides, referred to here as **organophosphates** (**OPs**), usually are esters, amides, or thiol derivatives of phosphoric acid. Figure 17.13 shows the chemical formulas for a phosphate (**Figure 13A**) and a phosphorothioate (**Figure 13B**) compound. Organophosphates have a phosphorus with a double bond to a terminal oxygen (an oxon), as represented by dichlorvos, or to sulfur (a thion), as represented by parathion.

The organophosphates in general are well absorbed via the oral, dermal, and inhalation routes. Metabolism occurs primarily in the liver by hydrolysis at the ester linkage, but the rate is highly variable among OPs. The resulting metabolites have relatively low toxicity.

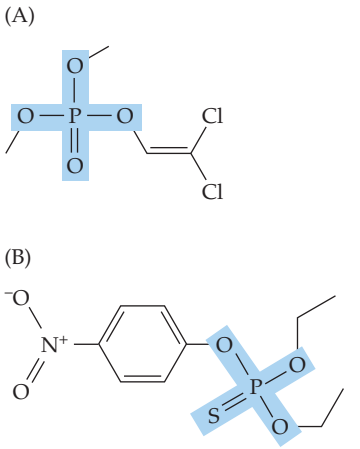


Figure 13 Organophosphates (OPs) (A) Dichlorvos (phosphoric acid, 2,2-dichloroethenyl dimethyl ester) is an example of a phosphate OP. (B) Parathion (phosphorothioic acid, O,O-diethyl O-[4-nitrophenyl] ester) is an example of a phosphorothioate OP.

The thions exhibit lower toxicity in mammals than the oxons and generally require metabolic transformation to the oxon form to inhibit the target enzyme, acetylcholinesterase (AChE). The normal acetylation of AChE by ACh is shown in **Figure 14**. In the presence of an OP, the enzyme is phosphorylated as opposed to being acetylated, as shown in **Figure 15**.

Not all OPs are capable of "aging" the enzyme. Only the phosphate and phosphonate OPs are capable of "aging" the enzyme, while the phosphinate OPs are incapable because they lack the possibility to be hydrolyzed at any site other than the AChE serine esteratic site.

Neurotoxicity in adults

OP inactivation of AChE causes accumulation of acetylcholine at cholinergic synapses and leads to overstimulation of muscarinic and nicotinic receptors. The signs and symptoms of OP poisoning are cholinergic in nature, as would be expected, and are referred to as **cholinergic syndrome**, as depicted in **Figure 16** and listed in **Table 2**.

In adults, acute poisoning with high doses of an OP (brain AChE inhibition exceeding 70%)[9] develops within minutes to hours of exposure, depending on the route of exposure (Clegg and Gemert, 1999). Overstimulation of the cholinergic system in both central and peripheral nervous systems is the primary form of toxicity exhibited with the OPs.

[9]Cholinesterase inhibition in red blood cells more closely reflects brain cholinesterase inhibition than plasma cholinesterase (pseudocholinesterase), although plasma cholinesterase is often used as an indicator of exposure.

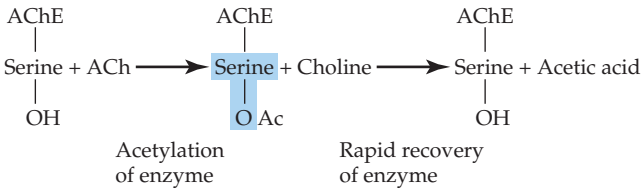


Figure 14 Acetylation of AChE by ACh and the rapid recovery of the enzyme following hydrolysis at the serine esteric site (highlighted in blue).

Prolonged effects can occur with irreversible inhibition of AChE. Death is usually the result of respiratory depression coupled with pulmonary secretions. Recovery is the result of new enzyme regeneration in critical tissues.

Following recovery (24 to 96 hours later) from an acute poisoning (cholinergic crisis), an intermediate syndrome has been described that is characterized by partial respiratory paralysis, reduced tendon reflexes, and muscular weakness (face, neck, proximal limbs) and lack of muscarinic symptoms (Christensen et al., 2009; Harper et al., 2009). This syndrome appears to be the result of pre- and post-synaptic dysfunction of neuromuscular transmission.

Some OPs also can induce a delayed neuropathy (OPIDN) that does not involve AChE inhibition, but rather, the inhibition of an enzyme called neuropathy target esterase (NTE). NTE deacetylates the major membrane phospholipid, phosphatidylcholine, and

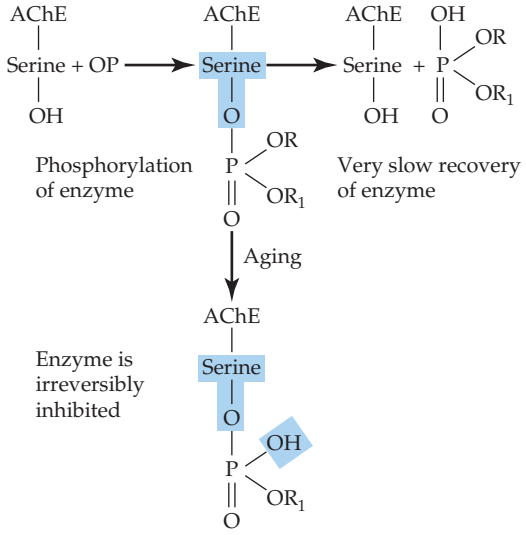


Figure 15 Phosphorylation of AChE by organophosphate OP and very slow recovery of the enzyme via hydrolysis at the serine esteric site. With some OPs, there may be complete and irreversible inhibition via hydrolysis at any other site (P–OH or P–OR_1), which results in strengthening of the bond to serine ("aging").

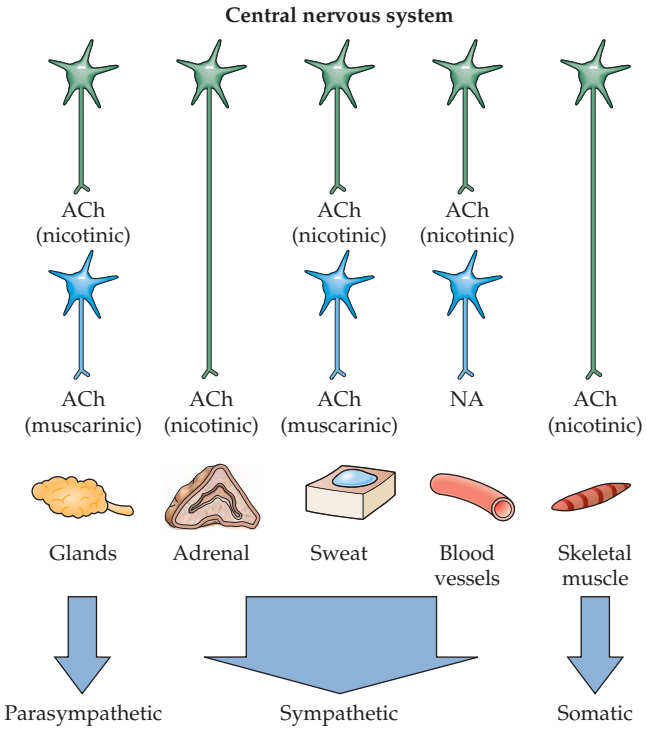


Figure 16 Cholinergic system Cholinergic system with receptor types that are overstimulated in the presence of AChE inhibition leading to acute cholinergic syndrome.

plays a major role in membrane homeostasis (Read et al., 2009). During neuronal differentiation, it regulates neurite outgrowth and process elongation. NTE inhibition results in axonal degeneration, which manifests chiefly as weakness or **paresthesia** (numbness and "pins and needles" feeling) and paralysis of the extremities, usually the legs.

Long-lasting behavioral effects have been reported in several human studies following recovery from intermediate syndrome or OPIDN (Bjorling-Poulsen, 2008). Although there has been concern for production of neurological effects following chronic, low exposure to OPs, the evidence is equivocal. In fact, chronic exposure may result in tolerance to AChE inhibition, as has been shown in animal studies, although the mechanism is unknown (Christensen et al., 2009; Harper et al., 2009).

TABLE 2 Clinical Signs and Symptoms of Acute OP Toxicity According to Receptor Type

	Peripheral	
Central muscarinic and nicotinic	Muscarinic	Nicotinic
Anxiety	Miosis	Muscle fasciculations
Ataxia	Blurred vision	Myoclonic jerks
Dysarthria (speech disorder)	Nausea	Muscle weakness
Confusion	Vomiting	Muscle rigidity
Headache	Diarrhea	Hyperreflexia
Fatigue	Salivation	Tremor
Drowsiness	Lacrimation	Paralysis
Difficulty concentrating	Rhinorrhea	Hypertension
Irritability	Bradycardia	Tachycardia
Emotional lability	Abdominal pain	Dysrhythmias
Delirium	Diaphoresis (profuse sweating)	Mydriasis (rare)
Toxic psychosis	Urinary incontinence	
Respiratory depression	Fecal incontinence	
Coma		
Seizures (occasional)		

Sources: ATSDR 2007a; Christensen et al., 2009; Harper et al., 2009; Kumar et al., 2010.

Neurotoxicity in children and the developing nervous system

Children with acute, high-dose poisoning can present with signs and symptoms somewhat different from those observed for adults (Sofer et al., 1989). In children, seizures, lethargy, and coma are more common.

Nineteen epidemiological studies of prenatal OP exposure reviewed by the Ontario College of Family Physicians (OCFP, 2012) included populations expected to be at higher risk for exposure; seven of the studies also examined another insecticide, which was usually a carbamate or pyrethrins (see OCFP, 2012 for summaries of individual studies). Most of the studies reviewed reported an association between OP exposure and impaired or delayed neurodevelopmental or behavioral outcomes. Prenatal OP exposure was associated with absent or hypotonic reflexes and deficits in attention to stimuli in neonates. In studies in which exposure was graded, more effects were observed with greater exposure. It was noted that deficits either were not measured or were not manifest at all time points in the longitudinal studies; thus it is difficult to evaluate the onset and persistence of some effects.

In studies from five countries of children over 3 years of age exposed postnatally to OPs, the neurological effects observed were inconsistent and were not related to OP exposure (OCFP, 2012). In what was deemed a high-quality study of Egyptian adolescent workers with high seasonal OP exposures, deficits were reported for all neurobehavioral measures evaluated compared with nonworker controls (Abdel Rasoul et al., 2008). Additionally, significantly more neurological symptoms were self-reported, such as difficulty concentrating, depression, and numbness. There was also a significant relationship between the years worked, the number of neurological symptoms reported, and performance on the Trails B test (an indicator of executive functioning). Other studies of children whose parents were exposed to pesticides, including OPs, showed a wide range of results from no effects to significant effects. These studies are largely uninterpretable because of study size and multiple confounding issues (OCFP, 2012).

In a study of 8- to 15-year-olds in which current exposure was evaluated, the increase in a urinary OP metabolite was associated with a significantly increased risk for the hyperactive/impulsive subtype of ADHD (Bouchard et al., 2010). The association with the combined subtypes was not statistically significant, but was in the same direction.

The developmental neurotoxicity of OPs is still relatively undefined in humans, in part because most studies reflect exposures to more than one pesticide. In California and New York City studies, an association was found between reflex abnormalities in neonates and increased concentrations of OP metabolites in maternal urine during pregnancy (Bjorling-Poulson et al., 2008). Similar associations between maternal urinary metabolites and reflex abnormalities were observed for an agricultural cohort from California (Young et al., 2005) and an inner city cohort from New York (Engel, 2007). Additionally, newborns of women who were slow OP metabolizers were more likely than newborns of normal or fast metabolizers to have abnormal reflexes.

Six cohort studies of prenatally exposed children examined up to 3 years of age in Ecuador, New York City, and California showed decreases in the Bayley Developmental Scales for Infant Development, which includes scores on the MDI and PDI scales. Most of the studies found that highly prenatally OP-exposed children scored lower on the Bayley MDI.

Studies of prenatally OP-exposed children at 3, 3.5, and 5 years show overall that high-exposure children were more likely to have attention problems. In one study, results reached statistical significance only for boys. Three studies examined the effects of prenatal OP exposure on the IQ of 6- to 9-year-olds using the Wechsler Intelligence Scale for children (WISC-IV). Two of the studies showed declines in full-scale IQ and the subscale of working memory. The third study showed nonsignificant trends toward lower IQ with higher OP exposure. Pesticide metabolite levels of urine in many of the studies have been reported to be similar to those measured in general populations in the United States and in E.U. countries (Bjorling-Poulson et al., 2008). Although the epidemiological evidence for the developmental neurotoxicity of OPs in humans is not without problems, there appears to be sufficient evidence that the OPs cause adverse effects. Additional well-controlled human studies are needed to define these neurotoxic effects.

The RfDs for the commonly used OPs range from about 10^{-2} mg/kg-day for less-toxic to about 10^{-5} mg/kg-day for more-toxic compounds.

Mechanisms of action

The primary mechanism for neurotoxicity is inhibition of AChE activity, as previously discussed. ACh, a neurotransmitter, has important functions during brain development that can be disrupted by inhibition of AChE. Other effects, as seen with chlorpyrifos (a phosphorothiate OP; **Figure 17**), suggest that mechanisms other than inhibition of AChE activity may, at least in part, be responsible for the

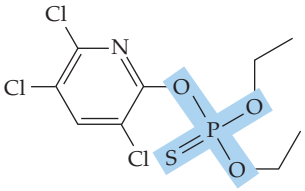


Figure 17 Chemical structure of chlorpyrifos (phosphorothioic acid, O,O-diethyl O-[3,5,6-trichloro-2-pyridinyl] ester).

developmental neurotoxicity of chlorpyrifos and possibly other OPs.

Chlorpyrifos is the most extensively studied OP with respect to developmental neurotoxicity in animals. Prenatal or neonatal exposure has resulted in a variety of behavioral abnormalities in rodents, including long-lasting effects on learning and memory (Aldridge et al., 2005; Canadas et al., 2005). These effects have been proposed to be the result of long-term alterations in 5-HT synaptic neurochemistry independent of AChE inhibition (Aldridge et al., 2005).

Prenatal exposure of rats to chlorpyrifos results in altered programming of synaptic development and deficits in brain cell numbers, neuritic projections, and synaptic communication (Qiao et al., 2003). The effects were first seen in adolescence and persisted into adulthood (i.e., the effects extend into relatively late stages of brain development). Neurobehavioral abnormalities can be induced as late as the second and third postnatal weeks in rats, which correspond to the neonatal stage of humans. Although this period occurs after the major phase of neurogenesis in most brain regions, it corresponds to the peak of gliogenesis and synaptogenesis. The developing glia are even more sensitive to chlorpyrifos than are the neurons. Antimitotic and pro-apoptotic mechanisms via directly targeted genes regulating the cell cycle and apoptosis during neurodifferentiation in the developing brain have been identified (Slotkin and Seidler, 2012). Deficits elicited by prenatal exposure to chlorpyrifos are seen even at exposures levels that do not inhibit AChE (Slotkin and Seidler, 2012).

Experiments with rat embryo cultures at concentrations relevant to humans have produced mitotic abnormalities and evidence of apoptosis during neural tube development (Ostrea et al., 2002). Significant effects have been seen at concentrations more than an order of magnitude *below* those present in human meconium (a fecal material that collects in the fetal intestine during development and is excreted shortly after birth) (Roy et al., 1998).

Pyrethrin and Pyrethroid Insecticides

The **pyrethroids** are synthetic analogs and derivatives of six naturally occurring **pyrethrins** from the *Chrysanthemum* genus of plants (ATSDR, 2003). This insecticidal class is quite diverse, but the pyrethroids have two common features—an acid moiety (e.g., a central ester) and an alcohol moiety. The pyrethrins and pyrethroids are generally classified into two groups (type I and type II) based on their structural and toxicological properties. Examples of type I and type II compounds are shown in **Figure 18**.

These compounds are readily degraded in the atmosphere, soil, and water and do not persist for longer than a few days to a few weeks. They are bound tightly to soil and do not "travel" or usually contaminate ground water. Likewise, they are not readily taken up by plant roots. They can bioconcentrate in aquatic organisms, however, and are toxic to fish. In spite of their lipophilicity, the pyrethroids do not bioaccumulate in human tissues because they are readily metabolized by hydrolases and cytochrome P450s (CYPs) (Soderlund et al., 2002).

These insecticides are used for both commercial and home applications. The general population is exposed to pyrethrins and pyrethroids primarily via foods, especially fruits and vegetables. Other sources of exposure include household insecticides, pet shampoos, and lice treatments. Occupational exposure can be the greatest, and dermal exposure is considered to be the most important (ATSDR, 2003). Several reviews are available for the interested reader (ATDSR, 2003; Breckenridge et al., 2009; Lautraite and Sargeant, 2009; Shafer et al., 2005; Soderlund et al., 2002).

Acute neurotoxicity

In rodents, type I pyrethroids typically induce aggressive behavior and increased sensitivity to external stimuli. At near lethal doses, fine tremor is observed followed by prostration and coarse whole body tremor, leading to coma and death. The term *T-syndrome*, for tremor, has been given to these type I responses (ATDSR, 2003).

The type II responses in rodents typically include pawing and burrowing behavior that is followed by profuse salivation, increased startle response, abnormal hand and limb movements and coarse whole body tremors that progress to serious writhing (choreoathetosis). Clonic seizures may be observed before death. The term *CS-syndrome*, for choreoathetosis and salivation, has been given to these type II responses. A few pyrethroids have demonstrated signs intermediate to the T- and CS-syndromes. Both syndromes are acute

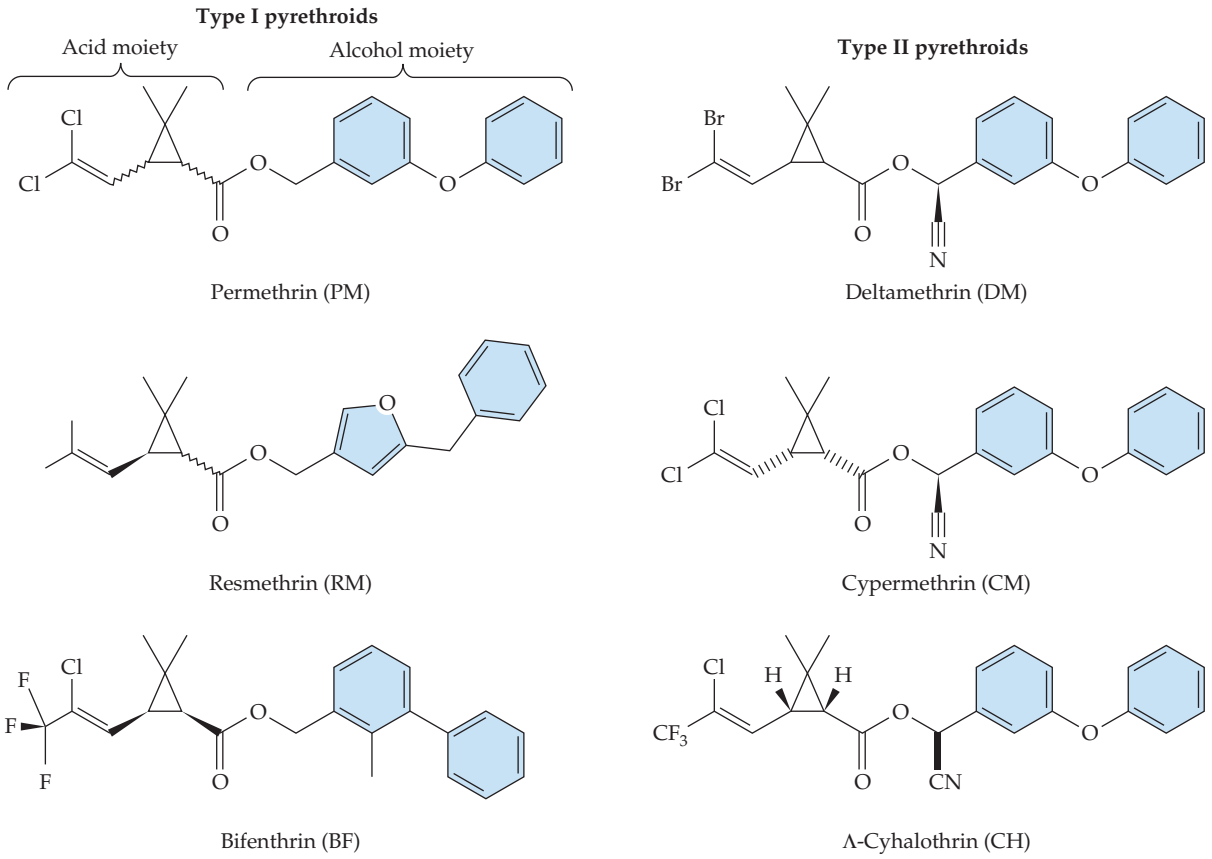


Figure 18 Representative structures of Type I and II pyrethroid pesticides

in nature, and chronic low-level exposures have not been reported to produce severe neurological effects (ATDSR, 2003).

Human pyrethroid poisoning is rare, and almost entirely involves type II pyrethroids. Occupational exposures have been the predominant source of pyrethroid poisoning. The main adverse effect of dermal exposure to type II pyrethroids is paresthesia, presumably due to a direct excitatory effect on small sensory nerve fibers in the skin (Lautraite and Sargeant, 2009). Dizziness, headache, and fatigue are common symptoms following ingestion and dermal exposure of type II pyrethroids. In severe cases, coma and convulsions are the principal life-threatening features (ATDSR, 2003). Increased acute peripheral nerve excitability has been reported for cotton workers exposed to deltamethrin over 3 days during spraying.

Developmental neurotoxicity

A series of 22 developmental neurotoxicity studies in animals have been summarized and critiqued by Shafer et al. (2005). The authors noted that there has been no systematic evaluation of exposure during various developmental periods, and no examination of the ontogeny of various behaviors and neurological endpoints. They also noted that there were inconsistencies in results even when similar neurobehavioral endpoints were evaluated. A few relatively consistent findings, however, were seen in studies in which the animals were evaluated following prenatal exposure: increased preweaning muscarinic ACh receptor (mAChR) expression in the cortex and increased motor activity and decreased habituation. Further work needs to be done to assess the potential for these insecticides to induce developmental toxicity in humans.

Mechanisms of action

The primary mechanism of action of the pyrethrins and pyrethroids is disruption of voltage-sensitive sodium channel (VSSC) function. The more potent the disruption of VSSC function, the more potent is the insecticidal and toxicological activity (Shafer et al., 2005). During development, perturbation of VSSC function impairs nervous system structure and function. VSSCs in mammals are composed of one α and two β subunits, with tissue specificity. The pyrethroids bind to the α subunit, which has been shown to have many variants in humans presumably contributing to the diversity seen in toxic responses.

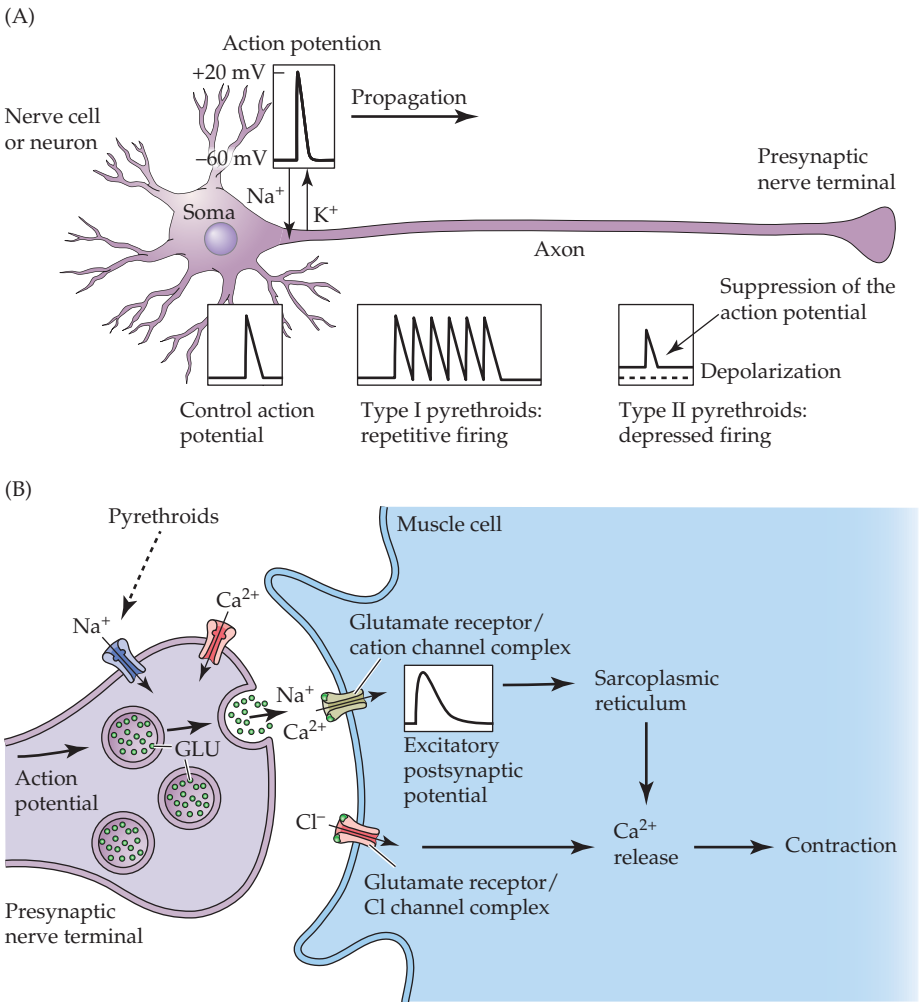


Figure 19 Neuromuscular transmission in the presence of pyrethroids (A) Depiction of propagation of an action potential down the presynaptic nerve axon. Under the axon the action potentials generated by type I and type II pyrethroids (i.e., repetitive firing and depressed firing) are shown relative to the control action potential (i.e., normal size and single action potential). The nerve terminal and muscle cell shown in (B) depict the normal release of glutamate (GLU, green circles) from the presynaptic terminal, their interaction with muscle cell receptor sites that open ion channels for the passage of N^{a+}, Ca^{2+} and Cl^{-} and the subsequent generation of the excitatory postsynaptic potential and the release of Ca^{2+} and contraction of the muscle cell. The site for action of the pyretheroids is shown at the presynaptic Na^{+} ion channel. (After Bloomquist, 2009.)

The pyrethroids slow the opening (activation) and closing (inactivation) of VSSCs and shift the membrane potential at which they open to more hyperpolarized potentials; that is, the sodium channels open after smaller depolarizing changes in membrane potential. The result is that more sodium ions cross the neuronal membrane and depolarize it. Type I compounds prolong channel opening just long enough to induce repetitive firing of action potentials, and type II compounds hold the channels open such that depolarization occurs and prohibits generation of action potentials (Shafer et al., 2005) (**Figure 19**).

The type II pyrethroids can bind to and block GABA receptors in in vitro mammalian brain preparations. Such blockade would be neuroexcititory in nature and is consistent with observed in vivo actions. Low potency, however, does not support this mechanism as a major role for acute toxicity (CS syndrome), although it could possibly be involved in developmentally induced neurotoxicity. It appears that pyrethrins and pyrethroids also affect calcium channel function; however, direct involvement in massive neurotransmitter release during pyrethroid intoxication has not been shown. There are some pyrethroids that have toxic effects that are intermediate between the two types.

Section Summary

- OPs produce acute neurotoxicity via inhibition of AChE and increased ACh concentrations at nicotinic and muscarinic receptors in the central and peripheral nervous systems.
- Prolonged toxicity with OPs occurs with irreversible inhibition of AChE, requiring the synthesis of new enzyme for normal function.
- OPIDN is produced by the irreversible inhibition of NTE, resulting in axonal degeneration and peripheral neuropathy.

- Studies of developmental neurotoxicity of OPs in humans are complicated by exposure to multiple pesticides. Effects on cognition and motor activity have been seen, although not consistently across studies. Prenatal chlorpyrifos exposure of rats at levels not causing AChE inhibition results in altered programming of synaptic development and deficits in brain cell numbers, neuritic projections, and synaptic communication.
- Pyrethrins and pyrethroids act through disruption of VSSC function, and severe poisonings of humans are seldom seen, but when they are, it is generally a type II compound. Neurotoxicity has not been reported following chronic low-level exposures.
- Developmental toxicity in humans has not been reported for pyrethroids. Animal studies of prenatal exposure have shown inconsistent effects except for increased preweaning mAChR expression in the cortex and increased motor activity and decreased habituation.

Toxic Metals

Lead, mercury, and arsenic are well-known environmental metals. (Arsenic is included in most discussions of toxic metals, but it is more appropriately referred to as a metalloid with properties in between those of metals and nonmetals.) Although the term *heavy metals* is often used in reference to the toxic environmental metals, it is an imprecise term that lacks a consistent and meaningful definition; thus the term *toxic metals* is more appropriately used.

Metals are naturally occurring and are among the oldest known toxicants. Hippocrates (460 to 377 BC) is credited with describing the symptoms of lead poisoning much as they are described today: "appetite loss, colic, pallor, weight loss, fatigue, irritability, and nervous spasm" (Lessler, 1988); however, it is questionable whether he recognized lead as the causative agent (Hernberg, 2000).

From an environmental perspective, metals are naturally redistributed in the environment by both geological and biological means, with human activity magnifying that distribution. The toxicity of many metals is determined by the oxidation state of the metal, its lipid solubility, the cellular dose achieved, the duration of exposure, and the extent of binding to the target biomolecule. The common mechanisms of metal-induced neurotoxicity are mediated through direct and indirect mitochondrial damage; oxidative stress and formation of ROS resulting in protein and lipid peroxidation; depletion of nonprotein sulfhydryls (e.g., glutathione, a naturally occurring antioxidant present in all cells); binding to protein sulfhydryl groups; substitution for key divalent cations, such as calcium (Ca^{2+}); and disruption of cellular signaling.

Lead (Pb)

Lead is found in the earth's crust primarily in areas with copper, silver, and zinc. Metallic (elemental) lead (zero oxidation state, Pb^0) is rare because it quickly oxidizes in the air. Lead is easy to extract and smelt and is highly malleable, which accounts for its extensive use through the millennia (Hernberg, 2000). Inorganic and organic compounds of lead are primarily in the +2 and +4 oxidation states, and Pb^{2+} is more common, being present in various ores around the world. In the environment, lead is strongly absorbed to soil.

In recent history, lead has been used in many products, including paints, gasoline, ceramics, pipes, solders, batteries, ammunition, and cosmetics. In the United States, lead exposure is most commonly from flaking and deteriorating lead-based paints used in older homes, contaminated soils and drinking water, lead crystal, and lead-glazed pottery (Sanders et al., 2009). The principal exposure source of lead for the general population is via food, and other sources are significant for certain populations. Contamination of soil from deteriorating lead-based paints and from the residual deposition of atmospheric lead from leaded gasoline is especially a concern for young children, who ingest soil and dust via their daily activities.

GI absorption of ingested water-soluble inorganic lead compounds is 3% to 10% in adults, and approximately 30% to 50% in infants and children (ATSDR, 2007b; Neal and Guilarte, 2012). Under circumstances where there is low dietary iron and calcium, lead absorption is significantly increased. In the blood, greater than 90% of the lead is contained in red blood cells, and less than 1% is in the plasma. From the blood, lead is distributed to the soft tissues and bone. It may be stored preferentially in the bone of adults because osteoclasts (the cells responsible for absorption of bone during normal turnover of bony tissues) can interchange Ca^{2+} and Pb^{2+}. Infants and children also store lead in bone, but their bone mass is small and the amount of stored lead as a percent of body burden is less than that of adults (73% versus 94%). Bone turnover due to skeletal growth in children and infants mobilizes Pb stores and may result in added exposure (Neal and Guilarte, 2012). Lead does not penetrate the blood–brain barrier of adults, but may

penetrate the more poorly developed blood–brain barrier of children. For adults, the half-life of lead in blood is about 1 month, and in the skeleton 20 to 30 years (ATSDR, 2007b).

Lead exhibits neurotoxic effects in the central and peripheral nervous systems that are dependent on the developmental period and the level and duration of exposure.

Neurotoxicity in adults

In adults, acute high-dose lead poisoning can cause encephalopathy (brain damage or malfunction) that manifests as an altered mental state, seizures, ataxia, and coma. Severe encephalopathy generally is observed only at extremely high blood levels (460 µg/100 ml [460 µg/dl]) (ATSDR, 2007b); however, less severe, overt encephalopathy has been reported at blood levels as low as 100 µg/dl. Chronic occupational exposures are associated with symptoms ranging from forgetfulness and irritability to weakness and paresthesia at blood levels from 40 to 120 µg/dl. Chronic lead exposure also is associated with inattentiveness, distractibility, hyperactivity, frustration, and aggression at blood levels as low as 10 µg/dl in some studies. Peripheral neuropathy in adults is associated with chronic exposure at blood levels of 70 µg/dl and greater (ATSDR, 2007b).

Neurotoxicity in children and the developing nervous system

In children, high-dose lead poisoning can lead to significant neurotoxic sequelae similar to what are observed in adults, but at lower doses. Overt encephalopathy in children, for instance, is associated with blood lead levels as low as 70 µg/dl, compared with 100 µg/dl in adults (ATSDR, 2007b).

As more data were gathered during the 1960s and later, it became apparent that the greatest concern for environmental lead exposure was for the prenatally and postnatally developing nervous system. In addition to the high-dose encephalopathic effects of lead, it was recognized that lower doses over a prolonged exposure period resulted in significant toxic effects. Between 1960 and 1991, the CDC blood lead level recommendation for individual clinical intervention in children was lowered from 60 to 25 µg/dl and again from 25 to 15 µg/dl in 1991. At the same time, 10 µg/dl was set as a risk management tool (i.e., not as a threshold for toxicity) (Sanders et al., 2009). In 2012, the CDC lowered the blood lead threshold in children younger than 6 years of age from 10 to 5 µg/dl based on a shift in policy from that of a clinical intervention to that of a public health approach focused on prevention (CDC, 2012b).

Blood lead levels of 10 µg/dl and higher that are associated with chronic lead exposure in early childhood are detrimental to neurodevelopment. The recognized adverse effects include impaired cognitive function, behavioral disturbances, attention deficits, hyperactivity, conduct problems, antisocial behavior, delinquency, and violence (Bellinger, 2009; Neal and Guilarte, 2012; Needleman et al., 2002; Sanders et al., 2009; Wright et al., 2008). In children, lead exposure has also been associated with increased risk of ADHD (Braun et al., 2006). Blood lead levels in young school-age children also predict neurologic deficits in children and young adults (Hornung et al., 2009). Newly identified neuroanatomical changes in young adults exposed to lead in childhood include reduced gray matter in the prefrontal region and white matter changes indicative of effects on myelination (Brubaker et al., 2009).

After decades of study, a nonlinear relationship between lead exposure and IQ decline in children has been recognized. It appears that the greatest rate of decline in IQ comes with the initial 10 µg/dl increase in blood lead levels (Neal and Guilarte, 2012). A pooled analysis of internationally conducted epidemiology studies calculated that a blood lead level of 10 µg/dl was associated with a 6-point decline in IQ relative to children with a 1 µg/dl blood level (Lanphear et al., 2005). Another study reported a similar decline in IQ points (7.4) with 10 µg/dl (Canfield et al., 2003).

Mechanisms of action

Lead has many interrelated mechanisms that are involved in its observed neurotoxicity; however, the primary mechanism may well be its effect on calcium metabolism via substitution for calcium and disruption of calcium homeostasis. Although not necessarily all of the following are related to disruption of calcium metabolism, lead has been shown to promote apoptosis, produce excitotoxicity, affect neurotransmitter storage and release, damage mitochondria and cause oxidative stress resulting in peroxidative damage to lipids and proteins, deplete antioxidants by binding to sulfhydryls (e.g., glutathione), inactivate antioxidative enzymes (e.g., glutathione reductase), deregulate cell signaling (e.g., activation of protein kinase C [PKC]), alter cellular membranes (e.g., cerebrovascular endothelial cells), impair synaptic transmission, and alter neurotransmitter concentrations, alter neurotransmitter receptor channel properties, and affect protein and gene expression (ATSDR, 2007b; Neal and Guilarte, 2012; Sanders et al., 2009) (**Figure 20**).

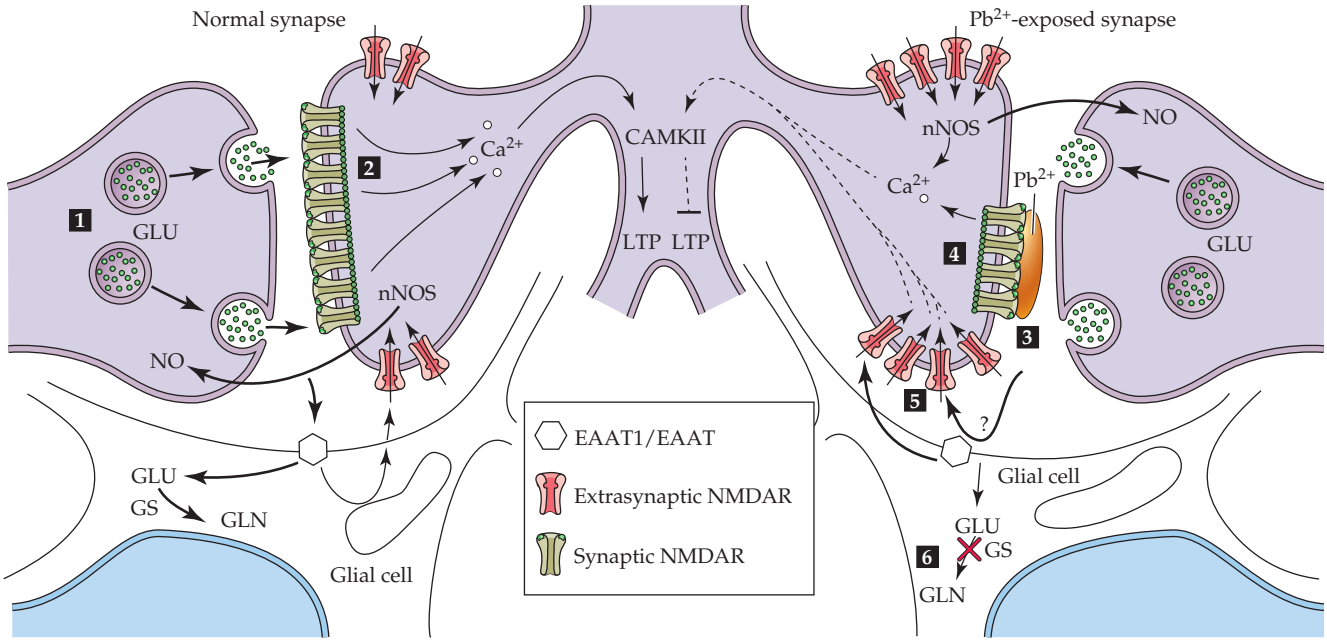


Figure 20 Pb^{2+} interaction at the synaptic level In a normal synapse, glutamate release (1) normal NMDAR density, and Ca^{2+} influx (2) through open NMDAR channels activate neuronal nitric oxide synthase (nNOS) and calcium/calmodulin kinase II (CAMKII), two enzymes involved in the induction and maintenance of long-term potentiation (LTP). Developmental exposure of Pb^{2+} leads to reduced numbers of NMDARs and potential blockage of the receptors by Pb^{2+} (3). Reduced Ca^{2+} influx (4) may occur as a result of fewer receptors and receptor blockage resulting in altered activation of nNOS and CAMKII, which affects LTP. (5) Glutamine synthetase (GS) is inhibited by Pb^{2+} and may result in an accumulation of GLU in glial cells which then could be available to activate extrasynaptic NMDAR subunits. (6) An alternative mechanism for GLU activation of extrasynaptic NMDARs is Pb^{2+} inhibition of the GLU transporters (EAAT1/EAAT), which would result in increased extracelluar concentrations of GLU. GLN, glutamine. (After Toscano and Guilarte, 2005.)

The consequences of some of these mechanisms are briefly cited to give the reader a feel, albeit superficial, for the profound effect that lead can have on the developing organism. Perturbations in normal Ca^{2+} signaling affect synaptic development and plasticity. Lead impairs timed programming of cell–cell connections, resulting in modification of neuronal circuitry. Lead induces precocious differentiation of the glia, whereby cells migrate to their eventual positions during structuring of the CNS. Learning and memory deficits may be related to inhibition of the *N*-methyl-D-aspartate receptor (NMDAR) in the hippocampus (Neal and Guilarte, 2012). It has been hypothesized that Pb^{2+} also delays the normal ontogeny and alters the distribution of NMDAR (**Figure 20**). The interrelationships among and between these individual mechanisms are considerable, and the interested reader is invited to review several articles addressing various aspects of the mechanisms of lead neurotoxicity (ATSDR, 2007b; Hsiang and Diaz, 2011; Neal and Guilarte, 2012; Sanders et al., 2009).

Mercury (Hg)

Elemental mercury (Hg^0), also known as quick silver, is a naturally occurring shiny, silver-white metal that is a liquid at room temperature. Natural releases from volcanoes and the earth's crust put metallic mercury vapor into the atmosphere, as do anthropomorphic releases from mining ore deposits, coal-burning power plants, and the incineration of waste. An example of mercury entering the environment through human activity via the recent upsurge in gold mining is depicted in **Figure 21**. Mercury circulates in the atmosphere until it eventually returns to earth, where it may settle in aquatic sediments and may be fixed by bacteria or plankton as methylmercury (ATDSR, 1999).

Mercury compounds are primarily in the +1 and +2 oxidation states, referred to as mercurous (Hg^+) and mercuric (Hg^{2+}) mercury, respectively. Mercuric mercury can form stable organic mercury compounds, such as methylmercury (CH_3Hg^+), which is done in association with either a simple anion, such as Cl^-, or a large, charged molecule, such as a protein.

Mercury historically has been used in thermometers and barometers, as topical antiseptics and preservatives (**Box 1**), and more recently in fluorescent light bulbs, laptop monitors, cell phones, and printed circuit boards. Although individual electronic devices contain a small amount of mercury (1 g mercury was calculated for a cell phone vintage 2000–2005, while other electronic devices cited contained 4 mg or more;

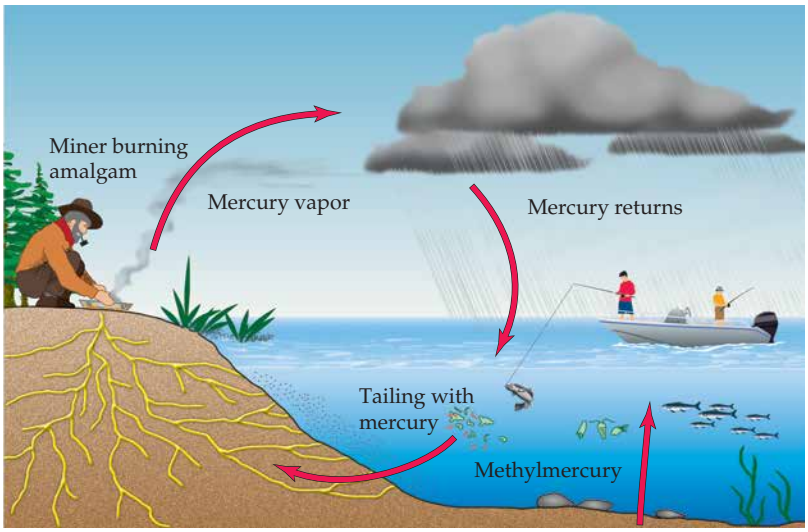


Figure 21 Release of mercury into the environment Mercury vapor enters the atmosphere as a result of mining activity where it can remain for some time before being deposited on land and surface waters (primarily through rainfall). Once mercury reaches surface water, it can settle into sediment, where it may be released through sediment resuspension, enter the food chain, or re-enter the atmosphere. (After UNIDO, 2006.)

EPA, 2007), their improper recycling has the potential to release elemental mercury vapor into the environment (Ramesh et al., 2007). This is especially a concern in third world countries, where environmental regulations are nonexistent or unenforced.

The primary source of human exposure to mercury is via methylmercury through consumption of fish and shellfish due to bioaccumulation because of its lipid solubility (EPA, 2012a). Consumption of large amounts of contaminated fish and/or shellfish can be sufficient to cause mercury poisoning in humans and animals. Although only a small percentage of metallic and mercuric mercury is absorbed from the adult human GI tract (approximately 0.01% and 15%, respectively), approximately 90% to 95% of methylmercury is absorbed (ATDSR, 1999). Methylmercury readily passes though the placenta, and infants can be exposed via the mother's milk. There appears to be very slow to no elimination of methylmercury for infants.

The tissue distribution of mercury is dependent on the speciation, lipid solubility, and route of exposure. Hg^0 is rapidly oxidized in red blood cells to inorganic mercury, and thus its distribution is similar to that of inorganic mercury. Hg^{2+} has a high affinity for sulfhydryl groups, and most all Hg^{2+} in the blood is bound to glutathione, cysteine, albumin, and other sulfhydryl-containing proteins.

Once methylmercury is absorbed, it can be transported across the blood–brain barrier via a carrier-mediated system (Aschner and Aschner, 1990). In the brain, methylmercury is metabolized to a limited extent to Hg^{2+}. Mercury toxicity in the brain is nonspecific in that it does not target a specific cell or receptor type. Its higher affinity for sulfhydryl groups, however, leads to its concentration in certain areas of the brain such as granule cells of the cerebellum and the calcarine region of the occipital cortex (Eto, 1997).

In 1995, the EPA lowered the allowable daily intake of methylmercury from 0.5 µg Hg/kg-day, a threshold established by the World Health Organization (WHO) in 1978, to 0.1 µg/kg-day based on adverse neurological effects in infants. The FDA and the EPA issued a joint advisory cautioning that "young children, women who are pregnant or who may become pregnant, and nursing mothers should avoid fish that contain high levels of methylmercury" (FDA, 2004). The species most likely to have these higher levels are shark, swordfish, king mackerel, and tilefish; shrimp, canned light tuna, salmon, Pollock, and catfish are the most common species to have low levels of mercury (EPA, 2012b; Neustadt and Pieczenik, 2007; NIEHS, 2012).

Neurotoxicity in adults

Neurotoxicity observed with mercury is similar for rodents, wild animals, and humans: ataxia, impaired gait, increased excitability, and tremors (ATSDR, 1999). Inhalation of metallic mercury vapor at high concentrations is associated with often acutely fatal interstitial pneumonitis. Acute high-level exposure of adults to mercury compounds via other routes generally results in paresthesia and ataxia that may be followed by visual field constriction and blindness. Lethal doses of organic mercury compounds have been estimated to range from 10 to 60 mg/kg for humans. For both inorganic and organic mercury, symptoms may not present for weeks to months after exposure. Neuropathology shows selective involvement of the cerebral and cerebellar cortices, focal necrosis, lysis, and phagocytosis in the visual cortex and cerebral granule cells (ATDSR, 1999). The neurons

BOX 1 Of Special Interest

Thimerosal in Vaccinations—Does It Cause Autism?

There has been controversy surrounding the use of thimerosal in childhood vaccines (Figure A). Thimerosal is a mercury-containing preservative that has been blamed for causing autism in children receiving the vaccines.

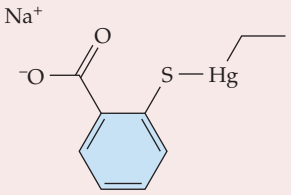
The controversy arose in the United States in the late 1990s and early 2000s with rising public concern about environmental mercury poisoning coupled with rising awareness of autism (the most severe of the autism spectrum disorders [ASDs]), rising incidence of autism, and an increase in the number of vocal advocacy groups of parents of autistic children. The tale of convergence of these factors is told by Baker (2008) in an article in the *American Journal of Public Health*.

In 1997, a rider was placed on the FDA Modernization Act that required the FDA to assess the mercury content of drug products. Assessment of vaccines in which thimerosal was used as a preservative began in early 1998. Thimerosal, as shown in Figure B, contains ethylmercury (CH_3CH_2Hg) attached to thiosalicylate; the mercury content is 49.6% by weight.

The FDA identified three vaccines routinely given to infants (diphtheria-tetanus-acellular pertussis, *Haemophilus influenzae* type b conjugate, and hepatitis B) that could potentially have thimerosal as a preservative. The analysis was completed in April 1999. The FDA had calculated that if infants received all the vaccines preserved with thimerosal over the first 6 months of life, the cumulative exposure could be 187.5 μg of ethylmercury, 200 μg if the influenza vaccine was also received (AAP, 1999). Moving rapidly, the American Academy of Pediatrics (AAP), the U.S. Public Health Service (PHS), and vaccine manufacturers decided in July 1999 that thimerosal should be removed from vaccines as a precautionary measure (CDC, 1999). This decision was reached in spite of the fact that thimerosal as a vaccine preservative had not caused any harm. The basis for the decision was the EPAs RfD for methylmercury (0.1 μg mercury/kg-day) since no standard for ethylmercury existed.

(A)

(B)



Thimerosal in vaccines (A) The only commonly recommended childhood vaccine that still contains thimerosal is the multidose vial of influenza vaccine. Single dose vials of the vaccine do not contain thimerosal. (B) The chemical structure of thimerosal (sodium ethylmercurithiosalicylate).

As chronicled in a review by Baker (2008), the efforts of activist parents of autistic children led to the publication of an article in *Medical Hypotheses* (Bernard et al., 2001) that compared various aspects associated with autism versus the signs and symptoms reported for mercury exposure. Although this article was not peer-reviewed, for many, especially the lay public, the publication legitimized the association between mercury and autism. Baker suggested that further complications arose when litigation muddied the scientific waters with "expert witness testimony."

So, what was the basis for the claim of a causal relationship between thimerosal and development of autism? The assumptions underlying a causal relationship were as follows: (1) ethylmercury and methylmercury are equivalent in absorption, distribution, metabolism, and excretion (ADME); (2) the signs and symptoms of mercury poisoning and autism are the same, so there is biological plausibility; and (3) the rise in the incidence of autism was caused by thimerosal.

So what does the science say? The scientific weight of evidence does not support a causal relationship, and furthermore, the underlying assumptions for a causal relationship were false. First, ethylmercury is not methylmercury, and their ADME profiles are not equivalent. At the time of the original evaluation, because of lack of data, it was presumed that the half-life of ethylmercury was similar to that of methylmercury. The half-life of ethylmercury, however, was

BOX 1 *(continued)*

subsequently shown to be much shorter. Comparing blood levels, which are assumed to reflect the total body burden, the half-life of methylmercury is about 50 days, and the half-life of ethylmercury from thimerosal in vaccines is 7 to 10 days. Therefore, in the 2 months between vaccinations at birth and 2, 4, and 6 months, the mercury would have been excreted (i.e., 6 to 8.5 half-lives would have occurred).

Second, the signs and symptoms of mercury poisoning are not the same as those of autism, so there is little to no biological plausibility (Gerber and Offit, 2009; Nelson and Bauman, 2003). Children with mercury poisoning exhibit characteristic changes in head circumference and neurological motor, speech, sensory, psychiatric, and visual changes or deficits that are different from or not seen in autistic children.

Third, the incidence of autism did not decrease but continued to increase after removal of thimerosal from vaccines; therefore, thimerosal could not be the cause of the increased incidence.

Furthermore, since the controversy arose, about a dozen studies have been performed in the United States, Canada, the United Kingdom, and Denmark. A few studies concluded that there was an association between thimerosal and autism but those studies have been evaluated in multiple review articles, and all reviews detail significant design flaws that invalidate a conclusion of causality.

Today, the multidose vial of influenza vaccine is the only commonly recommended childhood vaccine that contains thimerosal in the United States and Canada. Despite all the scientific evidence that does not support the role of thimerosal in vaccines in the causation of autism, many articles in the lay press and on the Internet keep the controversy alive. The advocates sound convincing and offer "evidence" to support their claim; however, close scrutiny reveals the underlying unsupported assumptions. The lesson? Look at the underlying assumptions, and do not accept them without getting the facts. Look to the scientific community, not to individuals or the lay press, to examine all

are replaced by supporting glial cells. The overall acute effect is cerebral edema, but the long-term effect is cerebral atrophy that results from prolonged destruction of gray matter and subsequent gliosis.

With chronic exposure to mercury, the first manifestation of major CNS effects is paresthesia of the hands, feet, and sometimes around the mouth; impairment of coordination, such as waking or writing; muscle weakness; mental disturbances (e.g., mood swings, memory loss); and impairment of speech, hearing, and peripheral vision. The lower toxicity of mercurous compounds relative to mercuric compounds is most likely attributable to their lower solubility.

There are two well-known mass poisonings related to methylmercury: one in Minamata Bay, Japan, in the mid-1950s, and another in Iraq in 1971–1972. The Japanese episode is an example of chronic exposure and poisoning from contaminated seafood; the Iraqi episode is an example of a more acute exposure and poisoning from contaminated grain (ATSDR, 1999; Grandjean and Herz, 2011).

In Minamata, following an extended period of exposure, severe poisoning (called Minamata disease) presented as ataxia, numbness of the extremities, muscle weakness, narrowing of the visual field, and damaged hearing and speech. Within a short period following symptom onset, some victims exhibited psychoses, paralysis, coma, and death. In Iraq, seed grain treated with a methylmercury fungicide was consumed as food. Symptoms were similar to those observed with Minamata disease, with the exception that blindness was also reported. The difference in visual effects between Minamata and Iraq is thought to be most likely due to the different nature of the exposures.

Developmental neurotoxicity

The developmental effects observed following in utero exposure to methylmercury in Japan gave rise to the term "fetal Minamata disease." The first neurological signs were usually seen in infants at an early age and included delayed movements, failure to follow visual stimuli, and uncoordinated sucking and swallowing. These signs were followed by persisting primitive reflexes and markedly impaired coordination. In the few autopsies that were performed, characteristic neuropathological changes were observed: bilateral cerebral atrophy and hypoplasia (fewer cortical nerve cells and malformed cells or processes); cerebellar atrophy and hypoplasia (reduced granule cell layer); abnormal cytoarchitecture; hypoplasia of the corpus callosum; defective myelination of white matter; and hydrocephalus (Matsumoto et al., 1965). The most characteristic abnormality reported was the poorly developed and inappropriately located and positioned neurons in the

CNS, which is most likely the result of disrupted neuronal migration and maturation.

Neurodevelopmental effects with high-level exposures are undisputed. Questions have been raised about the neurodevelopmental effects of exposure to low to moderate levels of methylmercury, however, because of different findings in studies of the Faroe Islands and the Seychelles (Chen et al., 2011). An association was seen in the Faroe Islands study between prenatal methylmercury exposure (4 µg/g maternal hair; 23 µg/l cord blood) and deficits in motor function, attention, and verbal domains in children up to 14 years of age. The Seychelles study, on the other hand, did not show an association between neurodevelopmental endpoints and prenatal methylmercury exposure (7 µg/g maternal hair) (Davidson et al., 2010; Myers et al., 2009). Neither study showed an association with postnatal methylmercury exposures (Faroe Islands: 3 µg/g hair; 9 µg/l blood at 7 years of age) (Seychelles: 6 µg/g hair at 9 years of age).

When the Faroe Islands and Seychelles studies were analyzed with a cohort from New Zealand, however, the overall change in child IQ was calculated as –0.18 points for each 1-µg increase in methylmercury per gram maternal hair.

Although no threshold has been determined for neurotoxic effects with mercury, several studies suggest that very low levels are without significant effect. In the United States for 2-year-old children, background levels of methylmercury in whole blood were approximately 0.5 µg/l. This level of exposure was not associated with adverse neurodevelopmental outcomes in children evaluated at 2, 5, and 7 years of age (Cao et al., 2010).

Mechanisms of action

The mechanisms for producing neurotoxicity are believed to be similar for inorganic and organic mercury. The relative toxicities of the different forms of mercury (e.g., metallic, mercurous, mercuric, inorganic, and methyl and other organic mercury compounds) are related in part to differential accumulation in sensitive tissues. It appears that chronic exposure to methylmercury results in an accumulation of inorganic as well as organic mercury in the brain (ATSDR, 1999). In studies of monkeys, it was observed that the brain elimination half-life of methylmercury was 35 days, and that of inorganic mercury was on the order of years. The presence of inorganic mercury was thought to be due to the in vivo demethylation of methylmercury.

In the adult brain, the underlying neurotoxic mechanism may be disruption in protein synthesis, which is among the earliest biochemical effects seen in animal studies. Cells with greatest repair capacity survive, while others die.

Mercury also can disrupt signaling pathways involved in cellular communication throughout the CNS and peripheral nervous system. One example is the muscarinic ACh (mACh) signaling pathway, where Hg^{2+} (as $HgCl_2$) and methylmercury inhibit binding of ACh to the receptor in the cerebellum and cerebral cortex in several species, including humans (Basu et al., 2005). $HgCl_2$ is more potent than methylmercury, lending further support to speculation that neurotoxicity from methylmercury is the result of its demethylation to Hg^{2+}. $HgCl_2$ at sublethal concentrations is also implicated in selective inhibition of another neurochemical signaling pathway called the JAK-STAT pathway (Monroe and Halvorsen, 2006). The JAK-STAT pathway is involved in cytokine and growth factor signal transduction from the plasma membrane to the nucleus for regulation of cell differentiation and proliferation, thus inhibition of this pathway could be important for the developmental neurotoxicity of $HgCl_2$.

At the cellular level, $HgCl_2$ also interferes with mitochondrial respiration, resulting in oxidative stress. Because neurons have a high mitochondrial density, they are especially susceptible, and some neurons (e.g., motor neurons) have limited antioxidant capabilities.

Disruption of neuronal migration and neural cytoarchitecture by methylmercury is related to alteration of neural cell adhesion molecules (NCAMs) and disruption of the neurocytoskeleton (microtubules), both of which are important for cellular movements and kinetics.

Arsenic (As)

Arsenic is widely distributed in nature and occurs as a metalloid or semi-metallic element (As^0); as organic and inorganic arsenite (As^{3+}), arsenate (As^{5+}), and arsenide (As^{3-}) compounds; and as arsine (AsH_3), an inorganic gas. Arsenic is difficult to characterize because of its complex chemistry and ability to form many compounds.

The major source of arsenic exposure for the general population is via food and contaminated drinking water from natural geological sources (ATSDR, 2007c). Arsenic is one of the top environmental health threats in the United States and worldwide. In the United States and Europe, public water supplies have a regulatory limit of 10 parts per billion (ppb) arsenic; however, private water wells are unregulated, as are

many water supplies worldwide. Thus, arsenic contamination affects hundreds of millions of people and is associated with an extensive list of disease risks.

Both As^{3+} and As^{5+} are well absorbed via inhalation and oral routes, and poorly absorbed via the dermal route. Water-soluble As^{3+} and As^{5+} compounds are 80% to 90% absorbed from the GI tract, but other arsenicals of lower solubility are less efficiently absorbed. Once absorbed, arsenates are partially reduced to arsenite, resulting in a mixture of As^{3+} and As^{5+} in the blood. As^{3+} compounds are the principal toxic forms; As^{5+} compounds are less toxic.

Metabolism of inorganic As^{3+} occurs in the liver, and some have speculated that the organic intermediary and end products formed by such metabolism may be more reactive and toxic than inorganic As^{3+} (Thomas et al., 2007). The biological half-life of orally ingested inorganic arsenic in the body is about 40 to 60 hours, and the half-life of arsenic metabolites is about 1 day (ATSDR, 2007c).

Although only the neurotoxic effects of arsenic are discussed here, it must be remembered that chronic arsenic exposure is associated with many diverse disease processes ranging from keratosis to cancer. The interested reader can examine a review that explores many aspects of arsenic neurotoxicity (Rodriguez et al., 2003).

Neurotoxicity in adults

Ingestion of large doses of arsenic in the range of 70 to 180 mg can induce encephalopathy and can cause death (ATSDR, 2007). If one recovers from severe acute toxicity, the most commonly observed neurological effect is sensory loss in the peripheral nervous system, which appears 1 to 2 weeks after the initial insult. The neuropathy results from degeneration of axons, which is potentially reversible if there is no additional exposure.

Acute inhalation exposure has been associated with severe nausea and vomiting, diarrhea, sleep disturbances, decreased concentration, disorientation, severe agitation, paranoid ideation, and emotional lability, which can be relieved by chelation therapy (ATSDR, 2007). Long-lasting effects such as severe impairment of learning and memory and mild impairment of visuoperception, visuomotor integration, psychomotor speed, and attention processes, however, have been observed even at 8 months post-exposure (Rodriguez et al., 2003).

Chronic exposure to inorganic arsenic compounds leading to neurotoxicity of both the peripheral and central nervous systems usually begins with sensory changes, paresthesia, and muscle tenderness, followed by weakness, progressing from proximal to distal muscle groups (ATSDR, 2007; Rodriguez et al., 2003). The sensory nerves are more sensitive, and neurons with large axons are more affected than those with short axons. Peripheral neuropathy is dose-dependent and may be progressive, involving both sensory and motor neurons and leading to demyelination of long axon nerve fibers.

In one report of chronic exposure to arsenic via contaminated well water, disturbances such as forgetfulness, confusion, and abnormal visual sensations were associated with a urinary arsenic of 488 μg/l, and peripheral neuropathy was diagnosed in another individual with 2260 μg As/l (Rodriguez et al., 2003). Occupational exposure to arsenic compounds has been associated with impairments of higher function, such as concentration, short-term memory, and learning (ATSDR, 2007; Rodriguez et al., 2003). Severity was associated with the duration of exposure, and most symptoms disappeared after exposure ceased.

Studies in rodents administered arsenic trioxide (As_2O_3) or sodium arsenite ($NaAsO_2$) orally have shown deficits in behavior, learning, and memory after 2 weeks to 3 months at doses that were not systemically toxic (Rodriguez et al., 2003).

Neurotoxicity in children and the developing nervous system

With acute exposures, children exhibit symptoms similar to those observed in adults. For chronic environmental exposures, children experience the same neurological effects as adults. In areas of endemically high arsenic in drinking water, arsenic concentrations in the human placental cord blood can be about as high as those in maternal blood (Concha et al., 1998), thus additional effects following exposure of the developing nervous system could be anticipated.

Several epidemiological studies of environmental arsenic exposure have evaluated neurotoxicity endpoints. A study of 720 children in China, aged 8 to 12 years, revealed decreased IQ scores with increased concentrations of arsenic in the drinking water (Wang et al., 2007). The mean IQ score in the control group (2 μg As/l water) was 105, and it was 101 and 95 for the medium (142 μg As/l) and high (190 μg As/l) arsenic exposed groups, respectively. These decreases were similar to those observed in a study of 201 10-year old children in Bangladesh (Wasserman et al., 2004) and in two small studies in Mexico (Calderon et al., 2001) and Taiwan (Tsai et al., 2003). Many factors affect IQ scores; decreasing scores from several studies are supportive but not conclusive evidence of a real effect. Other epidemiological studies of arsenic exposure via

drinking water have not shown significant neurological effects, possibly as the result of confounding due to the inability to quantify past exposure (ATSDR, 2007). Hearing impairment has also been associated with airborne arsenic in chronically exposed 10-year-old children.

The physical malformations reported in animal studies have not been reported for humans exposed to equally high blood arsenic concentrations from contaminated drinking water. The differences between animal studies and the human experience may be due to the form of the arsenic. In humans, the organic arsenic metabolite dimethylarsenic acid (DMA) predominates with chronic exposure. DMA has been shown to be less toxic than inorganic As^{3+} compounds in developmental animal studies, which may explain the lack of malformations in humans.

Mechanisms of action

A number of mechanisms have been proposed for the ability of arsenic to cause such diverse adverse effects. These include alterations in cell signaling, cell cycle control, oxidative stress, DNA repair, and others. Arsenic binds to a number of sulfhydryl-containing proteins and enzymes, including mitochondrial enzymes, resulting in impaired tissue respiration, which is related to the cellular toxicity of arsenic. Arsenic also inhibits mitochondrial energy-linked functions by competition with phosphate during oxidative phosphorylation and inhibition of mitochondrial adenosine triphosphate (ATP) production, resulting in increased ROS generation (Hughes, 2002).

Disruption of hormone signaling may be a key component of arsenic-induced developmental effects. Arsenic alters steroid hormone receptor (SHR)-mediated gene regulation at very low, environmentally relevant concentrations in cell cultures and animal models (Bodwell et al., 2004, 2006; Davey et al., 2007). All five SHRs (i.e., glucocorticoid, androgen, progesterone, mineralocorticoid, and estrogen hormones) are affected in a similar manner, suggesting a broad effect on these pathways, and also suggesting a common mechanism for these effects. Additional work is needed to elucidate endocrine disruption effects in the etiology of arsenic-induced neurotoxicity.

Section Summary

- Lead produces neurotoxic effects ranging from fatigue and confusion to encephalopathy at acute high-level exposures. Chronic lower-level exposures can result in cognitive deficits and peripheral neuropathy. Children are more sensitive than adults. Exposure of the developing nervous system can produce long-lasting neurological effects, including cognitive deficits.
- Mercury causes neurotoxic effects following acute high-level exposure and chronic low-level exposures in children and adults. The major source of exposure is from methylmercury in food. Paresthesia of the hands and feet is often the first manifestation of CNS effects in adults and children. Severe poisonings proceed to psychoses, paralysis, coma, and death. Neurodevelopmental effects at high exposure levels are undisputed. Neurodevelopmental effects following chronic low-level exposure are less conclusive but there are sufficient studies to suggest adverse effects on cognition, attention, and motor function.
- Arsenic causes acute neurotoxicity in adults and children at high exposures. Chronic exposure at significant levels is generally through contaminated drinking water and can induce neurotoxicity that first manifests as sensory changes that may progress to peripheral neuropathy. Neurodevelopmental studies of chronic exposure to low to moderate arsenic levels have been complicated by the inability to determine past exposure. There is suggestive evidence from several studies showing decreased IQ scores of children.

Recommended Readings

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