



Bioaccumulation of persistent toxic substances and its implication in human health -a review

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ABSTRACT

Anthropogenic activities such as pesticide use, coal-burning, and manufacturing introduce harmful substances that have high resistance to degradation by abiotic and biotic factors, and as such persist in the environment. They build up in the environment when decomposers are unable to break them down. Plants and fish take up these substances which are then transferred along the food chain until they reach the highest trophic level. These substances are collectively known as Persistent bioaccumulative toxic substances (PBTs). They typically accumulate in fatty tissues of humans and other species and are slowly metabolized, often increasing in concentration within the food chain. PBTs have been linked to a range of adverse effects in humans, including nervous system disorders, reproductive and developmental problems, cancer, gene mutation, alteration of sexual characteristics and other hormonal functions.

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Introduction

Chemicals encountered in the environment can find their way into plants and animals, and into humans. Most of the chemicals taken in by humans either from eating, drinking, breathing or even touching, are broken down and excreted or exhaled; however some substances are not broken down or excreted so readily leading to their build up and storage in fatty tissue. This process is known as bioaccumulation (USEPA, 2010). As the concentrations increase, a health risk could arise no matter whether the substance is "foreign" to the body (like lead or mercury) or whether it is needed by the body at lower concentrations (like vitamins or trace elements, e.g., selenium) (Barron, 1995).

Many human activities such as the use of pesticides and coal-burning introduce harmful substances including Dichlorodiphenyltrichloroethane (DDT), methyl-mercury and other organic chemicals into the environment, especially in aquatic ecosystem. These substances are not degraded easily into non-harmful metabolites in the environment and are collectively known as Persistent bioaccumulative toxic substances, or PBTs (Detzell *et al.*, 1994; UNEP, 2005). Pollution of the aquatic ecosystem with persistent bioaccumulative toxic substances is growing at an alarming rate and has become an important worldwide problem with increase in population, urbanization, industrialization and agricultural practices aggravating the situation (USEPA, 2010).

Extensive damage to organisms and declines in wildlife populations have been observed together with long-term bioaccumulation and biomagnifications of PBTs, with substantial evidences supporting long-term harm to human health and the environment (Mitrou *et al.*, 2001).

Bioaccumulation

Bioaccumulation is defined as the process by which organisms accumulate chemicals both directly from the abiotic environment (i.e., water, air, soil) and from dietary sources (trophic transfer) (Barron, 1995). It refers to the gradual build-up of pollutants in living organisms. It occurs when an organism absorbs a toxic substance at a rate greater than that at which it is

lost, degraded, or metabolized (Beek, 2000; USEPA, 2010). Once absorbed, the chemical must accumulate in the body to sufficient levels to elicit toxicity. PBTs are largely taken up by organisms through the process of passive diffusion. Primary sites of uptake include membranes of the lungs, gills, and gastrointestinal tract (USEPA, 2010).

Aquatic organisms pass tremendous quantities of water across their respiratory membranes (i.e., gills) allowing for the efficient extraction of PBTs from the water (Hutzinger, 1980^b). Plants also take up PBTs through their root systems and across their leaf cuticles. The mechanisms by which plants take up systemic pesticides and herbicides, which become distributed within the plant, have been studied very intensively (Beek, 2000).

Bioaccumulation Process

Bioaccumulation is a normal and essential process for the growth and nurturing of organisms. All animals, including humans, daily bioaccumulate many vital nutrients, such as vitamins A, D and K, trace minerals, and essential fats and amino acids. However, emphases are placed on the bioaccumulation of toxic substances to levels in the body that can cause harm. Bioaccumulation is the net result of the interaction of uptake, storage and elimination of a chemical (Beek, 2000; USEPA, 2010).

Uptake

The absorption of toxic chemicals from the environment into an organism's cells is known as uptake. The movement of chemicals is usually from a region of higher concentration to that of a low concentration. The chemical potential which is the force of pressure tends to move a chemical from the outside to the inside of an organisms' body (Beek, 2000). A number of factors may increase the chemical potential of certain substances. For example, some chemicals do not mix well with water. They are called lipophilic, meaning "fat loving," or hydrophobic, meaning "water hating." In either case, they tend to move out of water and enter the cells of an organism, where there are lipophilic microenvironments (Beek, 2000; USEPA, 2010).

Storage

Chemicals which are attracted to certain tissues, organs or organelles in the body; bind to proteins or dissolves in fats are temporarily stored in those sites (Beek, 2000; Mitrou *et al.*, 2001). One factor important in storage is water solubility and compounds that are highly water soluble have a low potential to be stored (or bioaccumulate) and do not leave water readily to enter the cells of an organism and once inside the organism, they are easily removed unless the cells have a specific mechanism for retaining them (Hutzinger, 1980^a). Heavy metals like mercury, copper, cadmium, lead; and certain other water-soluble chemicals are such an exception, because they bind tightly to specific sites within the body and accumulate there despite their water solubility. Similar accumulation processes occur for mercury, (Mitra, 1986).

Many fat-loving (lipophilic) chemicals pass into organism's cells through the fatty layer of cell membranes more easily than water-soluble chemicals. Once inside the organism, these chemicals may move through numerous membranes until they are stored in fatty tissues and begin to accumulate (Beek, 2000; Mitrou *et al.*, 2001).

Elimination

Another factor affecting bioaccumulation is whether an organism can break down and/or excrete a chemical. Metabolism varies among individual organisms and species and also depends on characteristics of the chemical itself (Hutzinger, 1980^a). Chemicals that dissolve readily in fat but not in water tend to be more slowly eliminated by the body and thus have a greater potential to accumulate (Beek, 2000).

Types of Bioaccumulation

Organismal bioaccumulation

This is a type of bioaccumulation in which compounds present in an organism's environment concentrate in the body of the organism over time. For example, fishes that swim frequently in contaminated water may build up pollutants in their fatty tissues (USEPA, 2010).

Trophic transfer bioaccumulation

This involves the transfer of chemicals/compounds from one organism to another (e.g. from prey to predator). The more preys that are eaten, the greater the magnification of the compound as it travels up the food chain. As such organisms at the top of the food chain including humans can receive the highest concentration of the chemical (Beek, 2000; USEPA, 2010).

Soil Bioaccumulation

Persistent bioaccumulative toxic substances (PBTs) that are dumped into surrounding environments from specific waste sites or that leak from specific factories are point-source pollutants. Often, these substances bind to soil particles and persist until they are removed through erosion, water percolation, or uptake by plants, microorganisms or animals in soils or sediments. Soil bioaccumulation is often the initial source of PBT exposure for terrestrial organisms (Detzell *et al.*, 1994; Robertson and Hansen 2001).

Sources of Persistent Bioaccumulative Toxic Substances

Worldwide, all industrial sectors use chemicals, but certain sectors are more likely to release PBTs. Environmental sources of PBTs can be categorized as either point sources or nonpoint sources. Point sources are discrete discharges of chemicals that are usually identifiable and measurable, such as industrial or municipal effluent/outfalls, chemical or petroleum spills and dumps, smokestacks and other stationary atmospheric discharges. Nonpoint sources are more diffuse inputs over large areas with no identifiable single point of entry such as

agrochemical (pesticide and fertilizer) runoff, mobile sources emissions (automobiles), atmospheric deposition, desorption or leaching from very large areas (contaminated sediments or mine tailings), and groundwater inflow (Schnoor, 1996).

Table 1. Common sources of PBTs to the environment

Sources	Contaminants
Mining and mineral processing	Heavy metals, hydrocarbon products resulting from spills and coal mining, and metallic salts.
Fossil fuel combustion	Polycyclic aromatic hydrocarbons and volatile organic compounds
Agriculture and forestry	Pesticides, green house gases, and mineral salts
Industrial production	Numerous synthetic organic and inorganic compounds, dioxins, heavy metals, organochlorines, hydrocarbons, chlorinated phenols, plastics, Pharmaceuticals, resins, surfactants, explosives, and natural organics.
Consumerism	Residential and commercial chemicals, pesticides, fertilizers, paints, hydrocarbons, solvents, medicines, volatile organic compounds, resins, Plastics and metals.

Source: United Nations Environmental Programme, 2005

After a pollutant is released from a source, it may act upon a receptor (elicit its effects on an organism) or may be deposited in a long-term sink such as aquatic sediments and soils (Hemond and Fechner, 1994; Schnoor, 1996).

A major concern with some PBTs is the ease with which they can move through the environment. PBTs make their way into remote regions by traveling long distances in a series of "hops" involving a complex cycle of long-range atmospheric transport, deposition and re-volatilization, collectively called the "grasshopper effect." Eventually, they accumulate in cold regions by a process called "global distillation" (Hemond and Fechner, 1994; Schnoor, 1996).

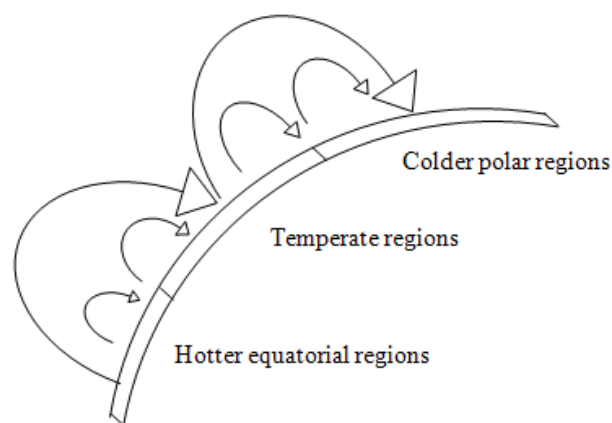


Figure 1. The grasshopper effect and global distillation (UNEP, 2010)

Factors Affecting Bioaccumulation of Persistent Toxic Substances

The propensity for an environmental contaminant to bioaccumulate is influenced by several factors. These factors include environmental persistence, bioavailability, lipophilicity, half life of the chemical, and the bioaccumulation factor of the chemical (LeBlanc, 1995).

Environmental persistence

The degree to which a chemical can bioaccumulate is dictated by the concentration present in the environment (UNEP,

2005). Contaminants that are readily eliminated from the environment will generally not be available to bioaccumulate. An exception would be instances where the contaminant is continuously introduced into the environment. PBTs resist degradative processes and accordingly persist in the environment for extremely long periods of time. Continued disposal of persistent toxic chemicals into the environment can result in their accumulation to environmental levels sufficient to pose toxicity. Such chemicals can continue to pose hazard long after their disposal into the environment has ceased.

Bioavailability

This is the tendency of a substance to enter an organism's system upon exposure. It describes the process by which toxic substances in water traverse fish gill epithelium and are transported by the blood through highly vascularized tissues to lipid tissue, which serves as a storage sink for hydrophobic substances. (Barron, 1990; LeBlanc, 1995).

Lipophilicity

The lipid solubility also influences the bioaccumulation of PBTs in an organism. Aquatic organisms can bioaccumulate lipophilic chemicals and attain body concentrations that are several orders of magnitude greater than the concentration of the chemical found in the environment. The degree to which aquatic organisms accumulate PBTs from the environment is largely dependent on the lipid content of the organism, since body lipids serve as the primary site of retention of the chemicals (Mitrou *et al.*, 2001).

Half life of the substance

The time between uptake and eventual elimination of a chemical directly affects bioaccumulation. The Half-life of a substance is the time it takes for the amount of the substance to decrease by half. If a pollutant is short-lived (short half life), it will be broken down before it can become dangerous. Persistent bioaccumulative toxic substances (PBTs) possess very long half life and as a result their degradation takes several years, enabling them to accumulate in the environment and in tissues of organisms (USEPA, 2012^a).

Bioaccumulation factor

Bioaccumulation factor is defined as the ratio of the chemical concentration in the organism (e.g., fish) and in the surrounding (water) at steady-state equilibrium. Persistent bioaccumulative toxic substances (PBTs) have high bioaccumulation factor and as a result are able to build up in fatty tissues of fish and other terrestrial organisms (LeBlanc, 1995).

Effects of persistent bioaccumulative toxic substances on human health

Heavy metals that can bioaccumulate and cause health problems in humans include cadmium, lead and mercury (Johnels and Westermarck, 1969; Goyer and Clarkson, 2001). Other PBTs implicated in human health include industrial chemicals such as organochlorine compounds [e.g. Dioxins, Polychlorinated Biphenyls, polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and tetrachlorodibenzo-*p*-dioxin (TCDD)] and agricultural chemicals such as Dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, chlordane, heptachlor and Hexachlorobenzene (Ecobichon, 2001, USEPA, 2012^b, Turgut *et al.*, 2009, USEPA, 2012^a, Carpenter, 2006). The various effects of PBTs include:

Interference with Enzyme Action

Enzymes are extremely important because they must function properly to enable essential metabolic processes to occur in cells. Substances that interfere with the proper action of enzymes obviously have the potential to be toxic (Mailman and

Lawler, 2001). Many xenobiotics that adversely affect enzymes are **enzyme inhibitors**, which slow down or stop enzymes from performing their normal functions as biochemical catalysts (Zoltán and Klaassen, 2001). The body contains numerous endogenous enzyme inhibitors that serve to control enzyme catalyzed processes. When a toxicant acts as an enzyme inhibitor, however, an adverse effect usually results. An important example of this is the action of ions of heavy metals, such as mercury (Hg^{2+}), lead (Pb^{2+}), and cadmium (Cd^{2+}), which have strong tendencies to bind to sulfur-containing functional groups, especially $-\text{SS}-$, $-\text{SH}$, and $-\text{S}-\text{CH}_3$ (Zoltán and Klaassen, 2001). These functional groups are often present on the active sites of enzymes, which, because of their specific three-dimensional structures, bind with high selectivity to the substrate species upon which the enzymes act. Toxic metal ions may bind strongly to sulfur-containing functional groups in enzyme active sites, thereby inhibiting the action of the enzyme (Mailman and Lawler, 2001; Zoltán and Klaassen, 2001).

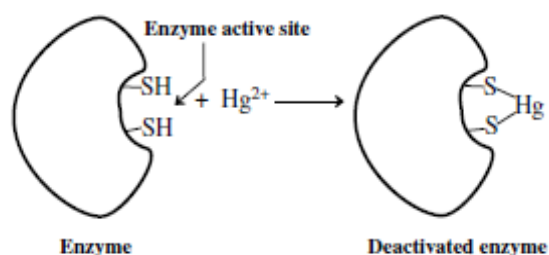


Figure 2. Enzyme inhibition by Hg^{2+} ion binding to sulfhydryl groups on an enzyme active site

Inhibition of Metalloenzymes

Substitution of foreign metals for the metals in metalloenzymes is an important mode of toxic action by metals (Mailman and Lawler, 2001). A common mechanism for cadmium toxicity is its substitution for zinc which is present in many metalloenzymes. This substitution occurs readily because of the chemical similarities between the two metals (for example, Cd^{2+} and Zn^{2+} behave alike in solution), and thus results in toxic effects (Timbrell, 1982). Some enzymes that are affected adversely by the substitution of cadmium for zinc are alcohol dehydrogenase and carbonic anhydrase. Another example is the displacement of zinc by lead in the zinc-dependent enzyme δ -aminolevulinic acid dehydratase (ALAD), thereby inhibiting the synthesis of heme, an important component of hemoglobin and heme-containing enzymes, such as cytochromes (Thayer, 1995).

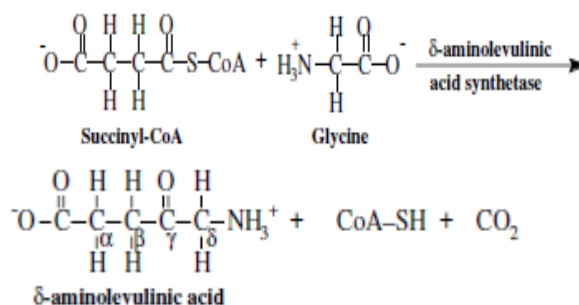


Figure 3. Path of synthesis of delta-aminolevulinic inhibited by Cadmium

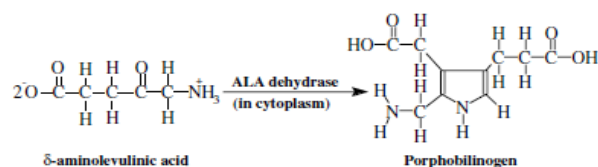


Figure 4. Synthesis of porphobilinogen from delta-aminolevulinic acid, a major step in the overall scheme of heme synthesis that is inhibited by lead in the body

Effect on Subcellular Organelle

Toxic metals may disrupt the structure and function of a number of organelles. For example, enzymes associated with the endoplasmic reticulum may be inhibited, metals may be accumulated in the lysosomes, respiratory enzymes in the mitochondria may be inhibited, and metal inclusion bodies may be formed in the nucleus (Thayer, 1995). Lead is taken up readily by the proximal tubule cells where it damages the mitochondria and inhibits mitochondria function, thereby altering the normal absorptive function of the cells of the proximal tubules (Thorne, 2001). Cadmium becomes localized in the lysosome of the proximal tubule cells of the kidney, inhibits the enzymes and thereby affecting the overall action of the cells (e.g. cell injury and loss of protein in the urine) (Thayer, 1995; Thorne, 2001). Mercury binds strongly to the –SH group of enzymes in the membrane of the proximal tubule cells thereby inhibiting the reabsorption of sodium and proteins by the proximal tubule cells and thus causing loss of protein in the urine-proteinuria (Thorne, 2001).

Ion Channel Modulators

Ion transport is central to nerve impulse transmission both along the axon and at the synapse. Many neurotoxicants elicit their effects by interfering with the normal transport of these ions (Hutzinger *et al.*, 1982). Neurotoxicity refers to the ability of an agent to adversely affect the structural or functional integrity of the nervous system. Alterations in nervous system function may occur through toxicant interactions with the normal signaling mechanisms of neurotransmission, resulting in little or no structural damage (Blake *et al.*, 2001). The action potential of an axon is maintained by the high concentration of sodium on the outside of the cell as compared to the low concentration inside. Active transporters of sodium (Na^+K^+ ATPases) that actively transport sodium out of the cell establish this action potential (Blake *et al.*, 2001). One action of the insecticide DDT resulting in its acute toxicity is the inhibition of the Na^+K^+ ATPases resulting in the inability of the nerve to establish an action potential. DDT also inhibits $\text{Ca}^{2+}\text{Mg}^{2+}$ ATPases, which are important to neuronal repolarization and the cessation of impulse transmission across synapses (Blake *et al.*, 2001; USEPA, 2012^b).

The gamma-aminobutyric acid (GABA_A) receptor is associated with chloride channels on the postsynaptic region of the neuron and binding of GABA_A to the receptor causes opening of the chloride channel. This occurs after transmission of the nerve impulse across the synaptic cleft and postsynaptic depolarization. Thus activation of GABA_A serves to prevent excessive excitation of the postsynaptic neuron. Many neurotoxicants function by inhibiting the GABA_A receptor, resulting in prolonged closure of the chloride channel and excess nerve excitation. Cyclodiene insecticides (i.e., dieldrin), the organochlorine insecticide lindane, and some pyrethroid insecticides all elicit acute neurotoxicity, at least in part, through this mechanism. Symptoms of GABA_A inhibition include dizziness, headache, nausea, vomiting, fatigue, tremors, convulsions, and death (Blake *et al.*, 2001).

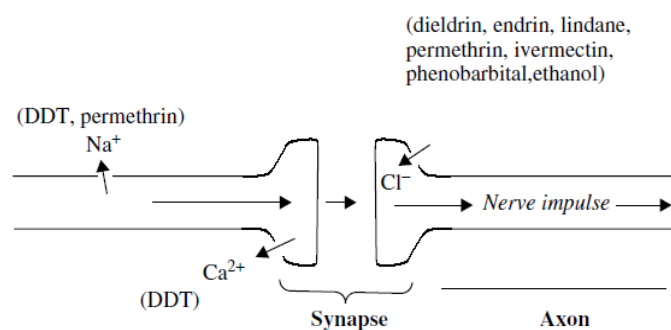


Figure 5. Ion channels that facilitate nerve impulse transmission which are susceptible to perturbation by various toxicants and drugs

Carcinogenicity

Cancer is the uncontrolled proliferation of cells of the body caused by chemical (carcinogens), physical (radiation, X-rays, UV light), and biological agents (viruses). A carcinogen is an agent that causes or induces neoplasia (Pitot and Dragon, 2001). Most carcinogens react with the growth control genes of the DNA of cells, causing mutations that lead to cancer. Other carcinogens cause cancer through other mechanisms that do not involve DNA. Some of these cause hormonal imbalances that cause rapid cell proliferation. One example is DDT which mimics the actions of the hormone estrogen (Pitot and Dragon, 2001). Estrogen stimulates cell division in the breasts and uteri of women. DDT is thought to cause certain forms of breast and uterine cancer. A number of metals have been shown to be carcinogenic in humans or animals. The carcinogenic action, in some cases, is thought to result from the interaction of the metallic ions with DNA (McKinney, 1981).

Effect on the Kidney

The kidney and bladder are very important in toxicology because they are the main route of elimination of hydrophilic toxicant and metabolites. Also damage to them in the form of impaired kidney function or bladder cancer is one of the major adverse effects of toxicants (Zoltán and Klaassen, 2001). Many heavy metals are potent nephrotoxicants, and relatively low doses can produce toxicity characterized by glucosuria, aminoaciduria, and polyuria. As the dose increases, renal necrosis, anuria, increased BUN, and death will occur (Schnellmann, 2001). Several mechanisms operate to protect the kidney from heavy metal toxicity. After low dose exposure and often before detectable signs of developing nephrotoxicity, significant concentrations of metal are found bound to renal lysosomes. This incorporation of metals into lysosomes may result from one or more of several mechanisms, including lysosomal endocytosis of metal-protein complexes, autophagy of metal-damaged organelles such as mitochondria, or binding of metals to lipoproteins within the lysosome. Exposure to high concentrations, however, may overwhelm these mechanisms, resulting in tissue damage (Goldstein and Schnellmann, 2001).

In humans, **Cadmium** is excreted in the urine mainly as a complex (CdMT) with the protein metallothionein (MT). MT is a low molecular weight protein synthesized in the liver and contains a large number of sulfhydryl groups that bind certain metals, including cadmium (Thayer, 1995). The binding of cadmium by MT appears to protect some organs such as the testes from cadmium toxicity. At the same time, however, the complex may enhance kidney toxicity because the complex is taken up more readily by the kidney than is the free metal ion (Schnellmann, 2001). Once inside the cell, it is thought that the cadmium is released, presumably by decomposition of the complex within the lysosomes. Cadmium has a long biological

half-life, 10 to 12 years in human kidney; thus low-level chronic exposure will eventually result in accumulation to toxic concentrations (Goldstein and Schnellmann, 2001).

Lead, as Pb^{2+} , is taken up readily by proximal tubule cells, where it damages mitochondria and inhibits mitochondrial function, altering the normal absorptive functions of the cell (Tarloff, 2001). Complexes of lead with acidic proteins appear as inclusion bodies in the nuclei of tubular epithelium cells (Porter, 1982).

Mercury exerts its principle nephrotoxic effect on the membrane of the proximal tubule cell. In low concentrations, mercury binds to the sulfhydryl groups of membrane proteins and acts as a diuretic by inhibiting sodium reabsorption (Porter, 1982; Tarloff, 2001). More recently organomercurial chemicals have been implicated as environmental pollutants, responsible for renal damage in humans and animals (Schnellmann, 2001; Tarloff, 2001).

Effect on the Nervous System

The nervous system is also a common target for toxic metals; particularly, organic metal compounds (Blake *et al.*, 2001). For example, methyl mercury readily crosses the blood-brain barrier and enters the nervous system. Inorganic lead also causes direct damage to myelinating cells. Oligodendrocytes appear more sensitive to lead toxicity than astrocytes or neurons. One mechanism for the devastating developmental effects of lead exposure may be the preferential inhibition of oligodendrocyte precursor (Blake *et al.*, 2001; Goyer and Clarkson, 2001). Lead readily crosses the placenta and in children, it penetrates the blood-brain barrier. It damages the arterioles and capillaries in the brain resulting in cerebral edema and neuronal degeneration (interferes with the function of neurotransmitters, including dopamine and GABA_A, and slows the function of neurotransmitters). This effect is fatal in infants and young children (Thorne, 2001).

Methyl mercury preferentially accumulates in astrocytes and to some extent in microglia, causing cellular swelling. The swelling is presumably the effect of methyl mercury interfering with ion channels (Blake *et al.*, 2001). Astrocytes are important reservoirs of excess glutamate, and swollen astrocytes release glutamate in and around synapses, potentially causing excitotoxicity. Astrocyte swelling also has effects on brain blood flow by increasing the distances substrates and waste products must diffuse to reach the bloodstream (Blake *et al.*, 2001; LeBlanc and Bain, 1997). Methyl mercury generally damages the blood-brain barrier and interferes with the regulation and transfer of metabolites such as amino acid to and from the brain thereby disrupting brain metabolic processes. Signs include tremor, ataxia, emotional instability such as irritability and lack of concentration (Blake *et al.*, 2001; Thayer, 1995).

Endocrine and Reproductive Effects

An endocrine disruptor has been broadly defined as an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones responsible for the maintenance of homeostasis and the regulation of developmental processes (Colburn *et al.*, 1993). Suspected endocrine-disrupting chemicals are found in insecticides, herbicides, fumigants, and fungicides that are used in agriculture as well as in the home. Other endocrine disruptors are found in industrial chemicals such as detergents, resins, plasticizers, organometals, halogenated aromatic hydrocarbons, and monomers in many plastics (Ecobichon, 2001; Krieger, 2001).

Xenobiotics have the ability to disrupt hormone activity through a variety of mechanisms, though the predominant

mechanisms appear to involve binding to the hormone receptor, either as an agonist or antagonist, or by modulating endogenous steroid hormone levels (Mailman and Lawler, 2001). Hormone receptor agonists “are compounds that bind to and activate a hormone receptor” and stimulate receptor-dependent physiological processes in the absence of the endogenous receptor ligand (hormone). Such inappropriate stimulation can result in the errant expression of hormone-dependent processes such as breast development in males (Mailman and Lawler, 2001). Receptor antagonists are defined as chemicals that bind to a hormone receptor but do not activate the receptor. Rather, these chemicals inhibit receptor activity by preventing the endogenous hormone from binding to and activating the receptor (Hutson *et al.*, 1989).

Effects on estrogen receptor

The estrogen receptor appears most susceptible to the action of xenobiotics. PCBs are example of environmental estrogen receptor antagonists. Consequences of estrogen receptor antagonism are typically considered de-feminization (loss of female traits) (Colburn *et al.*, 1993). In laboratory animal studies, estrogen receptor antagonists have been shown in females to disrupt estrous cycles, impair fertility, increase pre-implantation loss, and cause embryo lethality (McKinney, 1981).

Effect on androgen Receptor

Environmental chemicals that have been shown to act as androgen receptor antagonists include the agricultural pesticide DDT metabolite *p*, *p*-DDE, and some hydroxylated PCBs. The consequence of androgen receptor antagonism is typically considered demasculinization (loss of male traits). Demasculinizing effects of androgens antagonist in laboratory animal studies have included reductions in the size of the ventral prostate and seminal vesicle weights along with deformities of the penis (McKinney, 1981).

Inducers of Hormone Clearance

In most species, steroid and thyroid hormones are inactivated and cleared from the body by the same biotransformation processes that are involved in chemical detoxification (Hodgson and Goldstein, 2001; Hutson *et al.*, 1989). Predominant among the hormone biotransformation processes in vertebrates are hydroxylation, glucuronic acid conjugation, and sulfate conjugation (LeBlanc and Dauterman, 2001). The thyroid hormones T3 and T4 are inactivated and cleared following sulfate and glucuronic acid conjugation, respectively. The glucuronosyl transferase enzymes that are responsible for the elimination of T4 are induced following exposure to Phenobarbital type inducers and Ah receptor ligands (Hodgson and Goldstein, 2001). Thus exposure to chemical such as some dioxins and PCBs can result in enhanced clearance of thyroid hormone resulting in low circulating thyroid hormone levels. The resulting hypothyroid state can result in a variety of pathological conditions (Colburn *et al.*, 1993; McKinney, 1981). In newborn infants, hypothyroidism is associated with cretinism. This organizational syndrome is characterized by mental retardation, short stature, and various neurological abnormalities. In children, hypothyroidism can cause delayed growth and mental development while advancing the onset of puberty in adolescents. Hypothyroidism in adults results activation of various abnormalities including impaired cardiovascular, pulmonary, intestinal, and renal function. Chronic fatigue, lethargy, and difficulty in concentration are also associated with hypothyroidism in adults (McKinney, 1981). Increased clearance of steroid hormones due to induction of hepatic biotransformation enzymes following chemical

exposure often has been cited as a possible mechanism by which toxicants could lower circulating testosterone or 17 β -estradiol levels (Colburn *et al.*, 1993; McKinney, 1981).

Enhanced clearance of sex steroids can contribute to endocrine disruption if the toxicity also results in impaired hormone synthesis (i.e., gonadal toxicity or interference with the feedback control of hormone synthesis). 2,3,7,8-Tetrachlorodibenzodioxin appears to lower circulating sex steroid levels via this dual effect (Zoltán and Klaassen, 2001). Cadmium is known to produce testicular injury after acute exposure (Thayer, 1995), and lead accumulation in the testes is associated with testicular degeneration, inhibition of spermatogenesis, and Leydig-cell atrophy (Hernberg, 2000). Because the male and female reproductive organs are under complex neuroendocrine and hormonal control, any toxicant that alters any of these processes can affect the reproductive system (LeBlanc and Bain, 1997).

Conclusion

Persistent bioaccumulative toxic substances (PBTs) have been demonstrated to cause a variety of serious health effects. Some Persistent bioaccumulative toxic substances have been shown to cause cancer and a number of serious non-cancer health effects in animals, including effects on the immune system, reproductive system, nervous system, excretory system, and endocrine system. Studies in humans provide supportive evidence for the potential carcinogenic and non-carcinogenic effects of persistent bioaccumulative toxic substances. The different health effects of PBTs may be interrelated, as alterations in one system may have significant implications for the other regulatory systems of the body. PBTs are a unique classification of chemicals that have and will continue to impact human health and the environment worldwide due to their environmental persistence, lipophilicity, and longer biological half-life.

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