

REVIEW ARTICLE

Exposure to lipophilic chemicals as a cause of neurological impairments, neurodevelopmental disorders and neurodegenerative diseases

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ABSTRACT

Many studies have associated environmental exposure to chemicals with neurological impairments (NIs) including neuropathies, cognitive, motor and sensory impairments; neurodevelopmental disorders (NDDs) including autism and attention deficit hyperactivity disorder (ADHD); neurodegenerative diseases (NDGs) including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). The environmental chemicals shown to induce all these diseases include persistent organic pollutants (POPs), the plastic exudates bisphenol A and phthalates, low molecular weight hydrocarbons (LMWHCs) and polynuclear aromatic hydrocarbons (PAHs). It is reported here that though these chemicals differ widely in their chemical properties, reactivities and known points of attack in humans, a common link does exist between them. All are lipophilic species found in serum and they promote the sequential absorption of otherwise non-absorbed toxic hydrophilic species causing these diseases.

KEY WORDS: neurological disease; Alzheimer's disease; Parkinson's disease; autism; ADHD; lipophilic chemicals; toxic chemicals

Introduction

Neurological impairments (NIs), neurodevelopmental diseases (NDDs) and neurodegenerative diseases (NDGs) continue to increase dramatically worldwide. From 1990 to 2010, mental and behavioral disorders increased by more than 37%, Parkinson's disease increased by 75%, Alzheimer's disease doubled, autism increased by 30% and attention deficit hyperactivity disorder (ADHD) increased by 16% (Murray *et al.*, 2012; Vos, *et al.*, 2012). The increases in many epidemic and pandemic diseases, including neurological disorders, have been attributed to environmental exposures to exogenous toxic chemicals. The World Health Organization estimates that "as much as 24% of environmental disease is caused by environmental exposures that can be averted" (WHO, 2006).

Previously reported results have demonstrated the connection between lipophilic chemical exposure and type 2 diabetes (Zeliger, 2013b) and also with a cardiovascular disease (Zeliger, 2013a). It is reported here that such a connection also exists between lipophilic exposure and neurological impairments, neurodevelopmental diseases and neurodegenerative diseases.

It has been previously shown that mixtures of lipophilic and hydrophilic chemicals are toxic to humans at concentrations that are far below those known to be toxic for each of the components of such mixtures alone (Zeliger, 2003; Zeliger, 2011).

It has also been previously reported that exposures to the hydrophilic and lipophilic chemicals need not occur simultaneously but can occur sequentially, with the lipophilic substance exposure coming first and the hydrophilic exposure occurring some time later, provided that the lipophilic species is still retained in the body (Zeliger *et al.*, 2012). Such a sequential phenomenon has been demonstrated for the induction of type 2 diabetes (Zeliger, 2013b) and of a cardiovascular disease (Zeliger, 2013a). The case for such a mechanism for the induction of neurological disorders is proposed here.

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The lipophiles associated with induction of neurological disorders can be long-lived persistent organic pollutants (POPs), which once absorbed can remain in the body's adipose tissue for up to 30 years or more and can be transferred to serum (Yu *et al.*, 2011). The lipophiles can also be intermediate-lived species, including polynuclear aromatic hydrocarbons (PAHs), bisphenol A (BPA) and phthalates, which can remain in the body for days or weeks (Stahlhut *et al.*, 2009; Kessler *et al.*, 2012; Li *et al.*, 2012). This applies also to low molecular weight hydrocarbons (LMWHCs), which are retained in body serum for days after absorption (Pan *et al.*, 1987; Zeliger *et al.*, 2012). The serum concentrations of the lower-lived species remain more or less in a steady state due to continuous exposure and absorption (Zeliger *et al.*, 2012), replacing the quantities lost via metabolism and elimination (Baselt, 2000).

Suggested mechanisms of neurotoxic action for some of these chemicals include oxidative stress, epigenetic effects and endocrine disruption (Kodavanti, 2005; Quaak *et al.*, 2013; Patri *et al.*, 2009; Lochhead *et al.*, 2010; Calderon-Garciduenas *et al.*, 2008; Colborn *et al.*, 1997; Patrick, 2009). Yet to date, no one mechanism can account for the neurological toxicity of this group of chemicals which differ widely in structure, chemical properties and reactivity. It is reported here, however, that there is indeed a unifying explanation for the induction of neurological diseases by this diverse group of chemicals. The studies referred to above show that accumulation of all of these chemicals in body serum was associated with increased incidence of neurological impairment, neurodevelopmental and neurodegenerative diseases. All these chemicals are lipophilic and all were shown to accumulate in body serum following exposure to them. Lipophilic chemicals were found to facilitate the absorption of hydrophilic chemicals across the body's lipophilic membranes (Zeliger, 2003; Zeliger, 2011). It is proposed here that the lipophilia of these exogenous chemicals induces neurological disorders by permeating lipophilic membranes, including the blood brain barrier, thus enabling the entry for toxic hydrophilic species that would otherwise not be absorbed.

Methods

The results presented here are based upon the literature review of numerous studies, published both by this author and by others, on toxic effects of the chemicals involved, including case studies and epidemiologic studies. Adverse effects on health were in all instances diagnosed by appropriate clinical examinations and tests and chemical analytical data were generated in accordance with accepted protocols.

The total lipophilic load in serum is postulated as responsible for the induction of cardiovascular diseases (CVD). As used here, total lipophilic load refers to the total concentration of all exogenous lipophilic chemicals found in serum, without specification of individual chemical species.

Results

As discussed below, exposures to POPs, plastic exudates, PAHs and LMWHCs have been found to be associated with neurological disorders. The POPs include polychlorinated biphenyls (PCBs), organochlorine pesticides (OCs), dioxins and furans and polybrominated diphenyl ethers (PBDEs). Plastic exudates include BPA and phthalates. LMWHCs include benzene, toluene, ethyl benzene, xylenes, C3–C8 aliphatics, gasoline, chlorinated methanes and ethanes and chlorinated ethylenes.

POPs, PAHs, LMWHCs, BPA and phthalates all have been shown to penetrate the blood-brain barrier (BBB) (Seelbach *et al.*, 2010; Qiu *et al.*, Escudar-Gilabert *et al.*, 2009; Gupta *et al.*, 1999; 2011; Hartz *et al.*, 2008; Calderon-Garciduenas *et al.*, 2008; Sun *et al.*, 2002; Szychowski & Wojtowicz, 2013).

I. Neurological impairments

NIs associated with lipophilic chemical exposure include central nervous system disorders (cognitive, motor and sensory), as well as peripheral nervous system maladies (neuropathies) (Gamble 2000; Baker 1988; Maruff *et al.*, 1988; Weintraub *et al.*; 2000; Lee *et al.*, 2008b; Sendur *et al.*, 2009; Gupta *et al.*, 2011; Kodavanti, 2005; Patri *et al.*, 2009; Gamble, 2000; White & Proctor, 1997; Burbacher, 1993).

Recent research has shown that neurological impairment prevalence is increased by exposure to a number of different chemicals. These include persistent organic pollutants (POPs) – polychlorinated biphenyls (PCBs) (Kodavanti 2005; Gascon *et al.*, 2013; Faroon *et al.*, 2001; Buters *et al.*, 2007; Fitzgerald *et al.*, 2012; Chia & Chu, 1984); organochlorine pesticides (OCs) (Jurewicz *et al.*, 2013b; Moses *et al.*, 2010; Iwaniuk *et al.*, 2006; Colosio *et al.*, 2003; Lee *et al.*, 2008b); dioxins and furans (Kodavanti 2005), and polybrominated biphenyl ethers (PBDEs) used as fire retardants (Kodavanti 2005; Buters *et al.*, 2007; Fitzgerald *et al.*, 2012; Widholm *et al.*, 2003; Thomke *et al.*, 1999; Michalek *et al.*, 2001; Sweeney *et al.*, 1993); BPA, widely used in the manufacture of plastic food containers and other applications (Viberg *et al.*, 2011; White *et al.*, 1997; Viberg *et al.*, 2012; Yolton 2011); phthalates, widely used as plasticizers for polyvinyl chloride (Jurewicz *et al.*, 2013a; Le Cann *et al.*, 2011; Yolton *et al.*, 2011), which are exuded from plastics; low molecular weight aliphatic and aromatic hydrocarbons (LMWHCs) and their chlorinated products which evaporate from gasoline, adhesives, paints and household products (Viaene, 2002; Maruff *et al.*, 1998; Burbacher, 1993; ATSDR, 2001; Lammers *et al.*, 2011); and polynuclear aromatic hydrocarbons (PAHs) which come from primary and secondary tobacco smoke inhalation and fuel combustion (ATSDR, 1995; He *et al.*, 2012; Patri *et al.*, 2009; Krivoshto *et al.*, 2008).

II. Neurodevelopmental diseases

NDDs associated with lipophilic chemical exposure include autism spectrum disorders (ASD) (Winneke 2011; Roberts *et al.*, 2007; Roberts *et al.*, 2013; Larsson *et al.*, 2010; de Cock *et al.*, 2012; Cheslack-Postova *et*

al., 2013; Quaak *et al.*, 2013; Pessah *et al.*, 2008; Roberts and English 2007; McCanlies *et al.*, 2012; Volk *et al.*, 2011); attention deficit hyperactivity disorder (ADHD) (Polanska *et al.*, 2012; Pessah *et al.*, 2008; Roze *et al.*, 2009; Sagiv *et al.*, 2012; Sagiv *et al.*, 2010; de Cock *et al.*, 2012; Winneke 2011; Lee *et al.*, 2007; Harley *et al.*, 2013; Kim *et al.*, 2009; Quaak *et al.*, 2013); mental retardation (Grandjean & Landrigan, 2006); cerebral palsy (Grandjean & Landrigan, 2006); neural tube defects (Renn *et al.*, 2001; Brender *et al.*, 2010); hearing loss (Weitzman *et al.*, 2013); and other conditions (Eskenazi *et al.*, 2009); (Parron *et al.*, 2011; Loane *et al.*, 2013; Chen *et al.*, 2013; Steenland *et al.*, 2012; Wang, *et al.*, 2011; Dardiotis *et al.*, 2013; Caudle *et al.*, 2012; Weisskopf *et al.*, 2010; Moulton & Yang, 2012; Mayeux & Stern, 2012; Zaganas *et al.*, 2013; Sienko *et al.*, 1990; Vincenti *et al.*, 2012).

III. Neurodegenerative diseases

NDGs associated with lipophilic exposure include Alzheimer's disease (Mates *et al.*, 2010; Chen *et al.*, 2013; Parron *et al.*, 2011; Steenland *et al.*, 2012; Zaganas *et al.*, 2013; Blanc-Lapierre *et al.*, 2012); Parkinson's disease (Caudle *et al.*, 2012; Wang *et al.*, 2011; Fleming *et al.*, 1994; Dardiotis *et al.*, 2013; Blank-Lapierre *et al.*, 2012); ALS (Vincenti *et al.*, 2012; Logroscino *et al.*, 2008; Uccelli *et al.*, 2007; Blanc-Lapierre *et al.*, 2012).

Table 1 summarizes the above findings associating NIs, NDDs and NDGs with the lipophilic chemicals identified as established or suspected causative agents of these diseases.

Discussion

The chemicals that are known to cause neurological diseases include POPs (PCBs, OCs, PBDEs, dioxins,

furans, PFOEs), phthalates, BPA and hydrocarbons. These chemicals come from a variety of chemical classes that include chlorinated and brominated hydrocarbons, esters, ethers, polynuclear aromatic hydrocarbons, mononuclear aromatic hydrocarbons and straight chain aliphatic hydrocarbons. These chemicals differ widely in chemical properties, reactivity and rates of metabolism and elimination from the body.

The lipophiles associated with induction of neurological disorders can be long-lived POPs, which once absorbed can remain in the body's adipose tissue for up to 30 years or more and can be transferred to serum (Yu *et al.*, 2011). The lipophiles can also be intermediate-lived species, including PAHs, BPA and phthalates, which can remain in the body for days or weeks (Stahlhut *et al.*, 2009; Kessler *et al.*, 2012; Li *et al.*, 2012), as well as LMWHCs, which are retained in body serum for days after absorption (Pan *et al.*, 1987; Zeliger *et al.*, 2012). The serum concentrations of the lower-lived species remain more or less in a steady state due to continuous exposure (Zeliger, *et al.*, 2012) and absorption that replaces quantities lost via metabolism and elimination (Baselt, 2000).

Mechanisms by which environmental chemicals trigger neurological diseases have been proposed. These include: oxidative stress (Uttara *et al.*, 2009; Bolanos *et al.*, 2009), epigenetic effects (Jakovcevski & Akbarian, 2012; Urdinguio *et al.*, 2009) and endocrine disruption (Weiss, 2012; Mostafalou & Abdollahi, 2013; Colborn *et al.*, 1997). Compelling evidence has been presented to give validity to these mechanisms in some instances (see for example Urdinguio *et al.*, 2013). Until now, however, no single mechanism that accounts for the induction of a broad spectrum of neurological diseases has been proposed. The association with the onset of widely differing NIs, NDDs and NDGs with exposures to POPs, BPA, phthalates, PAHs and LMWHCs, chemicals which differ widely from

Table 1. Neurological disorders associated with lipophilic chemical exposures.

	POPS				PLASTIC EXUDATES		HYDROCARBONS	
	PCBs	OCs	PBDEs	Dioxins/ Furans	phthalates	BPA	PAHs	LMWHCs
NI								
Cognitive effects	*	*	*	*	*	*	*	*
Motor deficits	*	*	*		*		*	*
Sensory deficits	*	*	*	*			*	*
Peripheral NS effects	*	*		*			*	*
NDD								
Autism	*	*	*		*	*	*	
ADHD	*	*	*	*	*	*	*	
NDG								
Alzheimer's disease		*		*	**	**	*	
Parkinson's disease	*	*	*	*	**	**	*	*
ALS		*		*				

* established relationship; ** suspected relationship

each other, yet all of them are able to penetrate the blood-brain barrier, strongly suggests a lipophile-dependent mechanism for the induction of CVDs. The concept of lipophilic chemicals serving to assist the penetration of hydrophilic therapeutic drugs through the blood-brain barrier is well established (Pardridge, 2012; Patel *et al.*, 2009; Filmore, 2002; Seelig *et al.*, 1994), lending credence to the mechanism suggested here.

It has been previously shown that mixtures of toxic chemicals containing at least one lipophilic and one hydrophilic agent produce effects not predictable from the known toxicology of the individual species. These effects include attack on organs and systems not known to be impacted by the individual species, low-level toxicity induced by exposures to concentrations far below those known to be toxic by single chemicals in the mixtures and enhanced toxicity to humans (Zeliger, 2003). The correlation presented here between lipophilic absorption with sequential hydrophilic absorption corroborates well these findings. In all the published studies, the levels of lipophiles in blood are far lower than those known to be acutely toxic for the individual species.

POPs are long-lived and accumulate in white adipose tissue (WAT) from which they can pass to the blood and be transported around the body (Yu *et al.*, 2011; Mullerova & Kopecky, 2007; Covaci *et al.*, 2002). Due to the slow rates of metabolism and elimination, once absorbed, POPs can persist in the body for 30 years or longer and can build up with time to toxic concentrations (Yu *et al.*, 2011; Gallo *et al.*, 2011). This bioaccumulation of POPs with time over many years accounts for the delayed onset of disease following initial exposure.

The lower molecular weight of NI, NDD and NDG inducing chemicals (phthalates, BPA, PAHs and LMWHs), absorbed even at toxic concentrations, are more rapidly metabolized/eliminated. Nevertheless, they persist in body serum for days to weeks (Stahlhut *et al.*, 2009; Koch *et al.*, 2004; Li *et al.*, 2012; Pan *et al.*, 1987). Accordingly, short-term toxic concentrations from single exposures to these are fairly rapidly reduced. All of these chemicals, however, are ubiquitous in the environment as air, water or food contaminants, resulting in fairly continuous absorption and maintenance of steady-state concentrations in the blood of those who are continually exposed. Such a scenario applies as well to those who take some pharmaceuticals on a regular basis and produce fairly constant levels of lipophiles in the blood stream (Zeliger *et al.*, 2012; and Culver *et al.*, 2012).

The chemicals described above have one characteristic in common, they are all lipophiles. Although the exposure levels of these lipophilic species are much lower than their known toxic levels, they are high enough to provide a vehicle for the sequential absorption of toxic hydrophilic species (Zeliger *et al.*, 2012; Zeliger, 2013b). It is well known that mixtures of lipophilic and hydrophilic species induce low-level toxic effects and unanticipated points of attack (Zeliger, 2003; Zeliger 2011). It is proposed here that combinations of low-level lipophilic/hydrophilic mixtures act as agents for neurological disease induction.

We suggest that the structure of the lipophile is not the critical point. Rather, it is the lipophilicity and total serum load of a lipophilic species that is the determining factor in triggering neurological disease. Once a steady-state critical dose of a lipophile is reached, the body is ripe for sequential attack by a hydrophilic species, with the mixture of a lipophilic and a hydrophilic species capable to attack even at low levels of exposure (Zeliger, 2003; Zeliger, 2011, Zeliger *et al.*, 2012).

Support for this proposal comes from a consideration of other environmental diseases that have been attributed to exposures to these chemicals. Exposures to POPs, hydrocarbons and plastic exudates have been associated with metabolic diseases including type 2 diabetes, metabolic syndrome and obesity (Zeliger, 2013b; Lee *et al.*, 2010; Carpenter 2008). Exposures to the lipophilic chemicals discussed above have also been associated with a broad spectrum of cardiovascular diseases (Humblet *et al.*, 2008). These include myocardial infarction (Mustafic *et al.*, 2012, Wichmann *et al.*, 2013); atherosclerosis (Whayne, 2011, Lind *et al.*, 2012); hypertension (La Merrill *et al.*, 2013; Sergeev & Carpenter, 2011; Lind & Lind, 2012; Ha *et al.*, 2009; Valera *et al.*, 2013), coronary heart disease (Shankar *et al.*, 2012, Lind and Lind 2012), peripheral heart disease (Shankar *et al.*, 2012; Lind & Lind, 2012); ischemic heart disease (Toren *et al.*, 2007; Costello *et al.*, 2013; Burstyn *et al.*, 2005); and impact on cardiac autonomic function (Wu *et al.*, 2012).

Other diseases associated with exposure to lipophilic chemicals include: immunological disorders (Hertz-Picciotto *et al.*, 2008; Noakes *et al.*, 2006; Tryphonas, 1998), musculoskeletal disorders (Lee *et al.*, 2007), reproductive interferences (EPA, 2008; Nishijo *et al.*, 2008; Herz-Picciotto *et al.*, 2008), endocrine disruption (Snyder & Mulder, 2001; Colborn *et al.*, 1997), autoimmune diseases (Koch *et al.*, 2013; Sozeri *et al.*, 2012; Farhat *et al.*, 2011; Gregory *et al.*, 2008; Dahlgren *et al.*, 2007;) and periodontal disease (Lee *et al.*, 2008a).

The onset of many different cancers has also been associated with exposures to the chemicals described here. A discussion of environmental causes of cancer, however, is beyond the scope of this presentation. Zeliger 2004 and Zeliger 2011 offer an introduction to this subject.

People are routinely exposed to many other lipophilic chemicals that are retained in body serum. These include mycotoxins produced by mold and found in wet environments and in contaminated food (Brasel *et al.*, Peraica *et al.*, 1999; 2004; Brasel *et al.*, 2004; Reddy & Bhoola, 2010; Bennett & Klich, 2003; Brewer *et al.*, 2013), anti-oxidants and other preservatives added to foods and cosmetics, including triclosan, an antibacterial compound widely used in tooth paste, cleaners and other consumer products (Queckenberg *et al.*, 2010; Sandborgh-Englund *et al.*, 2006), butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Surak *et al.*, 1977; Verhagen *et al.*, 1989; Conning & Phillips, 1986). Other compounds are chlorinated derivatives of methane that are byproducts (DBPs) of the disinfection of water by chlorine, including chloroform and the bromo-chloro-methanes (Zeliger,

2011), the chlorinated derivatives of ethane, including 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene that arise from cleaning products and contamination of aquifers (Zeliger, 2011), pharmaceuticals that are found in contaminated drinking water in many cities (Donn, 2008); antioxidants put into foods and cosmetics for preservation purposes, including BHA and BHT (Conning & Phillips, 1986; Verhangen *et al.*, 1989), brominated vegetable oil, used to stabilize citrus-flavored soft drinks (Bernal *et al.*, 1986; Bendig *et al.*, 2013) and lipophilic pharmaceuticals, examples of which are statins, taken regularly (Culver *et al.*, 2012; Zeliger *et al.*, 2012).

The prevalence of neurological diseases discussed here as well as the other diseases cited have all increased dramatically in the past half century. For example, the prevalence of the bipolar disorder and of schizophrenia has increased in the range of 40% from 1990 to 2010 (Murray *et al.*, 2012), the prevalence of Alzheimer's disease is expected to double every 20 years (Mayeux & Stern, 2012). Such an increase can only be explained by environmental consideration and it corresponds to the worldwide increased use of POPs, plastic additives and other chemicals, fossil fuel and the environmental pollution associated with their use and discharge (EIA, 2013; Chen & McCarl, 2001; Colborn *et al.*, 1997).

As previously discussed, PAHs emanating from the combustion of fossil fuels and tobacco are considered to induce many environmental diseases. Several of the studies cited have made the association with inhalation of fine particles rather than with the PAHs (Costello *et al.*, 2013; Toren *et al.*, 2007). It has been shown, however, that the toxicity of the particles is due to the adsorption of the PAHs on the solid particles and the subsequent partitioning from such particles onto and through lipophilic membranes (Yokota *et al.*, 2008). The fine particles serve as vehicles to deliver the PAHs deep into the lungs, where these compounds are absorbed.

As seen in Table 1, not all of the lipophiles identified here have been associated with all of the diseases noted. This is due to the fact that causative studies are yet to be carried out for many chemical species.

It is to be noted that although the literature relating neurological disease to other exogenous lipophilic chemicals is scanty, mycotoxin exposures have been associated with neurological disease (Pestka *et al.*, 2008; Doi & Uetsuka, 2011; Moldes-Anaya *et al.*, 2012). Mycotoxins, as well as the widely used lipophilic disinfectant triclosan have been shown to accumulate in serum (Brewer *et al.*, 2013; Queckenberg *et al.*, 2010; Sandborgh-Englund *et al.*, 2006) and as such, they contribute to the total lipophilic load.

Conclusion

The prevalence of neurological diseases, including NIs, NDDs and NDGDs is increasing rapidly throughout the world. The evidence presented here strongly suggests that this increase is due in large part to increased exposure to exogenous lipophilic chemicals which, though varying

widely in structure, toxicology, chemical reactivity and retention time in the body, render the body susceptible to attack via subsequent exposure to low levels of hydrophilic toxins that would otherwise not be absorbed. The lipophilic chemicals can be POPs that are metabolized and eliminated slowly, or BPA, phthalates, PAHs, LMWHs and other lipophilic species that are eliminated from the body more rapidly, but are constantly replenished in the body from polluted air and water and contaminated food. The accumulation of lipophilic chemicals in the body proceeds until a critical lipophilic load level is reached, at which point the body is vulnerable to attack by low levels of toxic hydrophilic chemicals that would otherwise not be toxic. Sequential absorption of lipophiles followed by hydrophiles provides a unified explanation of how low levels of rather different environmental pollutants are responsible for the alarming increase of neurological diseases.

REFERENCES

- ATSDR. (1995). *Toxicological profile for polycyclic aromatic hydrocarbons*. Agency for Toxic Substances and Disease Registry. Atlanta, GA.
- ATSDR (2001). *Toluene toxicity*. Agency for Toxic Substances and Disease Registry. Atlanta, GA.
- Baker EL. (1988). Organic solvent neurotoxicity. *Ann Rev Pub Health* **9**: 223–232.
- Baselt RC. (2000). *Disposition of toxic drugs and chemicals in man*, 5th ed. Chemical Toxicology Institute. Foster City, CA.
- Bendig P, Maier Lehnert K, Knapp H, Vetter W. (2012). Mass spectra of methyl esters of brominated fatty acids and their presence in soft drinks and cocktail syrups. *Rapid Commun Mass Spectrom* **27**(9): 1083–1089.
- Bennett JW, Klich M. (2003). Mycotoxins. *Clin Microbiol Rev* **16**(3): 497–516.
- Bernal C, Basilio MZ, Lombardo YB. (1986). Toxicological effects induced by the chronic intake of brominated vegetable oils. *Arch Latinoam Nutr* **36**(3): 432–442.
- Bolanos JP, Moro MA, Lizasoain I, Almeida A. (2009). Mitochondria and reactive oxygen and nitrogen species in neurological disorders and stroke: Therapeutic implications. *Adv Drug Deliv Rev* **61**(14): 1299–1315.
- Blanc-Lapierre A, Bouvier G, Garrigou A, Canal-Raffin M, Raheison C, Brouhard P, Baldi I. (2012). Chronic central nervous system effects of pesticides: state-of-the-art. *Rev Epidemiol Sante Publique* **60**(5): 389–400.
- Brasel TL, Campbell AW, Demers RE, Ferguson BS, Fink J, Vojdani A, *et al.* (2004). Detection of trichothecene mycotoxins in sera from individuals exposed to *Stachybotrys Chartum* in indoor environments. *Arch Environ Health* **59**(6): 317–323.
- Brender JD, Felkner M, Suarez L, Canfield MA, Henry JP. (2010). Maternal pesticide exposure and neural tube defects in Mexican Americans. *Ann Epidemiol* **20**(1): 16–22.
- Brewer JH, Thrasher JD, Strauss DC, Madison RA, Hooper D. (2013). Detection of mycotoxins in patients with chronic fatigue syndrome. *Toxins* **5**: 605–615.
- Burbacher TM. (1993). Neurotoxic effects of gasoline and gasoline constituents. *Env Health Perspect* **101**(Suppl 6): 133–141.
- Burstyn I, Kromhout H, Partanen T, Svane O, Langard S, Ahrens W, *et al.* (2005). Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. *Epidemiology* **16**(6): 744–750.
- Buters JT, Schober W, Gutermuth J, Jakob T, Aguilar-Pimentel A, Huss-Marp J, *et al.* (2007). Toxicity of parked motor vehicle indoor air. *Environ Sci Technol* **41**(7): 2622–2629.
- Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, *et al.* (2008). Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid b-42 and a-synuclein in children and young adults. *Toxicologic Pathology* **36**: 289–310.

- Carpenter DO. (2008). Environmental contaminants as risk factors for developing diabetes. *Rev Environ Health* **23**(1): 59–74.
- Caudle WM, Guillot TS, Laxo C, Miller GW. (2012). Parkinson's disease and the environment: Beyond pesticides. *Neurotoxicology* **33**: 178–188.
- Chen CC, McCarl BA. (2001). An investigation of the relationship between pesticide usage and climate change. *Climatic Change* **50**: 475–87.
- Chen R, Wilson K, Chen Y, Zhang D, Quin X, He M, et al. (2013). Association between environmental tobacco smoke exposure and dementia syndromes. *Occup Environ Med* **70**: 63–79.
- Cheslack-Postava K, Rantakokko PV, Hinkka-Yi-Salomaki S, Surcel HM, Mckeague IW, Kiviranta HA, et al. (2013). Maternal serum persistent organic pollutants in the Finnish Prenatal Study of Autism: A pilot study. *Neurotoxicol Teratol* **38**: 1–5. doi: 10.1016/j.ntt.2013.04.001.
- Chia LG, Chu FL. (1984). Neurological studies on polychlorinated biphenyl (PCB)-poisoned patients. *Prog Clin Biol Res* **137**: 117–26.
- Colborn T, Dumanoski D, Myers JP. (1997). *Our stolen future*. Penguin Books, New York.
- Colosio C, Tiramani M, Maroni M. (2003). Neurobehavioral effects of pesticides: state of the art. *Neurotoxicology* **24**(4–5): 577–591.
- Conning DM, Phillips JC. (1986). Comparative metabolism of BHA, BHT and other phenolic antioxidants and its toxicological relevance. *Food Chem Toxicol* **24**(10–11): 696–702.
- Costello S, Garcia E, Hammond SK, Eisen EA. (2013). Ischemic heart disease mortality and PM(3.5) in a cohort of autoworkers. *Am J Ind Med* **56**(3): 317–325.
- Covaci A, de Boer J, Ryan JJ, Voorspoels S, Schepens P. (2002). Distribution of organobrominated and organochlorinated contaminants in Belgian human adipose tissue. *Environ Res* **88**(3): 210–218.
- Culver AL, Ockene IS, Balasubramanian R, Oldenski BC, Sepavich DM. (2012). Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Int Med* **172**(2): 144–52.
- Dahlgren J, Takhar H, Anderson-Mahoney P, Kotlerman J, Tarr J, Warshaw R. (2007). Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study. *Environ Health* **6**: 8–23.
- Dardiotis E, Xiromerisiou G, Hadjichistodoulou C, Tsatsakis AM, Wilks MF, Hadjigeorgiou GM. (2013). The interplay between environmental and genetic factors in Parkinson's disease susceptibility: the evidence for pesticides. *Toxicology* **307**: 17–23. doi: 10.1016/j.tox.2012.12.016.
- De Cock M, Maas YG, van de Bor M. (2012). Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. *Acta Paediatr* **101**(8): 811–818.
- Doi K, Uetsuka K. (2011). Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. *Int J Mol Sci* **12**(8): 5213–52037.
- Donn J. (2008). *Philly finds 56 drugs in its water*. Assoc Press.
- EIA (2013). U.S. Energy Information Administration. International energy outlook. July 25, 2013. <http://www.eia.gov/forcasts/ieo/> (last accessed 10/23/13)
- Escudar-Gilbert L, Villanueva-Camanas RM, Sagrado S, Medina-Hernandez MJ. (2009). Permeability and toxicological profile estimation of organochlorine compounds by biopartitioning micellar chromatography. *Biomed Chromatogr* **23**(4): 382–89.
- Farhat SC, Silva CA, Orione MA, Campos LM, Sallum AM, Braga AL. (2011). Air pollution in autoimmune rheumatic diseases: a review. *Autoimmun Rev* **11**(1): 14–21.
- Faroon O, Jones D, de Rosa C. (2001). Effects of polychlorinated biphenyls on the nervous system. *Toxicol Ind Health* **16**(7–8): 305–333.
- Filmore D. (2002). Breaching the blood-brain barrier. *Mod Drug Discov* **5**(6): 22–27.
- Fitzgerald EF, Shrestha S, Gomez MI, McCaffrey RJ, Zimmerman EA, Kannan K, Hwang S. (2012). Polybrominated biphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and neuropsychological status among older adults in New York. *Neurotoxicology* **33**(1): 8–15.
- Fleming L, Mann JB, Bean J, Briggie T, Sanchez-Ramos JR. (1994). Parkinson's disease and brain levels of organochlorine pesticides. *Ann Neurol* **36**(1): 100–103.
- Gallo MV, Schell LM, DeCaprio AP, Jacobs A. (2011). Levels of persistent organic pollutants and their predictors among young adults. *Chemosphere* **83**(10): 1374–1382.
- Gamble JF. (2000). Low-level hydrocarbon solvent exposure and neurobehavioral effects. *Occupat Med* **50**(2): 81–102.
- Gascon M, Verner MA, Guxens M, Grimalt JO, Forn J, Ibarluzea J, et al. (2013). Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children. *Neurotoxicology* **34**: 9–15. doi: 10.1016/j.neuro.2012.10.006.
- Grandjean P, Landrigan PJ. (2006). Developmental neurotoxicity of industrial chemicals. *Lancet* **368**(9553): 2167–2178.
- Gregory AC 2nd, Shendell DG, Okosun IS, Gieseker KE. (2008). Multiple sclerosis disease distribution and potential impact of environmental air pollutants in Georgia. *Sci Total Environ* **396**(1): 42–51.
- Gupta A, Agarwal R, Shukla GS. (1999). Functional impairment of blood-brain barrier following pesticide exposure during early development in rats. *Hum Exp Toxicol* **18**(3): 174–79.
- Gupta SR, Palmer Cam Cure JK, Balos LL, Lincoff NS, Kline LB. (2011). Toluene optic neurotoxicity: magnetic resonance imaging and pathologic features. *Hum Pathol* **42**(2): 295–298.
- Ha, MH, Lee DH, Son HK, Park SK, Jacobs DR. (2009). Association between serum concentrations of persistent organic pollutants and prevalence of newly diagnosed hypertension: results from the National Health and Nutrition Examination Survey 1999–2002.
- Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, Eskenazi B. (2013). Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. *Environ Res* **126**: 43–50. Doi: 10.1016/j.envres.2013.06.004
- Hartz AMS, Bauer B, Block ML, Hong JS, Miller DS. (2008). Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. *FASEB J* **22**: 2723–33.
- He C, Wang C, Zhou Y, Li J, Zuo Z. (2012). Embryonic exposure to benzo(a)pyrene influences neural development and function in rockfish (*Sebastes marmoratus*). *Neurotoxicology* **33**(4): 758–762.
- Hertz-Picciotto, Park HY, Dostal M, Kocan A, Trnovec Y, et al. (2008). Pre-natal exposure to persistent and non-persistent organic compounds and effects on immune system development. *Basic Clin Pharmacol Toxicol* **102**(2): 146–154.
- Humblet O, Birnbaum L, Rimm E, Mittleman MA, Hauser R. (2008). Dioxins and cardiovascular disease mortality. *Environ Health Perspect* **116**(11): 1443–48.
- Iwaniuk AN, Koperski DT, Cheng KM, Elliot Je, Smith LK, Wilson LK, Wylie DR. (2006). The effects of environmental exposure to DDT on the brain of a songbird: changes in structures associated with mating and song. *Behav Brain Res* **173**(1): 1–10.
- Jakovcevski M, Akbarian S. (2012). Epigenetic mechanisms in neurological disease. *Nat Med* **18**(8): 1194–1204.
- Jurewicz J, Polanska K, Hanke W. (2013a). Exposure to widespread environmental toxicants and children's cognitive development and behavioral problems. *Int J Occup Med Environ Health* **26**(2): 185–204.
- Jurewicz J, Polanska K, Hanke W. (2013b). Chemical exposure early in life and the neurodevelopment of children – an overview of current epidemiological evidence. *Ann Agric Environ Med* **20**(3): 465–86.
- Kessler W, Numtip W, Volkel W, Seckin E, Csanady GA, Putz C, et al. (2012). Kinetics of di(ethylhexyl) phthalate (DEHP) and mono(2-ethylhexyl) phthalate in blood and of DEHP metabolites in urine of male volunteers after single ingestion of ring-diluted DEHP. *Toxicol Appl Pharmacol* **264**(2): 284–291.
- Kim BH, Cho SC, Kim Y, Shin MS, Kim JW, Yang YH, et al. (2009). Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. *Biol Psychiatry* **66**(10): 958–963.
- Koch HM, Bolt HM, Angerer J. (2004). Di(2-ethylhexyl)phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium-labeled DEHP. *Arch Toxicol* **78**(3): 123–130.
- Koch MW, Metz LM, Agrawal SM, Yong VW. (2013) Environmental factors and their regulation of immunity in multiple sclerosis. *J Neurol Sci* **324**: 10–16.
- Kodavanti PRS. (2005). Neurotoxicity of persistent organic pollutants: possible mode(s) of action and further considerations. *Dose-Response* **3**: 273–305.
- Krivoshko BA, Richards JR, Albertson TE, Derlet RW. (2008). The toxicity of diesel exhaust: Implications for primary care. *J Am Bd Fam Med* **21**(1): 55–62.
- La Merrill M, Cirillo PM, Terry MB, Krigbaum NY, Flom JD. (2013). Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: A longitudinal birth control study. *Environ Health Perspect* **116**(11): 594–599.
- Lammers JHCM, Muijser H, Owen DE, Kulig BM, McKee RH. (2011). Neurobehavioral effects of acute exposure to normal (n-) paraffins. *Int J Toxicol* **30**(1): 47–58.

- Larsson M, Hagerhed-Engman L, Kolarik B, James P, Lundin F, Janson S, *et al.* (2010). PVC – as flooring material – and its association with incident asthma in a Swedish child cohort study. *Indoor Air* **20**: 494–501.
- Le Cann P, Bonvallet N, Glorennec P, Deguen S, Goeury C, Le Bot B. (2011). Indoor environment and children's health: recent developments in chemical, biological, physical and social aspects. *Int J Hyg Environ Health* **215**(1): 1–18.
- Lee DH, Jacobs DR, Porta M. (2007). Association of serum concentrations of persistent organic pollutants with the prevalence of learning disability and attention deficit disorder. *J Epidemiol Community Health* **61**: 591–596.
- Lee DH, Steffes MW, Jacobs DR. (2007). Positive association of serum concentration of polychlorinated biphenyls or organochlorine pesticides with self-reported arthritis, especially rheumatoid type in women. *Environ Health Perspect* **115**(6): 883–888.
- Lee DH, Jacobs DR, Kocher T. (2008a). Associations of serum concentrations of persistent organic pollutants with the prevalence of periodontal disease and subpopulations of white blood cells. *Environ Health Perspect* **116**(11): 1558–1562.
- Lee DH, Jacobs DR Jr, Steffes M. (2008b). Association of organochlorine pesticides with peripheral neuropathy in patients with diabetes or impaired fasting glucose. *Diabetes* **57**(11): 3108–3111.
- Lee DH, Steffes MW, Sjoden A, Jones RS, Needham LL, *et al.* (2010). Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. *Environ Health Perspect* **118**(9): 1235–1242.
- Li Z, Romanoff L, Bartell S, Pittman EN, Trinidad DA, McLean M, *et al.* (2012). Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chem Res Toxicol* **25**(7): 1452–1461.
- Lind PM, van Bavel B, Salihovic S, Lind L. (2012). Circulating levels of persistent organic pollutants (POPs) and carotid atherosclerosis in the elderly. *Environ Health Perspect* **120**(1): 38–43.
- Lind PM, Lind L. (2012). Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease? *J Intern Med* **271**(6): 537–553.
- Lochhead JL, McCaffrey G, Quigley CE, Finch J, DeMarco KM, Nametz N, Davis TP. (2010). Oxidative stress increases blood-brain barrier permeability and induces alterations in occluding during hypoxia-reoxygenation. *J Cerebral Blood Flow Metab* **30**: 1625–1636.
- Logroscino G, Traynor BJ, Hardiman O, Chio' A, Couratier P, Mitchell JD, *et al.* (2008). Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* **79**(1): 6–11.
- Maruff P, Burns CB, Tyler P, Currie BJ, Currie J. (1998). Neurological and cognitive abnormalities associated with chronic petrol sniffing. *Brain* **121**: 1903–1917.
- Mates JM, Segura JA, Alonso FJ, Marquez J. (2010). Roles of dioxins and heavy metals in cancer and neurological diseases using ROS-mediated mechanisms. *Free Rad Biol Med* **49**(9): 1328–41.
- Mayeux R, Stern Y. (2012). Epidemiology of Alzheimer's disease. *Cold Spring Harb Perspect Med* **2**(8). doi: 10.1101/cshperspect.a006239.
- McCanlies EC, Fekedulegn D, Mnatsakanova A, Burchfiel CM, Sanderson WT, Charles LE, Herts-Picciotto I. (2012). Parental occupational exposures and autism spectrum disorder. *J Autism Dev Disord* **42**(11): 2323–2334.
- Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. (2001). Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand. *Neurotoxicology* **22**(4): 479–90.
- Moldes-Anaya A, Rundberget T, Faeste CK, Eriksen GS, Berhoft A. (2012). Neurotoxicity of penicillium crustosum secondary metabolites: tremorgenic activity of orally administered penitrem A and thomitrem A and E in mice. *Toxicol* **60**(8): 1428–1435.
- Moses V, Peter JV. (2010). Acute intentional toxicity: endosulfan and other organochlorines. *Clin Toxicol (Phila)* **48**(6): 539–544.
- Mostafalou S, Abdollahi M. (2013). Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicol Appl Pharmacol* **268**(2): 157–77.
- Mullerova D, Kopecky J. (2007). White adipose tissue: storage and effector site for environmental pollutants. *Physiol Res* **56**(4): 375–381.
- Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, *et al.* (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**: 2197–2223.
- Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, *et al.* (2012). Main air pollutant and myocardial infarction: a systematic review and meta-analysis. *JAMA* **307**(7): 713–721.
- Nishijo M, Tawara K, Nakagawa H, Honda R, Kido T, *et al.* (2008). 2,3,7,8-tetrachlorodibenzo-p-dioxin in maternal breast milk and newborn head circumference. *J Expo Sci Environ Epidemiol* **18**(3): 246–251.
- Noakes PS, Taylor P, Wilkinson S, Prescott SL. (2006). The relationship between persistent organic pollutants in maternal and neonatal tissues and immune responses to allergens: a novel exploratory study. *Chemosphere* **63**(8): 1304–1311.
- Pan Y, Johnson AR, Rea WJ. (1987). Aliphatic hydrocarbon solvents in chemically sensitive patients. *Clin Ecol* **5**(3): 126–131.
- Pardridge WM. (2012). Drug transport across the blood-brain barrier. *J Cereb Blood Flow Metab* **32**(11): 1959–72.
- Parron T, Requena M, Hernandez AF, Alarcon R. (2011). Association between environmental exposure to pesticides and neurodegenerative diseases. *Toxicol Appl Pharmacol* **256**(3): 379–385.
- Patel MM, Goyal BR, Bhadada SV, Bhatt JS, Amin AF. (2009). Getting into the brain: approaches to enhance drug delivery. *CNS Drugs* **23**(1): 35–58.
- Patri M, Padmini A, Babu PP. (2009). Polycyclic aromatic hydrocarbons in air and their neurotoxic potency in association with oxidative stress: a brief perspective. *Ann Neurosci* **16**(1): 1–9.
- Patrick L. (2009). Thyroid disruption: mechanisms and clinical implications in human health. *Alt Med Rev* **14**(4): 326–346.
- Peraica M, Radic B, Pavlovic M. (1999). Toxic effects of mycotoxins in humans. *Bull World Health Org* **99**(7): 754–766.
- Pessah IN, Seegal RF, Lein PJ, LaSalle J, Yee BK, Van De Water J, Berman RF. (2008). Immunologic and neurodevelopmental susceptibilities of autism. *Neurotoxicology* **29**(3): 531–544.
- Pestka JJ, Yike I, Dearborn DG, Ward MD, Harkema JR. (2008). Stachybotrys, trichothecene mycotoxins, and damp building-related illness: new insights into a public health enigma. *Toxicol Sci* **104**(1): 4–26.
- Polanska K, Jurewicz J, Hanke W. (2013). Review of current evidence on the impact of pesticides, polychlorinated biphenyls and selected metals on attention deficit / hyperactivity disorder in children. *Int J Occupat Med Environ Health* **26**(1): 16–38.
- Quaak I, Brouns MR, Van de Bor M. (2013). The dynamics of autism spectrum disorders: How neurotoxic compounds and neurotransmitters interact. *Int J Environ Res Pub Health* **10**: 3384–3408.
- Queckenberg C, Meins J, Wachall B, Doroshenko O, Tomalik-Scharte D, Bastian B, *et al.* (2010). Absorption, pharmacokinetics, and safety of triclosan after dermal administration. *Antimicrobial Agents and Chemotherapy* **54**(1): 570–572.
- Qiu C, Cheng S, Xia Y, Peng B, Tang Q, Tu B. (2011). Effects of subchronic benzo(a)pyrene exposure on neurotransmitter receptor gene expression in the rat hippocampus related with spatial learning and memory change. *Toxicology* **289**(2–3): 83–90.
- Ren A, Qiu X, Jin J, Li Z, Ma J, Zhiwen L, *et al.* (2011). Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects. *Proc Natl Acad Sci USA* **108**(31): 12770–12778.
- Reddy L, Bhoola K. (2010). Ochratoxins – food contaminants: impacts on human health. *Toxins* **2**: 771–779.
- Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, *et al.* (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. (2013): *Environ Health Perspect* **121**(8): 978–984.
- Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C. (2007). Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ Health Perspect* **115**(10): 1482–1489.
- Roze E, Meijer L, Bakker A, Van Braechel KN, Sauer PJ, Bos AF. (2009). Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. 2009. *Environ Health Perspect* **117**(12): 1953–1958.
- Sagiv SK, Thurston SW, Bellinger DC, Altschul LM, Korrick SA. (2012). Neuropsychological measures of attention and impulse control among 8-year old children exposed prenatally to organochlorines. *Environ Health Perspect* **120**(6): 904–909.
- Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altschul LM, Korrick SA. (2010). Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. *Am J Epidemiol* **171**: 593–601.
- Sandborg-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. (2006). *J Toxicol Environ Health A* **69**(20): 1861–1873.

- Seelbach M, Chen L, Powell A, Choi YJ, Zhang B, Hennig B, Toborek M. (2010). Polychlorinated biphenyls disrupt blood-brain barrier integrity and promote brain metastasis formation. *Environ Health Perspect* **118**(4): 479–84.
- Seelig A, Gottschlich R, Devant RM. (1994). A method to determine the ability of drugs to diffuse through the blood-brain barrier. *Proc Natl Acad Sci USA* **91**: 68–72.
- Sendur OF, Turan Y, Bal S, Gurgan A. (2009). Toxic neuropathy due to N₆hexane: report of three cases. *Inhal Toxicol* **21**(3): 210–214.
- Sergeev AV, Carpenter DO. (2011). Geospatial patterns of hospitalization rates for stroke with comorbid hypertension in relation to environmental sources of persistent organic pollutants: results from a 12-year population-based study. *Environ Sci Pollut Res Int* **18**(4): 576–585.
- Shankar A, Teppala S. (2012). Urinary bisphenol a and hypertension in a multiethnic sample of U.S. adults. *J Environ Public Health* **2012**: 481641. doi: 10.1155/2012/897134.
- Snyder MJ, Mulder EP. (2001). Environmental endocrine disruption in decapod crustacean larvae: hormone titers, cytochrome P 450, and stress protein responses to heptachlor exposure. *Aquat Toxicol* **55**(3–4): 177–190.
- Sozeri B, Gulez N, Aksu G, Kutukculer N, Akalin T, Kandiloglu G. (2012). Pesticide-induced scleroderma and early intensive immunosuppressive treatment. *Arch Environ & Occupat Health* **67**(1): 43–47.
- Stahlhut RW, Welshons WV, Swan SH. (2009). Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. *Environ Health Perspect* **117**(5): 784–789.
- Steenland K, Wesseling C, Roman N, Quiros I, Juncos JL. (2013). Occupational pesticide exposure and screening tests for neurodegenerative disease among an elderly population in Costa Rica. *Environ Res* **120**: 96–101. Doi: org/10.1016/j.envres.2012.08.014.
- Sun Y, Nakashima MN, Takahashi M, Kuroda N, Nakashima K. (2002). Determination of bisphenol A in rat brain by microdialysis and column switching high-performance liquid chromatography with fluorescence detection. *Biomed Chromatogr* **16**(5): 319–26.
- Surak JG, Bradley RL Jr, Branan AL, Maurer AJ, Ribelin WE. (1977). Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) effects on serum and liver lipid levels in Gallus domesticus. *Poult Sci* **56**(3): 747–753.
- Sweeney MH, Fingerhut MA, Arezzo JC, Hornung RW, Connolly LB. (1993). Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD). *Am J Ind Med* **23**(6): 845–58.
- Szychowski KA, Wojtowicz AK. (2013). Components of plastic disrupt the function of the nervous system. *Postepy Hig Med Dpsw* **67**: 499–506.
- Thomke F, Jung D, Besser R, Roder R, Konietzko J, Hopf HC. (1999). Increased risk of sensory neuropathy in workers with chloracne after exposure to 2,3,7,8-polychlorinated dioxins and furans. *Acta Neuro Scand* **100**(1): 1–5.
- Toren K, Bergdahl A, Nilsson T, Jarvholm B. (2007). Occupational exposure to particulate air pollution and mortality due to ischaemic heart disease and cerebrovascular disease. *Occup Environ Med* **64**: 515–519.
- Tryphonas H. (1998). The impact of PCBs and dioxins on children's health: immunological considerations. *Can J Pub Health* **89**(May–June): 554–557.
- Verhagen H, Beckers HH, Comuth PA, Maas LM, ten Hoor F, Henderson PT, Kleinjans JC. (1989). Disposition of single oral doses of butylated hydroxytoluene in man and rat. *Food Chem Toxicol* **27**(12): 765–772.
- Uccelli R, Binazzi A, Altavista P, Belli S, Comba P, Mastrantonio M, Vanacore N. (2007). Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. *Eur J Epidemiol* **22**(11): 781–790.
- Urduinguo RG, Sanchez-Mut JV, Esteller M. (2009). Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. *The Lancet Neurol* **8**(11): 1056–1072.
- Uttara B, Singh AV, Zamboni P, Mahajan RT. (2009). Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* **7**(1): 65–74.
- Verhagen H, Beckers HH, Comuth PA, Maas LM, ten Hoor F, et al. (1989). Dispositions of single oral doses of butylated hydroxytoluene in man and rat. *Food Chem Toxicol* **27**(12): 765–772.
- Viberg H, Fredriksson A, Buratovic S, Eriksson P. (2011). Dose-dependent behavioral disturbances after a single neonatal Bisphenol A dose. *Toxicology* **290**(2–3): 187–194.
- Viaene MK. (2002). Overview of the neurotoxic effects in solvent-exposed workers. *Arch Pub Health* **60**: 217–232.
- Viberg H, Lee I. (2012). A single exposure to bisphenol A alters the levels of important neuroproteins in adult male and female mice. *Neurotoxicology* **33**(5): 1390–1395.
- Vincenti M, Bottecchi I, Fan A, Finkelstein Y, Mandrioli J. (2012). Are Environmental exposures to selenium, heavy metals and pesticides risk factors for amyotrophic lateral sclerosis? *Rev Environ Health* **27**(1): 19–41.
- Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnel R. (2011). Residential proximity to freeways and autism in the CHARGE study. *Environ Health Perspect* **119**(6): 873–877.
- Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**: 2163–96.
- Wang A, Costello S, Cockburn N, Zhang X, Bronstein J, Ritz B. (2011). Parkinson's disease risk from ambient exposure to pesticides. *Eur J Epidemiol* **26**(7): 547–555.
- Weintraub E, Gandhi D, Robinson C. (2000). Medical complications due to mothball abuse. *South Med J* **93**(4): 427–429.
- Weiss B. (2012). The intersection of neurotoxicology and endocrine disruption. *Neurotoxicology* **33**(6): 1410–19.
- Weitzman M, Govil N, Liu YH, Lalwani AK. (2013). Maternal prenatal smoking and hearing loss among adolescents. *JAMA Otolaryngol Head Neck Surg* **139**(7): 669–677.
- White RF, Proctor SP. (1997). Solvents and neurotoxicity. *Occup Med* **349**: 1239–1243.
- Whane TF. (2011). Atherosclerosis: current status of prevention and treatment. *Int J Angiology* **20**(4): 213–222.
- Widholm JJ, Seo BW, Strupp BJ, Seegal RF, Schantz SL. (2003). Effects of perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin on spatial and visual reversal learning in rats. *Neurotoxicol Teratol* **25**(4): 459–71.
- WHO. (2006). *Almost a quarter of all disease caused by environmental exposure*. World Health Organization, Geneva, Switzerland. Available from <http://www.who.int/mediacentre/news/releases/2006/pr32/index.html> (Accessed September 8, 2013).
- Wichmann J, Folke F, Torp-Pedersen C, Lippert F, Ketzler M, et al. (2013). Out-of-hospital cardiac arrests and outdoor air pollution exposure in Copenhagen, Denmark. *PLoS One* **8**(1): e53684.
- Winneke G. (2011). Developmental aspects of environmental neurotoxicology: lessons from lead and polychlorinated biphenyls. *J Neurol Sci* **308**(1–2): 9–15.
- Wu S, Deng F, Liu Y, Shima M, Niu J, et al. (2012). Temperature, traffic-related air pollution, and heart variability in a panel of healthy adults. *Environ Res* **120**: 82–89.
- Yokota S, Ohara N, Kabayashi T. (2008). The effects of organic extract or diesel exhaust particles on ischemia/reperfusion-related arrhythmia and on pulmonary function. *J Toxicol Sci* **33**(1): 1–10.
- Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. (2011). Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. *Neurotoxicol Teratol* **33**(5): 558–566.
- Yu GW, Laseter J, Mylander C. (2011). Persistent organic pollutants in serum and several different fat compartments in humans. *J Environ Public Health* **2011**: 417980. doi: 10.1155/2011/417980.
- Zaganas I, Kapetanaki S, Mastorodemos V, Knavouras K, Colosio C, Wilks MF, Tsatsakis AM. (2013). Linking pesticide exposure and dementia: What is the evidence? *Toxicology* **307**: 3–11. Doi: 10.1016/j.tox.2013.02.002.
- Zeliger HI. (2003). Toxic effects of chemical mixtures. *Arch Environ Health* **58**(1): 23–29.
- Zeliger HI. (2004). Unexplained cancer clusters: common threads. *Arch Environ Health* **59**(4): 172–176.
- Zeliger HI. (2011). *Human toxicology of chemical mixtures*, 2nd ed. Elsevier, London.
- Zeliger HI. (2012). *Statin use and risk of diabetes*. *Arch Int Med* **171**(11): 896–897.
- Zeliger HI, Pan Y, Rea WJ. (2012). Predicting co-morbidities in chemically sensitive individuals from exhaled breath analysis. *Interdiscip Toxicol* **5**(3): 123–126.
- Zeliger HI. (2013a). Lipophilic chemical exposure as a cause of cardiovascular disease. *Interdiscip Toxicol* **6**(2): 55–62.
- Zeliger HI. (2013b). Lipophilic chemical exposure as a cause of type 2 diabetes (T2D). *Rev Environ Health* **28**(1): 9–20.