HOUSEHOLD ENVIRONMENTAL TOXINS AND NEURODEVELOPMENT IN CHILDREN

by

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Brittany Lee Brandt

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ABSTRACT

Neurodevelopmental disorders diagnosed in children, such as ADHD, autism, Tourette's syndrome, learning disabilities, dyslexia, mental retardation, and cerebral palsy, are thought to arise from complex interactions between genetic, social and environmental factors. The increasing prevalence of some of these disorders in children over the past thirty years has precipitated more research into preventable environmental causes. Environmental toxins, such as heavy metals and synthetic chemicals, are among the targets of investigation by researchers. This literature review examines what is known from current research about neurodevelopment and exposure to the following household environmental toxins: PBDEs, pesticides, mercury, lead, and bisphenol A. Variables reviewed include source, neurological effects, and ways to reduce exposure to each toxin. Relevant articles were retrieved through keyword search of Medline database. Online government databases were also utilized. Results of the literature review indicate adverse neurological effects of developmental exposure to PBDEs, pesticides, mercury, lead and bisphenol A are similar to diagnostic features of some neurodevelopmental disorders. Adverse effects associated with exposures include: hyperactivity, aggression, decreased IQ, and impairments in attention, memory, fine and gross motor skills, social behavior, and communication. Nurses are often the first and sometimes the only health care provider working with children and families. As such, they are in an ideal position to address possibly harmful environmental exposures. Including screening for toxic exposures and addressing prevention is recommended during all primary care visits with children and is increasingly considered an expected practice by leading health care institutions.

INTRODUCTION

Background

Over the last 30 years, behavioral and learning disorders have developed into major chronic conditions in children. Both educators and pediatricians have reported seeing increases in the number of children with these disorders, and special education programs have seen major expansion during this time period (CDC, 2008). Indeed, one in six children has a developmental disability, the majority affecting the nervous system. These disorders, affecting memory, behavior, or ability to learn, include Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorders (ASD), Tourette's syndrome, Learning Disabilities (LD), dyslexia, mental retardation, and cerebral palsy (P. Grandjean, & Landrigan, P.J., 2006; Szpir, 2006; B. Weiss, & Landrigan, P.J, 2000).

The prevalence of some neurodevelopmental disorders appears to be increasing. Using 2006 data from the Autism and Developmental Disabilities Network (ADDM), the CDC now estimates that, on average, 1 in 110 children aged 8 in the United States (US) has an Autism Spectrum Disorder (ASD). This represents a 57% increase from 2002 (CDC, 2009b). Approximately 5% of school-age children have been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), and an additional 4% carry both the diagnosis of ADHD and Learning Disability (LD). This works out to a 3% increase in ADHD diagnoses each year between 1997 and 2006 (CDC, 2008).

Whether increases in reported prevalence represent true increases in the disorders has been widely debated. Changes in reporting and diagnostic criteria likely account for some of the increase in prevalence of ASD and ADHD, but true increases cannot be ruled out (CDC, 2009b; Stein, Schettler, Wallinga, & Valenti, 2002). According to Martha Herbert, a pediatric neurologist at Harvard Medical School, even though certainty about changes in true prevalence has not been ascertained, "there are enough studies coming in with higher numbers that we should take it seriously" (Szpir, 2006, p. A102).

Costs associated with care for individuals with neurodevelopmental disorders carry a heavy burden for individuals, families, and society at large. It is estimated that the annual societal cost for ADHD alone is between $36 and $52 billion dollars. This represents an annual average of $14,576 per individual and includes the costs of treatment and health care, education, parental work loss and juvenile justice (Pelham, 2007). Lifetime societal costs for a person with an ASD are estimated to be $3.2 million. This includes the cost of medical care, non-medical care, and loss of productivity (Ganz, 2007).

The cause of over 75% of neurodevelopmental disorders is unknown (B. Weiss, & Landrigan, P.J, 2000). However, a body of evidence has emerged over the past several decades that shows developmental disabilities arise from complex interactions between genetic, social, and toxicological (chemical) factors (P. Grandjean, & Landrigan, P.J., 2006; Stein, et al., 2002). It is estimated that between 3% and 10% of neurobehavioral disorders/ developmental disabilities are directly

linked to exposure to toxic substances in the environment. This works out to a cost of at least $9.2 billion that is spent annually on the portion of these disorders directly attributable to environmental toxins (Landrigan, 2002). Another 25% of developmental disabilities come about as a result of interaction between genetic, social, and toxic environmental exposures (P. Grandjean, & Landrigan, P.J., 2006; Landrigan, 2002). The environmental portion of these disorders is of key interest since these exposures are largely preventable (P. Grandjean, & Landrigan, P.J., 2006; Landrigan, 2002; Stein, et al., 2002). Research into environmental causation/contributing factors should be a priority (Szpir, 2006).

Over 80,000 new synthetic chemicals have been introduced into the environment over the past 50 years. Of these, the ones produced in the largest quantities pose the greatest risk for children. They are the ones most likely to be distributed in the air, water, food, homes, and communities. Fifteen thousand chemicals are produced at quantities greater than 10,000 pounds per year and 2,800 are produced at over a million pounds per year. Eighty percent of these high volume chemicals have no information on pediatric or developmental toxicity, and half of them have no basic toxicity data available whatsoever (D. C. Bellinger, 2007; P. Grandjean, & Landrigan, P.J., 2006; Landrigan, 2002; B. Weiss, & Landrigan, P.J, 2000).

Children's developing brains are particularly susceptible to insult from toxic chemical exposures, much more so than the adult brain. During the nine months of prenatal life, the human brain develops from "a strip of cells along the dorsal

ectoderm of the fetus into a complex organ consisting of billions of precisely located, highly interconnected, and specialized cells" (P. Grandjean, & Landrigan, P.J., 2006, p. 2167). Any disruption during this highly precise and tightly controlled process can have major consequences on brain functioning (P. Grandjean, & Landrigan, P.J., 2006; Landrigan, 2002; Stein, et al., 2002; WHO, 2006). There is some protection offered by the placenta, but it is incomplete. Many environmental pollutants, including metals, are able to cross the placenta into the developing fetus. The period of heightened vulnerability continues after birth, through infancy, and into early childhood when glial cells are growing and myelinization of axons continues to occur. The blood brain barrier offers little protection until it is completely developed, when the infant is around six months old (P. Grandjean, & Landrigan, P.J., 2006).

Infants and young children are also more susceptible to toxic exposures because their developing bodies absorb toxins at a greater rate and have less ability to detoxify compared to adults (P. Grandjean, & Landrigan, P.J., 2006). In addition, behavioral characteristics of this population make exposure to toxins more likely. Infants and young children spend more time on or near the floor where pollutants can be found in house dust or tracked in from outdoors. This, combined with normal developmental hand-to-mouth behavior, puts young children at greater risk for ingesting toxins. Children also eat and drink more in proportion to their body weight which increases the degree to which children are exposed to toxins in food and water sources (WHO, 2006).

Despite increasing concern in the scientific community about environmental exposures and their potential effects on child neurodevelopment, many parents remain uniformed about this connection. According to Kathy Lawson, the director of the Healthy Children Project at the Learning Disabilities Association of America, "I've discovered that people are completely unaware that there is a connection between environmental toxicants and their health. Even pediatricians don't know about these things" (Szpir, 2006, p. A107). It's no wonder when 75% of medical schools only require seven hours of education devoted to environmental medicine over a course of four years. Nurses also receive minimal to no environmental health training while in school (NEEF, 2008a). This is concerning since many Americans look to their health care provider to inform them about threats to their health. Leading health institutions, including the American Medial Association (AMA), the American Academy of Pediatrics (AAP), and the American Nurses Association (ANA) have called for improvements in environmental health content in all levels of medical and nursing education. Improvement in environmental health education is critical in order for information about potential health threats to be disseminated to the public.

Purpose Statement

The purpose of this paper is to review neurodevelopmental effects associated with exposure to five environmental toxins: polybrominated diphenyl ethers (PBDEs), pesticides, mercury, lead, and bisphenol A. Variables reviewed include 1)

the source of the toxin, 2) neurological effects linked to exposure, and 3) ways to reduce exposure.

Method

The toxins included in this review are all potentially found in the indoor home environment, since that is where infants and young children spend the majority of their time (Davis, 2007). The Medline database was searched using keywords “neuro*” “neurodevelopment” “autism” “attention deficit hyperactivity disorder” “child*” “lead” “mercury” “PBDE” “flame retardant” “pesticide*” “organochlorine*” “organophosphate*” “bisphenol A” “BPA” and “exposure” in various combinations. The asterisk (*) was used in some instances as a wildcard character to expand the search. Secondary searches were conducted using the MeSH headings “pregnancy” “prenatal exposure, delayed effects” “child” “infant/newborn” “child development” and “environmental exposure.” Article searches were limited to those written in the English language and those written between the years 1990 and 2012. Article titles and abstracts were scanned for relevance to the topic. Online government databases from the CDC, NIH, ATSDR, FDA, and EPA were also utilized. In addition to database searches, the process of “snowballing”, using reference lists from key publications, was employed as a research technique.

RESULTS

Polybrominated Diphenyl Ethers

Source

Polybrominated Diphenyl Ethers (PBDEs) are organobromine compounds that were developed in the 1970s for use as flame retardant additives in various consumer products including electronics, plastics, textiles, carpets, building materials, and polyurethane foam (Costa & Giordano, 2007; Darnerud, Eriksen, Jóhannesson, Larsen, & Viluksela, 2001; P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001; Herbstman, et al., 2009; Imm, Knobeloch, Buelow, & Anderson, 2009; McDonald, 2002). There are 209 possible congeners, or molecular combinations, of PBDEs. They are classified according to number of attached bromine atoms, with ten possible per molecule. This results in ten possible PBDE congener groups, (monobrominated through decabrominated) (Bakker, et al., 2008; Costa & Giordano, 2007; Darnerud, et al., 2001; H. Viberg, Fredriksson, & Eriksson, 2003).

Three different mixtures of PBDEs are generally found in commercial products: penta BDE, octo BDE, and deca BDE (Costa & Giordano, 2007; Darnerud, et al., 2001). Penta BDE mixtures are primarily comprised of penta BDE, but they also contain tetra BDE through hexa BDE congeners (ATSDR, 2004; Darnerud, et al., 2001). They are found in bedding and polyurethane foams that are used in furniture and vehicle upholstery (Imm, et al., 2009). Octo BDE mixtures are primarily comprised of octo BDE, but they also contain hexa through nona BDE congeners

(ATSDR, 2004; Darnerud, et al., 2001). They are found in personal computers and small appliances (Imm, et al., 2009). Deca BDE mixtures are over 97% deca BDE but they also contain some nona BDE (ATSDR, 2004). Deca mixtures are found in wire insulation, back coatings for upholstery, and plastics used in TV cabinets, auto and airplane interiors, and consumer electronics (Imm, et al., 2009).

PBDEs are structurally similar to a group of polychlorinated hydrocarbons that include polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), and dibenzofurans (PCDFs). The health hazards linked to these similar compounds have been well researched (Darnerud, et al., 2001; P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001). PBDEs in particular have received recent increased scrutiny because, unlike their counterparts, documented levels in humans have been increasing (Costa & Giordano, 2007; Darnerud, et al., 2001; Dingemans, et al., 2007; P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001; Kuriyama, et al., 2007; Toms, et al., 2009; H. Viberg, et al., 2003).

PBDEs, like these other compounds, are considered persistent organic pollutants (POPs) because they resist metabolization, are lipophilic, bioaccumulate, and bioconcentrate in human and animal tissue (they have been measured in human blood, adipose tissue, and breast milk). The lower brominated PBDE molecules absorb and bioaccumulate to a much greater degree than the higher brominated ones (ATSDR, 2004; Costa & Giordano, 2007; Darnerud, et al., 2001; Imm, et al., 2009; McDonald, 2002). Decabrominated BDE, in particular, is largely resistant to absorption and degradation (ATSDR, 2004). However, debromination from higher

to lower PBDE molecules can occur with exposure to sunlight and has been shown to occur in rodents and fish (Darnerud, et al., 2001; McDonald, 2002).

Five tetra, penta, and hexa BDEs are the predominant ones found in human tissues. These are congeners 47, 99, 100, 153, 154 (Bakker, et al., 2008; Costa & Giordano, 2007; Dufault, Poles, & Driscoll, 2005; P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001; Kuriyama, et al., 2007). Penta and octa congeners have been banned from use in the European Union (EU) since 2004 because of concerns about adverse health effects (Bakker, et al., 2008; Costa & Giordano, 2007). Their use has also been banned in several states in the US including California, Maine, Hawaii, and Washington (Costa & Giordano, 2007). Additionally, the US producer of penta and octa BDE voluntarily stopped production of these congeners in the US market at the end of 2004 (Bakker, et al., 2008; Costa & Giordano, 2007; Imm, et al., 2009). Products manufactured previous to this will continue to be exposure reservoirs (Imm, et al., 2009).

Since PBDEs are polymer additives, not chemically bound to the substances on which they are applied, they can be released into the environment (Alm, et al., 2006; Bakker, et al., 2008; P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001). Incineration, leaching from landfills, and volatilization (formation of dust) over a lifetime of use are thought to be ways in which this process occurs (Bakker, et al., 2008; Darnerud, et al., 2001; McDonald, 2002). PBDEs have been detected on computers and electronics, on surface water, in soil, sediment, sludge, and indoor and outdoor air samples (even in remote locations). They have also been found in fish, birds, and

mammals. Humans and animals become exposed when they inhale air or ingest food or dust that has been contaminated with PBDE molecules (Alm, et al., 2006; Bakker, et al., 2008; Costa & Giordano, 2007; Darnerud, et al., 2001; Dufault, et al., 2005; Gee & Moser, 2008; Imm, et al., 2009; McDonald, 2002; H. Viberg, et al., 2003). Dietary intake of fatty fish, meat, and dairy is thought to be a main source of human exposure (ATSDR, 2004; Darnerud, et al., 2001). Studies differ, however, in their estimates of exposure percentages attributed to diet, dust ingestion and inhalation (Bakker, et al., 2008).

Most studies show documented tissue levels of lower brominated PBDEs to be a factor 10-100 higher in the US than in other regions of the world (ATSDR, 2004; Costa & Giordano, 2007; Dufault, et al., 2005; Imm, et al., 2009). The highest levels are found in infants and toddlers. The high levels in this population are attributed to placental transfer, breastfeeding, and dust ingestion (Costa & Giordano, 2007; Costa, Giordano, Tagliaferri, Caglieri, & Mutti, 2008; Toms, et al., 2009).

Based on two studies of human breast milk conducted in Sweden in the late 1990s, it is estimated that infant intake of PBDEs (average of 5-8 congeners, predominantly BDE 47) from mothers' milk alone is 0.11 mcg/day (Darnerud, et al., 2001). Daily intake may be much higher for infants of North American women since levels here are 3-100 times higher than those tested elsewhere in the world (Dufault, et al., 2005).

Toms et al. (2009) found that blood levels of four PBDE congeners (47, 99, 100, 153) increased from birth to peak at age 2.6 to 3 years. Peaking levels in this age

group, later than when most mothers stop breastfeeding, suggests that toddlers have higher levels of exposure to these chemicals and/or a lower capacity to eliminate them. Dust ingestion may be a major exposure source for toddlers as hand to mouth exploration of the environment is a developmental characteristic of this age group (Toms, et al., 2009).

In June 2008, the US EPA set safe daily exposure levels of 0.1, 0.1, 0.2, and 7 mcg/kg body weight for BDE congeners 47,99, 153, and 209 respectively (Imm, et al., 2009). It is possible, based on documented breast milk and blood levels found in infants and toddlers, that exposure levels in this population are greater than those deemed safe by the EPA. This is especially concerning since infants and toddlers are more at risk for the adverse effects associated with exposure because their brains are in such a rapid state of development.

Neurological Effects

Animal Studies. Behavioral studies conducted in rodents under differing exposure protocols indicate that PBDEs cause alterations in neurobehavioral development. Changes in motor activity and cognition have been documented following PBDE exposure (Costa & Giordano, 2007; Darnerud, et al., 2001).

A group of Swedish researchers has conducted most of the studies on the developmental neurotoxicity of various PBDEs. In their experiments, neonatal mice or rats were given a single oral dose of a PBDE, usually on postnatal day (PND) 10. The timing of the exposure is significant as it corresponds to the period of rapid

growth in the neonatal mouse brain, or brain growth spurt (BGS), which occurs in rodents during the first three to four weeks of life. The researchers consider PND 10, at the height of the BGS, to be the time when the brain is the most sensitive to disruption by PBDEs. In humans the BGS begins in the third trimester and continues through the first two years of life (H. Viberg, et al., 2003).

The PBDEs tested by this group were BDE 47, 99, 153, 183, 203, 206, and 209. Exposure to all of the tested PBDEs resulted in long lasting changes in spontaneous locomotor behavior, namely hyperactivity (decreased habituation) (P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001; P. Eriksson, Viberg, Jakobsson, Orn, & Fredriksson, 2002; Gee & Moser, 2008; H. Viberg, 2009; H. Viberg, et al., 2003; H. Viberg, Fredriksson, A., Eriksson, P., 2004a, 2004b, 2007; H. Viberg, Fredriksson, A., Jakobsson, E., Orn, U., Eriksson, P, 2003; H. Viberg, Johansson, N., Fredriksson, A., Eriksson, J., Marsh, G., Eriksson, P, 2006). The PBDE exposed mice were initially hypoactive but then became hyperactive compared to controls (P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001). These changes in locomotor activity, in some cases, worsened with time (H. Viberg, et al., 2003; H. Viberg, Fredriksson, A., Jakobsson, E., Orn, U., Eriksson, P, 2003). Two of the PBDEs, BDE 209 and 183, did not cause the changes when given on PND 10 but did when given on PND 3. This is thought to be due to differences in how fast these PBDEs, or their metabolites, accumulate in the brain (H. Viberg, Fredriksson, A., Jakobsson, E., Orn, U., Eriksson, P, 2003).

Some of the tested PBDEs (BDE 99, 153, 203) were also found to cause

cognitive impairment. This was demonstrated by decreased spatial memory in a swim (Morris) maze (P. Eriksson, Jakobsson, E, & Fredriksson, A, 2001; H. Viberg, et al., 2003; H. Viberg, Johansson, N., Fredriksson, A., Eriksson, J., Marsh, G., Eriksson, P, 2006). In another study, rats were administered a penta BDE mixture from PND 6 to 12 and then tested in a visual discrimination learning task starting on day 30. The treated animals performed significantly worse than controls (Dufault, et al., 2005).

Information on possible mechanisms for the developmental neurotoxicity of PBDEs is still limited, but two general schools of thought are emerging. One is that the neurodevelopmental changes are related to effects PBDEs have on thyroid hormones, and the other is that PBDEs exert direct effects on the developing brain. Indeed, these ways of action are not mutually exclusive; both mechanisms may be at work (Costa, et al., 2008; McDonald, 2002).

Thyroid hormones are crucial to normal brain development starting in-utero and continuing for the first two years of life. Disruption, even temporary disruption, of thyroid levels can negatively impact brain development. Thyroid hormones are essential for normal assembly and stability of the cytoskeletal system. They control the proliferation, migration, and differentiation of neurons to different regions of the brain. They also regulate the cholinergic and dopaminergic transmitter systems which supply the hippocampus and the cerebral cortex (Porterfield, 2000)

PBDE exposure has been shown to disrupt thyroid hormone homeostasis. Most rodent studies show reduced concentrations of T_4 after rodents were exposed to differing PBDEs on various timelines (Ellis-Hutchings, 2006; Kuriyama, et al.,

2007; T. Zhou, Ross, D., DeVito, M., Crofton, K, 2001; T. Zhou, Taylor, M., Devito, M., Crofton K., 2002). Rats given an octo BDE mixture (DE 71 or 79) from gestational day (GD) 6 to PND 21 showed significantly decreased T_4 levels in the dam, fetuses, and pups on GD 20, PND 4, and PND 14 with recovered levels by PND 36 (T. Zhou, Taylor, M., Devito, M., Crofton K., 2002). Another study yielded similar results on PND 18 when rats were given DE 71 on GD 6 to PND 18. Levels recovered by PND 31 (Ellis-Hutchings, 2006). A single low dose exposure to PDE 99 elicited decreased T_4 levels in pups (Kuriyama, et al., 2007). It is thought that the changes in T_4 levels may be due to increased metabolism/excretion of circulating T_4 and/or that PBDEs may interfere with the thyroid transport protein, transthyretin (TTR) (Costa, et al., 2008).

PBDEs may also have direct neurotoxic effects on glial and neuronal cells (Costa, et al., 2008). Alterations in various brain proteins have been demonstrated post PBDE exposure. One study of mice exposed to BDE 209 on PND 3 showed changes in proteins involved with survival, growth, and synaptogenesis of neurons (H. Viberg, Mundy, W., Eriksson, P, 2008). Another study showed changes in proteins involved with neurodegeneration and neuroplasticity in the striatum and those involved metabolism and energy production in the hippocampus after a single dose of BDE 99 given during the BGS (Alm, et al., 2006). Additionally, a decrease in the density of cholinergic nicotinic receptors was found in the hippocampus of mice exposed to BDE 153 (H. Viberg, et al., 2003).

Epidemiological Studies. Only a couple of epidemiologic studies reporting neurodevelopmental effects associated with PBDE exposure have been conducted. One was a prospective study conducted on 62 Dutch children. The mothers of the children in this study were determined to have blood levels of BDE 47, 99, 100, 153, and 154 during week 35 of pregnancy. Correlations were then made between exposure and over 20 indices of child development and behavior at age 5-6. PBDE exposure was associated with mixed adverse (worse attention and fine motor skills) and beneficial (better visual perception and behavior) effects on development. No significant association was found between exposure and cognitive impairment as indicated by the WPPSI-R (Weschler Preschool and Primary Scale of Intelligence-Revised) test domains (Roze, 2009).

Another prospective study, initiated in Manhattan after 9/11/01, included 329 children. Cord blood was analyzed for PBDE congeners 47, 99, and 100. The participants were then assessed for neurodevelopmental effects at ages 1, 2, 3, 4, and 6. Children with higher concentrations of these PBDEs scored lower on tests of physical and mental development at 1-4 and 6 years of age (Herbstman, et al., 2009). Herbstman hypothesizes that the inconsistency in findings between the two studies may be due to differences in exposure levels, sample size, and statistical analyses performed.

Ways to Reduce Exposure

Increasing public awareness of the health concerns related to PBDE exposure is the first step toward reducing exposure. One organization working toward that

end is the Environmental Working Group (EWG). A portion of their website is dedicated to the risks associated with PBDEs and how to reduce exposure. Their suggestions primarily concern foam products and electronics. New foam products (purchased after 2005) should not have been treated with a penta BDE mixture, but products purchased before this probably have been. EWG recommends inspecting older foam items and replacing anything misshapen or breaking down. They also advise against reupholstering any old foam items. Using a vacuum with a hepa filter is recommended since they are more efficient at trapping smaller particles. In terms of electronics, some companies have made commitments to eliminating deca BDE mixtures from their products. Supporting these companies not only reduces PBDE exposure but sends a message that consumers want PBDEs out of products (EWG, 2008).

Dust ingestion is thought to be a major source of exposure for babies and toddlers. It is important, then, to encourage parents to frequently wash their children's hands since this population spends more time on the floor/ ground and hand-to mouth exploration of the environment is common. Parents may also want to consider reduction in duration of breastfeeding and consumption of fatty meat, fish, and dairy products. In most cases, however, the benefits of breastfeeding are thought to outweigh the risks. Parents who work with the production or disposal of PBDEs, or PBDE containing products should be mindful that they can carry PBDEs home to their families on their clothes or bodies. As a result, parents should shower/change clothes before leaving work. Work clothes should also be kept and

laundered separately from other clothes (ATSDR, 2004).

Some nutrient deficiencies in pregnancy may put pregnant women and fetuses at a greater risk for the adverse effects associated with PBDE exposure. PBDEs have been shown to affect thyroid homeostasis. Nutrient deficiencies, such as iodine and vitamin A, can stress an already taxed thyroid system and enhance the susceptibility for thyroid hormone disruption (Ellis-Hutchings, 2006; McDonald, 2002).

Pesticides

Source

Pesticides encompass a diverse group of products that have the general purpose of preventing, repelling, mitigating, or destroying pests (Davis, 2007; Rosas & Eskenazi, 2008; B. Weiss, Amler, & Amler, 2004). Some are broad-spectrum, treating a wide range of insects, whereas others are more selective, targeting specific ones (Jurewicz & Hanke, 2008). Over a billion pounds of pesticides are applied in the United States each year (B Eskenazi, Bradman, & Castorina, 1999; Brenda Eskenazi, et al., 2007; B. Weiss, et al., 2004; Young, et al., 2005). Three-quarters of conventional pesticides are used in agriculture. The remaining amounts are used in industrial, governmental, commercial, and residential settings (Rosas & Eskenazi, 2008; B. Weiss, et al., 2004). A 2006 study by the Environmental Protection Agency (EPA) estimated that 75% of US households had used one or more pesticides indoors in the past year (Davis, 2007; Weiss, Amler, & Amler, 2004). Another EPA study estimated that 80% of all pesticide exposures happen indoors

(Davis, 2007; Korrick & Sagiv, 2008; Rosas & Eskenazi, 2008). In humans, pesticides and their metabolites have been detected in amniotic fluid, meconium, blood (including umbilical cord blood, maternal and placental blood), ovarian follicular fluid, semen, breast milk, and urine (Colborn, 2006; Rosas & Eskenazi, 2008).

There are four main types of pesticides—organochlorines (OC), carbamates, pyrethroids, and organophosphates (OP) (Davis, 2007; B. Weiss, et al., 2004). Organochlorines, introduced in the 1940s, are an older class of pesticides. The use of many OCs has been restricted by the EPA due to concerns about their persistence in the environment and adverse effects on wildlife and human health. DDT (dichlorodiphenyltrichloroethane), one of the most researched OC pesticides, was banned from use in the US in 1972 for this very reason. It is still used on a limited basis in some third world countries for disease vector control (Rosas & Eskenazi, 2008). Like PBDEs, organochlorines are lipophilic and bioaccumulate. Human exposure, therefore, comes primarily from fatty foods in the diet such as dairy products and fish. In general, usage restrictions in the US and other developed countries have been associated with decreasing serum levels of these types of pesticides (CDC, 2009a).

Carbamates have been widely used in the United States and worldwide. They have been used in agriculture and on lawns, golf courses, and nurseries. Carbamate use in agriculture, however, has been decreasing with the increasing popularity of pyrethroids and other insecticides. Carbamates do not persist in the environment and have a low potential for bioaccumulation. The general population is exposed to

carbamates when they are applied in residential settings. To a lesser extent, contaminated foods can also be a source. Carbamates can be absorbed dermally, through ingestion, and inhalation (CDC, 2009a).

Pyrethroids, synthetic analogues of naturally occurring chemicals in the chrysanthemum flower, are used to control insects in a variety of residential, commercial, and public settings. They are also used as ingredients in anti-lice shampoos and topical scabies treatments (CDC, 2009a; Rosas & Eskenazi, 2008; B. Weiss, et al., 2004). In general, pyrethroids are not persistent in the environment and rapidly degrade within days to months. Pyrethroids have low toxicity in mammals and birds but are highly toxic to fish and some aquatic invertebrates. Therefore, usage is restricted near water. The general population is exposed to pyrethroids through residential use and contaminated foods. Absorption occurs primarily through ingestion and inhalation, pyrethroids are not well absorbed through the skin. After absorption, pyrethroids are rapidly metabolized and eliminated in urine and bile over several days (CDC, 2009a).

Organophosphates (OP) are the class of pesticides most used in U.S. agriculture, comprising about half of the insecticides used in this country (Rosas & Eskenazi, 2008; B. Weiss, et al., 2004). Most residential uses of OP pesticides, however, have been phased out as a result of the Food Quality Protection Act of 1996. Exposure to the general population occurs through contaminated food and hand to mouth contact from contaminated surfaces. OP pesticides can be absorbed through dermal contact and inhalation, but their primary route is through ingestion.

The elimination half lives for OP pesticides in mammals can range from hours to weeks (CDC, 2009a).

Children, for multiple reasons, are particularly susceptible to pesticide exposure. In fact, "it is fairly safe to say that every child conceived today in the Northern hemisphere is exposed to pesticides from conception throughout gestation and lactation regardless of where it is born" (Colborn, 2006, p. 10). Children are exposed to pesticides in-utero. Maternal exposure to pesticides can reach the developing fetus through the placenta and the immature blood brain barrier (Brenda Eskenazi, et al., 2007). Dietary pesticide sources can be especially significant for children (Brenda Eskenazi, et al., 2007; B. Weiss, et al., 2004). Infants can be exposed to pesticides through breast milk and children in general eat, drink, and breathe proportionately more than adults, thus increasing the degree to which they are exposed (B Eskenazi, et al., 1999; Brenda Eskenazi, et al., 2007; Rosas & Eskenazi, 2008; B. Weiss, et al., 2004; WHO, 2006). Pesticides used indoors can be released into the air from where they are initially applied and then settle into toys, bedding, furniture, and carpeting and become part of house dust (Davis, 2007; B. Weiss, et al., 2004). Parents who work occupationally with pesticides can carry residue home on their bodies and clothes (Rohlman, et al., 2005). Behaviors and qualities that are inherent to young children such as hand-to-mouth exploration of their environment, eating or mouthing non-food items, and having breathing zones close to the ground also increase chances for exposure (B Eskenazi, et al., 1999; Rosas & Eskenazi, 2008; B. Weiss, et al., 2004).

Neurological Effects

The four classes of pesticides work in different ways. OC pesticides act on the central nervous system by interfering with the movement of ions through neuronal membranes. They delay the closing of the sodium ion channels, prevent potassium channels from fully opening, and inhibit neuronal transport of calcium ions. The net result of these actions is to keep the neuron in a state of depolarization, potentiating the release of neurotransmitters, and effectively leading to a state of central nervous system excitation. This manifests as symptoms of hyperexcitability, convulsions, and tremors (ATSDR, 2002; Rosas & Eskenazi, 2008). Pyrethroids work by prolonging sodium channel opening when a nerve cell is depolarized. There may be other actions on neuroreceptors and ion channels as well (CDC, 2009a; B. Weiss, et al., 2004). OP and carbamate pesticides inhibit acetylcholinesterase. This results in accumulation of the neurotransmitter acetylcholine in neuronal junctions of the central and peripheral nervous systems. The net result of this action is continuous stimulation and then suppression of neurotransmission (Dam, 2003; Brenda Eskenazi, et al., 2007; Rosas & Eskenazi, 2008; Slotkin, 2006; B. Weiss, et al., 2004).

Fetuses, infants and young children have an increased susceptibility to the neurotoxic effects of pesticides (Brenda Eskenazi, et al., 2007; P Grandjean, Harari, Barr, & Debes, 2006). The fact that the brain is rapidly growing—replicating, differentiating, forming synapses and axons-- means small disturbances could have significant consequences on development. In addition, the developing brain is immature (Brenda Eskenazi, et al., 2007; P Grandjean, et al., 2006). The blood brain

barrier is not fully formed until about six months of age and, thus, is not able to protect itself as effectively as it can later in development (P Grandjean, et al., 2006). The mechanisms by which some pesticides work are enhanced during fetal life and early childhood. Levels of acetylcholinesterase are already reduced during pregnancy and fetuses and young children have lower levels of enzymes that deactivate OP pesticides (B Eskenazi, et al., 1999; Brenda Eskenazi, et al., 2007).

Neurological effects can result from both acute and chronic exposure to pesticides (Ruckart, Kakolewski, Bove, & Kaye, 2004; B. Weiss, et al., 2004). Acute exposure to OP and carbamate pesticides can result in loss of consciousness, dizziness, headache, confusion, loss of coordination, twitching of muscles, muscle weakness, tremor, convulsions, nausea/vomiting, abdominal cramps, blurred vision, diarrhea, excessive salivation and perspiration, and even death (Davis, 2007; Ruckart, et al., 2004). Acute pyrethroid exposure can result in tremor, seizures, choreathetosis, and salivation. Generally, potential effects are worse with increasing levels of exposure (Davis, 2007).

Much less is known about the neurological effects of chronic, low levels of exposure to pesticides (Brenda Eskenazi, et al., 2007; Handal, Lozoff, Breilh, & Harlow, 2007; B. Weiss, et al., 2004). In neonatal rats, repeated low level in-utero exposure to OP pesticides has been linked to impaired maze performance, balance, and locomotion (B Eskenazi, et al., 1999). Chronic exposures have also been associated with subtle changes in short term memory and attention, cognitive

dysfunction, motor skill and sensory symptoms, behavioral problems, and mental and emotional disorders (Davis, 2007; Handal, et al., 2007; Ruckart, et al., 2004).

Epidemiological Studies. Relatively few epidemiological studies have assessed the neurodevelopment of newborns and young children after exposure to low levels of pesticides (Brenda Eskenazi, et al., 2007; P Grandjean, et al., 2006; Handal, et al., 2007). Studies conducted have generally focused on populations of children considered to be at higher risk of pesticide exposure than the general population (Bouchard, Bellinger, Wright, & Weisskopf, 2010; Jurewicz & Hanke, 2008; Rosas & Eskenazi, 2008; Young, et al., 2005).

Two such studies involved the children of agricultural workers from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort. The Salinas Valley in California is a major center for agricultural production in the United States. Approximately 500,000 pounds of OP pesticides are applied here each year (Brenda Eskenazi, et al., 2008; Young, et al., 2005). One study of this cohort examined the association between OP pesticide exposure, as determined by urinary dialkylphosphate (DAP) metabolites, and children's development at 6, 12, and 24 months. In general, the investigators found that pregnancy DAP metabolite levels were associated with mental development problems but child levels were not. Neither pregnancy nor child DAP levels were associated with psychomotor development or attention problems. Both prenatal and child DAP metabolite levels, however, were associated with risk of pervasive developmental disorders at 24 months of age (Brenda Eskenazi, et al., 2007).

In another CHAMACOS birth cohort study, Young et al. (2005) examined urinary DAP metabolite levels of 381 infants at 14 weeks and 26 weeks gestation and 7 days postpartum. Rising average prenatal metabolite levels were associated with and increased number of abnormal reflexes and an increased proportion of infants with more than three abnormal reflexes. In a similar cohort study, conducted at Mt. Sinai Children's Environmental Health Center in New York City, indoor pesticide use and child neurodevelopment was examined. Investigators found that increasing levels of urinary OP metabolites were associated with increasing numbers of abnormal reflexes (Engel, et al., 2007).

A 2005 study compared children from agricultural communities in North Carolina and Oregon with those from non-agricultural communities. A number of neurobehavioral tests were performed on 78 children, ages 48 to 71 months. Analysis of the resulting data showed that children from the agricultural communities demonstrated poorer performance on the measures of response speed and latency (Rohlman, et al., 2005).

Another study examined the association between indoor OP pesticide use and neurodevelopment. Methyl parathion, an OP pesticide not licensed for indoor use, was sprayed illegally for cockroaches in at least nine states including Mississippi and Ohio. The study compared exposed children, six years old or younger at the time of spraying, with unexposed ones (exposure was determined by urinary metabolite levels and environmental wipe samples). Results suggested that long term effects of exposure may include subtle changes in short term memory,

attention, and may add to some motor skill and behavioral problems. No differences in integration of visual and motor skills, multi-step processing, or general intelligence were found (Ruckart, et al., 2004).

Organophosphate pesticides are heavily used in Ecuador, where agricultural products comprise the majority of exports. The cut-flower industry, which greatly relies on OP pesticides, has become the country's third most valuable export. Two studies looked at the neurodevelopment of children in this region. The first study compared a high potential exposure group of children, living in a community dominated by the cut-flower industry, with lesser-exposed group living in a more rural setting. The Ages and Stages Questionnaire (ASQ) was administered to all the children. Results from the 3-23 month old group showed an association between high potential exposure and delays in the domains of communication, gross motor skills, fine motor skills, resolution of problems, and socio-individual skills. The 24-61 month old high potential exposure group showed delays in the domains of communication and gross motor skills. The effects were worse in those children who also showed signs of malnourishment in the form of growth stunting (Handal, et al., 2007).

Another study of Ecuadorian children looked at 72 second and third grade children whose mothers were or were not occupationally exposed to OP and carbamate pesticides during pregnancy. Thirty-seven children, whose mothers worked at a floriculture plantation while pregnant, were considered exposed. Results showed that the children with prenatal exposure had increases in

abnormalities on neurologic exam and on the Stanford-Binet copying test. Current exposure, as determined by urinary DAP metabolite levels, was associated with increased reaction time. The researchers also concluded that the effects of pesticide exposure may add to the already deleterious effects of malnutrition on neurodevelopment (P Grandjean, et al., 2006).

Recently, a study was conducted on children considered to have average levels of pesticide exposure. A cross-sectional study, using data from the National Health and Nutrition Examination Survey (2000-2004), looked at the association between urinary DAP metabolite levels and Attention Deficit Hyperactivity Disorder in 1139 children, ages 8 to 15. The investigators found that children with higher urinary DAP levels were more likely to be diagnosed with this disorder. This study is significant because it is more applicable to the general US population. The results reflect data from a nationally representative sample instead of one with higher exposure levels (Bouchard, et al., 2010).

Ways to Reduce Exposure

Evidence suggests that pesticide exposure is harmful to the brain, especially the developing one. It is therefore wise for people to reduce their exposure to pesticides. Using integrative pest management practices (IPM) and eating organic food are two ways to achieve this goal.

Integrative pest management is defined as minimizing pest infestations by the coordinated use of knowledge about the pests themselves, their environment, and pest prevention/control strategies in order to minimize damage to people,

property, and environment (EPA, 2009). Upon reviewing the evidence, an expert panel concluded that IPM is indeed effective at decreasing pesticide residue exposure (Sandel, et al., 2010). In practice, IPM entails identifying the pest, learning its habits, and making structural or sanitation improvements to combat the pest, such as sealing cracks in the home and removing trash. If preventative measures are ineffective, using living biological or mechanical controls, like traps, is the next logical step. If these control methods are ineffective, proceeding to the limited use of pesticides is the next control measure advised. Limited use means using the smallest amount possible of the least toxic pesticide to control the pest. When pesticides are required, avoidance of use around children and storage out of their reach is essential (Davis, 2007; B. Weiss, et al., 2004).

Eating organic food is another way of reducing exposure to pesticide residue. In 2008, the U.S. Department of Agriculture found pesticide residue on 7 out of every 10 conventionally-grown fruit and vegetable samples analyzed (EWG, 2010). Although current levels of pesticide residue in the food supply are thought to be below regulatory thresholds for the general population, concerns have been raised that regulatory thresholds are not sufficient for children given their unique biologic and developmental characteristics (CDC, 2009a). Organic food is grown without the use of synthetic pesticides, and eating organically has been shown to reduce children's pesticide body burdens. If organics aren't available or economically feasible, the environmental working group (EWG) provides a list of the worst twelve and best fifteen fruits and vegetables in terms of pesticide residue. The EWG

estimates that pesticide consumption can be reduced by nearly four fifths just by avoiding the most contaminated and eating the least contaminated fruits and vegetables (EWG, 2010).

Mercury

Source

Mercury is a naturally occurring metal that has always been released into the environment through volcanic eruptions and the erosion of mercury-containing rocks and soil. Relatively recent human activities, however, now account for 80% of mercury releases into the air (ATSDR, 1999; Davidson, Myers, & Weiss, 2004). Fossil fuel combustion, waste incineration, and mining/smelting account for the majority of these releases. Mercury can be found in its elemental, or metallic, form as well as several other inorganic and organic chemical compositions (ATSDR, 1999; CDC, 2009a; Counter & Buchanan, 2004; Davidson, et al., 2004).

Elemental mercury is a silvery liquid at room temperature. It is acquired primarily through the process of refining mercuric sulfide in cinnabar ore (ATSDR, 1999; CDC, 2009a). Elemental mercury is used in production of chlorine gas and caustic soda. It is also used in thermometers, sphygmomanometers, batteries, electrical switches, fluorescent lights, and substances used in some Latin American and Caribbean rituals (ATSDR, 1999; CDC, 2009a; Counter & Buchanan, 2004; Davidson, et al., 2004). A major source of elemental mercury exposure in humans is the placement and wearing down of dental amalgams (ATSDR, 1999; CDC, 2009a;

Davidson, et al., 2004). Inhalation is the major route of elemental mercury absorption. Gastrointestinal absorption, by contrast, is poor. Eighty percent of inhaled mercury vapors are readily absorbed (ATSDR, 1999; CDC, 2009a; Counter & Buchanan, 2004). Once in the body, elemental mercury oxidizes into various inorganic forms. Blood concentrations decline with an initial rapid half-life of 1-3 days and a slower secondary half-life of 1-3 weeks. It settles with greatest concentrations in the kidneys, but can also cross the blood-brain and placental barriers to accumulate in the brain (CDC, 2009a; Counter & Buchanan, 2004). Excretion occurs primarily through the urine (CDC, 2009a).

Inorganic mercury compounds form when elemental mercury combines with other elements like sulfur, oxygen, or chlorine. In the past, inorganic mercury compounds, or mercury salts, were widely used in laxatives, teething powders and worming medications. Safer and more effective agents are used in these products today. However, inorganic mercury is still being used in fungicides, skin lightening creams, batteries, pigments, and some alternative medications (ATSDR, 1999; CDC, 2009a; Davidson, et al., 2004). Since inorganic mercury compounds are powders and do not typically vaporize, they do not easily enter the body through inhalation. The primary route of absorption for inorganic mercury is through ingestion. Approximately 7-15% of an ingested dose becomes absorbed, however, in some cases absorption can be up to 40%. Dermal absorption from applied inorganic compounds is at 2-3% (Counter & Buchanan, 2004). Half-life is similar to the secondary phase of elemental mercury, around 1-3 weeks. Inorganic compounds

settle primarily in the kidney and do not readily cross the blood-brain or placental barriers. Excretion is by both renal and fecal routes (ATSDR, 1999; CDC, 2009a; Counter & Buchanan, 2004).

Organic mercury compounds are still in use today as preservatives and topical antiseptics. Thimerosal, containing 50% ethylmercury, has been used as a preservative in vaccinations. Its use in US pediatric vaccine formulations, however, has been greatly reduced or eliminated over the past decade (CDC, 2009a; FDA, 2010b). The organic mercury compound methylmercury is the most researched and main source of mercury exposure for the general population (CDC, 2009a; Counter & Buchanan, 2004). Humans are exposed to methylmercury by consuming contaminated fish. Elemental and inorganic mercury released into the environment ends up in bodies of water where it is converted to methylmercury by phytoplankton, bacteria, and fungi. It is then ingested and stored in fish tissue where it bioaccumulates and biomagnifies up the food chain. It is found in the most toxic concentrations in the largest and oldest predatory fish (ATSDR, 1999; Anna F. Castoldi, et al., 2008; CDC, 2009a; Counter & Buchanan, 2004). There are varying levels of methylmercury in shellfish and sea mammals as well (Anna F. Castoldi, et al., 2008; Davidson, et al., 2004).

The human gastrointestinal tract absorbs 95% of the methylmercury that is ingested. Once in the bloodstream, methylmercury readily crosses the blood brain and placental barriers. It concentrates in the brain where it is found at levels five times higher than those in the blood. Additionally, fetal cord blood levels of

methylmercury are proportional or higher than those found in maternal blood. There is greater risk to the fetus through in utero exposure to methylmercury than through breast milk, but some mercury does pass through the breast milk and represents potential postnatal exposure (Anna F. Castoldi, et al., 2008; CDC, 2009a; Counter & Buchanan, 2004). The average half-life of methylmercury in the body is 50 days but can be anywhere between 20-70 days. The main route of excretion is through the feces (Davidson, et al., 2004).

Neurological Effects

Infants are primarily exposed to mercury through maternal ingestion of fish during gestation and breastfeeding. As children grow older, they can continue to be exposed from their own fish consumption. Since ingestion of contaminated fish and seafood constitutes the greatest source of mercury exposure in children, the following review will be limited to what is known about the neurological effects of methylmercury.

The neurotoxic effects of high levels of methylmercury exposure have been well documented. Mass poisoning in Japan in the 1950s and 1960s and in Iraq in the 1970s provided much of that knowledge. In Japan, fish consumed from waters heavily contaminated with mercury-laden industrial discharge poisoned thousands of villagers. In Iraq, thousands were sickened and hundreds died after consuming bread made from grain treated with an organomercury fungicide. Children who were in-utero at the time of the poisoning had much more significant neurological

damage than the adults (A. F. Castoldi, Coccini, Ceccatelli, & Manzo, 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; FDA, 2010b; Spurgeon, 2006).

Poisoned adults showed damage to focal areas of the brain including the visual cortex and the cerebellum as well as peripheral sensory nerves. The damage to the developing brain, by contrast, was diffuse and widespread, even occurring when the mother showed no overt signs of poisoning. The neurodevelopmental effects of high dose exposure to methylmercury included microcephaly, cerebral palsy, severe mental retardation, seizures, blindness, deafness, dysarthria, abnormal reflexes, and gross impairments of mental and motor development (A. F. Castoldi, et al., 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; Davidson, et al., 2004; FDA, 2010b). In vitro and in vivo animal studies suggest the mechanisms of methylmercury's effects include neuronal cell necrosis and apoptosis, disruptions in calcium channel signaling, microtubule disruption, oxidative stress injury, and damage to the glutamatergic, muscarinic cholinergic, and dopaminergic neurotransmitter systems (A. F. Castoldi, et al., 2001).

Whereas the neurotoxic effects of high dose exposure to methylmercury are not disputed, findings are inconsistent when it comes to lower level chronic exposures. Some studies show associations between mercury exposure and impaired neurodevelopment whereas others do not (A. F. Castoldi, et al., 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; Davidson, et al., 2004; FDA, 2010b). The Faroe Islands investigation and the Seychelles study, which make up the bulk of what is known about low-level methylmercury exposure and

neurodevelopment, had divergent findings. Both studies were longitudinal and of high methodologic quality (Counter & Buchanan, 2004; Spurgeon, 2006).

Epidemiological Studies. The Faroe Islands are located in the North Atlantic between Iceland and Scotland. The Faroese are exposed to methylmercury from ingestion of pilot whale meat and blubber as well as fish. The Faroe Islands investigation enrolled a birth cohort of 1022 children in the study between 1986 and 1987. Testing of the children was done at 12 months, 7 years, and 14 years. Methylmercury exposure was determined by measurement of cord blood and maternal hair mercury levels at birth. At ages 7 and 14, methylmercury exposure was positively associated with impairments in attention, language, verbal memory, motor speed and visuospatial function (A. F. Castoldi, et al., 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; Davidson, et al., 2004; FDA, 2010b; Spurgeon, 2006).

Numerous cross sectional studies have also found associations between methylmercury exposure and neurodevelopment. Of these, one frequently cited took place in New Zealand. In 1977-1978 a group of 237 children were identified as high, medium, or low methylmercury exposure based on maternal hair mercury levels and maternal diet questionnaires. At age four, increased prevalence of abnormal results on the Denver Developmental Screening Test was found in highly exposed children. When the children were six to seven years old, 26 psychological and scholastic tests were administered to the children. Maternal hair mercury levels were associated with decrements in six of these tests measuring full-scale IQ,

language development, gross motor skills, and visual-spatial performance (A. F. Castoldi, et al., 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; Crump, Kjellstrom, Shipp, Silvers, & Stewart, 1998).

Another, more recent, cross-sectional study took place in Poland between 2001 and 2003. Maternal and cord blood mercury levels were tested in a cohort of 233 children at birth. At one year of age, the children were tested for neurobehavioral outcomes using the Bayley Scales of Infant Development. Mean maternal and cord blood mercury levels were higher in those children with delayed performance than in those with normal neuro-cognitive performance. The differences were significant for maternal blood levels and borderline significant for cord blood levels (Jedrychowski, et al., 2006; Mozaffarian & Rimm, 2006).

Grandjean et al. found significant associations between hair mercury concentrations and reduced abilities on neuropsychological tests assessing attention, motor function, and visuospatial performance in 351 children, ages 7 to 12, in Brazil (A. F. Castoldi, et al., 2001; P. Grandjean, White, Nielsen, Cleary, & de Oliveira Santos, 1999). Two other studies conducted by Steuerwald et al. and Mckeown-Eyssen et al. reported positive associations between methymercury exposure and abnormalities on neurological exam in children less than three years of age. Both, however, express some reservations on the strength of their findings (Anna F. Castoldi, et al., 2008; Spurgeon, 2006).

Other studies have reported no significant association between methylmercury exposure and neurodevelopment, including the Seychelles Child

Development Study. The Seychelles Islands are located approximately 1000 miles to the east of the African mainland. Fish consumption accounts for methylmercury exposure in this population where 85% of the people eat marine fish daily. Marine mammals are not eaten (Counter & Buchanan, 2004). The Seychelles Child Development Study was a large, high quality longitudinal investigation that included a pilot study that began in 1987 and a main study that began in 1989. Both studies enrolled over 700 children. Exposure was determined by measurement of mercury levels in maternal and child hair samples. In the pilot study, infants were enrolled at 5-109 weeks, and followed at 66 months and 108 months. No significant association was found between maternal hair mercury and overall neurological evaluation, increased deep tendon reflexes or muscle tone in children at 5-109 weeks. In the main study, various neurodevelopmental tests were conducted at 6 months, 19 months, 29 months, 66 months, 107 months, and 11 years. No significant adverse neurodevelopmental effects were found to be associated with methylmercury exposure regardless of age at testing (A. F. Castoldi, et al., 2001; Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; Davidson, et al., 2004; FDA, 2010b; Spurgeon, 2006).

A cross sectional study of 131 mother-child pairs, conducted in Peru by Marsh et al., found no association between methymercury exposure and neurological outcomes. Murata et al. conducted another cross sectional study on the island Madeira (Portugal). They performed neurological, neurodevelopmental, and neurophysiological tests on 149 first graders, using the child's hair as biomarker for

exposure. They found no clear association between methymercury exposure and neurodevelopment (Counter & Buchanan, 2004; Spurgeon, 2006).

Counterintuitively, some test results have, in fact, shown enhancements with low-level methylmercury exposure. In the Seychelles study, two endpoints, language function at 66 months and ADHD index at 107 months, were improved with exposure (Davidson, et al., 2004; Spurgeon, 2006). In French Guiana, Cordier et al. also found that results of one test were enhanced with methylmercury exposure in children ages 9 months to 12 years (Spurgeon, 2006).

A cross-sectional US pregnancy and child cohort study in eastern Massachusetts examined associations between maternal fish intake during gestation and maternal hair mercury at delivery with infant cognition. The study, conducted between 1999 and 2003, examined 135 infants at six months of age. Maternal fish consumption was positively associated with infant visual recognition memory scores, but mercury levels were negatively associated (Mozaffarian & Rimm, 2006; Oken, et al., 2005).

Numerous explanations have been proposed for the inconsistencies seen in these studies. The enhanced test results associated with methylmercury exposure have been attributed to breastfeeding or the nutrients in the fish, such as omega 3 fatty acids selenium, and vitamin E. In some studies, selenium and/or vitamin E have even been shown to confer some protection against the neurotoxicity of methylmercury (Anna F. Castoldi, et al., 2008; Mozaffarian & Rimm, 2006; Oken, et al., 2005).

It is hypothesized that the associations found in the Faroe Islands study were a result of the higher levels of methylmercury and other toxins, such as polychlorinated biphenyls (PCBs), in whale meat and blubber, not from the lower methymercury levels found in fish. Experimentally, PCBs have been shown to interact with methymercury in a synergistic, additive, and antagonistic manner. The limited experimental and epidemiological evidence that exists, however, does not indicate that PCB co-exposure markedly worsens the toxicity of methymercury (Anna F. Castoldi, et al., 2008). Upon reviewing the evidence, the U.S. National Academy of Sciences concluded that the adverse outcomes seen in the Faroe Islands study were not due to PCB co-exposure (Counter & Buchanan, 2004; Davidson, et al., 2004).

Patterns of exposure may also complicate the interpretation of the data. Differences in frequency, source, and amount of methymercury exposure were found among the populations studied. Episodic higher-level exposures are thought to be more detrimental than continuous lower level exposures, despite similar body burden levels. Timing of exposure may also affect outcomes, given the “windows” of fetal brain development that occur at different times during gestation (Anna F. Castoldi, et al., 2008).

Other confounders include gender and delayed onset of effects. Numerous studies have indicated that boys appear more vulnerable to the effects of methylmercury than girls. In addition, some studies have shown that the effects of

prenatal exposure to methylmercury did not become apparent until adulthood (Anna F. Castoldi, et al., 2008).

Lack of homogeneity among studies may also account for the seemingly contradictory results. The studies vary in design (longitudinal vs. cross sectional), mercury assessment methods (hair vs. blood samples), type of mercury measured (organic, inorganic, total), timing of assessment (infancy vs. childhood), confounding variable control, type of outcome testing, and statistical analysis methods used. Such differences limit the ability to make comparisons across studies (Mozaffarian & Rimm, 2006; Spurgeon, 2006).

Ways to Reduce Exposure

The EPA's reference dose for methylmercury of 0.1 mcg/kg of body weight per day was reviewed by the National Academy of Sciences in 2000. After reviewing the New Zealand, Faroe Islands, and Seychelles studies, it was determined that there is scientific evidence to deem this dose likely be without appreciable harmful effects over a lifetime. The Faroe Islands investigation was the critical study used to make this determination (Anna F. Castoldi, et al., 2008; Counter & Buchanan, 2004; FDA, 2010b).

The EPA and the FDA have issued guidelines regarding fish consumption to women who may become pregnant, pregnant women, nursing mothers, and young children based on this reference dose. They state that fish and shellfish contain nutrients, such as protein and omega 3 fatty acids, that are important the growth and development of children. In order to reduce exposure to methylmercury while

still obtaining the nutritional benefits of fish, they recommend the following: 1) Do not eat fish known to have high levels of mercury such as shark, swordfish, king mackerel, and tilefish. 2) Up to 12 ounces of fish and shellfish lower in mercury, such as light tuna, salmon, pollock, shrimp, and catfish, may be consumed per week. Albacore "white" tuna is higher in mercury and therefore the recommendation is to not eat more than six ounces of this per week. 3) Advice from local advisories should be sought for fish caught in local rivers, lakes, and coastal areas. Barring none, up to six ounces can be consumed if no other fish will be consumed that week (EPA, 2004).

The Environmental Working Group (EWG) issued a report in 2001 stating that the FDA/ EPA guidelines fall short, that the current guidelines could expose one in four newborns to unsafe levels of methylmercury for at least one month of pregnancy. The current recommendation, they argue, is calculated to protect a 150-pound man, half of the women in the United States weigh less than this. The FDA/EPA guideline also does not take into account the mercury already present in a woman's body prior to pregnancy. According to the CDC, 10% of women of childbearing age in the United States have blood mercury levels that the National Academy of Sciences deem potentially hazardous to the developing fetus. The EWG's analysis took into account real differences among women and their risks from mercury exposure instead of using a hypothetical "average." They matched this with a database of fish contamination test results from seven different government sources. What resulted was the creation of a distribution of blood methylmercury

levels comparable to that found in the general population of women (J. W. Houlihan, R., 2001).

The resulting EWG recommendations for fish consumption among women of childbearing age are more stringent. In addition to the four fish already contraindicated by the EPA/FDA, the EWG recommends women considering pregnancy, pregnant and nursing women, and young children should not eat tuna steaks, sea bass, oysters (Gulf of Mexico), marlin, halibut, pike, walleye, white croaker, and large mouth bass. The following fish should be consumed for no more than one meal per month: canned tuna, mahi mahi, blue mussels, eastern oyster, cod, pollock, salmon (Great Lakes), blue crab (Gulf of Mexico), channel catfish, and lake whitefish. The EWG recommends the following fish as species that are the least contaminated by methylmercury: farmed trout, farmed catfish, shrimp, fishsticks, flounder, wild pacific salmon, croaker, blue crab (mid-Atlantic), and haddock (J. W. Houlihan, R., 2001).

Improvements in disseminating information about methymercury levels in seafood to women of childbearing age are needed. Education and outreach to pregnant women about methymercury risks have been inadequate (J. W. Houlihan, R., 2001). Health care providers for women of childbearing age, pregnant women, and children need to be aware of the risks posed by methymercury exposure in order to properly educate their patients about safe levels of fish consumption.

Lead

Source

Lead is a heavy metal element found in the earth's crust usually as an ore, a combination of lead and another element. Due to human activity, environmental levels of elemental lead have increased a thousand-fold over the past three centuries. Recognition of the neurotoxic effects of lead has precipitated its removal from paint, gasoline and water pipes over the past three decades. As a result, US children's blood lead levels have been significantly reduced. Past uses of lead, however, continue to represent potential exposure sources for children (ATSDR, 2007; D. Bellinger, 2004; Koller, Brown, Spurgeon, & Levy, 2004).

Lead was used as a pigment in interior and exterior paints until it was banned in 1978. The lead paint that remains in many older homes in the US continues to be the most significant source of lead exposure for children. Lead does not degrade and therefore chipping and peeling paint can contaminate the soil outside, and the house dust inside, affected homes (ATSDR, 2007; D. Bellinger, 2004; Koller, et al., 2004). In fact, house dust represents 50% of a young child's total intake of lead (Koller, et al., 2004). Young children are especially at risk for exposure because of their greater tendency to play at ground level and put non-food items in their mouths (ATSDR, 2007; D. Bellinger, 2004; Koller, et al., 2004).

Between the years 1950 to 2000, releases of lead into the environment were at their highest because of lead added to gasoline. Use of lead in gasoline was gradually phased out and completely banned by the EPA for use in highway

transportation beginning January 1, 1996. Since the reduction and subsequent elimination of lead from gasoline, atmospheric levels of lead have decreased substantially. The EPA estimated that emissions decreased 93% between 1982 and 2002. Soil near roadways, however, can still contain high levels of lead. In addition, lead may still be used as an additive in gasoline used by airplanes and off-road vehicles (ATSDR, 2007).

Exposure to lead can also occur from the leaching of lead into drinking water from lead-containing water pipes, fixtures, and or solder. Since 1988, the use of lead in plumbing has been strictly regulated. The Safe Drinking Water Act, enacted in 1998, further restricted lead use by mandating that water pipes, fixture, and solder be lead-free. Although many older homes have had their lead pipes replaced by copper, galvanized, and plastic ones, the lead pipes that remain continue to exist as an exposure source for some families. It is estimated that less than 1% of US water systems have water entering the distribution system with lead levels greater than 5 μg/L. Acidic water, however, increases pipe corrosion which could result in potentially higher levels of lead-contaminated water in homes where this is a factor (ATSDR, 2007).

Use of lead in other products is declining as well. Lead was eliminated from pesticides in the 1950s and from the solder in food cans in 1989, thereby reducing food sources of lead. Plants grown in lead-containing soils remain a potential food source of lead. Plants and animals bioconcentrate lead, but, unlike mercury, it is not thought to biomagnify in the food chain. Lead in ammunition, sinkers, and in

ceramic paints, glazes, and dyes is being phased out due to human and environmental health concerns (ATSDR, 2007).

Currently, the largest use of lead is in automobile batteries. It is also still being used in X-ray shielding, some non-Western medicines and folk remedies, hair dyes, some glass production, inexpensive metallic jewelry, and in the production of lead alloys, soldering and other building materials. Mining and smelting of lead-containing ore, combustion of coal and oil, waste incineration, and manufacture of lead-containing products continue to release lead into the environment (ATSDR, 2007).

The route of absorption for lead is primarily ingestion and inhalation. Dermal absorption is much less efficient. Submicron sized particles of inorganic lead may be inhaled, and almost completely absorbed, by the respiratory tract. Larger particles may be ingested. Rates of absorption after ingestion vary depending on characteristics of the lead particle and the individual consuming it, including age and nutritional status. Absorption of lead may be increased during pregnancy. Studies also indicate that absorption rates of ingested lead in children are 40-50% as compared to 3 to 10% in fed adults. Absorption rates appear to be higher in individuals who are deficient in iron and calcium. The presence of food in the gastrointestinal tract also has an effect, absorption is increased with fasting and decreased with the presence of a meal (ATSDR, 2007).

Soon after lead is absorbed into the body, the blood transports it to soft tissues and various organs such as the brain, liver, kidneys, lungs, spleen, and heart.

Some maternal blood lead can be transferred to the fetus through the placenta and to the infant through breast milk. After several weeks, blood lead moves into the bones and teeth. The amount of lead stored here, however, varies between adults and children. Children store less lead in bones and teeth than adults, 73% compared to 94%. Bone lead can be mobilized back into the blood during certain circumstances such as pregnancy, lactation, osteoporosis, and after a broken bone. The excretion of the lead not stored in bone occurs primarily through the urine and feces. Children and adults, however, differ in excretion rates. Ninety nine percent of lead taken in by adults will be excreted as waste whereas only 32% of the lead taken in by children will be (ATSDR, 2007).

Neurological Effects

The neurological effects of acute lead toxicity have been known for thousands of years. Symptoms of encephalopathy following lead ingestion were documented by Nikander, a Greek physician, as far back as the second century B. C. Symptoms of encephalopathy occur with high level lead exposures with manifestations that include clumsiness, staggering, headache, and behavioral changes. High-level exposure can progress to altered level of consciousness, stupor, convulsions, and death. These overt symptoms of lead toxicity generally occur when blood levels reach >100 μg/dl in adults and > 70 μg/dl in children (ATSDR, 2007; Needleman, 2004). Over the past century, there has been emerging recognition of asymptomatic lead toxicity. Even at blood levels less than 10 μg/dl, children

exposed to lead can manifest impaired cognition, attention and behavior (Needleman, 2004).

The mechanisms of lead's neurotoxicity are multifold. Lead's ability to substitute for calcium and zinc accounts for many of these effects. Calcium is involved in many cellular processes including cell-signaling pathways. One such process that has been a focus of research is the activation of protein kinase C. Interference of lead in this pathway can affect long-term potentiation, memory processes, and spatial learning. Lead also alters astroglia, oligodendroglia, and cerebrovascular endothelial cells, which can affect blood-brain barrier formation and function. Most neurotransmitter systems are affected by lead, but the dopaminergic, cholinergic, and glutamatergic systems are thought to be the most impacted. Alterations in these systems are known to affect learning, cognition, and memory (ATSDR, 2007; Lidsky & Schneider, 2003).

Children are more susceptible to the neurotoxic effects of lead than adults. As already discussed, young children explore their environment with hand-to-mouth activity, which may result in ingestion of lead contaminated dust or soil. Blood lead levels likely peak between the ages of 1 and 3 years old due to this very behavior. In addition, children's gastrointestinal tracts absorb a larger fraction of ingested lead than adults. The forming nature of children's brains also puts them more at risk. Interference with trimming and pruning of synapses, neuronal migration, and neuron/glia interactions during development can alter neuronal connections

resulting in possibly permanent changes in brain formation (ATSDR, 2007; D. Bellinger, 2004; Needleman, 2004).

Though the neurological effects of acute lead toxicity have been known for centuries, its effects on children were not formally recognized until the 1890s when J. Lockhart Gibson indentified lead paint, used on porches and rails of homes in Brisbane, Australia, as the cause of the severe neurological disease seen in numerous children (D. Bellinger, 2004; Koller, et al., 2004; Lidsky & Schneider, 2003; Needleman, 2004). Since that time, knowledge of the clinical effects of lead on children's neurodevelopment has advanced significantly. Initially, acute lead toxicity in children was thought to result in either death or complete recovery without sequelae. This notion was rejected when, in 1943, follow up of children who had recovered from acute lead toxicity demonstrated considerable deficits including behavioral disorders, learning problems, and school failure. These deficits, however, were thought to exist only in those children who suffered symptoms of encephalopathy during the acute phase. Not until the 1970s did studies begin to demonstrate that children had deficits in IQ scores, attention, and behavior even without ever showing signs of acute toxicity (ATSDR, 2007; Needleman, 2004).

Advancing knowledge of lead toxicity resulted in a downward shift of guidelines for unacceptable blood levels of lead from >60 μg/dl in the 1960s, >40 μg/ dL in 1971, >30 μg/dL in 1978, >25 μg/dL in 1985, to its current level of >10 μg/dl (D. Bellinger, 2004; Koller, et al., 2004; Needleman, 2004). Numerous studies, both prospective and cross-sectional, have shown that lead exposure affects

children's cognition. Indeed, enough studies have been conducted to make meta-analyses possible. The preponderance of evidence suggests that a 10 μg/dl increase in blood lead is associated with a 1 to 5 point decrease in IQ (e.g. from 10μg/dL to 20 μg/dL) (ATSDR, 2007; D. Bellinger, 2004).

Beyond IQ, lead exposure has been shown to affect children's behavior. Though age at exposure and magnitude of exposure are often highly confounded, contributing to the difficulty in discerning a consistent "behavioral signature" of lead exposure, impairments in attention, executive function, visual-motor reasoning skills, vestibular-proprioceptive control, and social behavior, appear to be key domains affected. Manifestations of impairments in attention include impulsivity, distractibility, and inability to follow simple or complex sequences of instructions. Additionally, children exposed to low levels of lead have also been shown to exhibit delinquent, antisocial, and aggressive behaviors. The neurobehavioral effects of lead exposure likely contribute, at least in part, to the decreases in IQ seen with lead exposure (ATSDR, 2007; D. Bellinger, 2004; Chiodo, 2004).

Since 1991, when the CDC established the 10 μg/dL threshold, further research has demonstrated neurological effects associated with blood lead levels well below 10 μg/dL. In fact, the relative impact on IQ may be greater at these very low level exposures. Indeed, emerging evidence indicates that there is no lead threshold that represents a safe blood level of lead (ATSDR, 2007; D. Bellinger, 2004; Koller, et al., 2004).

Epidemiological Studies. A study by Lanphear et al. found deficits in academic achievement or cognitive functioning in children with blood lead levels < 10 μg/dL. Investigators used information from the Third National Health and Nutrition Examination Survey (NHANES III) on 4,853 children, ages 6-16. The Wide Range of Achievement Test-Revised (WRAT) and the Block Design and Digit Span subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R) were used as well as cognitive subtests. Adjustment was made for multiple potential confounders such as child's gender, race, iron status, contine level (metabolite of tobacco smoke), region of country, marital status of "family reference person" (usually head of household), educational level of this person, Poverty Index Ratio, in-utero and postnatal exposure to tobacco, birth weight, and admission to NICU. Adjustment was not made for maternal intelligence and measure of the home environment. Investigators found an inverse relationship between blood lead levels and all four measures of cognitive function, non-verbal reasoning, short-term memory, reading and arithmetic skills, in children with blood lead concentrations <10 μg/dL. Additionally, reading and arithmetic skills were shown to be impacted even with blood levels < 5 μg/dL (B. P. Lanphear, Dietrich, K., Auinger, P., & Cox, C, 2000).

A limitation of this study, as with many other cross-sectional studies, is that blood lead histories of the children are not available. A study of school-age children, such as this, may reflect damage done by higher blood lead levels at an earlier age (ATSDR, 2007; D. Bellinger, 2004). An investigation by Chen et al., however, seems

to indicate that concurrent, rather than past, blood lead levels are more predictive of later IQ scores. Data were analyzed from a clinical trial of 780 children who were treated for elevated lead levels (20-44 μg/dL) at around two years of age. The children were then followed with serial blood lead levels and IQ measurements until seven years of age. Blood lead levels were 12 μg/dL at age 5 and 8 μg/dL at age 7. Concurrent blood lead levels (those taken close to IQ measurement) were always more strongly associated with IQ, the relationship growing stronger as the children got older. These results support the idea that not all lead-associated damage is done by the time a child is age two or three, it continues to be toxic as they reach school age (ATSDR, 2007; Chen, Dietrich, Ware, Radcliffe, & Rogan, 2005).

Other studies indicate that lead's neurodevelopmental effects are not only seen below blood levels of 10 μg/dL, but the slope of the association, or degree of effect, appears to be greater at these lower levels than in those > 10 μg/dL. A frequently cited study by Canfield et al. measured blood lead levels in 172 children from the Rochester longitudinal study at 6, 12, 18, 24, 36, 48, and 60 months of age. The study adjusted for multiple variables including child's sex, birth weight, iron status, and mother's IQ, race, years of education, tobacco use during pregnancy, yearly household income, and Home Observation for Measurement of the Environment Inventory (HOME) score. The Stanford-Binet Intelligence Scale was given at the ages of 3 and 5 years. Consistent with prior studies, investigators found that blood lead levels were significantly inversely associated with IQ, each 10 μg/dL increase was associated with a 4.6 point IQ decline. For a subgroup of children

whose blood lead levels never exceeded 10 μg/dL, IQ declined an average of 7.4 points (Canfield, 2003).

A pooled analysis of 1,333 children from seven international prospective cohorts represents, perhaps, the strongest evidence for effects of low levels of lead on intelligence and support for a non-linear dose-response. The children, from sites in Boston, Massachusetts; Cincinnati and Cleveland, Ohio; Rochester, New York; Mexico City; Port-Pirie, Australia; and Kosovo, Yugoslavia were followed from birth or infancy until 5-10 years of age. Full-scale IQ was the primary outcome measure and adjustment was made for covariates. The investigators found that, given an increase in blood lead, associated declines in IQ were significantly greater in children whose maximal blood lead levels never exceeded 7.5 μg/dL than in those who had maximal blood lead levels ≥7.5 μg/dL. Estimated reductions in IQ for blood lead levels of 2.4 to 10 μg/dL, 10 to 20 μg/dL, and 20 to 30 μg/dL were 3.9, 1.9, and 1.1 points respectively (ATSDR, 2007; B. P. Lanphear, et al., 2005).

A study by Chiodo et al. examined neurobehavioral deficits in children exposed to very low levels of lead. The study consisted of 237 African American, inner city children. Blood lead levels were taken at age 7.5. Numerous potential confounders were considered including alcohol and drug use, socioeconomic status, age, marital status, and years of education of primary caregiver, child's gender and parity, number of children in the house, HOME score, assessment of parenting quality, primary caregiver vocabulary, caregiver level of depression, crowded living conditions, disruption in care-giving, caregiver anxiety/hostility, caregiver

personality disorder (if any), family function, life events for caregiver and child, domestic violence experienced by mother, age of child at 7.5 year visit, and the examiner. Consistent neurobehavioral deficits were found even in children with blood lead concentrations as low as 3 μg/dL. These deficits included overall IQ, performance IQ, reaction time, visual-motor integration, fine motor skills, off-task behaviors, attention, executive function, and withdrawn behaviors (Chiodo, 2004).

Ways to Reduce Exposure

Children's greatest risk of lead exposure occurs through ingestion of lead paint particles in house dust and soil surrounding older homes. Parents can help prevent lead exposure by getting their home tested for lead if it was built before 1978. In homes fitting this profile, repainting should be done if the current paint is peeling, chipping or flaking. Any remodeling requiring paint removal, including sanding, could cause high-level exposures. These jobs should be left to professional contractors who know how to minimize potential exposures. Frequent dusting and floor cleaning in the home can also reduce exposures. Additionally, parents can be mindful to discourage children from mouthing painted surfaces or eating non-food items, such as soil. Frequent hand and face washing, especially before meals, is another helpful measure (ATSDR, 2007).

Families who live in homes where plumbing was installed before 1930 likely have high levels of lead in their pipes. Since lead leaches from pipes more easily in warm water, it is recommended that pipes be flushed with cold running water for up to two minutes to flush out possible lead (ATSDR, 2007). Purchasing a reverse

osmosis water filter for home use may be worthwhile investment in these cases if feasible.

Children can also be potentially exposed to lead through a parent's occupation. A parent who works around lead dust can change clothes, shower at work, and place dirty clothes in a secured bag until laundered. Lead exposure can also occur from products still containing lead such as ceramic glazes, hair or makeup pigments, and non-Western folk remedies. Parents should be made aware of current lead-containing products so they can reduce or eliminate these potential exposure sources for their children (ATSDR, 2007).

Finally, making sure children have adequate nourishment through a balanced diet with no nutritional deficiencies can have a protective effect against the absorption of lead. Adequate intake of vitamins and minerals, iron and calcium in particular, is especially important. Calcium supplementation during lactation has also been shown to decrease lead levels in maternal blood and breast milk (ATSDR, 2007).

Bisphenol A

Source

Bisphenol A (BPA) is a synthetic chemical compound with estrogenic properties that was first produced in 1891. In the 1930s, its usefulness in the manufacturing of epoxy resins was discovered. About 20 years later, chemical engineers found that BPA could be polymerized to form polycarbonate plastics

(Palanza, Gioiosa, vom Saal, & Parmigiani, 2008; Wolstenholme, Rissman, & Connelly, 2011). Additional uses for BPA have subsequently been discovered. Currently, BPA is one of the highest volume chemicals produced. In the United States, production of BPA is estimated to be 2.3 billion pounds annually and worldwide production exceeds 6.4 billion pounds (Erler & Novak, 2010; Shelby, 2008; vom Saal & Hughes, 2005).

Polycarbonate plastics, usually marked with a "7" or "PC" near the recycle symbol, are used in many consumer products including water bottles, baby bottles, tableware, food containers, compact discs, medical devices, and impact-resistant safety equipment. Polycarbonate plastics, used in combination with other materials, form molded parts for mobile phones, automobiles, and household products. Epoxy resins coat the metal surfaces of products such as canned food, canned baby formula, bottle tops, water pipes, and wine vats. Epoxy resins are also found in some paints, floorings, and dental sealants (CDC, 2009a; Erler & Novak, 2010; Shelby, 2008).

Bisphenol A residue is also found in paper and cardboard food containers. It is used in the production of thermal paper, a type of paper used in some receipts, fax paper, and self-adhesive labels. Additionally, BPA is used in the manufacture of polyvinyl chloride plastics, polyester resins, polyacrylate resins, and some flame retardants (CDC, 2009a; Shelby, 2008).

Although routes of exposure to bisphenol A (BPA) can include inhalation and dermal contact from particles in air, dust, or water, most daily human exposure

occurs through the ingestion of contaminated food and beverages. Bisphenol A from polycarbonate plastic or epoxy resin-lined containers has been shown to migrate into the food or beverage they hold. This leaching is accelerated in heat and when in contact with acidic or basic compounds. It occurs regardless, however, with simple product wear and use over time (Shelby, 2008; vom Saal & Hughes, 2005). Once ingested, most BPA is quickly metabolized with help of liver enzymes and eliminated through the urine. The remaining amount, known as free BPA, is considered active and available to interact with biological processes in the body (Shelby, 2008).

Human exposure to BPA is widespread. BPA has been detected in urine, blood and other body fluids and tissues including amniotic fluid, placental tissue, and breast milk. In the NHANES 2003-2004 study, BPA and/or its metabolites were detected in the urine of 92.6% of all participants. Since most BPA is metabolized rapidly in the body, such high levels of detection of the compound in the participants suggest that human BPA exposure is continuous and occurs from many sources (vom Saal & Hughes, 2005). Study results also showed higher urine BPA concentrations in children than in adolescents, and higher levels in adolescents than adults. Females had higher levels than males, and urinary concentrations were lowest for those with a household income greater than $45,000 a year (Calafat, Ye, Wong, Reidy, & Needham, 2008). Evidence also suggests that BPA exposure may be increasing. Median urinary BPA levels doubled and the 95th percentile values tripled from NHANES III (1988-1994) to the 2003-2004 NHANES study (Shelby, 2008).

Although the NHANES study did not include children younger than six, it is estimated that the highest daily intake of BPA occurs in infants and young children. This is because of potential exposures through canned baby formula, polycarbonate baby bottles, polycarbonate tableware, and canned food (Shelby, 2008). Formula-fed babies, aged 0-6 months, are estimated to ingest 1-11 μg/kg/ day of BPA. Breastfed babies of the same age are estimated to ingest 0.2-1 μg/kg/day of BPA. Intake estimates for babies aged 6-12 months range from 1.65-13 μg/kg/day. Children age 1.5 to 6 years have an estimated daily intake of 0.043-14.7 μg/kg/day. Adult intake is estimated at 0.008-1.5 μg/kg/day (Shelby, 2008).

As mentioned in the prior discussion of other toxins, characteristics of infants and young children also place them at greater risk for exposure. Pound per pound, they eat, drink and breathe more per kilogram of body weight than adults. They also explore their environment with hand to mouth activity, including mouthing of plastic items that may be sources of exposure. Evidence from studies on laboratory rodents also shows that young animals metabolize bisphenol A less efficiently than adult ones (Shelby, 2008).

Neurological Effects

As determined by the EPA, BPA has a Lowest Observed Adverse Effect Level (LOAEL) of 50 mg/kg/day. Numerous studies have demonstrated adverse effects with high dose BPA at or above this level. High-level BPA exposure during pregnancy and lactation has been shown to decrease survival (≥ 500 mg/kg/day), reduce growth (≥ 300 mg/kg/day), and delay onset of puberty (≥ 50 mg/kg/day) in

both male and female laboratory mice and rat pups. These effects are well documented and not considered controversial within the scientific community. Exposures at this level, however, are well above estimated daily intake for both children and adults (Shelby, 2008).

Based on the LOAEL, the EPA calculated the oral reference dose for BPA to be 50 μg/kg/day. The oral reference dose is presumed to be the "safe" dose, a daily exposure level without appreciable risk of deleterious effects over a lifetime. This dose is similar to current human exposure levels. Research findings over the past 20 years have raised concerns about low dose BPA exposure. Adverse effects on laboratory animal have been observed with exposure levels at or lower than the current oral reference dose (Shelby, 2008). Inconsistency in study findings, however, has led to disagreement within the scientific community about the level of concern necessitated by low dose BPA exposure. Whereas some studies have demonstrated adverse effects, others have shown no toxicity, or have inconclusive results based on major methodological flaws (Arnich, et al., 2011).

Within the past five years, both the National Toxicology Program (NTP) (a division of the NIH) and the FDA have reviewed current evidence and concluded there is valid concern about low dose BPA exposure (defined by the NTP as doses ≤ 50 μg/kg/day), especially as it relates to brain and reproductive development of fetuses, infants and young children (FDA, 2010a; Shelby, 2008). Since the development of the central nervous system is highly dependent on the effects of endogenous hormones, there is concern that endocrine disrupting chemicals, such

as BPA, have the potential to permanently alter hormonal signaling, especially at critical periods of brain development (Richter, et al., 2007; Shelby, 2008). Indeed, studies examining low dose BPA exposures have revealed adverse neurological effects including alterations in hormone receptors, neurotransmitters and their receptors, and neuroendocrine function. Evidence for altered brain structure and behavior has also been reported (Richter, et al., 2007; Shelby, 2008).

Animal Studies. The estrogenic effects of BPA have been well documented; numerous *in vivo* and *in vitro* studies have reported its estrogen mimicking effects. More recent studies have shown that BPA also has the ability to antagonize the activity of estrogen. Attributing the adverse effects of BPA solely on estrogen activity, however, is likely overly simplistic. Increasing numbers of studies have demonstrated BPA interacting with a variety of other cellular targets besides estrogen receptors. BPA has been shown to interact with many other receptors involved in brain function including gamma aminobutyric acid type A ($GABA_A$) receptors, progesterone receptors, aryl hydrocarbon receptors, retinoic acid receptor alpha, retinoid X receptor alpha, and thyroid receptors (Shelby, 2008). Alterations in the dopaminergic system, the hypothalamus-pituitary-gonad, and hypothalamus-pituitary-thyroid axis have also been reported (Richter, et al., 2007).

A common theme among studies examining the brain structure of male and female rat and mice pups following BPA exposure is the reduction or loss of sexual dimorphisms. Sexual dimorphisms are the normal sex differences seen in size, cellular composition, or molecular expression patterns of specific structures or

regions of the brain. Areas of the brain where this reduction has been observed include the locus ceruleus (involved in mediating response to stress), the bed nucleus of the stria terminalis (involved in emotional regulation), and the anteroventral periventricular nucleus (a region that provides input to gonadotropin-releasing hormone neurons). The alterations in behavior that have been observed following developmental exposure to low dose BPA include changes in play, aggression, anxiety and fear, cognition, motor activity, impulsivity, exploration, novelty seeking, reward response, pain response, and social interactions. Of note, many of these behaviors, including novelty seeking, activity level, exploration, and anxiety, have some degree of sexual dimorphism associated with them (Richter, et al., 2007; Shelby, 2008).

Epidemiological Studies. Only a few studies have examined neurodevelopmental effects of BPA in children. The first study, reported by Braun et al. in 2009, used data from the ongoing prospective birth cohort study in Cincinnati, Ohio. Data from 249 mothers and their children was examined. BPA concentrations in maternal urine were quantified at 16 and 26 weeks gestation as well as at birth. Assessment of child behavior was conducted at two years of age using the Behavioral Assessment System for Children (BASC-2). Adjustment was made for numerous confounders including maternal age, race, education, household income, HOME score, marital status, and maternal depression during pregnancy. The investigators found an association between mean prenatal BPA concentrations and externalizing behaviors (such as hyperactivity and aggression) among female

children. The association was strongest with urine measurement ≤ 16 weeks gestation among all children (Braun, et al., 2009).

The second study, reported in 2011 by many of the same investigators, examined the impact of gestational and childhood BPA exposure on three year old children's behavior and executive function. The study employed the same Cincinnati prospective birth cohort, this time using data from 244 mothers and their three year-old children. Maternal BPA urine concentrations were quantified at 16 and 26 weeks gestation as well as at birth. Child urine BPA concentrations were measured at one, two, and three years of age. Measurement of behavior and executive function was conducted using BASC-2 as well as the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P) tools. Adjustment was made for potential confounders including maternal race, education, marital status, household income, depression during pregnancy, HOME score, gestational tobacco smoke exposure, and gestational urinary low molecular weight phthalate concentration. Results showed associations with each 10-fold increase in gestational BPA concentration of increased anxious and depressed behavior on the BASC-2 and poorer inhibition and emotional control on the BRIEF-P. This positive association was seen with girls' scores, whereas the association with boys score was null or negative. Scores were especially pronounced for hyperactivity, with girls demonstrating marked increases in hyperactivity and boys showing decreased hyperactivity with gestational BPA exposure. Childhood BPA exposure was not associated with changes in neurobehavior for either boys or girls (Braun, et al., 2011).

A third study, reported in 2010 by Miodovnik et al., looked at the impact of prenatal exposure to endocrine disruptors, namely bisphenol A and phthalate esters, on social behavior. The study utilized data from the Mount Sinai Children's Environmental Health Study, which is a prospective multiethnic cohort study of women who delivered babies between May 1998 and July 2002. Urine samples of 404 women were analyzed and phthalate metabolites and bisphenol A levels were quantified. The mother-child pair was invited to return for three follow-up visits when the child was between four and nine years of age. At the last visit (when the child was between seven and nine years of age), the mother completed the Social Responsiveness Scale (SRS). The SRS is a well-validated tool for detecting and measuring autistic behaviors and their severity. A positive association was found with phthalate concentrations and greater social deficits. No significant association with BPA was found. The authors report, however, that when influential outliers were removed, the magnitude of the BPA association was similar to that of low molecular weight phthalates (Miodovnik, et al., 2011).

Animal studies have shown that low dose BPA exposure impacts neurodevelopment in mice and rats. The few epidemiological studies that have been conducted seem to suggest that children are also affected. More studies are needed to confirm and further elucidate findings (FDA, 2010a; Shelby, 2008).

Ways to Reduce Exposure

The 2008 NTP report reviewing the evidence on adverse effects associated with low dose BPA prompted a number of actions nationally aimed at banning or

limiting children's exposure. Manufacturers Playtex and Nalgene declared they were shifting to BPA-free products, and major retailers including Walmart and Toys-R-Us announced they would be phasing out BPA containing baby bottles. In 2009, more manufacturers including Avent, Disney First Years, Gerber, Dr. Brown, and Evenflow, announced they would stop using BPA based plastic in baby bottles made for the U.S. market (Erler & Novak, 2010; J. Houlihan, Lunder, S., & Jacob, A, 2008).

In May 2008, the House Energy and Commerce Committee wrote to the major formula companies requesting they remove BPA from their packaging. Four companies, Abbott (Similac), Nestle, Mead-Johnson (Enfamil), and PBM (maker of store brands) responded, indicating they are exploring different packaging options for their products (J. Houlihan, Lunder, S., & Jacob, A, 2008). In 2009, Similac announced that their powdered and ready-to-eat formula were repackaged using no BPA (concentrated formula still packaged in BPA lined cans) (J. Houlihan, Lunder, S., & Jacob, A, 2008).

In 2009, over 20 states proposed legislation to ban or restrict BPA containing products. Since then additional legislation has been proposed, and eleven states; California, Connecticut, Delaware, Maryland, Washington, Maine, Massachusetts, New York, Minnesota, Wisconsin, and Vermont, have succeeded in banning BPA in baby bottles and sippy cups. In 2010, Canada became the first country to ban BPA. Since then, BPA has also been banned in the European Union, China, and the United Arab Emirates (J. Houlihan, Lunder, S., & Jacob, A, 2008; Shader, 2011).

Although concerted efforts have been made nationally to reduce children's BPA exposure, parents can reduce risk of exposure even further. It is recommended that mothers breastfeed for 12 months or longer when possible. When breastfeeding is not an option, use powdered infant formula instead of liquid. If liquid formula is used, avoid heating the cans on the stove or in boiling water (HHS, n.d.).

Avoid buying polycarbonate bottles or cups, which contain BPA. Use glass bottles or safer plastics such as those with recycling labels #1, #2, #4 or #5 (EWG, 2007). Parents can recognize polycarbonate plastic by its appearance and label. Although items containing BPA can come in many colors, the plastic is usually rigid and clear (not cloudy). Plastics containing BPA are usually labeled with the letters PC and/or recycling label #7. If polycarbonate bottles/cups are used, do not use in the microwave or pour boiling or very hot liquids into them. Any scratched BPA containing bottles or cups should be discarded immediately (HHS, n.d.).

Pregnant women and children should also limit or avoid canned food consumption. A study conducted by the Environmental Working Group (EWG) tested 97 cans of fruit, vegetable, pasta, soup, soda, and other commonly eaten foods. They found detectable levels of BPA in over half of the cans tested. The highest levels of BPA were found in canned soups and pastas, the lowest levels were found in canned sodas (EWG, 2007). Some companies are finding alternatives to bisphenol A for use in their canned food. Eden Organics uses an oleoresinous c-enamel instead of bisphenol A in all of their canned beans, chilies, and rice and

beans. Muir Glen has found a safe alternative to bisphenol A for use in the can liners of their organic tomatoes (Organic, 2012; Organics, 2010).

DISCUSSION

Implications for Nursing Practice

Although environment has been recognized as one of nursing's foundational concepts since the time of Florence Nightingale; nursing schools, both at the undergraduate and graduate level, include little to no environmental health content in their curriculum. Lack of knowledge and awareness translates into nurses who are inadequately informed and prepared to address environmental health issues when they get into practice. Since nurses are often the first and sometimes the only contact individuals have with the health care system, it is critical for them to be able to recognize and help prevent toxic environmental exposures (McCurdy, 2004).

Improved dissemination of environmental health concepts into nursing education, practice and research has been advocated by leading health institutions and delineated by several national initiatives. The Institute of Medicine (IOM) initiative has developed specific environmental health competencies for nurses, including basic knowledge and concepts; assessment and referral; advocacy, ethics, and risk communication; and legislation and regulation (NEEF, 2008a). The Environmental Health Nursing Initiative, developed by the Agency for Toxic Substances and Disease Registry (ATSDR), provides environmental health educational opportunities for nursing students and practicing nurses with an additional goal of identifying research gaps and improving collaboration between agencies concerned with environmental hazards. The National Institute of Nursing

Research (NINR) initiative emphasizes the role of nursing research in identifying health consequences of environmental exposures (Larsson, 2002). Since the launch of these initiatives in the 1990s, much work has been done to better incorporate environmental health into nursing practice, education, and research. Some of these accomplishments are documented in a 2002 ATSDR publication entitled "Nurses and Environmental Health: Success Through Action." Although these accomplishments are to be celebrated, more work is needed in order for environmental health to be recognized as a critical part of mainstream nursing practice.

Nurse Practitioners, as primary care providers, are increasingly expected to be capable of addressing environmental health problems in practice. In fact, the U.S. Department of Health and Human Services Division of Nursing has made the ability to recognize environmental health problems and provide health protective interventions an essential primary care nurse practitioner competency (NEEF, 2008a). Recognition of environmental health problems begins with taking a good environmental health history. The Pediatric Environmental Health Initiative, a multi-year campaign brought about by the National Environmental Education Foundation (NEEF), aims to make environmental history taking a routine practice for health care providers. NEEF encourages integrating environmental health questions into both well and sick child visits and suggests that the child's age and developmental stage guide the provider in prioritizing the most appropriate content to be addressed (NEEF, 2008c). Given that many toxins can be detrimental to the

developing fetus, pre-conception and prenatal visits are prime opportunities for addressing potential toxic exposures as well.

A printable environmental history form, that can help facilitate pediatric environmental health history taking, is available on the NEEF website (NEEF, 2008b). This form contains questions that would alert the practitioner to numerous potential environmental health hazards including pesticide, mercury, and lead exposures. The questions regarding pesticides address whether or not pesticides are used inside or outside the home, where they are stored, what type of produce is eaten and whether it is washed prior to consumption. The questions focusing on mercury ask what type and how much seafood is consumed per month. The questions addressing lead ask about the year the home was built and if any family member or friend has ever had an elevated blood lead level. Content about PBDEs and bisphenol A on the NEEF history form is lacking, however, likely due to less accumulated and more controversial evidence on these two toxins. To screen for potential PBDE and bisphenol A exposure, include questions about foam products, electronics, and animal fats in the diet as well as types of bottles/cups used, formula (if any), and canned food consumed.

Helping families protect their children from adverse health effects associated with toxins begins by educating them about children's increased vulnerability. As mentioned throughout this review, children are at greater risk of harm from toxic exposures for many reasons. Behavioral characteristics of young children such as spending more time on the floor, hand-to-mouth activity, and the fact that they eat

and drink more in proportion to their body weight increase their likelihood of ingesting toxins. Biological characteristics of children, including the highly sensitive nature of the developing brain to disruption and immature detoxifications systems, increase their risk of developing significant adverse effects from any toxic exposure.

Communicating specific ways to prevent or reduce toxic exposure to families is another part of prevention. Measures to reduce exposure to PBDEs, pesticides, mercury, lead, and bisphenol A have been thoroughly discussed in this review. Two major themes of prevention have emerged from the research, dietary modifications and household surface cleaning. Food is a main source of exposure for many of the toxins discussed. Reduction in consumption of animal fats, fish, and canned formula/food can go a long way to reducing PBDE, mercury, and bisphenol A exposure. Eating organic food can reduce exposure to pesticide residue. Additionally, having a healthy, well-rounded diet seems to confer protection against the adverse effects of some toxins. Poorer outcomes on neurological testing following exposures have been documented in children with nutrient deficiencies, including calcium, iron, vitamin A, iodine, or malnutrition in general.

Since young children are more often playing on the floor, frequent surface cleaning/dusting can help reduce exposure to toxins found in house dust including PBDEs, pesticides, and lead. Taking shoes off before entering the house can prevent toxins, such as lead or pesticides, from being tracked inside. Washing children's hands frequently throughout the day, especially before meal, as well as trying to limit mouthing of non-food items can also help prevent ingestion of toxins. Parents

who work occupationally with any toxic substance need to be especially vigilant about not bringing home residue on their bodies and clothes. In these cases, parents are advised to shower and change clothes before returning home after work. The potentially contaminated clothes should be transported in a sealed plastic bag and laundered separately from family clothes.

Conclusion

Findings from current research indicate adverse neurological effects of developmental exposure to PBDEs, pesticides, lead, mercury, and bisphenol A are similar to diagnostic features of some neurodevelopmental disorders. Adverse effects associated with exposures include: hyperactivity, aggression, decreased IQ, and impairments in attention, memory, fine and gross motor skills, social behavior, and communication. By screening for these exposures and discussing prevention in primary care visits with children and pregnant women, nurses can have a significant impact toward reducing neurological injury, disease, and disability in children.

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