

Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders

Developed by the Collaborative on Health and the Environment's Learning and Developmental Disabilities Initiative November 7, 2007

Given the established knowledge, protecting children from neurotoxic environmental exposures from the earliest stages of fetal development clearly is an essential public health measure if we are to help prevent learning and developmental disorders and create an environment in which children can reach and maintain their full potential.

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1 Introduction

This consensus statement outlines the current scientific understanding of the links between [environmental factors](#) and [learning and developmental disabilities](#). It also identifies important research areas that hold promise of further advancing our understanding of these links. This statement is intended as a guide to scientists, medical professionals, policymakers, public health advocates, and the general public in advancing their efforts to address the important individual and social issues raised by [learning and developmental disabilities](#). Terms in [orange underlined font](#) are defined in a Glossary of Terms and Term Usage specific to this document, beginning on page 19.

1.1 Purposes of the document

To review findings from diverse research disciplines concerning environmental contaminants and the biological basis of compromised learning and development, with special attention to critical recent discoveries in related basic sciences;
 To identify conclusions that could be drawn with confidence from existing data;
 To identify critical knowledge gaps and areas of uncertainty;
 To establish key elements of a coherent research agenda to help fill these gaps and resolve uncertainties;
 To form a foundation of current scientific knowledge upon which to make policy decisions that promote and protect an environment in which all children can reach and maintain their full potential.

1.2 Scope and incidence of disorders

Within the human brain lies our capacity to learn, talk, read, calculate, memorize, conceptualize, organize, pay attention, utilize motor skills, interact socially and behave appropriately. We cannot reach our full potential with a damaged brain or nervous system.

Though many of the environmental contaminants discussed in this document can also undermine the healthy development of other biological systems in the body, such as the reproductive, endocrine and immune systems, this consensus statement is focused solely on the developing brain and nervous system. This distinction is somewhat artificial since the impact of toxicants upon these other systemic processes may have effects that feed back and impact brain function. Although it is often believed that endocrine function, for example, is independent of brain development, it is now clear that they are so closely entwined that endocrine toxicants are, in essence, neurodevelopmental toxicants.

Children are not little adults

Environmental exposures start early: preconception, during gestation (*in utero* exposure), via breast milk, infant formula and then through contact with the environment.

For their body weight, children eat and breathe more than adults, thus a small exposure translates into a big dose.

Their organ systems, particularly the nervous system, are forming and are thus more susceptible to the effects of chemicals.

Young children are prone to hand-to-mouth behaviors that expose them to higher levels of ambient chemicals.

Children rely on adults to ensure that they develop in an environment in which they can reach and maintain their full potential.

Other neurologically based disorders have also been shown to have environmental contributors, especially Parkinson's disease (1-4), mental illness including schizophrenia (5), cerebral palsy (6) and epilepsy. This document focuses on learning and developmental disorders and does not address these conditions.

1.2.1 Definitions of LDDs

In this report, we define learning and developmental disorders broadly as conditions resulting from interference of normal brain development and function that adversely affect an individual's performance.

[Learning and developmental disabilities \(LDDs\)](#) include but are not limited to deficits in learning and memory, reduced IQ, [attention deficit hyperactivity disorder \(ADHD\)](#), [autism spectrum disorder](#), [conduct disorders](#) and [developmental delays](#).

1.2.2 Overview of brain development

The development of the human brain begins in utero and continues through adolescence, following a precise and delicate step-by-step sequence involving complex neurobiological processes including the formation of the neural tube, cell proliferation, differentiation, migration and selection, synapse formation, development of neurochemical systems, cell pruning; and myelination. These processes ultimately involve 10 to 100 billion neuronal cells with many trillions of connections. The long and complex development of the brain and nervous system leaves it susceptible to the adverse effects of chemical exposures.

Even minor changes in the structure or function of the nervous system can have profound consequences for neurological, behavioral and related body functions. Disruption of the brain's normal development can happen in utero as a baby develops within the mother's body or as the brain continues to develop from

infancy through adolescence. Brain function can also be impacted in adulthood from an accident, trauma or exposure to [neurotoxicants](#).

1.2.3 Incidence

[Autism](#), [attention deficit hyperactivity disorder \(ADHD\)](#), [dyslexia](#), [mental retardation](#), lowered IQ and other disorders of learning and behavior are highly prevalent among American children. The incidence of [learning and developmental disabilities \(LDDs\)](#) appears to be rising, affecting between five and 15 percent of all children under the age of 18 in the United States, or more than 12 million children under 18 (7). In general, disabilities have increased significantly over the past four decades (8).

These disabilities include disorders of learning, attention, emotional state and behavior. [Mental retardation](#) impacts two percent of children, or approximately 1.4

Critical recent discoveries

Even very low doses of some biologically active contaminants can alter gene expression important to learning and developmental function. Exposures during fetal development can adversely affect learning and development of the individual and last a lifetime.

Humans are exposed to complex mixtures of chemicals that can interact to enhance adverse effects.

Due to genetic variation ([polymorphisms](#)) people differ in susceptibility to exposures. Not identifying and studying susceptible subgroups can result in failure to protect those at high risk.

Children are often more susceptible than adults to the effects of exposure to [environmental agents](#).

million children (9-12). [ADHD](#) is conservatively estimated to occur in three to six percent, or approximately two million children (13) (14). A more recent study in the [National Health and Nutrition Examination Survey \(NHANES\)](#) found 8.7 percent of 8- to 15-year-old children met the Diagnostic and Statistical Manual of Mental Disorders ([DSM-IV-TR](#)) criteria for ADHD based on parent recall (15).

[Autism spectrum disorder](#) is estimated to affect approximately 0.7 percent, or 450,000 children and appears to be 10 times more prevalent today than it was in the 1980s (16), although that estimate is still debated.

These nonfatal disabilities that affect an individual for a lifetime can be classified as the "new morbidities," and the prevalence in children is summarized in Figure 1 below. This figure presents a compilation of data from different sources (7, 15, 17-19), demonstrating the interrelation of these childhood conditions.

Prevalence of the "New Morbidities" in United States Children

Attempts to calculate the costs of these childhood "morbidities" have only recently been undertaken (20, 21). Providing special education services to students with disabilities amounted to \$77.3 billion, or an average of \$12,474 per student in 1999-2000, almost twice the cost per regular education student, which is almost 22 percent of the 1999-2000 total spending on all elementary and secondary educational services in the US (22) (for additional information see the Center for Special Education Finance (CSEF) at <http://www.csef-air.org/>).

Prevalence % of Children

1.2.4 Impacts on individuals, families and society

In children, developmental, learning, attention and behavioral problems can cause tremendous challenges for the affected children, their families and communities. Consequences include psychological and economic costs associated with learning delays, aggressive or otherwise inappropriate behavior, school dropout, teen parenting, substance abuse, unemployment, welfare dependency and involvement with juvenile and adult criminal justice systems (20).

2 Historical Perspective

The effects of chemicals on the nervous system have been recognized since ancient times. Most of the early reports were the results of high exposures in workers that led to debilitating conditions or even death. For example, 2000 years ago people knew that lead exposure "makes the mind give way." As

Autism Conduct Learning ADHD Preterm Disorder Disability Birth

Figure 1.

science progressed, it was recognized that even small doses of some chemicals result in subtle nervous system impacts that affect an individual's performance. Despite this knowledge, lead was added to paint and gasoline, removed only following considerable research that confirmed what was already known. Many investigations have now demonstrated that even small amounts of lead affect the developing nervous system (23).

Similarly, the adverse effects of exposure to elemental mercury, recognizable because of its liquid silver appearance, which evaporates at room temperature and can be inhaled, were recognized in miners well before the common era. Subsequently, workers in the felt-hat industry, where

mercury was used to process the fur, succumbed to its **neurotoxic** effects – truly an example of “mad hatters” (see *Alice’s Adventures in Wonderland* by Lewis Carroll). Organic mercury, formed by the conversion of inorganic mercury to methylmercury by bacteria, **bioaccumulates** in fish and is readily absorbed. Organic mercury exposures in Iraq in 1971 and in Minimata, Japan, beginning in the late 1950s revealed both the overt and more subtle effects of organic mercury on development and the nervous system. Even low doses of methylmercury damage the nervous system and cause neurobehavioral deficits (24-28).

Exposure to a wide range of potentially hazardous chemicals from conception to death is now unavoidable. Approximately 3,000 chemicals are produced in quantities greater than one million pounds per year. For the majority of these chemicals little information exists about the potential effects on learning and development. There is good evidence that about 200 of these chemicals are adult neurotoxicants and another 1000 are suspected of affecting the nervous system (29) (see Figure 2, in part from (29)). Overall there has been a gross failure to require developmental neurotoxicity testing.

What we don’t know about chemicals

Figure 2.

As our testing methods have become more sophisticated, the recognition of individual sensitivity and, in particular, the sensitivity of the developing nervous system to the effects of **environmental agents** has grown. The causes of and initiatives to prevent **LDDs** have received increased attention from national organizations (30-32), the government and academic researchers (20, 29, 33). A substantial recent initiative, the **National Children’s Study**, will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21, with the goal of improving the health and well-being of children (<http://www.nationalchildrensstudy.gov/>).

3 Environmental Contributors to Disorders

Many factors – heredity, gene expression, socioeconomic environment, infectious disease, nutrition, stress, drugs and chemical contaminants – contribute in complex ways to brain development and thus to the genesis of **LDDs**. There is growing evidence that the interaction of these factors is associated with or exacerbates a variety of developmental disorders (34-37). Of all the factors contributing to **LDDs**, chemical contaminants in the environment have historically been the least studied despite being the most preventable. We now have solid scientific evidence that a variety of **environmental agents** can adversely affect the nervous system. The impact of chemical contaminants on children is a worldwide issue and the focus of this document.

The susceptibility of the developing nervous system to the adverse effects of environmental agents, and the need to take preventive measures were recently recognized by international researchers in the Faroes Statement (38). International groups have also developed statements on the developmental effects of metals and the need to take preventive action to protect public health (39). In addition, comprehensive reports have documented the effects of environmental agents on development (40).

3.1 Timing of exposure

A child’s developing nervous system is more sensitive to chemical exposures than the adult nervous system. This can be seen in the effects of alcohol: a pregnant woman who drinks enough to become intoxicated may suffer a hangover, but her fetus may suffer permanent brain damage resulting in fetal alcohol spectrum disorder (41). Also, in both the Iraq and Minimata methylmercury disasters, pregnant women showed minimal signs of toxicity, but their children displayed effects ranging from cerebral palsy to delayed development (6). Extensive animal data also establish the effects of mercury exposure on the developing nervous system.

Research on brain development has mapped out the progression of the proliferation, differentiation and migration of different cell types into selected regions of the brain. This work has been extended as neurotoxicologists have examined the effects of exposure to chemicals at different points during development (42-45). Vulnerability to chemical exposure varies across the stages of brain development (43) such that exposure at three months gestation may result in a different effect than exposure to the same chemical at six months gestation or at two years of age.

3.2 Bioaccumulation and mixtures

Concentrations and/or potency of **environmental agents** can be amplified because of **persistence** (**biomagnification** and **bioaccumulation**) and because agents occur in **mixtures**. Mercury accumulation in fish is a well known example of both **biomagnification** and **bioaccumulation** (24, 46). Fish can also be contaminated with other compounds, such as **polychlorinated biphenyls (PCBs)**; thus we are often consuming a **mixture** of compounds. Recent **biomonitoring** studies reveal the range of compounds we are exposed to and that accumulate in our bodies.

Experiments with single chemicals can underestimate the effects of these chemicals in **mixtures**.

The interplay among multiple toxicants whether stored or through ongoing exposures, and other environmental factors can cumulatively interfere with the brain’s development and exacerbate the impact. For example, there is good evidence that lead exposure and maternal stress interact, and there is some evidence of **potentiated** effects of combined exposures of the pesticides paraquat and maneb during development (47).

3.3 Mechanisms of disruption

Brain development is a long and complex process that involves cellular proliferation, migration, differentiation, synaptogenesis, myelination and apoptosis (programmed cell death). Chemicals can interfere with or stop these processes through the extended period of brain development from conception to adolescence (43). There are multiple mechanisms by which chemicals can disrupt neurological development,

including gene expression acting on protein pathways (48) (49, 50) and hypothyroidism (51-53). Recent research has focused on how genes act on protein pathways, determining how tissue and cells form and grow. The expression of multiple genes can affect multiple protein pathways. A single contaminant that influences gene expression can affect [endpoints](#) in more than one tissue. Some contaminants have been shown to alter the expression of hundreds of genes, and effects can vary with the timing and dose of the contaminant.

3.4 Variable sensitivity

Genetic variation, or DNA [polymorphisms](#), within populations (humans, wildlife and laboratory animals) can result in greater sensitivity to specific contaminants in some individuals. Specific [genetic polymorphisms](#) are linked to increased risk to various disorders such as fetal alcohol spectrum disorder

(54) and are associated with increased susceptibility to organophosphate pesticide toxicity (55-57). Genetic variations are also associated with increased susceptibility to higher blood-lead levels (58, 59).

The effects of environmental agents, particularly endocrine disruptors, have recently been shown to promote epigenetic transgenerational effects – changes passed down to subsequent generations. [Epigenetics](#), a molecular phenomenon, typically methylation of the genome, regulates gene expression without alterations to the DNA sequence (60, 61). Recent studies have demonstrated that the commonly used fungicide vinclozolin has produced epigenetic transgenerational effects on development and cancer (62-64). Epigenetic effects may explain in part the transgenerational effects of the synthetic estrogen diethylstilbestrol (65). The low-dose effects of endocrine disruptors are being actively explored (66, 67).

3.5 Evidence of exposures (body burden)

Recent measurements of contaminants in people demonstrate that humans are exposed, starting at conception, to hundreds of chemicals simultaneously – and some at levels within ranges known individually to affect neurological development (68-70).

Chemicals may also be passed from one generation to the next, from mother to developing child, as chemicals stored in or consumed by the mother cross the placenta or are incorporated into breast milk. While breast milk is clearly the best food for infants and breast feeding is almost always recommended, [persistent, bioaccumulative](#) chemicals stored in a woman's body fat are mobilized during breast feeding and excreted in breast milk.

3.6 Other environmental factors

There are many other chemicals of concern, as well as other environmental factors that interact with chemicals, that can affect development and contribute to LDDs. We include a brief discussion of some of these factors due to increasing evidence of their interactions with chemical agents and their contribution to LDDs.

3.6.1 Pharmaceuticals

A wide range of drugs have [neurotoxic](#) side effects in children when consumed by a pregnant mother, infant or child. When these drugs are given to children (even when needed) and not adequately monitored, serious lifetime disabilities can result. A classic example is aminoglycoside antibiotics, which can cause severe hearing loss and subsequent learning and development challenges. We know much less about the long-term effects of psychoactive compounds. There is evidence that thalidomide or valproate exposure during pregnancy increases the risk of autism (71-74).

3.6.2 Genetic factors

With [autism](#) in particular, new research is beginning to reveal that the disorder involves the whole body, a complex interaction of genes and the environment, and perhaps many factors working in concert with one another (75, 76). While the low-dose effects of endocrine disruptors are still being explored, some have argued that genetic susceptibility plays an important role in the etiology of autism (76).

3.6.3 Environmental justice: socioeconomic, nutrition and stress

Six million children live in poverty in the United States, increasing the likelihood of exposures and heightened vulnerability to [environmental agents](#) that adversely affect learning and development. Economically disadvantaged children are more likely to live in older homes contaminated with lead, live in neighborhoods and around schools where pesticides have traditionally been applied, and have diets that are less nutritious. Additionally, there is growing evidence that stress combined with environmental exposures increases susceptibility to developmental disorders (36, 47). Recent research indicates that stress and social ecology can play an important role in developmental disorders (36).

Children lacking certain nutrients are more vulnerable to toxicants. For example, iron and/or calcium deficiency affects the absorption and toxicity of heavy metals such as lead (77) and manganese (78, 79).

Lead is stored in bone and may be mobilized with calcium from bone to the fetus during pregnancy. The role of nutrition in mitigating exposure to environmental agents is an important public health issue (80).

4 Status of Evidence on Environmental Agents

Research definitively shows that [environmental agents](#) such as lead, mercury, manganese, arsenic, [PCBs](#), alcohol, toluene, tobacco smoke and many pesticides are capable of disrupting human brain development, resulting in negative impacts on the functions controlled by the brain. Additional environmental chemicals and pollutants, other solvents and other heavy metals have been shown to disrupt brain development in animal studies and are suspected of having similar effects in humans.

4.1 Human and animal assessment of learning and development

Evaluating the potential [neurotoxic](#) effects of a compound often requires evaluating animal data and then incorporating any human data into the assessment.

Given the large number of compounds with limited or no data on nervous system effects, it is important to consider [in vitro testing](#). [In vitro](#) systems typically use cell culture techniques for initial assessment of [neurotoxic](#) potential. New tests utilizing cell lines are now used to assess the effects of chemicals on eye irritation or damage. Cell lines are available with which to examine a variety of [endpoints](#) on neuron or glial cells. [Endpoints](#) include proliferation, migration, synaptogenesis and apoptosis. Well-characterized [in vitro](#) testing systems have a number of potential advantages including minimizing the use of animals, reducing costs and increasing adaptability to rapidly screen agents for potential cellular effects. [In vitro](#)

tests are not sufficient for setting exposure standards, but they can provide a rapid assessment that further testing is needed.

It is also possible to use *in vitro* models to examine chemical mixtures, such as additives, on neuronal cells (81). There are, however, a number of challenges with *in vitro* neurotoxicity testing, such as characterizing cell migration and interconnection (82).

Several different tests are used to assess neurotoxic effects in adult and developing animals. Functional assessment can be supplemented with morphological assessment of the nervous system (83) although conventional pathological assessments are relatively insensitive and may not detect subtle adverse cellular changes. A basic screen for behavioral function and neurological involvement is the functional observational battery (FOB) (84). The FOB is typically used to evaluate the need for more sophisticated neurotoxicity testing.

The US Environmental Protection Agency (EPA) and the Paris-based Organisation for Economic Cooperation and Development (OECD) established a protocol for the evaluation of developmental neurotoxicity (DNT) in laboratory animals (US EPA 870.6300 and OECD 426) (85, 86). These protocols include tests of neurobehavioral function, auditory startle (hearing), learning and memory function, changes in motor activity, neuropathologic examination and morphometric analysis. For examples and comments on the testing protocols see papers by Claudio et al., Cory-Slechta et al., Dorman et al., Garman et al. and Mileson and Ferenc (87-91).

Testing involving animals, including nonhuman primates, has been invaluable in evaluating the effects of a number of neurotoxicants (92). Recent studies have examined the neurotoxicity of pesticide mixtures in animals (93), and protocols are available to examine cognitive effects on weanling rodents (94). Advanced assessment of learning and memory in rodents has been used to evaluate the effects of lead (95). Tests of specific functions using nonhuman primates are used to evaluate the low-level effects of neurotoxicants, such as mercury, on vision, auditory function and vibration sensitivity (96-99) or lead on learning and memory (100, 101). The concordance between human and animal neurotoxicity assessment is remarkable as demonstrated for lead, mercury and PCBs (102, 103).

Despite significant challenges, human testing for the neurotoxic effects of occupational exposures to chemicals is steadily

Environmental agents that

advancing (104-107). These procedures have also been used to we are confident cause

examine the neurotoxic effects of the stress and hazards of war

learning and developmental

(108, 109), which demonstrates broadening utility and acceptance

disabilities in humans

of these testing procedures. The World Health Organization

• Alcohol

(WHO) recommended a neurobehavioral test battery for humans

• Lead

(110) and test batteries for assessing children (111). Notable

• Mercury

examples of childhood neurotoxic evaluation include examination of the effects of low-level lead exposure (112, 113) and mercury • PCBs exposure (114). • PBDEs

• Manganese

4.2 High-confidence conclusions • Arsenic

Solvents

PAHs

Many environmental contaminants have been conclusively shown to affect the developing nervous system, causing a range of

• Pesticides

performance deficits (29, 115).

• Nicotine & ETS

4.2.1 Alcohol

The effects of ethyl alcohol on brain development and function are well established. Fetal Alcohol Syndrome (FAS), now considered part of Fetal Alcohol Spectrum Disorder (FASD), is the most preventable form of behavioral and learning disabilities. In the US, FASD is estimated to affect 9.1 per 1000 infants (41), with even higher rates in other parts of the world (116). Even low or moderate consumption of alcohol during pregnancy can cause subtle and permanent performance deficits (117, 118). Specific genetic polymorphisms enhance the risk of FASD (54).

4.2.2 Lead

Lead is probably the most studied of environmental contaminants in both humans and animals. Its effects on learning and development are undisputed. Recent research indicates that there is no safe level of lead exposure for children (112, 119, 120). Lead exposure impairs overall intelligence as measured by IQ, learning and memory and is associated with ADHD even at minute exposures. Efforts to prevent lead exposure provide an outstanding example of the struggle when science meets policy (23, 121, 122). Figure 3 (right) documents the gradual recognition of the harmful effects of lead at ever lower exposures. This debate is still unfolding: the US Centers for Disease Control and Prevention (CDC) has not adjusted the blood-lead action level since 1990 despite scientific evidence of behavioral effects well below 10 micrograms per deciliter ($\mu\text{g}/\text{dL}$). Arguments have been made to reduce the CDC blood-lead action level to 2 $\mu\text{g}/\text{dL}$ (23).

4.2.3 Mercury

There is no doubt that mercury exposure causes learning and developmental disorders; the controversy regards the level of exposure. We are all exposed to some form of mercury. Inorganic mercury is the liquid silver form and is used in dental amalgams. Mercury is also present in

coal, and coal-burning electric utilities facilities are a significant source of atmospheric environmental mercury. While much of the mercury falls close to the facility, mercury can be carried long distances to pollute water supplies and, ultimately, contaminate the food supply. Inorganic mercury is converted to the organic methylmercury and **bioaccumulates** in the flesh of fish, being **biomagnified** up the food chain. Methylmercury contamination often results in fish-consumption advisories, particularly for women and children. The knowledge (and concern) that methylmercury exposures affect the developing nervous system resulted in several very sophisticated studies designed to assess the effects of very low-level exposures on a range of learning and memory tests and on other performance-based tests (6, 27, 28, 46, 102, 103, 123-127). These tests typically included age-related assessment of learning and memory, reading, IQ and other neurological functions.

4.2.4 PCBs

Polychlorinated biphenyls (PCBs) are **mixtures** of chlorinated compounds that were once used as cooling and insulating fluids in electrical transformers and other electronic components. Because they are very **persistent**, **PCBs** have become widely distributed in the environment despite being banned in the 1970s. Because **PCBs bioaccumulate** in fat, human exposure continues through the food supply, and infant exposure continues through contaminated breast milk. Numerous studies have documented that **PCB** exposure can adversely affect motor skills, learning and memory as shown in lower full-scale and verbal IQ scores and reading ability (103, 128-134).

4.2.5 PBDEs

Polybrominated diphenyl ethers (PBDEs) have been used commonly as flame-retardant chemicals for several decades. PBDEs, structurally similar to PCBs, bioaccumulate in animals and humans, and are excreted in human breast milk. Recent studies have left little doubt that PBDEs are developmental neurotoxicants in animals and lead to changes in motor activity and reduced performance on learning and memory tests (135, 136).

4.2.6 Manganese

Manganese is a trace element which is necessary in small amounts for growth and development. Recent studies indicate that high levels of manganese exposure, either from inhalation (welding fumes) (137, 138) or through drinking water, can damage the developing nervous system (139, 140) as measured in full-scale IQ and verbal tests (139, 141-146). For example, a case study documented memory effects in a child exposed to manganese in drinking water (142), and a more recent study confirmed similar effects (140). The US EPA advises that water levels of manganese should not exceed 300 µg Mn/L, but approximately six percent of domestic household wells exceed this level (146).

4.2.7 Arsenic

Arsenic is commonly found in drinking water around the world, sometimes in concentrations high enough to cause cancer (147). Recent studies have found a dose-response relationship between exposure to arsenic and intellectual impairment (141, 148-151). While additional studies assessing the impact of low levels of arsenic in drinking water are needed, it is clear that arsenic affects the neurodevelopment of children.

4.2.8 Solvents

Solvents include a broad array of different compounds including toluene, benzene, alcohol, turpentine, acetone and tetrachloroethylene (TCE) (see Table 1), with more than 50 million metric tons used in the US and more than 10 million people exposed in the workplace. Solvent **neurotoxicity** is well recognized in adult workers (152). Ethyl alcohol is a widely used and consumed solvent with clear learning and developmental effects (see above). Recent

Table 1. Examples of Solvents

studies indicate that occupational exposure to solvents in salons and laboratories can result in visual deficits in offspring (153-156). Several reports have documented that the adverse developmental effects of maternal toluene exposure include low birth weight, decreased head circumference and **developmental delays** (157, 158). **Awareness of developmental effects of solvent exposure has resulted in increasing concern for women working in nail and beauty salons. Some solvents, such as toluene, have also been abused by pregnant women who purposely sniff them.**

4.2.9 PAHs

Polycyclic aromatic hydrocarbons (PAHs) are widely distributed air pollutants and well-recognized human mutagens and carcinogens. PAHs are generated during combustion of fuels from motor vehicles, coal-fired power plants, residential heating and cooking and are also present in tobacco smoke. Recent studies have indicated that elevated exposure to PAHs results in lower birth weight (159) and affects cognitive development (160).

4.2.10 Pesticides

Major classes of pesticides are specifically designed to kill insects, plants, fungi or animals. Agricultural and residential application of pesticides in the US totals more than one billion pounds per year, with thousands of people exposed every year. Data from acute exposure incidents leave no doubt that some pesticides, particularly insecticides, are **neurotoxic**. There is now evidence that childhood exposure to pesticides, such as organophosphates, enhances the risk for developmental disorders including deficits in memory (161), poorer motor performance (111, 162) and an array of other conditions (163-171). A recent study documented the developmental effects of the pesticide chlorpyrifos on inner-city children (172). There is also evidence of specific genetic susceptibility to pesticide exposure and related health effects (55-57, 163).

4.2.11 Nicotine and environmental tobacco smoke

Many studies link maternal smoking during pregnancy to behavioral disorders in children (37, 173-175), and **developmental delays** caused by environmental tobacco smoke (ETS, also known as secondhand smoke) are costly and preventable (176). Furthermore, new data indicates that childhood exposure to ETS is associated with neurobehavioral effects (177). There is growing recognition of subsequent behavioral disorders in young adults following exposures either prenatally or as children. (175, 178, 179). The CDC reported in 2002 that 11.4 percent of all women giving birth in the United States smoked during pregnancy (180). Clearly this highly preventable form of developmental disorder

requires that parents, both male and female, be educated about the harmful effects of tobacco.

4.3 Other contributors and emerging evidence

It is not possible to address all the chemicals that might be associated with causing learning and developmental disorders. A more comprehensive assessment of developmental [neurotoxicity](#) of chemicals was undertaken by Grandjean and Landrigan (29) in which they pointed out that, for the majority of chemicals, we do not have the data necessary to conclude there are no adverse developmental effects. They estimate that more than 200 chemicals are known to cause neurotoxic effects in adults and that, for many of these chemicals, developmental effects have not been examined. In addition, very few studies have focused on the potential synergistic impacts of chemicals in [mixtures](#). Highlighted below are just a few agents that are of significant concern.

4.3.1 Endocrine disruptors

Animal studies have documented that a wide range of chemicals have the ability to disrupt endocrine function in animals and affect cognitive function (50). [Endocrine disruptors](#) include [phthalates](#), [PCBs](#) and [polychlorinated dibenzodioxins](#), [brominated flame retardants](#), [dioxins](#), [DDT](#), [perfluorinated compounds \(PFCs\)](#), [organochlorine pesticides](#), [bisphenol A](#) and some metals. The controversy around the effects of [endocrine disruptors](#) is perhaps best illustrated by research on [bisphenol A](#) (181, 182) whose estrogenic activity was first reported in 1936. It was subsequently found to stabilize polycarbonates and resins and is now widely used in many products including food-can liners. There is a growing body of evidence related to the very low-dose effects of [bisphenol A](#) (66, 67, 183). The very low-dose effects of [endocrine disruptors](#) can not be predicted from high-dose studies, which contradicts the standard “dose makes the poison” rule of toxicology. Nontraditional dose-response curves are referred to as [nonmonotonic dose-response curves](#).

4.3.2 Fluoride

Fluoride is commonly added to municipal drinking water across the US based on data that it reduces dental decay. In addition to drinking water, fluoride is also present in a range of consumer products including toothpaste and mouthwashes. Excessive fluoride ingestion is known to lower thyroid hormone levels, which is particularly critical for women with subclinical hypothyroidism: decreased maternal thyroid levels adversely affect fetal neurodevelopment. In addition, a study in China reported decreased child IQ levels associated with fluoride in drinking water (184, 185). The question is what level of exposure results in harmful effects to children. The primary concern is that multiple routes of exposure, from drinking water, food and dental care products, may result in a high enough cumulative exposure to fluoride to cause developmental effects. In 2006 the National Academy of Sciences (NAS) produced a report, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* (185), reviewing the appropriateness of EPA's four parts per million (ppm) maximum contaminant level goal for fluoride in drinking water. The NAS was not directed to conduct a risk assessment of the effects of low-level fluoride exposure. It is not clear that the benefits of adding fluoride to drinking water outweigh risks of neurodevelopment or other effects such as dental fluorosis (186).

4.3.3 Food additives

Artificial or synthetic food colors and additives are ubiquitous in the food supply and have long been suspected of causing [conduct disorders](#). Their use has encouraged treatments such as the Feingold Diet (187, 188) in which many food additives are removed from the diet of individuals with [ADHD](#). Previous and recent carefully conducted double-blind human studies have confirmed that artificial food colorings such as sunset yellow, tartrazine, carmoisine and ponceanu, as well as the preservative sodium benzoate, can cause [conduct disorders](#) (187-192). Recent studies using well-designed randomized, double-blind, placebo-controlled, crossover trials show that artificial food colors and additives cause increased hyperactivity in three-year-old children (192). This has the potential to become a serious issue given the large number of children diagnosed with [ADHD](#).

5 Call for Further Research

Further research into the links between [environmental agents](#) and [LDDs](#) is urgently needed, as is regulatory action in those cases in which the weight of evidence is sufficient now, to reduce exposures. Cumulative exposures (from different chemicals with similar modes of action) and aggregate exposures (from all sources of exposure to a chemical such as via dust, food, air, water), as well as direct exposure from items in the home environment and from food, must be taken into account in assessing risk and devising appropriate action.

5.1 Better assessment tools and procedures

While some progress in testing methodology has been made, few chemicals have been evaluated using the Developmental Neurotoxicity Test (DNT) to date, although it has been determined as one of the most sensitive tests, in some cases showing adverse effects at lower levels of exposure than other tests. There is a growing demand to gather data on and screen compounds for effects on the nervous system. More sophisticated methodologies for testing humans and animals are also required, including testing procedures that address specific neurological disorders. New methods will be necessary to gather data as most high-volume chemicals have little or no developmental or neurotoxicity data.

5.2 In vitro (test-tube) screening of both new and old compounds

For most chemicals there are very little data on the potential to cause learning or developmental disorders or even basic data on potential neurotoxicity. Basic research is needed to develop reliable and reproducible [in vitro](#) tests that accurately predict the potential for [neurotoxic](#) effects. Development of these tests will also help reduce the need for animal-based research studies. Relatively quick and inexpensive [in vitro](#) tests will need to be followed by more efficient, integrated neurobehavioral test methods if indicated (see the National Research Council report on toxicity testing (193)).

5.3 Chronic effects of hazardous chemicals

While the acute high-dose effects of exposure to some chemicals are well documented, the learning and developmental effects of chronic, low-level exposure to pesticides, endocrine disruptors, flame retardants and other chemicals need further research.

5.4 Multiple exposures

More research is needed on the consequences of exposure to multiple chemicals and cumulative exposures as children and adults are exposed to low levels of a variety of chemical agents throughout life. More data are needed on the interaction of the chemicals and their effects on development, and better risk-assessment procedures are needed to evaluate multiple exposures (194).

5.5 Low-level exposures

Many animal and human studies have examined the effects of relatively high exposures. There is increasing evidence that low-level exposures to a variety of environmental toxicants (such as lead or tobacco) are associated with adverse consequences. In some cases the deficits are proportionately greater at lower levels. These new data indicates that studies should be designed specifically to examine the effects in representative samples, such as in the [National Children's Study](#).

5.6 Interactions with socioeconomic factors (environmental justice)

Disadvantaged groups are at a higher risk for learning and developmental disorders. More research is needed to determine the mechanisms and relationship by which socioeconomic factors and stress interact with chemical exposures to produce learning and developmental disorders. Furthermore, we must develop tools and systemic models for prevention.

5.7 Effects of endocrine disruption on cognitive deficits

Children and adults are exposed to a wide range of chemicals that affect the endocrine system and which can cause a range of learning and developmental disorders. Additional research is needed to evaluate the effects of low-level exposures and ascertain possible mechanisms of action and better characterize the adverse effects.

5.8 Interactions with genetics and identification of susceptible subpopulations

There is increased need to identify subpopulations who, due to genetic contributors and susceptibility to developmental disorders, may be vulnerable to chemical exposure or other factors, including stress, that exacerbate the onset of these disorders.

5.9 World Health Organization research recommendations

Research recommendations on evaluating children's risk to exposure to environmental chemicals are defined in a recent report by the World Health Organization (195).

6 Ethical and Policy Considerations

6.1 Ethical considerations

There is growing recognition that ethical, legal and social considerations play a crucial role in public- and child-health decision making that involves conflicts between individual, corporate, human rights and social-justice goals (196-200). Knowledge of the causes of learning and developmental disabilities implies an ethical duty and responsibility to act to protect children's health and well-being (122, 201). Accepting childhood exposure to contaminants that result in compromised learning and behavioral abilities violates the basic tenets of biomedical ethics. The principle of beneficence ("do good") requires that the benefits be maximized while the harm be minimized or eliminated. Respect for autonomy or personhood is violated when children are unnecessarily exposed to harmful substances. Respect of person also implies informed consent, and no child has given the informed consent for exposure to harmful chemicals. Finally, the principle of justice requires that burdens be shared equally, and because children are more vulnerable they endure a greater burden. In addition there are disparities related to socioeconomic status demonstrated by the increased burden of lead exposure in children of poverty (202). Perhaps America's first bioethicist Aldo Leopold said it best when he wrote in 1949: "A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise" (203). It is wrong to allow the exposure of children to environmental agents that cause learning and developmental disorders.

6.2 Policy considerations

Recognition of the contribution of chemical contaminants to [LDDs](#) has increased substantially in recent years as new evidence has emerged both about the ability of neurotoxic chemicals to interfere with brain development and the susceptibility of the brain to chemicals (29). Given this established knowledge, it is clear that protecting children from [neurotoxic](#) environmental exposures from the earliest stages of fetal development is an essential public health measure if we are to help prevent [LDDs](#) and create an environment in which children can reach and maintain their full potential.

There is a vast amount of information already available upon which to base sound policy decisions. As Garrett Hardin observed in 1968, many problems cannot be solved by technical solutions or additional research but only through responsible management of the problem (204). Our society is still contending with the effects of adding lead to paint and gasoline, even though its toxic effects were well documented at the time. Knowledge was sufficient, but management was not. To protect children, a precautionary approach is required that shifts the burden of responsibility to producers or manufacturers to demonstrate safety prior to potential exposure.

The researchers and reviewers for this statement are developing a companion document outlining specific policy recommendations based on the status of scientific knowledge outlined in this statement.

7 Conclusions

The scientific evidence we have reviewed indicates environmental contaminants are an important cause of [learning and developmental disabilities](#). The proportion of environmentally induced [LDDs](#) is a question of profound human, scientific and public policy significance. Existing animal and human data suggest that a [greater proportion is environmentally influenced than has yet been generally realized or than can be demonstrated with scientific certainty](#). The consequences of [LDDs](#) are most significant for the affected individual but also have profound implications for the family, school system,

local community and greater society. Despite some uncertainty, there is sufficient knowledge to take preventive action to reduce fetal and childhood exposures to environmental contaminants. Given the serious consequences of **LDDs**, a precautionary approach is warranted to protect the most vulnerable of our society.

8 Resources: Children and Environmental Agents

American Association on Intellectual and Developmental Disabilities (AAIDD)

www.aaid.org/

American Pediatric Association

www.aap.org

Autism Society of America

www.autism-society.org

Center for Health, Environment and Justice

www.chej.org/

Children's Environmental Health Network

www.cehn.org

Collaborative on Health and the Environment

www.healthandenvironment.org

Greater Boston Physicians for Social Responsibility

<http://psr.igc.org/>

Healthy Child, Healthy World

<http://healthychild.org/>

Healthy Schools Network, Inc.

www.healthyschools.org

Institute for Children's Environmental Health

www.iceh.org

Learning and Developmental Disabilities Initiative

www.iceh.org/LDDI.html

Learning Disabilities Association of America's Healthy Children Project

www.healthychildrenproject.org

Learning Disabilities Association of Canada (LDAC)

www.ldac-taac.ca

Mt. Sinai Children's Environmental Health Center

www.cehcenter.org/

The National Association for the Dually Diagnosed

www.thenadd.org

National Institute for Environmental Health Science Centers for Children's Environmental Health & Disease

Prevention Research

www.niehs.nih.gov/research/supported/centers/prevention/

Preventing Harm: A Resource and Action Center on Children and the Environment

www.preventingharm.org

Toxipedia

<http://toxipedia.org/>

University of Tennessee Youth Environment and Health Research Group

<http://utyeah.utk.edu>

US Environmental Protection Agency Office of Children's Health Protection

<http://yosemite.epa.gov/ochp/ochpweb.nsf/content/homepage.htm>

9 Glossary of Terms and Term Usage Specific to This Statement

(A number of the definitions were taken in whole or in part from the Vallombrosa Consensus Statement on Environmental Contaminants and Human Fertility Compromise October 2005.)

Attention deficit hyperactivity disorder (ADHD) – The principal characteristics of ADHD are inattention, hyperactivity and impulsivity. According to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (**DSM-IV-TR**) (205), there are three patterns of behavior that indicate ADHD. People with ADHD may show several signs of being consistently inattentive. They may have a pattern of being hyperactive and impulsive far more than others of their age. Or they may show both types of behavior. This means that there are three subtypes of ADHD recognized by professionals. These are the predominantly hyperactive-impulsive type (that does not show significant inattention); the predominantly inattentive type (that does not show significant hyperactive-impulsive behavior) sometimes called ADD – an outdated term for this entire disorder; and the combined type (that displays both inattentive and hyperactive-impulsive symptoms) (see also a document from the National Institute of Mental Health (13)).

Autism spectrum disorders – The Diagnostic and Statistical Manual of Mental Disorders **DSM-IV-TR** (205) includes autism as one of the five pervasive developmental disorders (PDD), more often referred to today as autism spectrum disorders (ASD). All these disorders are characterized by varying degrees of impairment in communication skills, social interactions and restricted, repetitive and stereotyped patterns of behavior (see also a document from the National Institute of Mental Health (16)).

Bioaccumulation – A process whereby contaminants taken up from the surrounding environment (air, food, water) are retained and concentrate in tissues at a rate faster than they can be broken down and excreted. With bioaccumulation, tissue levels of a contaminant become greater than surrounding environmental levels.

Biomagnification – A process whereby the concentration of contaminants increases up the food chain due to larger organisms ingesting smaller organisms containing contaminants. Humans and other predatory organisms accumulate the highest concentrations of contaminants.

Biomarker – A biological substance found in body fluids (blood, urine, breast milk) or tissues (fat) that can be measured and is associated with exposure to a contaminant. Biomarkers can help monitor exposure to contaminants and may help characterize individual susceptibilities to exposure. A biomarker of exposure is a measure of either the contaminant or a metabolite occurring shortly after exposure. A biomarker of effect is an enduring genetic change caused by a contaminant exposure that can be measured by changes in DNA or chromosome structures (such as [genetic mutations](#)). Biomarkers of effect are not necessarily specific to contaminant exposure. A biomarker of susceptibility is a gene or expression of a gene ([polymorphism](#)) that renders an individual more vulnerable to the adverse effects of contaminant exposure. For example, due to differences in enzymes some individuals may not be able to detoxify a contaminant as efficiently as others, resulting in higher levels of exposure and greater toxicity.

Biomonitoring – The assessment of exposure to contaminants by measuring [biomarkers](#) of exposure in body tissues or fluids (such as blood, urine, breast milk, amniotic fluid, hair, adipose tissue, bone). Biomonitoring can be used to monitor not only exposures in populations but also changes in levels of contaminants over time.

Bisphenol A – A common chemical compound that forms the building block of polycarbonate plastics and epoxy resins. Bisphenol A is used in polycarbonate plastic in food containers, water bottles, baby bottles, compact disk cases, eyeglass lenses, the lining of food cans and as a dental sealant. It binds with nuclear and extracellular estrogen receptors.

Conduct disorders – Refers to behavior characterized by hostility and aggression.

Developmental delays – Refers to development which is delayed compared with age peers. Developmental delays can be associated with varied or negative effects in multiple areas such as sensory, motor, language, social, reading and emotional areas. These are also referred to as neurodevelopmental delays.

Dioxins – A class of hundreds of related [persistent](#) chemicals, some of which are known to be highly toxic, that result from industrial combustion/incineration processes; burning of household trash or fuels such as wood, coal and oil; chlorine bleaching of pulp/paper; and some types of chemical manufacturing. Cigarette smoke also contains dioxins.

DSM-IV-TR – The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2013) is a handbook for mental health professionals that lists categories of mental disorders and the criteria for diagnosing them according to the American Psychiatric Association. It is used worldwide by clinicians and researchers as well as insurance companies, pharmaceutical companies and policymakers.

Dyslexia – A specific learning disability that manifests primarily as a difficulty with written language, particularly with reading and spelling. Dyslexia is the result of a neurological difference but is not an intellectual disability. Most people with dyslexia have average or above-average intelligence.

Endocrine disruptors – Environmental compounds that interfere with the normal function of endogenous hormones (those produced by an organism). Endocrine disruptors can stimulate or block the actions of hormones or can interfere with their metabolism. Endocrine disruptors continue to be discovered but have been recognized to include a diverse range of chemicals including pesticides, plasticizers, flame retardants, industrial byproducts, pharmaceuticals and plant-derived compounds.

Endpoints – In a scientific study, the outcome that is being measured. In the field of environmental health, this could be a [biomarker](#), toxic effect, disease outcome or other measure anticipated to differ between exposed and unexposed populations.

Environmental agents – These include natural or synthetic chemicals, heavy metals (such as lead, mercury, cadmium), and naturally occurring compounds such as plant-derived estrogens.

Environmental factors – In this document, “environmental factors” refers to a broader range of possible environmental influences than the environmental agents listed above. Environmental factors include pharmaceutical use, stress, other chemical agents or physical conditions that adversely affect learning or development.

Epigenetics – The molecular phenomena that regulate gene expression without alterations to the DNA sequence.

Genetic mutation – A change in the nucleotide sequence of a DNA molecule. Genetic mutations are a kind of [genetic polymorphism](#). Genetic mutation refers to changes in DNA sequence which are not present in most individuals of a species and either have been associated with disease (or risk of disease) or have resulted from damage inflicted by external agents (such as viruses or radiation).

Genetic Polymorphism – A difference in DNA sequence among individuals, groups or populations (for example, a genetic polymorphism might increase susceptibility to Fetal Alcohol Spectrum Disorder). Genetic polymorphisms may be the result of chance processes, may be inherited or may be induced by external agents (such as viruses or radiation), which is then referred to as a genetic mutation.

In vitro testing – Generally refers to experiments done in a test tube, outside a living organism. *In vitro* systems typically use cell culture techniques for initial assessment of harmful effects.

Learning and developmental disabilities (LDDs) – Conditions resulting from interference of normal brain development and function that adversely affect an individual’s performance. [Learning and developmental disabilities](#) include but are not limited to deficits in learning and memory, reduced IQ, [attention deficit hyperactivity disorder](#), [autism spectrum disorder](#), [conduct disorders](#) and [developmental delays](#), but do not consider effects of the peripheral nervous system.

Mental retardation – According to the American Association on Intellectual and Developmental Disabilities

(AAIDD), mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills (see www.aaidd.org/Policies/faq_mental_retardation.shtml).

Mixtures – In this context, “mixtures” indicates the effects of two or more contaminants in which the outcome of exposure is different from their separate effects. The interaction could be additive (a sum of individual effects), subtractive (one substance is stimulatory and another inhibitory), or multiplicative (the effect is greater than the sum of individual effects).

Morphometric – Generally refers to procedures that count or quantitatively assess the number of specific cell types.

National Health and Nutrition Examination Survey (NHANES) – A program designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC), US Public Health Service, and has the responsibility for producing vital and health statistics for the nation (www.cdc.gov/nchs/nhanes.htm).

National Children’s Study – Led by a consortium of US government agencies (<http://nationalchildrensstudy.gov>), this study aims to examine the effects of **environmental factors** on the health and development of more than 100,000 children from before birth to age 21.

Neuropathology/neuropathological – The microscopic study of cells of the brain or nervous system.

Neurotoxic / neurotoxicity – An adverse change in the chemistry, structure or function of the nervous system, during development or at maturity, following exposure to a chemical or physical agent.

Neurotoxicant – A chemical or physical agent that produces **neurotoxicity**.

Nonmonotonic dose-response curve (NMDR) – A traditional dose-response curve in toxicology assumes that the response to exposure will increase with increasing dose. This is known as a monotonic curve, one in which the slope of the dose-response curve does not change from positive to negative or vice versa. In a nonmonotonic dose-response curve, the slope of the dose-response curve changes sign as the level of exposure increases. Some NMDR curves are shaped like a U, while others are shaped like an inverted U. NMDR curves are important from a public-health perspective because in dose-response curves that are nonmonotonic, low-dose effects cannot be predicted from high-dose testing. The traditional assumption that higher doses cause greater harm (“the dose makes the poison”) is used in standard risk-assessment studies to identify the level of a chemical exposure beneath which contamination should cause no effect. This old assumption may be true for many chemicals and for many classic health effects, but it can be misleading for exposures that have a nonmonotonic dose-response curve.

Octyl/nonyl phenols – Chemicals that belong to a broader class of compounds known as alkylphenol ethoxylates (APEs). APEs are high-volume chemicals that have been used for more than 40 years as detergents, emulsifiers and wetting and dispersing agents. These chemicals are used as ingredients in spermicides, cosmetics and detergents and as inert ingredients in pesticides. Some are **endocrine disruptors**. Several are noted contaminants in aquatic environments.

Perfluorinated compounds (PFCs) – **Persistent, bioaccumulative** chemicals found in a wide array of products including stain-resistant coatings for carpets and clothing (Gore-Tex), nonstick cookware (Teflon), and insecticides. Widespread contamination of human tissues has been documented, with some of the highest levels found in US populations. PFCs have been linked to neuroendocrine and reproductive effects.

Persistence – This refers to the stability of a contaminant in the environment. Persistent contaminants are characterized by their ability to resist natural degradation so that they build up in the environment with time. Persistent contaminants often are transported globally on currents of wind or water.

Phthalates – Chemicals added to personal-care products to enhance penetration and hold scent/color and used as plasticizers in rigid plastics such as polyvinyl chloride (PVC) to create flexibility. Phthalates are found in numerous and diverse consumer products including vinyl flooring, plastic shower curtains, cosmetics and fragrances, shampoos and lotions, toys, pharmaceutical and herbal pill coatings – and in hospital equipment including intravenous bags and tubing.

Polybrominated diphenyl ethers (PBDEs) – **Persistent, bioaccumulative** chemicals added to electronics, upholstery foam, textiles and numerous other materials to make them more flame-resistant. PBDEs have a chemical structure very similar to **PCBs** and have been rapidly accumulating in wildlife and human tissues.

Polychlorinated biphenyls (PCBs) – There are 209 individual chlorinated PCB compounds (known as congeners) that are **persistent** and **bioaccumulative**. Manufacture was banned in the US in the late 1970s, although PCBs are still found in some products, and widespread environmental contamination still exists. PCBs were used in hundreds of commercial and industrial applications, including as lubricants, plasticizers, insulators for electrical applications, caulking and paint. Health effects of PCB exposure include acne-like skin conditions in adults and neurobehavioral and immunological changes in children. PCBs cause cancer in animals (see ATSDR fact sheet www.atsdr.cdc.gov/tfacts17.html).

Polymorphism – see genetic polymorphism above.

Potentiated or potentiating – To enhance or increase the effect of a drug or chemical, which results in an increased response or undesired action or effect.

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