TRAINING FOR THE HEALTH SECTOR

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CHILDREN AND NEURODEVELOPMENTAL BEHAVIOURAL INTELLECTUAL DISORDERS (NDBID)

Children's Health and the Environment

WHO Training Package for the Health Sector

World Health Organization

www.who.int/ceh

October 2011

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<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the problem. Present only those slides that apply most directly to the local situation in the region.>>

<<NOTE TO USER: This module presents several examples of risk factors that affect neurodevelopment, you can find more detailed information in other modules of the training package that deal with specific risk factors, such as lead, mercury, pesticides, persistent organic pollutants, endocrine disruptors; or prenatal exposures and developmental effects.>>

Children & neurodevelopmental behavioural intellectual disorders

OBJECTIVES

- To define & describe common Neurodevelopmental Behavioral Intellectual Disorders (NDBID) and their prevalence.
- To understand the neurodevelopmental process in the context of basic science and environmental data.
- To discuss key epidemiological studies addressing environmental risk factors.
- To gain insight into environmental neurotoxic potential exposures and complexities of attributing causality.

<<READ SLIDE>>

Children & neurodevelopmental behavioural intellectual disorders

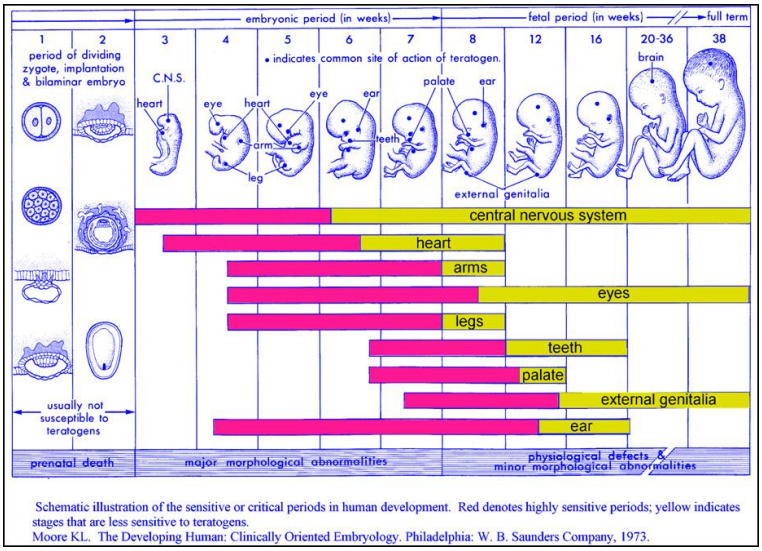
OVERVIEW

- Descriptions of common Neurodevelopmental Behavioral Intellectual Disorders (NDBID).
- Brief epidemiology of Neurodevelopmental Behavioral Intellectual Disorders.
- Summary of neurodevelopmental processes.
- Discussion of environmental linkages.
- Impacts of Neurodevelopmental Behavioral Intellectual Disorders and challenges of adequately protecting children.

<<READ SLIDE>>

Children & neurodevelopmental behavioural intellectual disorders

WINDOWS OF DEVELOPMENT



Schematic illustration of the sensitive or critical periods in human development. Red denotes highly sensitive periods; yellow indicates stages that are less sensitive to teratogens.
Moore KL. The Developing Human: Clinically Oriented Embryology. Philadelphia: W. B. Saunders Company, 1973.

Moore, Elsevier Inc, 1973

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Physiological differences between children and adults are not only manifest in immature metabolic pathways. Because important systems are still differentiating and growing, children have unique susceptibilities not seen in adults — and critical time windows for those susceptibilities. The critical times are as follows:

•preconception

•gestation (susceptibility to: thalidomide, DES, ionizing radiation, methylmercury, lead)

•postnatal (susceptibility to: SHTS (second-hand tobacco smoke), lead.

There has been an explosion of knowledge about child development in past decade or so, and it is hard to remember that it was only about 50 years ago that the discovery was made that the fetus is vulnerable to exposures. The phocomelia epidemic resulting from use of thalidomide by pregnant women was an early and dramatic example of the ability of chemicals to traverse the placenta and damage the fetus. Additionally, thalidomide administered during a small, 4-day window between gestational days 20 and 24, may increase the risk of autism *(Stromland, 1994).* More than one system can be susceptible and different pathology may occur depending upon the dose and timing of exposure.

Now we know that other exposures during gestation, some of which are listed here, can harm the systems of the developing child. We also know that preconception exposure of parents, as well as postnatal exposure of both parents, can harm children.

<<NOTES TO USER: It is important to point out the different responses to insults shown on the bottom bar of the figure. Significant insult during the embryonic phase will result in pregnancy loss (first 2 weeks) or major organ malformation. During the fetal stage, damage is more subtle and related to system dysfunction.>>

Ref:

•Stromland. Autism in thalidomide embryopathy: a population study. *Developmental Medicine & Child Neurology,* 1994, 36:351.

Of a population of 100 Swedish thalidomide embryopathy cases, at least four met full criteria for DSM-III-R autistic disorder and ICD-10 childhood autism. Thalidomide embryopathy of the kind encountered in these cases affects fetal development early in pregnancy, probably on days 20 to 24 after conception. It is argued that the possible association of thalidomide embryopathy with autism may shed some light on the issue of which neural circuitries may be involved in autism pathogenesis.

Figure: Reprinted from Moore. *The developing human.* Elsevier Inc., 1973. *Used with copyright permission (2004) from Elsevier.*

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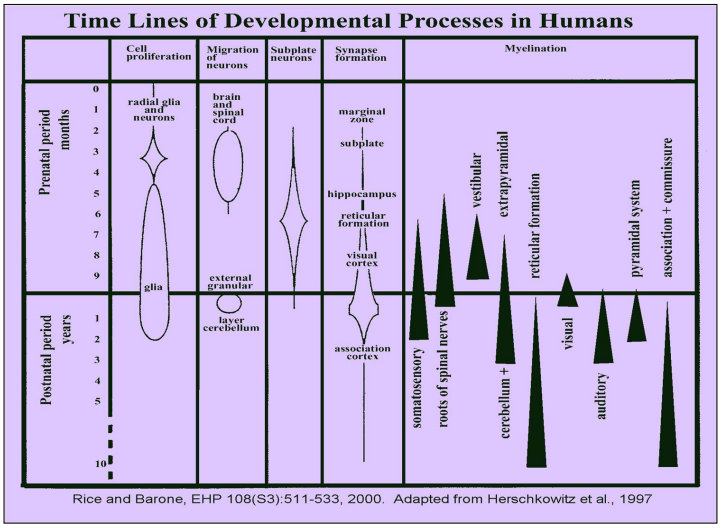
NEURODEVELOPMENTAL PROCESSES



Rice D. Environ Health Perspectives, 2000;108(S3)

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Neurodevelopment begins in the early prenatal stage with a complex neurological development that begins with proliferation of radial glia and neurons. These continue to develop in the postnatal years. This process is not complete until almost 3 years of age.

Migration of neurons, which occurs from the 2nd to the 6th month of gestation, and again within the cerebellum postnatally, is a very important and complex process.

Synapse formation, which occurs essentially in the last trimester as well as in the first 2 years of life, is critical to ongoing functioning and development.

Myelination is an important process that begins in the second half of gestation and goes on to adolescence, with different systems myelinating at different times, as shown in the diagram.

Ref:

•Rice D, Barone Jr S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environmental Health Perspectives*, 2000, 108(S3):511-533.

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NEURODEVELOPMENTAL PROCESSES

Cortex maturation from ages 5 to 20 years: "synaptic pruning" of unused neural connections

- **Abnormalities in maturation may underlie neurodevelopmental disorders**
- **Increased pruning with childhood-onset schizophrenia; decreased with autism**

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Refs:

•Gogtay N et al. From the Cover: Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, 2004, 101: 8174-8179

•National Institute of Mental Health (NIMH) / University of California Los Angeles (UCLA). Time-lapse imaging tracks brain developing from ages 5 to 20. NIMH/UCLA Project visualizes maturing brain - available at *www.loni.ucla.edu/~thompson/DEVEL/PR.html* - accessed 15 June 2011

The brain's center of reasoning and problem solving is among the last to mature. The decade-long magnetic resonance imaging (MRI) study of normal brain development, from ages 4 to 21, by researchers at NIH's National Institute of Mental Health (NIMH) and University of California Los Angeles (UCLA) shows that such "higher-order" brain centers, such as the prefrontal cortex, don't fully develop until young adulthood. A time-lapse 3-D movie that compresses 15 years of human brain maturation, ages 5 to 20, into seconds shows gray matter - the working tissue of the brain's cortex - diminishing in a back-to-front wave, likely reflecting the pruning of unused neuronal connections during the teen years. Cortex areas can be seen maturing at ages in which relevant cognitive and functional developmental milestones occur.

The researchers scanned the same 13 healthy children and teens every two years as they grew up, for 10 years. After co-registering the scans with each other, using an intricate set of brain anatomical landmarks, they visualized the ebb and flow of gray matter - neurons and their branch-like extensions - in maps that, together, form the movie showing brain maturation from ages 5 to 20.

It was long believed that a spurt of overproduction of gray matter during the first 18 months of life was followed by a steady decline as unused circuitry is discarded. Then, in the late 1990s, NIMH's Dr. Jay Giedd, a co-author of the current study, and colleagues, discovered a second wave of overproduction of gray matter just prior to puberty, followed by a second bout of "use-it-or-lose-it" pruning during the teen years.

The new study found that the first areas to mature (e.g. extreme front and back of the brain) are those with the most basic functions, such as processing the senses and movement. Areas involved in spatial orientation and language (parietal lobes) follow. Areas with more advanced functions -- integrating information from the senses, reasoning and other "executive" functions (prefrontal cortex) - mature last

Thompson says that researchers debate whether teens are actually losing tissue when the gray matter disappears, trimming connections, or just coating gray matter with insulation. Imaging doesn't provide high enough resolution to distinguish among the possibilities, he notes: "Right now we can image chunks of millions of neurons, but we can't look at individual cells."

Tremendous rate of growth in areas of vision and sensation occur in the early school years. In middle school areas in language development show repid growth. Late teens exhibit rapid growth in areas controlling inhibition, judgment. Healthy development means an increase and loss of neurological tissue.

Maturation of the central nervous system is critical in the development of neurodevelopmental disorders. Cell pruning or synapse pruning, which occurs between the ages of 5 – 20 years appears to be a critical process whereby if increased may be linked with childhood onset schizophrenia and if decreased may be linked with autism.

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NEURODEVELOPMENTAL PROCESSES CLINICAL MILESTONES

WHO

A newborn baby, although fully formed, is born with an immature neurological system which does not allow the baby to be anything more than helpless. There is poor head control, the limbs are flexed and newborn babies have no opportunity to defend themselves from harm other than by crying.

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NEURODEVELOPMENTAL PROCESSES CLINICAL MILESTONES

WHO

4 months

- Good head control, supports self on forearms
- Fixes, follows and takes interest in surroundings with eyes
- Hearing – brightens to sounds
- Cooing

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Development occurs very quickly as the neurological system matures in the first few years and months of life. By 4 months of age, a baby is able to hold his/her head against gravity when in the prone position, is fixing on and following objects with their eyes, responding to sounds and even beginning to grab at toys. In the sitting position a 4 month baby brightens to sounds, coos and interacts socially.

By 9 months of age the baby is sitting unsupported, is able to pick up toys, transfers them from hand-to-hand and is able to pick up very small objects between the thumb and first finger. At this time they are babbling consonants and vowels and modulating pitch and volume. They are able to make their needs understood for eating, drinking and the need for diaper change.

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NEURODEVELOPMENTAL PROCESSES
CLINICAL MILESTONES

WHO

18 months

- Walks up stairs
- Takes off shoes and socks
- Opens box, puts toys in and takes them out
- Says 10 – 20 words, understands phrases

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By 18 months of age a child is walking and running, can throw a ball and kick a ball, can stack toys, can walk up stairs, help with dressing and undressing and is able to say 10 – 20 words and understand more complex phrases.

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NEURODEVELOPMENTAL PROCESSES
CLINICAL MILESTONES

WHO

3 years

- Rides a tricycle
- Speaks in sentences (subject, verb, & object)
- Asks: *What? Where?* and *Who?* questions
- Understands three points

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By 3 years of age a child has the ability to ride a tricycle, speak sentences using a subject, verb and object which is understandable by strangers, asks questions what, where and who and understands more complex instructions.

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NEURODEVELOPMENTAL PROCESSES
CLINICAL MILESTONES

4 years

WHO

- Hops on one foot
- Climbs a ladder
- Asks: *When? Why?* and *How?* questions
- Understands opposites
- Understands four points

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By 4 years of age, the neurological system is becoming quite complex in that the child can hop on one foot, can climb a ladder, asks more complex questions when, why and how, understands opposites and is able to follow full instructions in a row.

NEURODEVELOPMENTAL BEHAVIORAL INTELLECTUAL DISORDERS

Inconsistencies in terminology and definitions

European Definition:

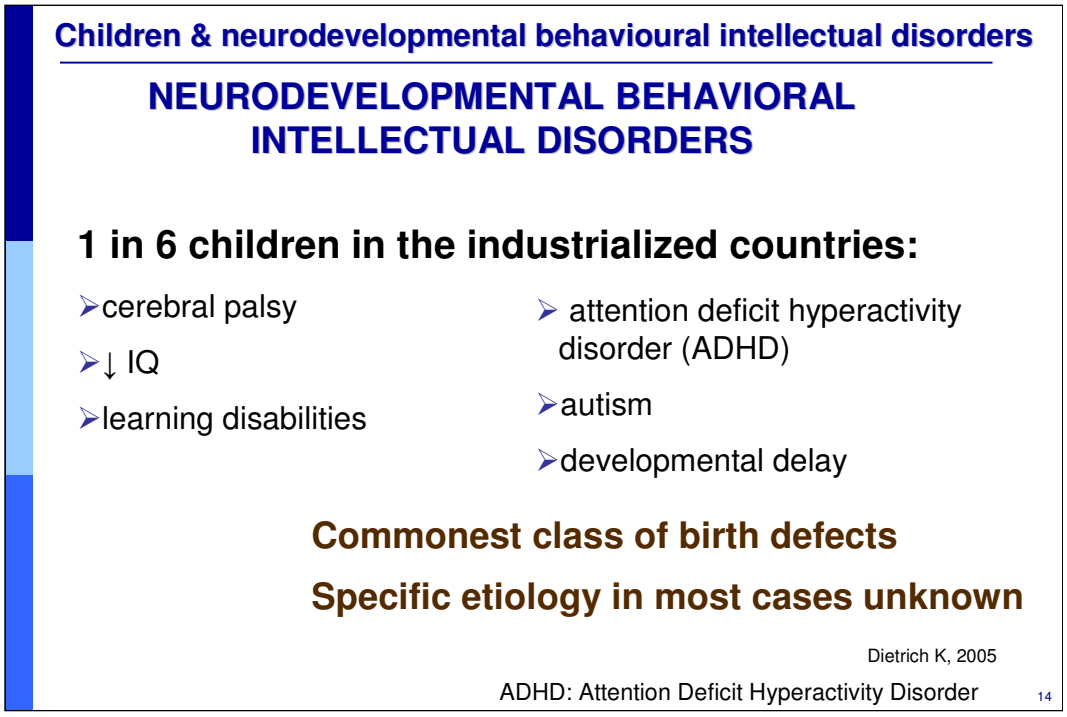
Neurodevelopmental disorders are disabilities in the functioning of the brain that affect a child's behaviour, memory or ability to learn e.g. mental retardation, dyslexia, attention deficit hyperactivity disorder (ADHD), learning deficits and autism.

Draft Baseline Report on Neurodevelopmental Disorders in the Framework of the European Environment and Health Strategy, 2003

Neurodevelopmental paediatrics is a developing field that addresses complex aspects of central nervous system (CNS) development in children. Some definitions include physical aspects consequent on early damage to the CNS e.g. cerebral palsy. Other definitions restrict themselves to functional impairment. The definition on this slide can be found in the draft baseline report on neurodevelopmental disorders in the framework of the European Environment and Health Strategy.

Ref:

•European Union. Draft Baseline Report on neurodevelopmental disorders in the framework of the European Environment and Health Strategy. Technical working group on priority diseases, subgroup neurodevelopmental disorders, 2003.



In North America, the definition of neurodevelopmental behavioural intellectual disorder has traditionally included physical as well as functional abnormalities.

Neurodevelopmental behavioural disorders occur commonly in industrialized countries. Figures as high as 15% of children are described as having learning disabilities, developmental delay, attention deficit hyperactivity disorder, autism, reduced intelligence quotient and cerebral palsy. In Aboriginal children, the prevalence is often much higher. Although some cases are linked to identified exposures, e.g. fetal alcohol, tobacco smoke, low birth weight and obstetric complications, in most cases specific etiology is unknown.

Ref:

•Dietrich K et al. Principles and practices of neurodevelopmental assessment in children: Lessons learned from the centers for children's environmental health and disease prevention research. *Environ Health Perspect*, 2005, 113(10):1437-1446.

NEURODEVELOPMENTAL BEHAVIORAL INTELLECTUAL DISORDERS - DEFINITIONS

Attention Deficit Hyperactivity Disorder (ADHD)

- A childhood mental disorder with onset before 7 years of age and involving impaired or diminished attention, impulsivity, and hyperactivity.

Autism

- A developmental disorder that appears in the first 3 years of life, and affects the brain's normal development of social and communication skills.

American Psychiatric Association, 2000
Mosby's Medical Dictionary, 2009
www.nlm.nih.gov/medlineplus/ency/article/001526.htm

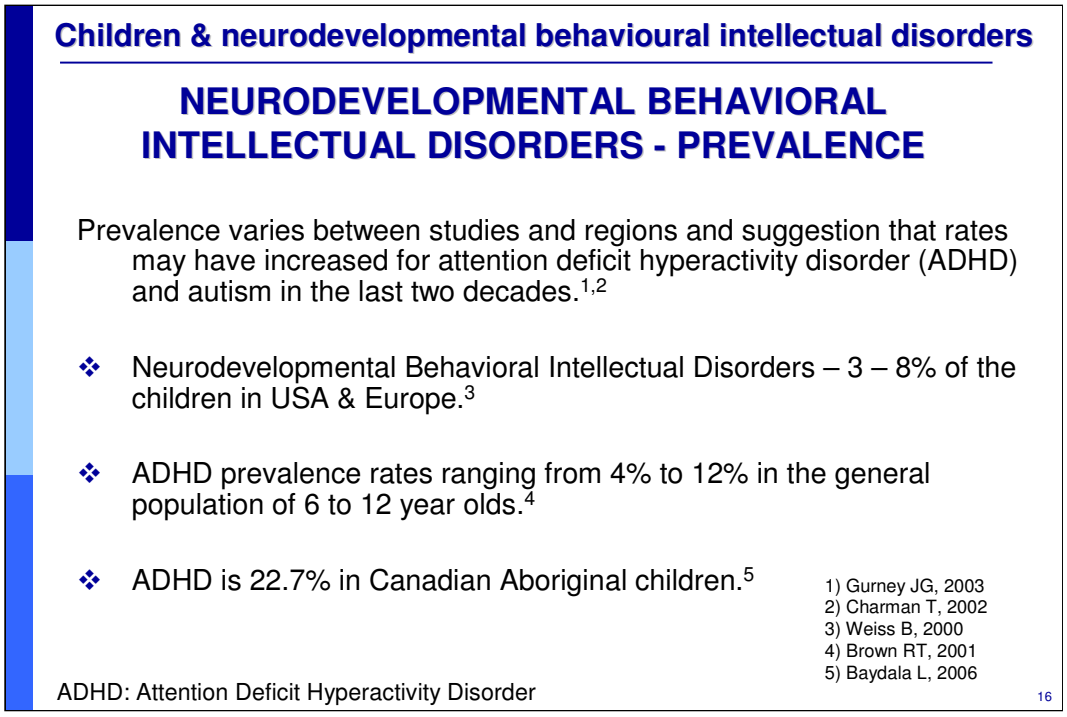
Neurodevelopmental behavioural intellectual disorders consist of many conditions. The commonest functional conditions identified are Attention Deficit Hyperactivity Disorder (ADHD) and autism which each now consist of various subgroups depending on an individual child's predominant symptomatology. For instance, Attention Deficit Disorder without hyperactivity is described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) typically diagnosed in older girls of about 9 years of age.

Refs:

•American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition. Washington, US. *American Psychiatric Association*, 2000.

•Kaneshiro NK. Autism. Available at *www.nlm.nih.gov/medlineplus/ency/article/001526.htm* - accessed 15 June 2011

•Mosby. ADHD. In: *Mosby's Medical Dictionary*, 8th edition, Elsevier, 2009.



Wide variations reported in previous rates due often to diagnostic and reporting variations. However, differences occur between gender (males higher than females), ethnic background (higher in Aboriginal children) and socioeconomic groups (higher in lower socioeconomic groups).

A study from Canada reports “findings suggest[ive] of either a high prevalence of attention deficit hyperactivity disorder (ADHD) in [Canadian] Aboriginal children or unique learning and behavioral patterns in Aboriginal children that may erroneously lead to a diagnosis of ADHD if screening questionnaires are used.” (Baydala, 2006)

Although increases noticed over the last 2 decades may reflect increased awareness of these disorders and broader diagnostic criteria, there is general concern about the possible implication of environmental factors in the etiology of neurodevelopmental disorders.

Refs:

•Baydala L et al. ADHD characteristics in Canadian Aboriginal children. *Journal of Attention Disorders*, 2006, 9(4):642-647.

•Brown RT, et al. Prevalence and assessment of Attention-Deficit/Hyperactivity Disorder in primary care settings. *Pediatrics*, 2001;107(3):E43.

•Charman T. The prevalence of autism spectrum disorders. Recent evidence and future challenges. *Eur Child Adolesc Psychiatry*, 2002, 11:249-256.

•Gurney JG et al. Analysis of prevalence trend of autism spectrum disorder in Minnesota. *Arch Pediatr Adolesc Med*, 2003, 157:622-7.

•Weiss B, Landrigan PJ. The developing brain and the environment: an introduction. *Environ Health Perspect*, 2000, 108(3):373-376.

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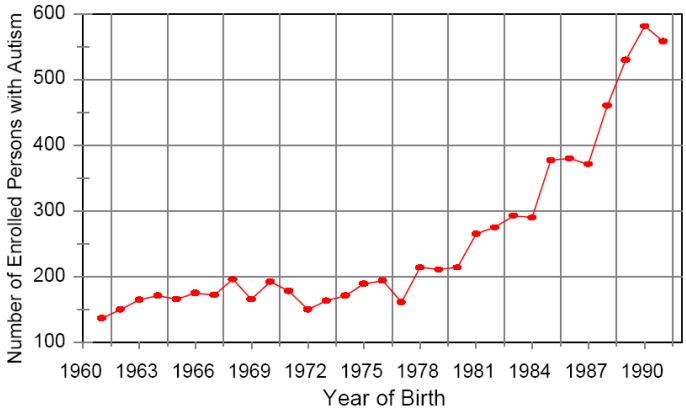
PREVALENCE OF AUTISM IN CALIFORNIA



www.dds.ca.gov/Autism/docs/autism_report_1999.pdf

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It is the perception of many general clinicians that the incidence of autism is rising. Until recently, genetics has been attributed as the major risk factor for development of autism in children which is commoner in certain ethnic backgrounds, e.g. Caribbean. There, however, are few databases to confirm this.

This graph from the State of California identifies a significant rise in cases of autism during the last 30 years.

Refs:

•Byrd RS. The epidemiology of autism in California: a comprehensive pilot study. Report to the legislature on the principal findings. *Medical Investigation of Neurodevelopmental Disorders (MIND) Institute, University of California*, Davis, 2002.

•Keen DV, Reid FD, Arnone D. Autism, ethnicity and maternal immigration. *Br J Psychiatry*, 2010, 196(4):274-81.

Image: California Department of Developmental Services. Changes in the population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998. A report to the Legislature. Sacramento CA: California Health and Human Services Agency, 1999. Available at www.dds.ca.gov/Autism/docs/autism_report_1999.pdf - accessed June 2011

NEURODEVELOPMENTAL BEHAVIORAL INTELLECTUAL DISORDERS

Co-morbidity and adult outcomes

- Anxiety/depression, oppositional defiant disorder, bipolar disorder, Tourette's Syndrome.
- Substance abuse, antisocial behavior, and even criminality are among the better-known problems persisting into adulthood.

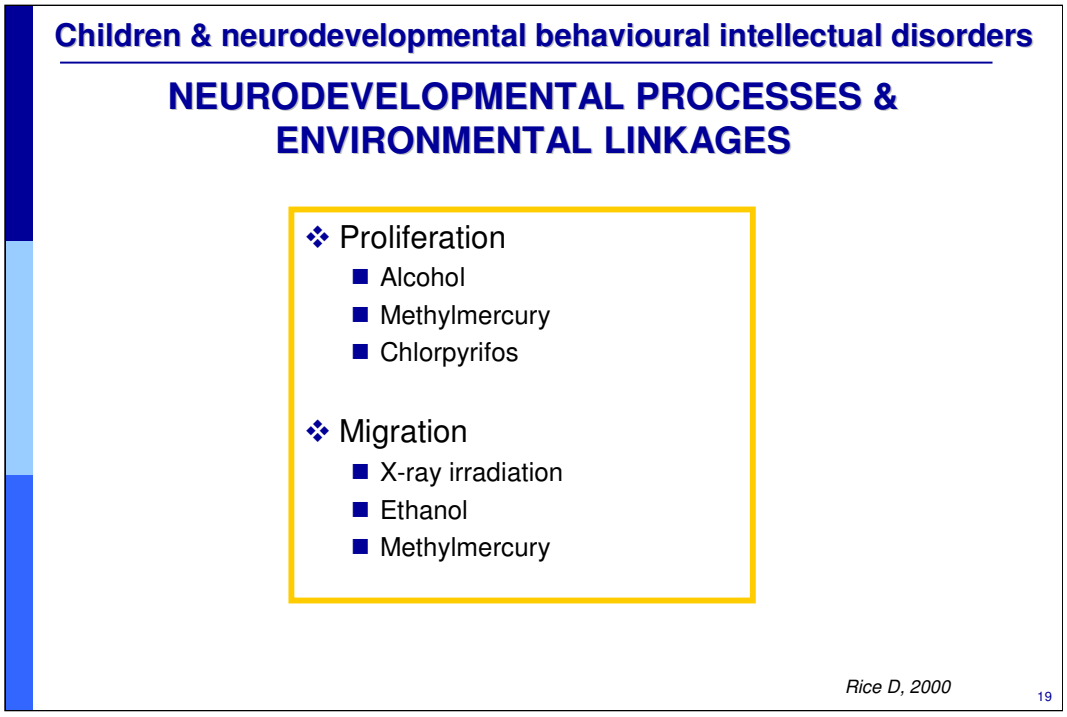
It is widely recognized that although some children with Neurodevelopmental Behavioral Intellectual Disorders, especially Attention Deficit Hyperactivity Disorder (ADHD), "grow out" of their condition, many remain affected and frequently develop co-morbidities i.e. oppositional defiant disorder, depression/anxiety, substance abuse, conduct disorder. This may lead to school failure and incarceration. Persistance of ADHD into adulthood is well-recognized although data collection and methodologies for reporting appear inconsistent.

Refs:

•Hechtman L, Weiss G, Perlman T. Hyperactives as young adults: Past and current substance abuse and antisocial behavior. *American Journal of Orthopsychiatry,* 1984, 54:415-425.

•Pliszka SR, Carlson CL, Swanson JM. ADHD with co-morbid disorders: Clinical assessment and management. *New York, The Guilford Press,* 1999.

•Rabiner D. How often does ADHD persist into adulthood? ADHD library. Available at *www.adhdlibrary.com/library/how-often-does-adhd-persist-into-adulthood* - accessed 15 June 2011

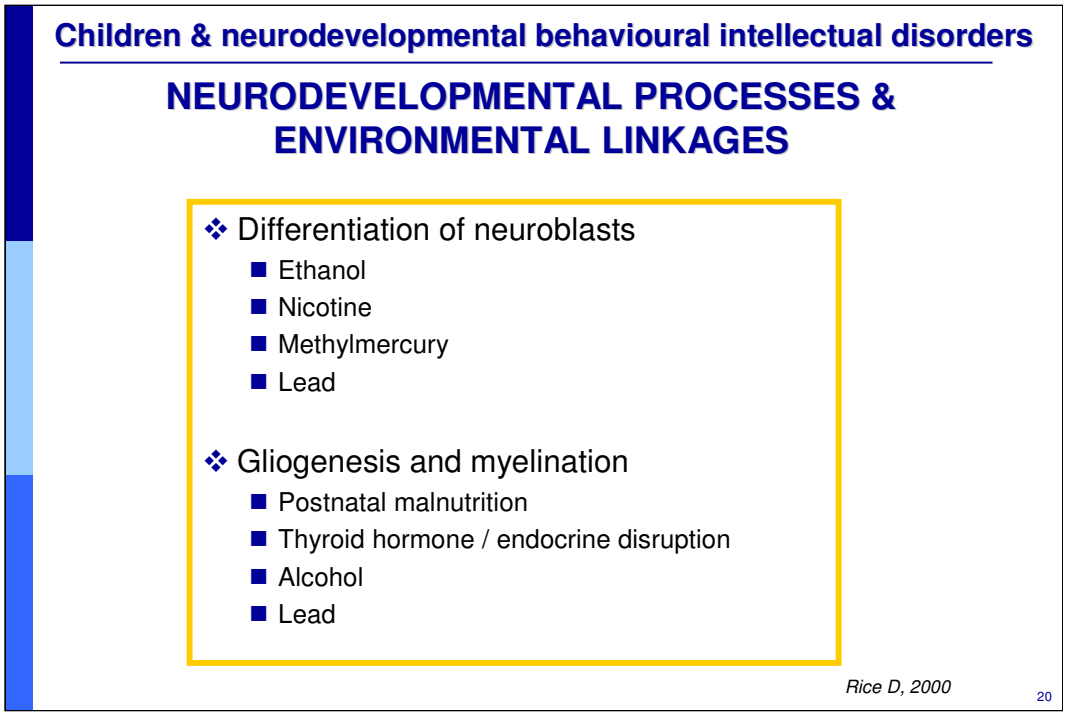


Cell proliferation may be adversely affected by alcohol intake, exposure to chlorpyrifos or methylmercury.

Migration of neurons may be affected by exposure to x-ray radiation, alcohol or methylmercury. Cell migration may be adversely affected by x-ray irradiation, ethanol and methylmercury.

Ref:

•Rice D, Barone Jr S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspectives*, 2000, 108(S3):511-533.

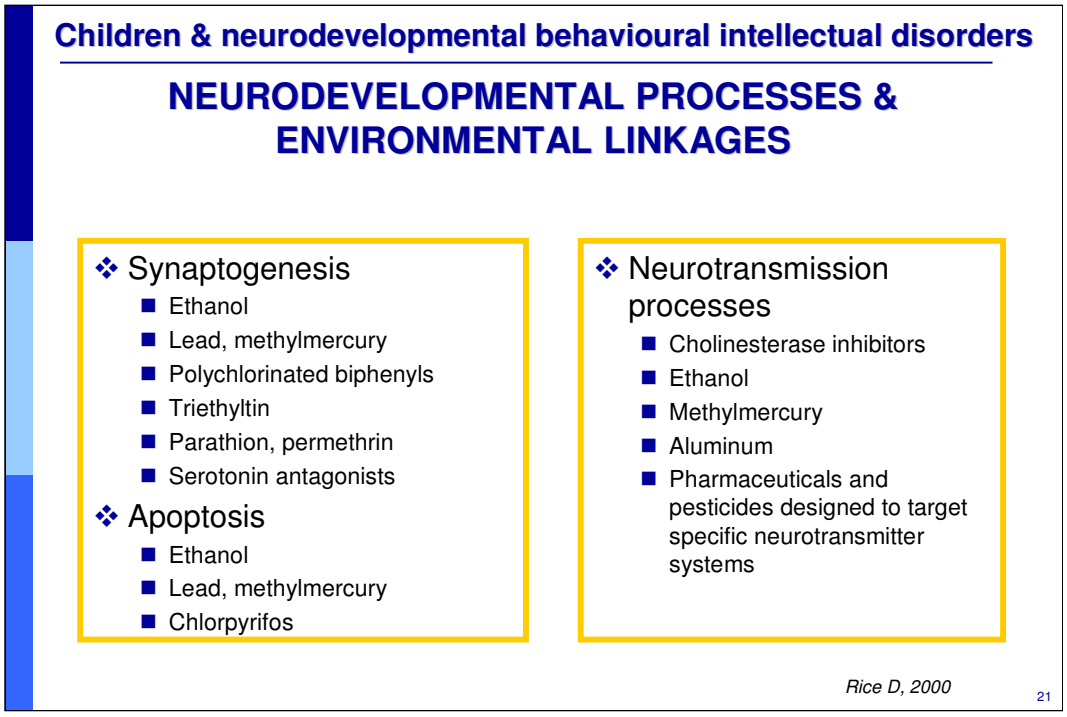


Differentiation of neuroblasts may be adversely affected by ethanol, nicotine, methylmercury and lead.

Gliogenesis and myelination may be adversely affected by postnatal malnutrition, thyroid hormone/endocrine disruption, exposures to alcohol, and lead.

Ref:

•Rice D, Barone Jr S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *EHP*, 2000, 108(S3):511-533.



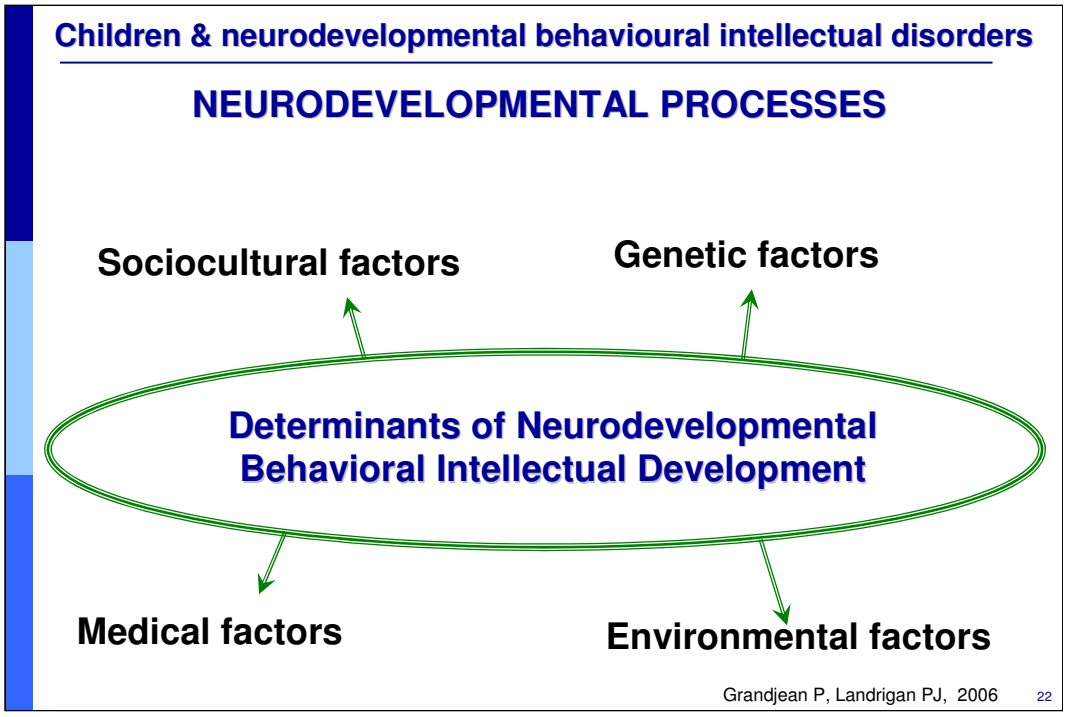
Synaptogenesis may be adversely affected by ethanol, lead, methylmercury, polychlorinated biphenyls (PCBs), triethyltin, parathion, permethrin, and serotonin antagonists.

Apoptosis or cell death is a complex process in which appropriate cells are removed to ensure optimal neurodevelopmental behavioural intellectual development. However, this intricate, balanced process may be adversely affected at critical stages of gestation and postnatal development by exposure to ethanol, lead, mercury and chlorpyrifos.

Neurotransmission processes may be adversely affected by cholinesterase inhibitors, ethanol, methylmercury, aluminum, as well as pharmaceuticals and pesticides designed to target specific neurotransmitter systems.

Ref:

•Rice D, Barone Jr S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspectives*, 2000, 108(S3):511-533.



Many important factors interact to determine the outcome of the neurodevelopmental process in each individual child. Determinants of Neurodevelopmental Behavioral Intellectual Development (NDBID) can be categorized according to the diagram.

Sociocultural factors may include nutrition, prenatal care, education, access to healthcare, maternal IQ, ethnicity, gender, culture, support networks, quality of childrearing.

Genetic factors may include chromosomal abnormalities, e.g. trisomy 21 Down's syndrome. Specific gene location (chromosomes 6, 15) are linked with reading disability. Girls with Turner's syndrome may exhibit specific visuo-spatial difficulties. Children with Fragile X syndrome may have specific language deficits.

Medical factors may include hypoxic ischemic encephalopathy, very low birth weight, severe intrauterine growth retardation, prenatal exposure to alcohol, tobacco and drugs, brain injury from head trauma intraventricular hemorrhage. Conductive hearing loss (from otitis media with effusion) may lead to language problems.

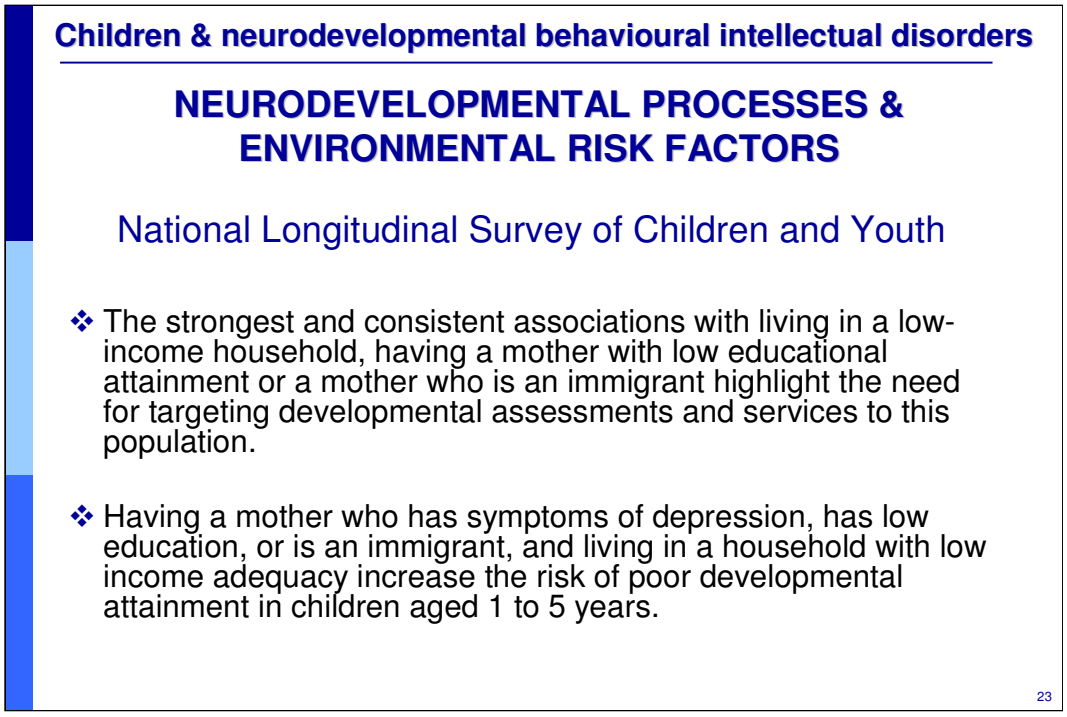
Environmental factors may lead to infections in early life e.g. AIDS, meningitis, septicemia may result in Neurodevelopmental Behavioral Intellectual Disorders. Many chemical exposures have been investigated. The community ones studied to date are environmental tobacco smoke, lead and mercury. Prenatal and early childhood offers windows of vulnerability for adverse effects on healthy neurodevelopment.

Concern is growing regarding high volume industrial neurotoxic emissions into the environment.

Refs:

•Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*, 2006, 368(9553):2167-2178.

•Kliegman RM et al. Nelson textbook of pediatrics. 18th edition. *Elsevier Health Sciences Division*, 2007.



A Canadian National Longitudinal Survey of Children and Youth which has been in effect for over 20 years, identifies various social factors influencing neurodevelopment. Poverty, maternal mental health and education are reported to be key determinants of neurobehavioural intellectual development. The survey showed that single mothers who are new immigrants to Canada are particularly at risk of having children with neurobehavioural intellectual developmental problems.

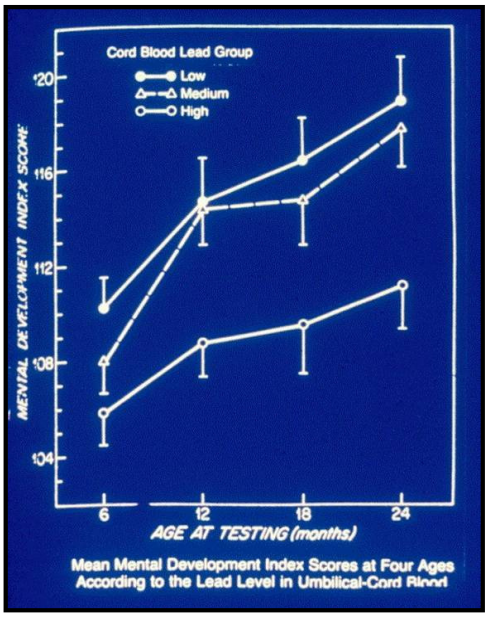
Refs:

•To T et al. Risk markers for poor developmental attainment in young children: results from a longitudinal national survey. *Archives of Pediatrics & Adolescent Medicine*, 2004, 158(7):643-9

•To T et al. What factors are associated with poor developmental attainment in young Canadian children? *Canadian Journal of Public Health. Revue Canadienne de Santé Publique*, 2004, 95(4):258-63

Children & neurodevelopmental behavioural intellectual disorders

CORD BLOOD LEAD LEVEL AND MENTAL DEVELOPMENT INDEX



Mean Mental Development Index Scores at Four Ages According to the Lead Level in Umbilical-Cord Blood

Bellinger, N Eng J Med. (1987)316:1037

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When lead poisoning begins in the womb, the most critical system is the central nervous system of the fetus.

This article, published in 1987, was essential in increasing understanding of the potential for lead to cause damage at levels much lower than those that cause overt symptoms. It showed a high correlation between blood lead level in the umbilical cord and mental development index at 2 years of age.

Ref:

•Bellinger D et al. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med,* 1987, 316:1037.

In a prospective cohort study of 249 children from birth to two years of age, we assessed the relation between prenatal and postnatal lead exposure and early cognitive development. On the basis of lead levels in umbilical-cord blood, children were assigned to one of three prenatal-exposure groups: low (less than 3 micrograms per decilitre), medium (6 to 7 micrograms per decilitre), or high (greater than or equal to 10 micrograms per decilitre). Development was assessed semiannually, beginning at the age of six months, with use of the Mental Development Index of the Bayley Scales of Infant Development (mean +/- SD, 100 +/- 16). Capillary-blood samples obtained at the same times provided measures of postnatal lead exposure. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The estimated difference between the overall performance of the low-exposure and high-exposure groups was 4.8 points (95 per cent confidence interval, 2.3 to 7.3). Between the medium- and high-exposure groups, the estimated difference was 3.8 points (95 per cent confidence interval, 1.3 to 6.3). Scores were not related to infants' postnatal blood lead levels. It appears that the fetus may be adversely affected at blood lead concentrations well below 25 micrograms per decilitre, the level currently defined by the Centers for Disease Control as the highest acceptable level for young children.

Children & neurodevelopmental behavioural intellectual disorders

ASSOCIATION BETWEEN DENTINE LEAD LEVEL AND CLASSROOM BEHAVIOUR

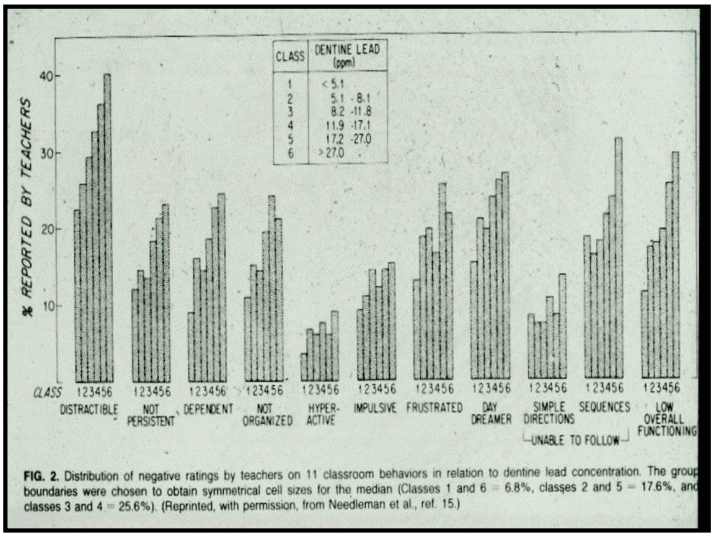


FIG. 2. Distribution of negative ratings by teachers on 11 classroom behaviors in relation to dentine lead concentration. The group boundaries were chosen to obtain symmetrical cell sizes for the median (Classes 1 and 6 = 6.8%, classes 2 and 5 = 17.6%, and classes 3 and 4 = 25.6%). (Reprinted, with permission, from Needleman et al., ref. 15.)

Needleman, N. Engl J Med. (1979);300(13):689.

25

Deficits in psychological and classroom performance of children with elevated lead levels in teeth was among the first evidence that low levels of lead intoxication caused loss of intellectual capacity and changes in behaviour.

Ref:

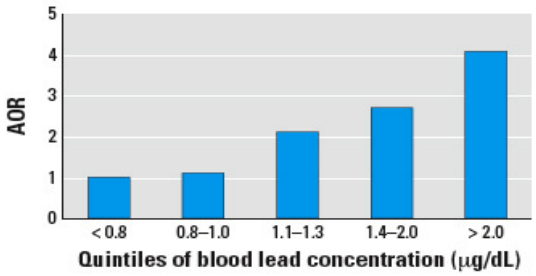
•Needleman. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *N Engl J Med,* 1979, 300:689.

To measure the neuropsychological effects of unidentified childhood exposure to lead, the performance of 58 children with high and 100 with low dentine lead levels was compared. Children with high lead levels scored significantly less well on the Wechsler Intelligence Scale for Children (Revised) than those with low lead levels. This difference was also apparent on verbal subtests, on three other measures of auditory or speech processing and on a measure of attention. Analysis of variance showed that none of these differences could be explained by any of the 39 other variables studied. Also evaluated by a teachers' questionnaire was the classroom behaviour of all children (2146 in number) whose teeth were analysed. The frequency of non-adaptive classroom behaviour increased in a dose-related fashion to dentine lead level. Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychological deficits that may interfere with classroom performance.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

Lead & attention deficit hyperactivity disorder (ADHD)



AOR for ADHD among U.S. children, NHANES 1999–2002, by blood lead concentration (µg/dL). The model was adjusted for child's age, sex, race/ethnicity, preschool attendance, serum ferritin, prenatal ETS exposure, smoker in the household, and insurance status.
p-value for trend = 0.012.

Braun J. *Environ Health Perspect.* 2006;114(12):1904-1909.

Lead is a well studied neurotoxin. This slide shows the association of rising blood lead concentrations and reduction of cognitive functioning in young children.

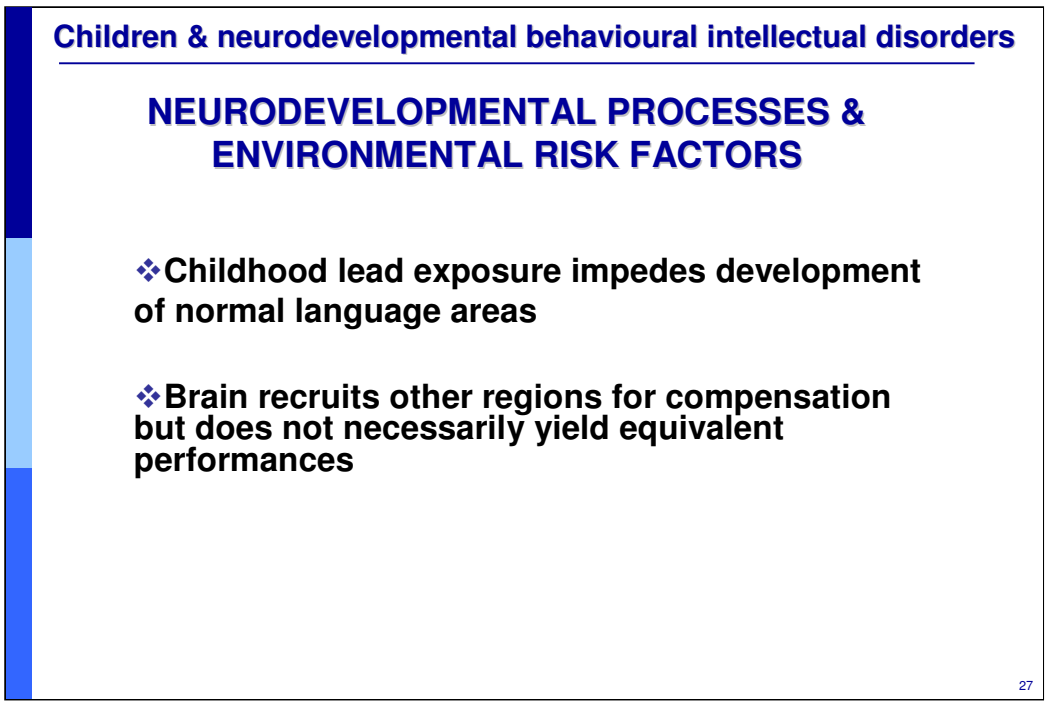
ETS: Environmental tobacco smoke / second-hand tobacco smoke

AOR: Adjusted odds ratio

Ref:

•Braun J et al. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environmental Health Perspectives*, 2006, 114(12):1904-1909.

<<NOTE TO USER: For more information see module on lead.>>



Lead has been identified as adversely affecting speech in young children. Functional magnetic resonance imaging (MRIs) in adolescents who showed levels of lead toxicity in young childhood affecting speech may show compensation in second language centres. This compensation may depend on type of insult, intensity and timing. However, performance may not be equivalent. Even low-level lead exposure can negatively affect a wide range of cognitive functions: attention, language, memory, cognitive flexibility, and visual-motor integration; underlying mechanism by which lead disrupts brain function in children, especially for low lead concentrations that do not produce noticeable physical signs.

It is suggested that as lead exposure impedes development of normal language areas, the brain recruits other regions for compensation but does not necessarily yield equivalent performances. The amount of compensation may not only depend on the type of insult but also on the timing, duration and intensity of insult as the brain develops. However, it should be noted that the compensatory alternative pathway does not necessarily yield equivalent performance to that achieved using the normative cortical circuitry for the same function. The degree to which this compensation mechanism is able to meet the demand for the development of language function is assumed to be associated not only with the type of insults, but also with the timing, duration, and intensity of the insult requiring further investigation.

Elevated childhood lead exposure exerts a substantial influence on the cortical organization of semantic language function in young adulthood, demonstrated by a selective, deleterious effect on normal language areas with concomitant recruitment of contralateral regions, resulting in striking, exposure-dependent patterns of recruitment for language function. These imaging data provide further confirmation of the adverse consequences of environmental lead exposure on cognitive abilities.

Refs:

•Yuan W. et al. Functional magnetic resonance imaging study of language function. The impact of early childhood lead exposure on brain organization. *Pediatrics*, 2006, 118:971-977

The purpose of this work was to assess the long-term impact of childhood lead exposure on the neurosubstrate of language function and brain organization.

METHODS. Young adults from the Cincinnati Lead Study were recruited to undergo functional magnetic resonance image scanning while performing a verb generation task. These subjects have been followed from birth through early childhood with extensive documentation of lead exposure, neuropsychology, and behavior. Forty-two subjects provided useful imaging data. The locale, strength, and the correlation between brain language activation and childhood blood lead concentration were studied.

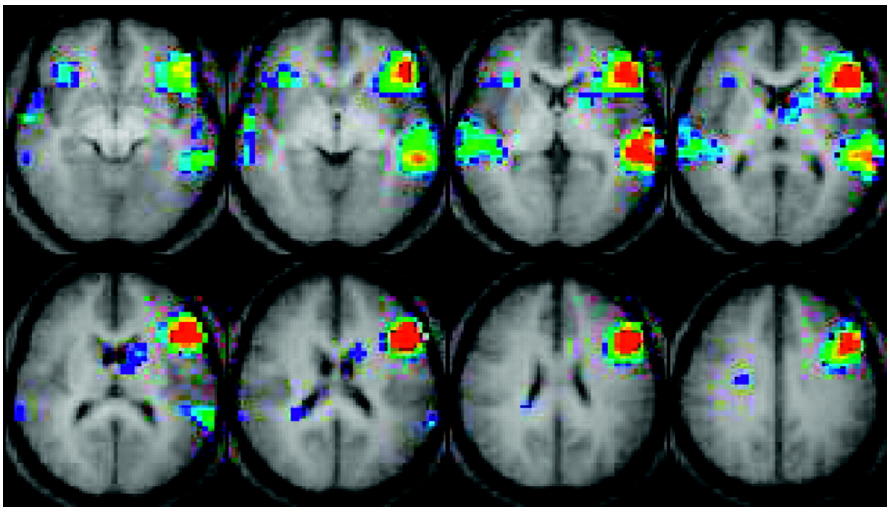
RESULTS. After adjusting for potential confounders, the activation in left frontal cortex, adjacent to Broca's area, and left middle temporal gyrus, including Wernicke's area, were found to be significantly associated with diminished activation in subjects with higher mean childhood blood lead levels, whereas the compensatory activation in the right hemisphere homolog of Wernicke's area was enhanced in subjects with higher blood lead levels.

CONCLUSION. This study indicates that childhood lead exposure has a significant and persistent impact on brain reorganization associated with language function.

•WHO. Childhood lead poisoning. *WHO*, 2010. Available at *www.who.int/ceh/publications/childhoodpoisoning/en/index.html* - accessed March 2011.

Children & neurodevelopmental behavioural intellectual disorders

Composite fMRI activation map for the verb generation task showing z-score statistics in young adults with childhood lead exposure (n = 42).



Yuan W et al. Pediatrics 2006;118:971-977

28

Composite fMRI activation map for the verb generation task showing z-score statistics in young adults with childhood lead exposure (n = 42). Most highly activated areas include left inferior frontal gurus, left medial temporal gyrus, and right medial temporal gyrus. The orientation of the images follows radiologic convention.

Ref:

Yuan W et al. The Impact of Early Childhood Lead Exposure on Brain Organization: A Functional Magnetic Resonance Imaging Study of Language Function. *Pediatrics*. 2006, 118(3):971-977

OBJECTIVES. The purpose of this work was to assess the long-term impact of childhood lead exposure on the neurosubstrate of language function and brain organization.

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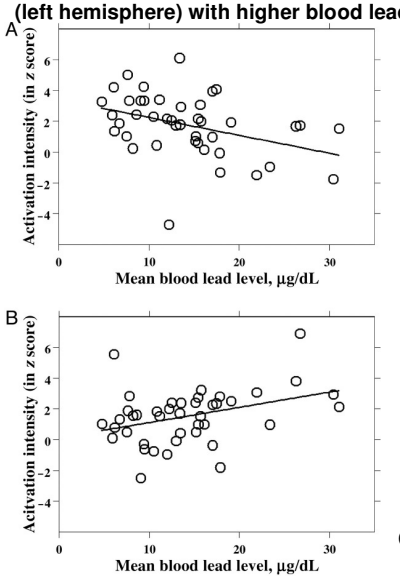
Children & neurodevelopmental behavioural intellectual disorders

Diminished activity of dominant language areas (left hemisphere) with higher blood lead level



A, Multivariate linear regression of brain activation in left inferior frontal gyrus (ROI_1) versus childhood mean blood lead level adjusted for confounders.

A, Multivariate linear regression of brain activation in left inferior frontal gyrus (ROI_1) versus childhood mean blood lead level adjusted for confounders. Partial R = –0.328; P = .039. B, Multivariate linear regression of brain activation in right middle temporal gyrus (ROI_2) versus childhood mean blood lead level adjusted for confounders. Partial R = 0.354; P = .025.

Compensatory activity of contralateral regions

Yuan W et al. Pediatrics 2006;118:971-977

29

Ref:

•Yuan W et al. The Impact of Early Childhood Lead Exposure on Brain Organization: A Functional Magnetic Resonance Imaging Study of Language Function. Pediatrics. 2006, 118(3):971-977

OBJECTIVES. The purpose of this work was to assess the long-term impact of childhood lead exposure on the neurosubstrate of language function and brain organization.

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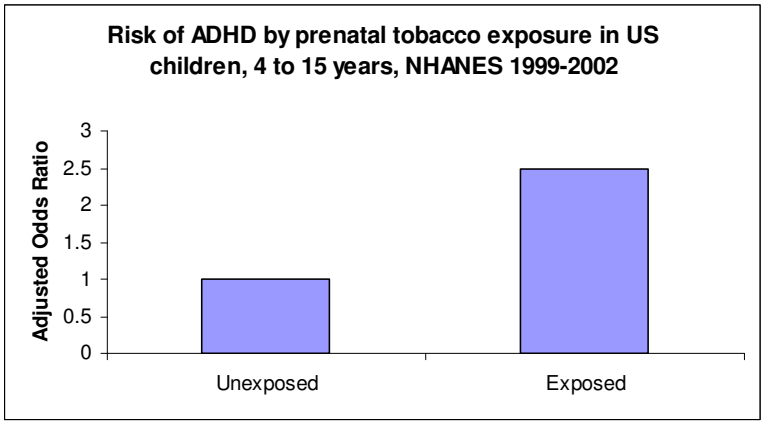
CONCLUSION. This study indicates that childhood lead exposure has a significant and persistent impact on brain reorganization associated with language function.

Figure from Yuan W et al. The Impact of Early Childhood Lead Exposure on Brain Organization: A Functional Magnetic Resonance Imaging Study of Language Function. Pediatrics. 2006, 118(3):971-977. Reproduced with permission from Pediatrics, Copyright 2010 by the American Academy of Pediatrics.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS



Braun J. *Environ Health Perspect*. 2006;114(12):1904-1909.

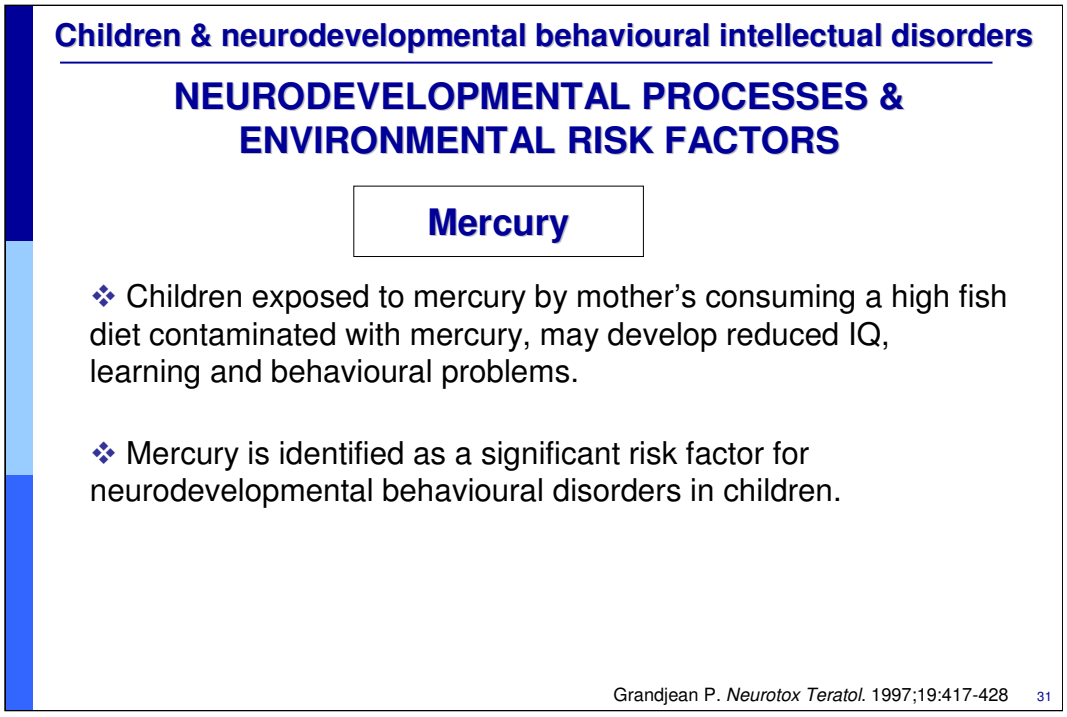
ADHD: Attention Deficit Hyperactive Disorder

30

There is now strong evidence that prenatal tobacco exposure is linked with the development of Attention Deficit Hyperactive Disorder (ADHD) in children whose mother either smoked or were exposed to second-hand cigarette smoke in the home. This study is one example.

Ref:

•Braun J et al. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environmental Health Perspectives*, 2006, 114(12):1904-1909.



Children exposed to mercury by mother's consuming a high fish diet contaminated with mercury, may develop reduced IQ, learning and behavioural problems. Mercury with its known neurotoxic properties is identified as a significant risk factor for neurodevelopmental behavioural disorders in children.

Refs:

•Grandjean P, et.al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotox Teratol.* 1997, 19:417-428

•WHO. Children's exposure to mercury compounds. *WHO*, 2010. Available at *www.who.int/ceh/publications* - accessed June 2011.

<<NOTE TO USER: For more information see module on mercury.>>

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

- Cohort of 1022 children born 1986-1987
- Exposure of mothers to methylmercury:
  - Pilot whale meat - episodic, and potentially high
    - Fish consumption - continuous, but low
- Neuropsychological dysfunctions (age 7)
  - Language
  - Attention
  - Memory
- Neurophysiologic dysfunctions (age 14)
  - Delayed brainstem auditory evoked potentials
  - Decreased autonomic heart rate variability
- Attributed to prenatal exposure

Faroe Islands study
Mercury

32

Refs:

•Grandjean P et al. Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. *J Pediatr.* 2004, 144(2):169.

•Grandjean P et al. Cognitive deficit in 7 year old children with prenatal exposure to methylmercury. *Neurotoxicology and teratology*. 1997, 19:417

A cohort of 1022 consecutive singleton births was generated during 1986-1987 in the Faroe Islands. Increased methylmercury exposure from maternal consumption of pilot whale meat was indicated by mercury concentrations in cord blood and maternal hair. At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Neuropsychological tests included Finger Tapping; Hand-Eye Coordination; reaction time on a Continuous Performance Test; Wechsler Intelligence Scale for Children-Revised Digit Spans, Similarities, and Block Designs; Bender Visual Motor Gestalt Test; Boston Naming Test; and California Verbal Learning Test (Children). Clinical examination and neurophysiological testing did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological dysfunctions were most pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. These associations remained after adjustment for covariates and after exclusion of children with maternal hair mercury concentrations above 10 microgram(s) (50 nmol/g). The effects on brain function associated with prenatal methylmercury exposure therefore appear widespread, and early dysfunction is detectable at exposure levels currently considered safe.

•Grandjean P. Neurodevelopmental disorders. In: *Children´s health and the environment: A review of evidence.* Tamburlini G, von Ehrenstein O, Bertollini R. (eds). WHO, Rome, 2002.

•Murata K et al. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr*, 2004, 144(2):177.

To determine possible exposure-associated delays in auditory brainstem evoked potential latencies as an objective measure of neurobehavioral toxicity in 14-year-old children with developmental exposure to methylmercury (MeHg) from seafood. Prospective study of a birth cohort in the Faroe Islands, where 878 of eligible children (87%) were examined at age 14 years. Latencies of brainstem evoked potential peaks I, III, and V at 20 and 40 Hz constituted the outcome variables. Mercury concentrations were determined in cord blood and maternal hair, and in the child's hair at ages 7 and 14. Results: Latencies of peaks III and V increased by about 0.012 ms when the cord blood mercury concentration doubled. As seen at age 7 years, this effect appeared mainly within the I-III interpeak interval. Despite lower postnatal exposures, the child's hair mercury level at age 14 years was associated with prolonged III-V interpeak latencies. All benchmark dose results were similar to those obtained for dose-response relationships at age 7 years. Conclusions: The persistence of prolonged I-III interpeak intervals indicates that some neurotoxic effects from intrauterine MeHg exposure are irreversible. A change in vulnerability to MeHg toxicity is suggested by the apparent sensitivity of the peak III-V component to recent MeHg exposure.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

- Cohort of 779 mother-infant pairs

Seychelles study
Mercury

- Exposure from mothers' high fish consumption
- At age 9: neuropsychological tests
- Neurodevelopmental risks due to prenatal MeHg exposure not seen

33

Refs:

•Grandjean P. Neurodevelopmental disorders. In: *Children´s health and the environment: A review of evidence.* Tamburlini G, von Ehrenstein O, Bertollini R. (eds). WHO, Rome, 2002.

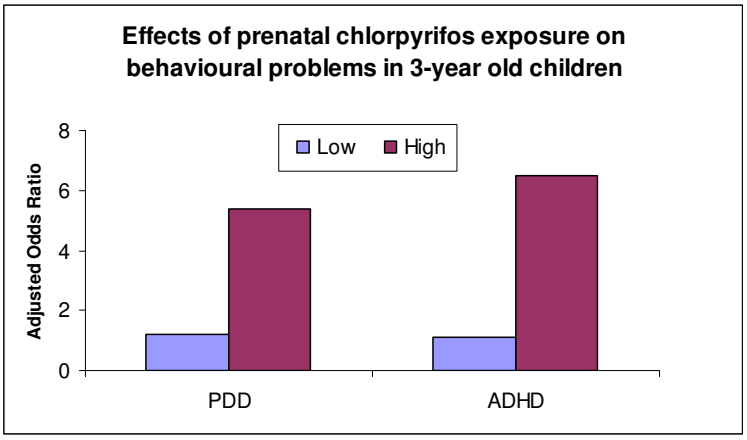
"A large prospective study in the Seychelles has not revealed any clear adverse effects related to maternal hair mercury concentrations"

•Myers GJ et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet,* 2003, 361:1686

Exposure to methylmercury (MeHg) before birth can adversely affect children's neurodevelopment. The most common form of prenatal exposure is maternal fish consumption, but whether such exposure harms the fetus is unknown. We aimed to identify adverse neurodevelopmental effects in a fish-consuming population. We investigated 779 mother-infant pairs residing in the Republic of Seychelles. Mothers reported consuming fish on average 12 meals per week. Fish in Seychelles contain much the same concentrations of MeHg as commercial ocean fish elsewhere. Prenatal MeHg exposure was determined from maternal hair growing during pregnancy. We assessed neurocognitive, language, memory, motor, perceptual-motor, and behavioural functions in children at age 9 years. The association between prenatal MeHg exposure and the primary endpoints was investigated with multiple linear regression with adjustment for covariates that affect child development. Mean prenatal MeHg exposure was 6.9 parts per million (SD 4.5 ppm). Only two endpoints were associated with prenatal MeHg exposure. Increased exposure was associated with decreased performance in the grooved pegboard using the non-dominant hand in males and improved scores in the hyperactivity index of the Conner's teacher rating scale. Covariates affecting child development were appropriately associated with endpoints. Interpretation: These data do not support the hypothesis that there is a neurodevelopmental risk from prenatal MeHg exposure resulting solely from ocean fish consumption.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS



Based on Rauh V. *Pediatrics*. 2006;118(6):e1845-e1859

PDD: Pervasive Developmental Disorder
ADHD: Attention Deficit Hyperactivity Disorder

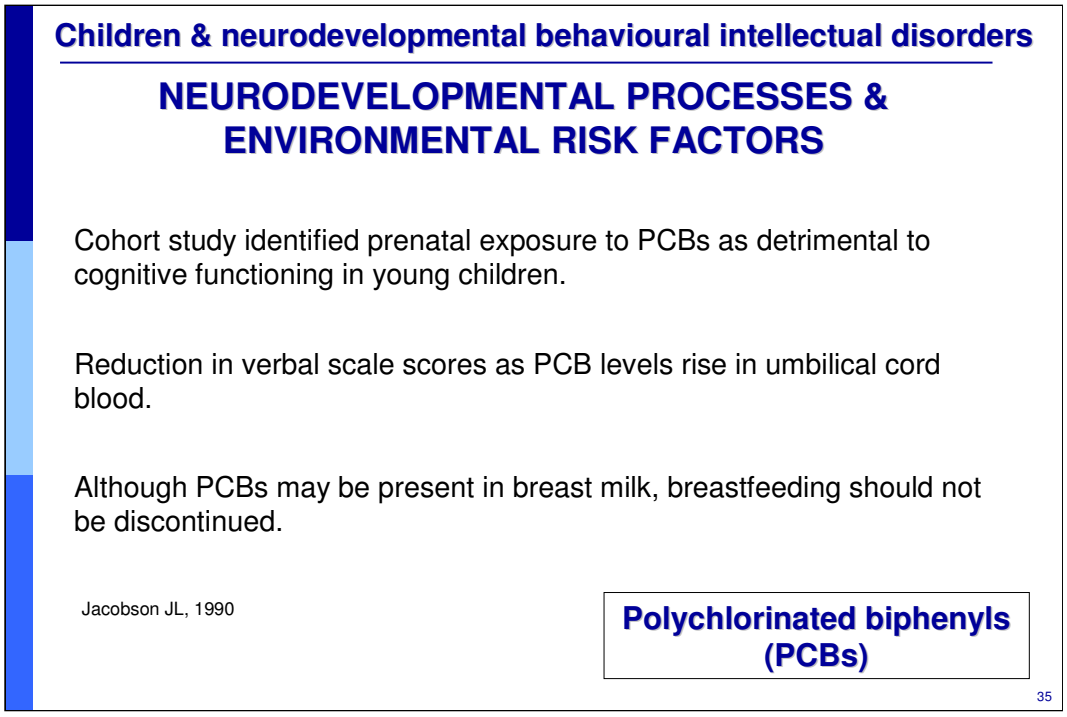
Chlorpyrifos

34

Women exposed in pregnancy to the pesticide chlorpyrifos have been studied and identified as having increased risk of producing children with autism and with Attention Deficit Hyperactive Disorder.

Image based on: Rauh V et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics, 2006, 118(6):e1845-e1859

<<NOTE TO USER: For more information see module on pesticides.>>



Polychlorinated biphenyls (PCBs): This cohort study identifies that prenatal exposure to PCBs is detrimental to cognitive functioning in young children. The study showed reduction in verbal scale scores as PCB levels rise in umbilical cord blood. Although PCBs may be present in breast milk, studies have shown that this postnatal exposure is far less harmful than prenatal intrauterine exposure. Breastfeeding should not be discontinued.

Ref:

•Jacobson JL, Jacobson SW, Humphrey HEB. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J of Paeds*, 1990, 116:38-45

Because prenatal exposure to polychlorinated biphenyls (PCBs) and related contaminants has been associated with reduced birth weight, neonatal behavioral anomalies, and poorer recognition memory in infants born to women who have consumed Lake Michigan sports fish, 236 children, previously evaluated for PCB-related deficits in infancy, were assessed at 4 years of age. Prenatal exposure (indicated by umbilical cord serum PCB level) predicted poorer short-term memory function on both verbal and quantitative tests in a dose-dependent fashion. These effects cannot be attributed to a broad range of potential confounding variables, the impact of which was evaluated statistically. Although much larger quantities of PCBs are transferred postnatally via lactation than prenatally across the placenta, exposure from nursing was unrelated to cognitive performance. The data demonstrate the continuation of a toxic impact received in utero and observed initially during infancy on a dimension of cognitive functioning fundamental to learning.

•WHO. Persistent organic pollutants: impact on child health. *WHO,* 2010. Available at *www.who.int/ceh/publications* - accessed June 2011.

<<NOTE TO USER: For more information see module on persistent organic pollutants.>>

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

Manganese & poor attention

A Canadian prospective epidemiological study (n= 247 pregnant women and their babies) identified exposure to manganese, mainly from manganese air pollution from gasoline containing methylcyclopentadienyl manganese tricarbonyl (MMT) and suggested a link with poor attention in young children.

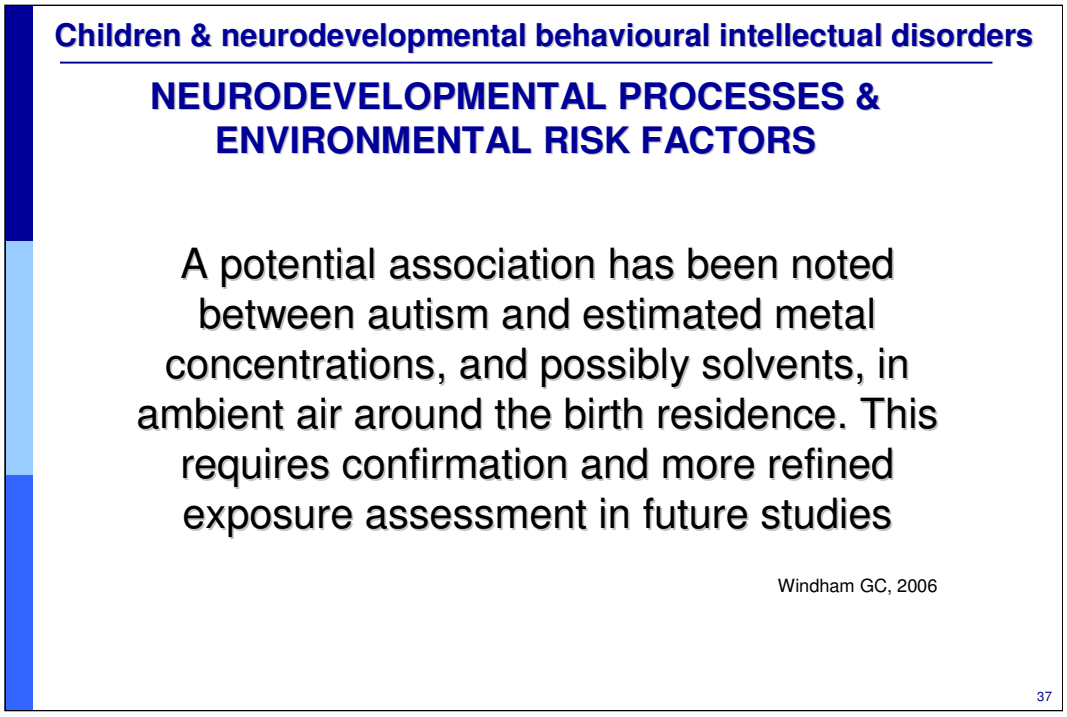
Takser, 2003

This Canadian study identifies exposure to manganese, mainly from manganese air pollution from gasoline containing methylcyclopentadienyl manganese tricarbonyl (MMT), and suggests a link with poor attention in young children.

Ref:

•Takser L et al. Manganese, monoamine metabolite levels at birth, and child psychomotor development. *NeuroToxicology*, 2003, 24:667-674.

Several studies have demonstrated neurobehavioral impairment related to manganese (Mn) exposure in the workplace. Exposure to high doses of manganese is associated with irreversible neurodegenerative disorders resembling idiopathic Parkinson disease. Although there is a risk of Mn accumulation in the foetus during pregnancy, little information exists about developmental effects of environmental low-level exposure in human. For this reason, we conducted a prospective epidemiological study in 247 healthy pregnant women and their babies to determine the long-term effect of in utero Mn levels on child's psychomotor development. Concurrently, we examined the relationship between Mn tissue levels at delivery and foetal plasma monoamine metabolites. Of the newborns, 195 were examined at 9 months, 126 at 3 years and 100 at 6 years. At 9 months, the Brunet–Lézine scales were administered. The McCarthy scales of children's abilities were used at 3 and 6 years. After adjustment for potential confounding co-factors (child's gender, mother's educational level), negative relationships were observed between cord blood Mn levels and several psychomotor sub-scales at age of 3 years: "attention" (partial r=–0.33, P<0.001), "non-verbal memory" (partial r=–0.28, P<0.01), and "hand skills" (partial r=–0.22, P<0.05). No significant relationships were observed between Mn measures at birth and the general psychomotor indices, Brunet–Lézine developmental quotient (DQ) at 9 months or McCarthy general cognitive index (GCI) at 3 and 6 years. Maternal blood Mn levels were negatively associated with foetal plasma HVA and 5-HIAA concentrations (adjusted for labour duration, child's gender, and smoking during pregnancy), but the adjustment for monoamine levels at birth did not change the association between the Mn levels and the psychomotor scores. These results suggest that environmental Mn exposure in utero could affect early psychomotor development.



This study from California, US, suggests there may be an association between metals, and possibly solvents in ambient air, around birth residence and development. Further studies are required for confirmation.

Ref:

•Windham GC et al. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area. *Environ Health Perspect*, 2006, 114(9):1438-1444.

Objective: To explore possible associations between autism spectrum disorders (ASD) and environmental exposures, we linked the California autism surveillance system to estimated hazardous air pollutant (HAP) concentrations compiled by the U.S. Environmental Protection Agency.

Methods: Subjects included 284 children with ASD and 657 controls, born in 1994 in the San Francisco Bay area. We assigned exposure level by census tract of birth residence for 19 chemicals we identified as potential neurotoxicants, developmental toxicants, and/or endocrine disruptors from the 1996 HAPs database. Because concentrations of many of these were highly correlated, we combined the chemicals into mechanistic and structural groups, calculating summary index scores. We calculated ASD risk in the upper quartiles of these group scores or individual chemical concentrations compared with below the median, adjusting for demographic factors.

Results: The adjusted odds ratios (AORs) were elevated by 50% in the top quartile of chlorinated solvents and heavy metals [95% confidence intervals (CIs), 1.1–2.1], but not for aromatic solvents. Adjusting for these three groups simultaneously led to decreased risks for the solvents and increased risk for metals (AORs for metals: fourth quartile = 1.7; 95% CI, 1.0–3.0; third quartile = 1.95; 95% CI, 1.2–3.1). The individual compounds that contributed most to these associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride.

Conclusions: Our results suggest a potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence, requiring confirmation and more refined exposure assessment in future studies.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

Air pollution

Prenatal exposure to environmental polycyclic aromatic hydrocarbons at levels encountered in New York City air may adversely affect children's cognitive development at 3 years of age. This may have implications for school performance.

Perera FP. *Environ Health Perspect.* 2006; 114(8):1287-1292.

38

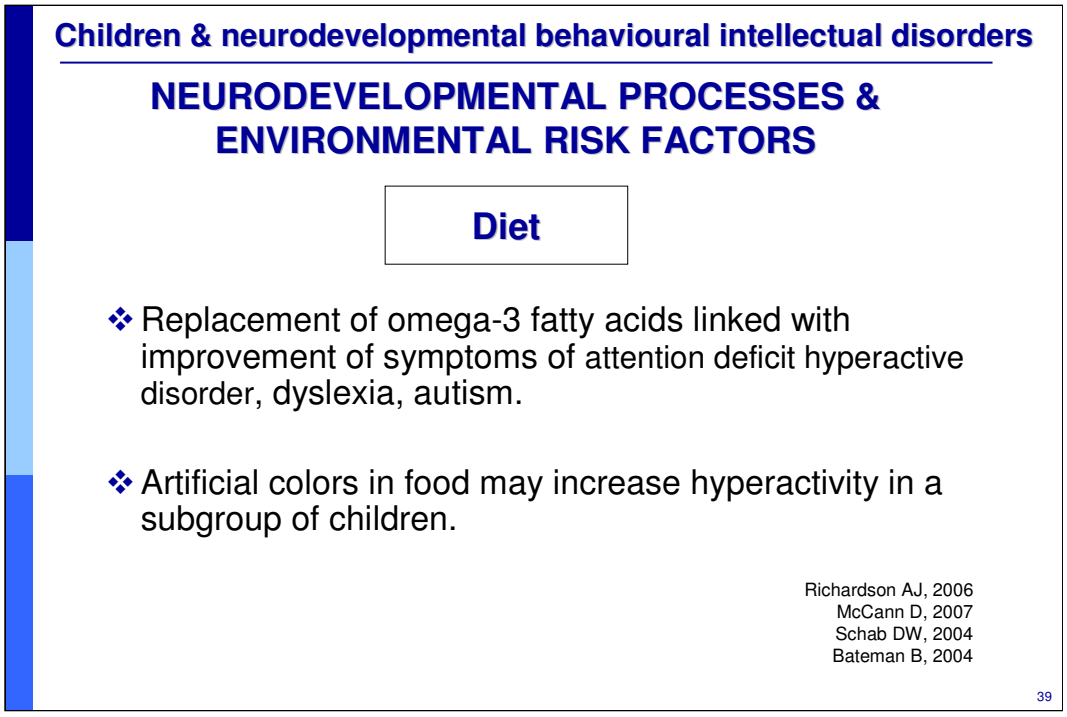
Following the events of 11 September in New York, US, polycyclic aromatic hydrocarbons (PAHs), in relation to children's cognitive development, through prenatal exposure have been studied. Results show that prenatal exposures at the levels recently encountered have implications for school performance.

Ref:

•Perera FP et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environ Health Perspect*, 2006, 114(8):1287-1292.

Our prospective cohort study of nonsmoking African-American and Dominican mothers and children in New York City is evaluating the role of prenatal exposure to urban pollutants, including polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS), and pesticides, in the pathogenesis of neurobehavioral disorders. We used the Bayley Scales of Infant Development to evaluate the effects on child mental and psychomotor development of prenatal exposure to airborne PAHs monitored during pregnancy by personal air sampling. Behavioral development was assessed by the Child Behavior Checklist. We adjusted for potential confounders including sociodemographic factors and prenatal exposure to ETS and chlorpyrifos. Prenatal exposure to PAHs was not associated with psychomotor development index or behavioral problems. However, high prenatal exposure to PAHs (upper quartile) was associated with lower mental development index at age 3 [β= –5.69; 95% confidence interval (CI), –9.05 to –2.33; p < 0.01]. The odds of cognitive developmental delay were also significantly greater for children with high prenatal exposure (odds ratio = 2.89; 95% CI, 1.33 to 6.25; p = 0.01). General estimated equation analysis showed a significant age × PAH effect on mental development (p = 0.01), confirming the age-specific regression findings. Further adjustment for lead did not alter the relationships. There were no differences in effect sizes by ethnicity. The results require confirmation but suggest that environmental PAHs at levels recently encountered in New York City air may adversely affect children's cognitive development at 3 years of age, with implications for school performance.

<<NOTE TO USER: For more information see modules on air pollution.>>



Evidence is accumulating that dietary factors may play a role in Neurodevelopmental Behavioral Intellectual Disorders in children. Diets with adequate omega-3 fatty acids and low in artificial food colors and preservatives may benefit children's behaviors and learning. Children with attention deficit hyperactive disorder (ADHD), dyslexia & autism have been studied and found to benefit from omega-3 replacement. Withdrawing fatty food coloring from the diet of children with ADHD symptoms may be beneficial in a small subgroup.

When dealing with Neurodevelopmental Behavioral Intellectual Disorders in children, health professionals could advise a diet with sufficient omega-3 fatty acids and low in food coloring.

Refs:

•Bateman B et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Arch Dis Child*, 2004, 89:506-511.

•McCann D et al. Food additives and hyperactive behaviour in 3 year old and 8/9 year old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet*, 2007, 370:1560-1567.

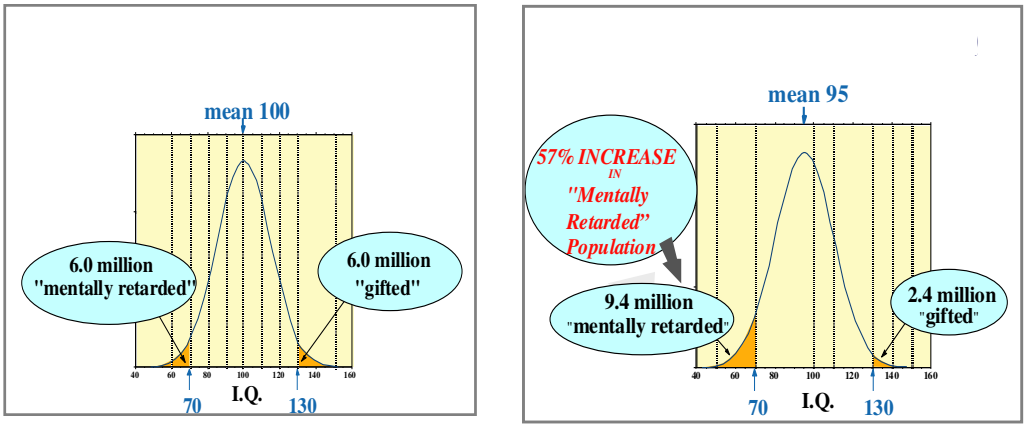
•Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *Int Rev Psych*, 2006, 18(2):155-172.

•Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blinded placebo-controlled trials. *J Developmental & Behavioral Pediatrics*, 2004, 25(6):423-434.

Children & neurodevelopmental behavioural intellectual disorders

NEURODEVELOPMENTAL PROCESSES & ENVIRONMENTAL RISK FACTORS

Significance of 5 point IQ reduction



Greater Boston Physicians for Social Responsibility, 2000

40

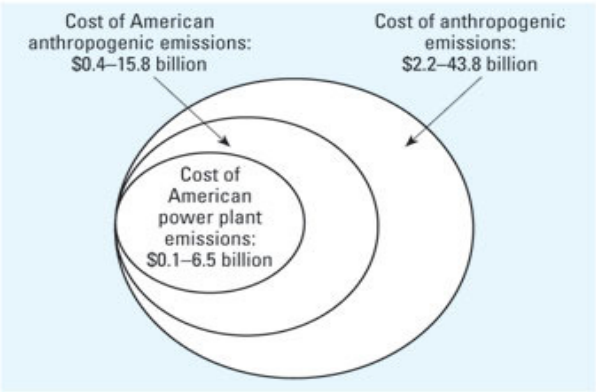
A 5-point loss in IQ might not affect the ability of an individual to live a productive life. But if that loss is experienced by an entire population, the implications for that society could be profound. Bernard Weiss, a behavioural toxicologist at the University of Rochester, US, examined the societal impact of seemingly small losses of intelligence. Imagine an unaffected population numbering 260 million people (such as that of the US) with an average IQ of 100 and a standard deviation of 15 (left-hand graph). In that population there would be 6 million people with IQs above 130 and 6 million below 70.

A decrease in average IQ of 5 points would shift the distribution to the left (right-hand graph). The number of people scoring above 130 would decline by 3.6 million while the number below 70 would increase by 3.4 million.

Picture adapted from Schettler T. *In harm' s way.* Greater Boston Physicians for Social Responsibility, 2000. *Used with permission.*

Children & neurodevelopmental behavioural intellectual disorders

CHALLENGES & IMPACTS OF NEURODEVELOPMENTAL BEHAVIORAL INTELLECTUAL DISORDERS



Portions of cost of methyl mercury exposure attributed to sources. Assumptions: 18–36% attributable to American sources; 41% of American emissions attributable to American power plants.

Public health and economic consequences of methylmercury toxicity to the developing brain

Trasande L, Landrigan PJ, Schechter C. *Environ Health Perspectives,* 2005, 113(5):590-596.

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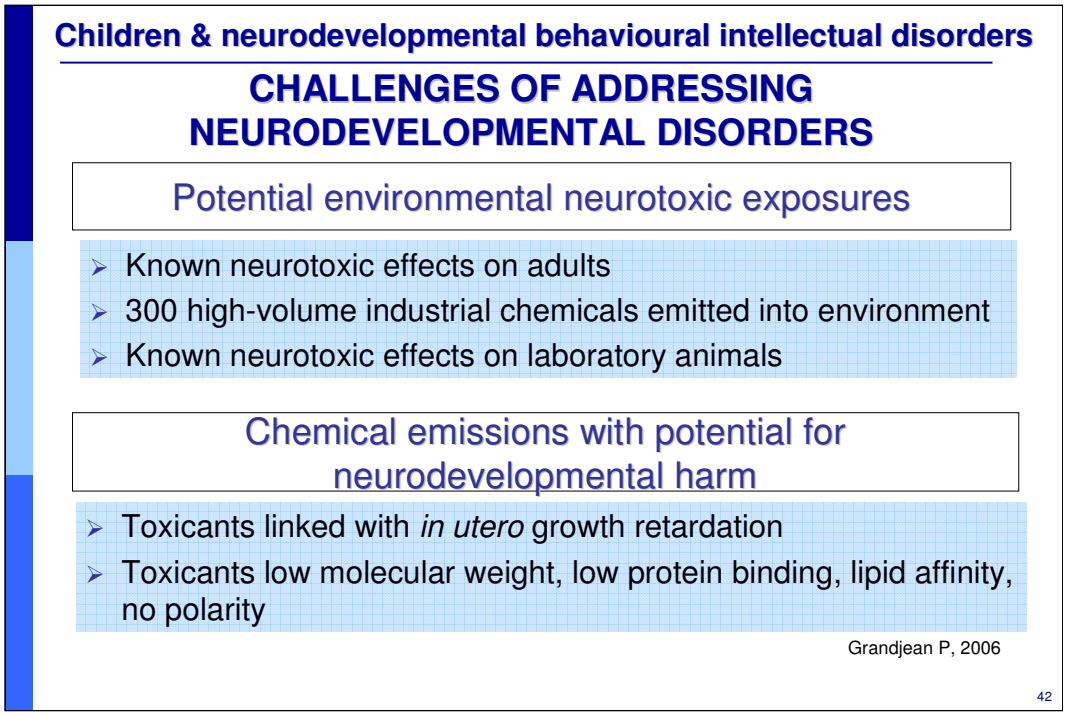
To focus specifically on the costs of fetal exposure to mercury released by U.S. coal-fired power plants, scientists examined the impact of the 41% of U.S. anthropogenic emissions of mercury attributable to these facilities. They estimate that the attributable cost of methylmercury exposure from U.S: electric generation facilities to the developing fetus is $1.3 billion. Applying a sensitivity analysis in this model, they find that the true cost of methylmercury exposure from electric generation facilities to the U.S. birth cohort ranges from $0.1 to $6.5 billion/year. Again, the major source of these costs is loss of earnings over a lifetime.

Ref:

•Trasande L, Schechter C, Landrigan PJ. Public health and economic consequences of environmental methyl mercury toxicity to the developing brain. *Environ Health Perspect*, 2005, 113:590-596.

Methyl mercury is a developmental neurotoxicant. Exposure results principally from consumption by pregnant women of seafood contaminated by mercury from anthropogenic (70%) and natural (30%) sources. Throughout the 1990s, the U.S. Environmental Protection Agency (EPA) made steady progress in reducing mercury emissions from anthropogenic sources, especially from power plants, which account for 41% of anthropogenic emissions. However, the U.S. EPA recently proposed to slow this progress, citing high costs of pollution abatement. To put into perspective the costs of controlling emissions from American power plants, we have estimated the economic costs of methyl mercury toxicity attributable to mercury from these plants. We used an environmentally attributable fraction model and limited our analysis to the neurodevelopmental impacts--specifically loss of intelligence. Using national blood mercury prevalence data from the Centers for Disease Control and Prevention, we found that between 316,588 and 637,233 children each year have cord blood mercury levels > 5.8 microg/L, a level associated with loss of IQ. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity is the major cost of methyl mercury toxicity, and it amounts to $8.7 billion annually (range, $2.2-43.8 billion; all costs are in 2000 US$). Of this total, $1.3 billion (range, $0.1-6.5 billion) each year is attributable to mercury emissions from American power plants. This significant toll threatens the economic health and security of the United States and should be considered in the debate on mercury pollution controls.



Approximately 300 high-volume industrial chemicals with neurotoxic properties are emitted into the environment with known neurotoxic effects on adults as well as known neurotoxic effects on laboratory animals. Researchers raised the question of whether each of these substances should be tested appropriately for neurodevelopmental effects on children or whether protective policies can be instituted in the absence of the detailed science that we currently have for lead, others.

Very few environmental neurotoxics have been studied to identify potential harmful effects on Neurodevelopmental Behavioral Intellectual Disorders processes in the fetus and the young child. Risk assessment methods for chemicals being released into the environment are not adequate to protect children from Neurodevelopmental Behavioral Intellectual Disorders. We are identifying increasing numbers of environmental chemicals that contribute to Neurodevelopmental Behavioral Intellectual Disorders damage in the fetus and the young child. Researchers need to ask the question "which chemicals do we need to study?". Many chemicals may have direct neurotoxic effects or indirect effects by contributing to causality of other risk factors of Neurodevelopmental Behavioral Intellectual Disorders, e.g. low birth weight.

Refs:

•Dietrich K et al. Principles and practices of neurodevelopmental assessment in children: Lessons learned from the centers for children's environmental health and disease prevention research. *Environ Health Perspect*, 2005, 113(10):1437-1446.

•Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *The Lancet,* 2006, 368:2167-2178.

Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (eg, lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays. Another 200 chemicals are known to cause clinical neurotoxic effects in adults. Despite an absence of systematic testing, many additional chemicals have been shown to be neurotoxic in laboratory models. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. The two main impediments to prevention of neurodevelopmental deficits of chemical origin are the great gaps in testing chemicals for developmental neurotoxicity and the high level of proof required for regulation. New, precautionary approaches that recognise the unique vulnerability of the developing brain are needed for testing and control of chemicals.

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CHALLENGES OF ADDRESSING NEURODEVELOPMENTAL DISORDERS

Prevention of exposures to neurotoxic pesticides

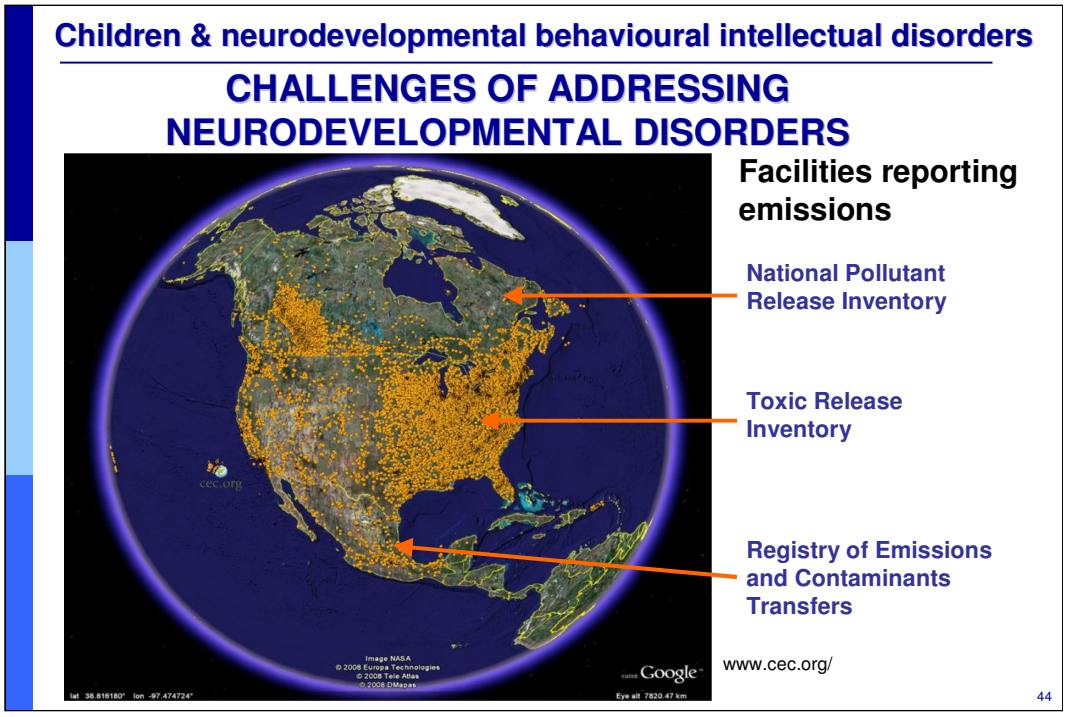
- Many pesticides target the nervous system of insect pests.
- Concerns have been raised that the developing brain may be particularly vulnerable to adverse effects of neurotoxic pesticides.

Bjoling-Poulsen M, 2008

Ref:

Bjoling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environ Health*, 2008, 7:50.

Pesticides used in agriculture are designed to protect crops against unwanted species, such as weeds, insects, and fungus. Many compounds target the nervous system of insect pests. Because of the similarity in brain biochemistry, such pesticides may also be neurotoxic to humans. Concerns have been raised that the developing brain may be particularly vulnerable to adverse effects of neurotoxic pesticides. Current requirements for safety testing do not include developmental neurotoxicity. We therefore undertook a systematic evaluation of published evidence on neurotoxicity of pesticides in current use, with specific emphasis on risks during early development. Epidemiologic studies show associations with neurodevelopmental deficits, but mainly deal with mixed exposures to pesticides. Laboratory experimental studies using model compounds suggest that many pesticides currently used in Europe – including organophosphates, carbamates, pyrethroids, ethylenebisdithiocarbamates, and chlorophenoxy herbicides – can cause neurodevelopmental toxicity. Adverse effects on brain development can be severe and irreversible. Prevention should therefore be a public health priority. The occurrence of residues in food and other types of human exposures should be prevented with regard to the pesticide groups that are known to be neurotoxic. For other substances, given their widespread use and the unique vulnerability of the developing brain, the general lack of data on developmental neurotoxicity calls for investment in targeted research. While awaiting more definite evidence, existing uncertainties should be considered in light of the need for precautionary action to protect brain development.



Canada, Mexico and the US maintain inventories of industrial toxic emissions. These include a number of neurotoxins. Industries that meet the criteria for reporting are legislated to submit an estimate of releases annually.

This is a Google-generated map identifying location (longitude & latitude) of industrial facilities that participate in these inventories. This data is publically available from *www.cec.org/* - accessed 15 June 2011.

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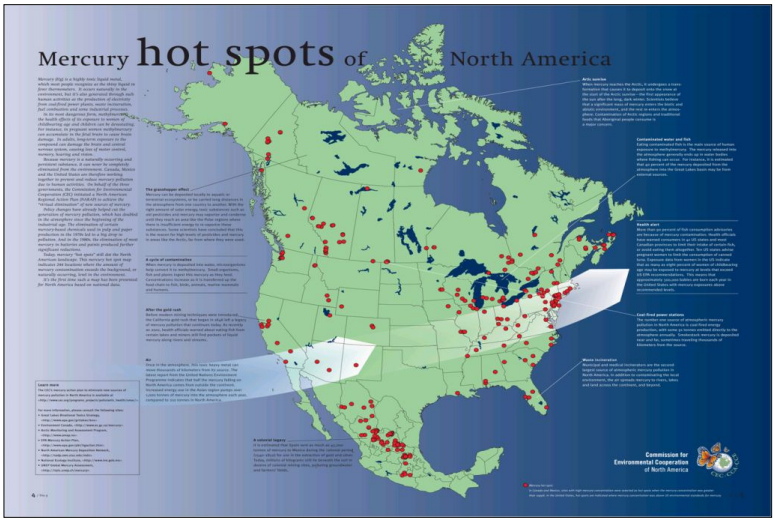

www.cec.org/

The Commission for Environmental Cooperation which is the environmental side arm of the North American Free Trade Agreement (NAFTA) produced this map from national emissions inventories to demonstrate visibly sources of emissions of mercury in North America. Inventories of this kind demonstrated on maps bring awareness to communities of sources of potentially harmful emissions. This information can be used for education, awareness and protective policies as well as ongoing research by scientists.

Image from www.cec.org/ - accessed 15 June 2011.

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UNEP GLOBAL MERCURY PARTNERSHIP

The overall goal is to protect human health and the global environment from the release of mercury and its compounds

UNEP Global Mercury Partnership www.chem.unep.ch/mercury

UNEP: United Nations Environment Programme

The United Nations Environment Programme (UNEP) Global Mercury Partnership is a voluntary initiative where government, non-government, public and private entities have agreed to work together in a systematic way to achieve the goal of the Partnership. The overall goal is to protect human health and the global environment from the release of mercury and its compounds by minimizing and, where feasible, ultimately eliminating global anthropogenic mercury releases to air, water and land.

Ref:

•UNEP Global Mercury Partnership. Available at *www.unep.org/hazardoussubstances/Mercury/tabid/434/language/en-US/Default.aspx* – accessed 15 June 2011

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WHO/UNEP GLOBAL ALLIANCE TO ELIMINATE LEAD PAINT

Key activities areas for the elimination of lead paints

a) Raising awareness of toxicity to human health and the environment and alternatives;

(b) Guidance and assistance to identify potential lead exposure;

(c) Assistance to industry (manufacturers, wholesalers and retailers);

(d) Prevention programmes to reduce exposure;

(e) Promotion of national regulatory frameworks.

UNEP: United Nations Environment Programme

www.unep.org/hazardoussubstances/LeadCadmium/PrioritiesforAction/GAELP/tabid/6176/Default.aspx 47

<<READ SLIDE>>

More information on the Global Alliance to Eliminate Lead Paint available at *www.unep.org/hazardoussubstances/LeadCadmium/PrioritiesforAction/GAELP/tabid/6176/Default.aspx* – accessed 15 June 2011

CHALLENGES OF ADDRESSING NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders are largely preventable. Countries can develop:

- Better surveillance
  - Access to environmental data
- Appropriate public health interventions
  - Relevant health databases, identification and action on all risk factors
- Coordinated research plan
  - Ecological, basic science, epidemiological & qualitative
- Adequate risk assessment, management & communication
- National, regional, global strategies

<<READ SLIDE>>

Refs:

•Neira M et al. Environmental threats to children's health – a global problem. *Int J Environment and Health*, 2008, 2(3/4):276.

•Pronczuk J, Bruné MN, Gore F. Children's environmental health in developing countries. In: *Encyclopedia of Environmental Health*. Nriagu J, ed. Elsevier, 2011.

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SUMMARY

1. Neurodevelopmental Behavioral Intellectual Disorders are common in industrialized countries.
2. The neurodevelopment process is a delicate, vulnerable, very complex process. It is affected by many genetic & environmental factors.
3. Neurodevelopmental Behavioral Intellectual Disorders carry an enormous economic and emotional impact on societies.
4. Exposures to environmental chemicals with potential for contributing to Neurodevelopmental Behavioral Intellectual Disorders are poorly understood.
5. Neurodevelopmental Behavioral Intellectual Disorders are largely preventable through a coordinated plan to identify and mitigate relevant risk factors.

<<READ SLIDE>>

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