Developmental neurotoxicity of industrial chemicals

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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.

Published Online
November 8, 2006
DOI:10.1016/S0140-6736(06)69665-7

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One in every six children has a developmental disability and in most cases these disabilities affect the nervous system.[1] The most common neurodevelopmental disorders include learning disabilities, sensory deficits, developmental delays, and cerebral palsy.[1] Some experts have reported that the prevalence of certain neurodevelopmental disorders—autism and attention deficit and hyperactivity disorder, in particular—might be increasing, but there are few data to sustain that position.[2] Treatment of these disorders is difficult, and the disabilities they cause can be permanent;[3] they are therefore very costly to families and to society.[4–6]

Evidence has been accumulating over several decades that industrial chemicals can cause neurodevelopmental damage and that subclinical stages of these disorders might be common. The possibility of a link between chemicals and widespread neurobehavioural changes was first raised by research showing that lead was toxic to the developing brain across a wide range of exposures.[7–10] That report was in accord with reports indicating that other environmental pollutants were also toxic to early brain development.[11] An expert committee from the US National Research Council concluded that 3% of developmental disabilities are the direct result of environmental exposure to such substances, and that another 25% arise through interactions between environmental factors and individual genetic susceptibility.[3] These estimates were based on scarce information about neurotoxicity and could therefore underestimate the true prevalence of chemically-induced abnormalities.

Neurobehavioural damage caused by industrial chemicals is, in theory, preventable. An essential prerequisite to prevention is recognition of a chemical's ability to harm the developing brain. Knowledge that a chemical is neurotoxic can prompt efforts to restrict its use and to control exposure. Previous evidence-based programmes of exposure prevention, such as those directed against children's exposure to lead, have been highly successful, although they were initiated after substantial delay.

The aims of this review are to characterise the vulnerability of the developing nervous system to chemical toxicity; to collate publicly available data for human neurotoxicity of industrial chemicals; to examine the possible extent of a developmental neurotoxicity pandemic; to describe the known consequences of developmental neurotoxicity for individuals and society; to examine the implications for human health of the dearth of toxicological information; and to consider prospects for prevention of exposure.

Vulnerability of the developing brain

The developing human brain is inherently much more susceptible to injury caused by toxic agents than is the brain of an adult.[12] This susceptibility stems from the fact that during the 9 months of prenatal life, the human brain must develop from a strip of cells along the dorsal ectoderm of the fetus into a complex organ consisting of billions of precisely located, highly interconnected, and specialised cells. Optimum brain development requires that neurons move along precise pathways from their points of origin to their assigned

Search strategy and selection criteria

We identified industrial chemicals that have caused neurotoxic effects in man from the hazardous substances data bank of the US National Library of Medicine, supplemented by fact sheets by the US Agency for Toxic Substances and Disease Registry, and the integrated risk information system of the US Environmental Protection Agency. We searched for the terms "neurotoxic", "neurological", and "neuro". For all neurotoxic substances identified, we then used synonyms, commercial names, and CAS (chemical abstracts service) numbers to search PubMed, TOXNET, and TOXLINE to identify published data for developmental neurotoxicity. The primary search terms were "prenatal exposure delayed effects"[MeSH] and "neurotoxicity syndromes"[MeSH]. Secondary searches used combinations of "maternal exposure" and "maternal fetal exchange" with "developmental disabilities/chemically induced" and "neurotoxins", all with the limiters "all child: 0–18 years", "most recent 10 Years", "English", and "human". We also used references cited in the chosen articles.

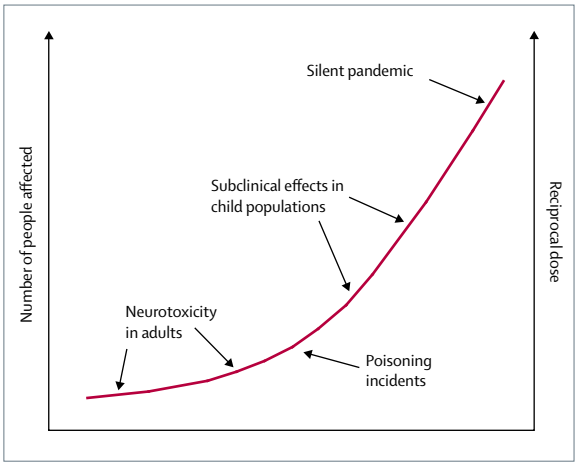

Figure 1: **The effects of a neurotoxic chemical on a population over time**
For identification of chemicals toxic to neurodevelopment, the first evidence dealt with adverse effects of high doses on the adult nervous system, and was followed by case reports and epidemiological evidence on developmental toxicity at successively lower doses, to which childhood populations of increasing magnitude were exposed. Recognition of inorganic lead, methylmercury, and polychlorinated biphenyls as neurotoxic followed this curve towards the right, and arsenic and toluene were later seen to match this curve. Documentation of most neurotoxicants is directed toward adults only and therefore many compounds remain far to the left on the timescale.

locations, that they establish connections with other cells, both nearby and distant, and that they learn to communicate with other cells via such connections.[12–14] All these processes have to take place within a tightly controlled time frame, in which each developmental stage has to be reached on schedule and in the correct sequence. Because of the extraordinary complexity of human brain development, windows of unique susceptibility to toxic interference arise that have no counterpart in the mature brain, or in any other organ. If a developmental process in the brain is halted or inhibited, there is little potential for later repair, and the consequences can therefore be permanent.[12,14]

During fetal development, the placenta offers some protection against unwanted chemical exposures, but it is not an effective barrier against environmental pollutants.[15] For example, many metals easily cross the placenta, and the mercury concentration in umbilical cord blood can be substantially higher than in maternal blood.[16] The blood-brain barrier, which protects the adult brain from many toxic chemicals, is not completely formed until about 6 months after birth.[17]

The human brain continues to develop postnatally, and the period of heightened vulnerability therefore extends over many months, through infancy and into early childhood. Although most neurons have been formed by the time of birth, growth of glial cells and myelinisation of axons continues for several years.[13,14]

The susceptibility of infants and children to industrial chemicals is further enhanced by their increased exposures, augmented absorption rates, and diminished ability to detoxify many exogenous compounds, relative to that of adults.[18,19] Persistent lipophilic substances, including specific pesticides and halogenated industrial compounds, such as PCBs, accumulate in maternal adipose tissue and are passed on to the infant via breast milk, resulting in infant exposure that exceeds the mother's own exposure by 100-fold on the basis of bodyweight.[20]

Recognition of neurotoxicity

Developmental neurotoxicity in children exposed to industrial chemicals is often first identified through recognition of obvious functional abnormalities after high-dose exposure that clearly caused poisoning. Good quality research later documented the presence of less striking, but nonetheless serious adverse effects at low doses of exposure (figure 1). This sequence of discovery led to the recognition that environmental pollutants exert a range of adverse effects—some are clinically evident, but others can be discerned only through special testing and are not evident on standard examination, hence the term subclinical toxicity. The underlying idea is that there is a dose-dependent continuum of toxic effects, in which clinically obvious effects have subclinical counterparts.[21] A pandemic of subclinical neurotoxicity is therefore likely to be silent—ie, not apparent from standard health statistics.

The notion of subclinical toxicity originates from the pioneering work of Landrigan[7] Needleman[8] and their colleagues, which, showed that children's exposure to lead could cause reductions in intelligence and changes in behaviour even in the absence of clinically visible symptoms of lead toxicity. The subclinical toxicity of lead in children has subsequently been confirmed in prospective epidemiological studies.[22,23]

Parallel findings have been reported on some other industrial chemicals, but their number is small. About 80 000 chemicals are registered for commercial use with the US Environmental Protection Agency, and 62 000 were already in use when the Toxic Substances Control Act was enacted in the USA in 1977.[24] The situation is similar in the EU, where 100 000 chemicals were registered in 1981.[25] The full extent to which these chemicals contribute to neurodevelopmental disorders and subclinical neurotoxicity is still unknown.

Neurotoxic agents

Identification

Studies in animals support the notion that a wide range of industrial chemicals can cause developmental neurotoxicity at low doses that are not harmful to mature organisms.[26,27] Such injury seems to result in permanent changes in brain function that might become detectable only when the animal reaches maturity. Because developmental neurotoxicity might not be apparent from routine toxicology tests,[28] identification of neurotoxic chemicals often rests on clinical and epidemiological data.

www.thelancet.com Published online November 8, 2006 DOI:10.1016/S0140-6736(06)69665-7

To identify environmental chemicals that are toxic to the human brain, we searched the hazardous substances data bank of the US National Library of Medicine, where substances are listed with their adverse effects in human beings. We checked the completeness of this list against other data sources and with a previous review of published data for clinical toxicity.[29] The panel shows the industrial chemicals known to be neurotoxic in human beings. We have excluded drugs, food additives, microbial toxins, and snake venoms and similar biogenic substances. This list excludes chemicals that have proved neurotoxic solely in laboratory animals, for which no systematic list exists. We mainly include acutely toxic substances that have caused serious accidents or have been used in suicide attempts, Neurotoxins that mainly cause chronic or delayed disease are likely to be underrepresented.[29] The largest groups of identified compounds are metals, solvents, and pesticides, but other chemicals with less documentation could have unrecognised effects. The list therefore should not be regarded as comprehensive.

These substance names (see panel) were used for searches of published data for developmental neurotoxicity. On the basis of our critical review, the few known chemicals causing neurodevelopmental abnormalities are highlighted in the panel. Many more chemicals that we have not listed are known to harm neurodevelopment in laboratory animals,[27] but no data about their potential toxic effects on human brain development are available.

Panel: Chemicals (n=201) known to be neurotoxic in man

Metals and inorganic compounds

- Aluminum compounds
- *Arsenic and arsenic compounds
- Azide compounds
- Barium compounds
- Bismuth compounds
- Carbon monoxide
- Cyanide compounds
- Decaborane
- Diborane
- Ethylmercury
- Fluoride compounds
- Hydrogen sulphide
- *Lead and lead compounds
- Lithium compounds
- Manganese and manganese compounds
- Mercury and mercuric compounds
- *Methylmercury
- Nickel carbonyl
- Pentaborane
- Phosphine
- Phosphorus
- Selenium compounds
- Tellurium compounds
- Thallium compounds
- Tin compounds

Organic solvents

- Acetone
- Benzene
- Benzyl alcohol
- Carbon disulphide
- Chloroform
- Chloroprene
- Cumene
- Cyclohexane
- Cyclohexanol
- Cyclohexanone
- Dibromochloropropane
- Dichloroacetic acid
- 1,3-Dichloropropene
- Diethylene glycol
- N,N-Dimethylformamide
- 2-Ethoxyethyl acetate
- Ethyl acetate
- Ethylene dibromide
- Ethylene glycol
- n-Hexane
- Isobutyronitrile
- Isophorone
- Isopropyl alcohol

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Lead

The neurotoxic effects of lead in adults were known in Roman times, but a report from Australia 100 years ago was the first description of epidemic lead poisoning in young children; the source of the outbreak was traced to ingestion of lead-based paint by children playing on verandas with peeling paint.[30] Further reports of childhood lead poisoning from the USA and Europe followed. Lead poisoning was at that time thought to be an acute illness, from which a child either recovered or died. Long-term sequelae were first documented in the 1940s, when 19 of 20 survivors of acute poisoning were noted to have severe learning and behavioural problems.[31]

Despite those early paediatric warnings, the largely unchecked use of lead in petrol, paints, ceramic glazes, and many other products through much of the twentieth century caused continued risk of lead poisoning. During the 1970s, widespread subclinical neurobehavioural deficits, including problems with concentration, memory, cognition, and behaviour, were documented in asymptomatic children with raised blood-lead concentrations.[7,8] Spurred by recommendations issued by the European Regional Office of WHO, studies were initiated in many countries; the results corroborated the previous conclusions.[32]

As a result of accumulating evidence, many sources of lead exposure became controlled, although not all sources, and not in all countries. A 90% reduction in childhood

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- Isopropylacetone
- Methanol
- Methyl butyl ketone
- Methyl cellosolve
- Methyl ethyl ketone
- Methylcyclopentane
- Methylene chloride
- Nitrobenzene
- 2-Nitropropane
- 1-Pentanol
- Propyl bromide
- Pyridine
- Styrene
- Tetrachloroethane
- Tetrachloroethylene
- *Toluene
- 1,1,1-Trichloroethane
- Trichloroethylene
- Vinyl chloride
- Xylene

Other organic substances

- Acetone cyanohydrin
- Acrylamide
- Acrylonitrile
- Allyl chloride
- Aniline
- 1,2-Benzenedicarbonitrile
- Benzonitrile
- Butylated triphenyl phosphate
- Caprolactam
- Cyclonite
- Dibutyl phthalate
- 3-(Dimethylamino)-propanenitrile
- Diethylene glycol diacrylate
- Dimethyl sulphate
- Dimethylhydrazine
- Dinitrobenzene
- Dinitrotoluene
- Ethylbis(2-chloroethyl)amine
- Ethylene
- Ethylene oxide
- Fluoroacetamide
- Fluoroacetic acid
- Hexachlorophene
- Hydrazine
- Hydroquinone
- Methyl chloride
- Methyl formate
- Methyl iodide
- Methyl methacrylate
- p-Nitroaniline
- Phenol

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blood-lead concentrations followed the termination of lead additives in petrol.[33] Now, research into lead neurotoxicity focuses on the shape of the dose-response curve at very low exposures that seem to cause surprisingly large functional decrements.[22] As convincing evidence was recognised, health agencies reduced the permissible concentration of lead in children's blood. However, up-to-date research[22] suggests that the current effects of lead exposure on human brain development could be even greater than previously thought.

Methylmercury

Toxic effects on the brain due to methylmercury were first established in men with occupational exposure.[34] The developmental toxicity of this organic mercury compound became evident in the 1960s in Minamata, Japan, where an epidemic of spasticity, blindness and profound mental retardation was seen in infants born to mothers who consumed fish from contaminated waters. After many years of clinical and experimental studies, the source proved to be mercury compounds released into Minamata Bay by a plastics plant.[35] Methylmercury accumulated and reached high concentrations in locally caught fish. Exposed adults, including mothers of poisoned children, were less seriously affected, if at all.[36] Similar outbreaks of profound neurodevelopmental disorders in the infants of seemingly unaffected mothers have arisen after maternal consumption during pregnancy of seed grain treated with methylmercury fungicides.[37,38] Studies of a serious poisoning incident in Iraq established a crude dose-response association between mercury concentrations in maternal hair and risk of neurological abnormalities in the children of the women.[39]

Recent studies have focused on prenatal exposures to reduced concentrations of methylmercury. They have examined populations with a high intake of seafood and freshwater fish with various degrees of methylmercury contamination. Prospective examination of a New Zealand cohort noted a three-point decrement in intelligence quotient (IQ) and changes in affect in children born to women with mercury concentrations in hair of grerater than 6 μg/g.[40] A large prospective study in the Faroe Islands noted evidence of dose-related impairments in memory, attention, language, and visuospatial perception in exposed children.[41] A third prospective cohort study in the Seychelles provided no support for prenatal neurotoxicity after adjustment for postnatal exposures.[42] Several cross-sectional studies recorded significant associations between methylmercury exposure and neurobehavioral impairment in young children.[43]

The US National Academy of Sciences reviewed these studies and concluded that strong evidence exists for fetal neurotoxicity of methylmercury, even at low exposures.[44] These findings have led food safety authorities to issue dietary advisories, and national and

www.thelancet.com Published online November 8, 2006 DOI:10.1016/S0140-6736(06)69665-7

international agencies (with coordination from the UN Environment Programme) now seek to control and restrict mercury releases to the environment. Substantial reductions have already been achieved in mercury use and release from hospitals and incinerators.[45] A related substance, ethylmercury, has been widely used as a preservative in vaccines, but neurotoxic risk has not been documented.[46]

Arsenic

Ingestion of arsenic-contaminated drinking water has long been recognised to cause peripheral neuropathy in adults.[47] Developmental neurotoxicity due to arsenic was reported in 1955 in Japan, where consumption of powdered milk contaminated with arsenic led to over 12 000 cases of poisoning and 131 deaths.[48] A follow-up study of three groups of adolescents born during the time of the milk contamination included one group that was fully breast-fed, one that was exposed to the tainted milk product, and one that received other supplements, but no tainted formula.[49] Compared with national rates, a ten-fold increase in mentally-retarded individuals was seen in the tainted milk group.[48] Poor school records, emotional disturbances, and abnormal or borderline electroencephalogram findings were also more common in the exposed group. Since these findings were initially reported in Japanese journals not easily available elsewhere,[48,49] they have often been overlooked, even in the most thorough risk assessments of environmental arsenic exposure.[50,51]

Arsenic is present in ground water worldwide, and industrial pollution is widespread. Cross-sectional studies of school-age children showed cognitive deficits associated with drinking water contamination[52] and raised urinary arsenic concentrations.[53] Similar results were obtained in children with arsenic exposure from a smelter.[54] Possible combined adverse effects on IQ caused by arsenic and manganese exposures was suggested by metal concentrations in hair in children living near a hazardous waste site.[55] Although evidence for subclinical neurodevelopmental neurotoxicity of arsenic is less well established than for lead and methylmercury, the data are consistent and fit with the high-exposure findings from Japan. Still, regulatory action does not emphasise the need to protect the developing brain against this neurotoxic substance.[50,51]

Polychlorinated biphenyls

PCBs used to be widely applied in electrical equipment as insulators. Human toxicity was first described from industrial exposures,[56] but neurological effects did not seem important. Developmental toxicity of PCBs was first seen in children exposed to high concentrations in two poisoning events in Asia, where cooking oil had been contaminated by PCBs and related substances during manufacturing. Prenatal exposure in one incident, in Taiwan, was associated with low birthweight, delayed

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- p-Phenylenediamine
- Phenylhydrazine
- Polybrominated biphenyls
- Polybrominated diphenyl ethers
- *Polychlorinated biphenyls
- Propylene oxide
- TCDD
- Tributyl phosphate
- 2,2′,2″-Trichlorotriethylamine
- Trimethyl phosphate
- Tri-o-tolyl phosphate
- Triphenyl phosphate

Pesticides

- Aldicarb
- Aldrin
- Bensulide
- Bromophos
- Carbaryl
- Carbofuran
- Carbophenothion
- α-Chloralose
- Chlordane
- Chlordecone
- Chlorfenvinphos
- Chlormephos
- Chlorpyrifos
- Chlorthion
- Coumaphos
- Cyhalothrin
- Cypermethrin
- 2,4-D
- DDT
- Deltamethrin
- Demeton
- Dialifor
- Diazinon
- Dichlofenthion
- Dichlorvos
- Dieldrin
- Dimefox
- Dimethoate
- Dinitrocresol
- Dinoseb
- Dioxathion
- Disulphoton
- Edifenphos
- Endosulphan
- Endothion
- Endrin
- EPN
- Ethiofencarb
- Ethion
- Ethoprop

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developmental milestones, and lower IQs in comparison with unexposed siblings.[57] Exposed boys (but not girls) showed deficits in spatial reasoning. A follow-up study showed growth impairment, slow development, lack of endurance, clumsy movement, and very low IQs.[58] In a similar incident in Japan, neurological damage seemed less prominent than that of the Taiwan contamination.[59] Because of the mixed exposures, the specific contribution by PCB to these adverse effects cannot be determined.

Epidemiological studies of asymptomatic populations exposed prenatally to PCBs and related contaminants through maternal diet were done in the USA. Subclinical developmental deficits were shown in the most highly exposed of these children[60,61] and were associated, at age 11 years, with an average IQ score 6·2 points below that of children with lower exposures.[62] A Dutch cohort included 418 healthy infants and noted subclinical decrements on neonatal neurological examination and in subsequent developmental tests related to increased PCB exposures.[63] Continued follow-up of this cohort suggested that the effects could be modified or masked with age, but were still detectable at age 9 years.[64] Results from a German cohort were in accord with these findings and also suggested that postnatal PCB exposure from breastfeeding contributes to cognitive deficits.[65] A possible mechanism through which PCBs injure the developing brain is by interference with maternal thyroid function,[13,66] which might not harm adult brain functions. Although PCB manufacture has been banned in most nations, and exposures are decreasing, exposures at currently prevalent concentrations could still cause developmental neurotoxicity.[67]

Solvents

Solvent neurotoxicity in adults is well known from acute poisoning cases and from occupational studies.[68] Ethanol is a solvent. Intermittent, low-level exposures produce mild inebriating effects, but do not lead to irreversible damage. However, heavy, long-term ethanol intake in adults can lead to serious injury, including Wernicke's syndrome but because such exposures are voluntary, ethanol is not included in the panel.

Fetal alcohol syndrome is qualitatively different from the syndrome in adults. It was originally described in infants of mothers with a serious drinking habit, and involves cognitive and behavioural deficits and changes in facial features. Permanent neurotoxic damage in the mother is not a prerequisite for irreversible effects in the child.[69] At low consumption, subtle but permanent neurotoxicity, including decreased IQ scores, has been seen.[70] Effects of alcohol on the fetus could be enhanced by specific genetic polymorphisms.[71]

Less reliable documentation is available for other solvents widely used in industry. Because of its anaesthetic effects, toluene has been abused by sniffing, and case reports have reported that infants of mothers who sniffed toluene in pregnancy had abnormally low scores on developmental tests and showed delayed development of speech and motor function.[72–74] Additional evidence of cognitive deficits in children comes from small studies of mothers who

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- Fenitrothion
- Fensulphothion
- Fenthion
- Fenvalerate
- Fonofos
- Formothion
- Heptachlor
- Heptenophos
- Hexachlorobenzene
- Isobenzan
- Isolan
- Isoxathion
- Leptophos
- Lindane
- Merphos
- Metaldehyde
- Methamidophos
- Methidathion
- Methomyl
- Methyl bromide
- Methyl demeton
- Methyl parathion
- Mevinphos
- Mexacarbate
- Mipafox
- Mirex
- Monocrotophos
- Naled
- Nicotine
- Oxydemeton-methyl
- Parathion
- Pentachlorophenol
- Phorate
- Phosphamidon
- Phospholan
- Propaphos
- Propoxur
- Pyriminil
- Sarin
- Schradan
- Soman
- Sulprofos
- 2,4,5-T
- Tebupirimfos
- Tefluthrin
- Terbufos
- Thiram
- Toxaphene
- Trichlorfon
- Trichloronat

*=substances that have been documented also to cause developmental neurotoxicity.

www.thelancet.com Published online November 8, 2006 DOI:10.1016/S0140-6736(06)69665-7

reported occupational exposure to solvents, including toluene, during pregnancy.[75–77] The women were apparently exposed within permissible workplace limits aimed at prevention of neurotoxicity in the workers themselves. However, these studies do not allow any definite conclusions on the specific hazard and the nature of dose-response associations for developmental neurotoxicity.

Pesticides

More than 600 pesticides are registered, and include insecticides, fungicides, and rodenticides. In the USA alone, about 500 million kg are applied yearly. Acute pesticide neurotoxicity is well known from occupational exposure studies, poisoning events, and suicide data;[29] such neurotoxicity is often caused by cholinesterase inhibition by organophosphates.

Developmental neurotoxicity was suggested by an anthropological study of two similar groups of asymptomatic, Yaqui children aged 4–5 years in Mexico.[78] Those with high exposure to a mix of pesticides, including organophosphates, had diminished short-term memory, hand-eye coordination, and drawing ability, whereas unexposed children of the same tribe showed normal development.[78] Likewise, preschool children from agricultural communities in the USA showed poorer performance on motor speed and latency than did those of urban communities.[79] Ecuadorean schoolchildren, whose mothers had been exposed to organophosphates and other pesticides from working in greenhouses during pregnancy, showed visuospatial deficits compared with their unexposed peers.[80] Current pesticide exposure, measured by urinary excretion of organophosphate metabolites, was associated with delays in the children's simple reaction times.[80] Acute exposure of American children to the organophosphate pesticide, methyl parathion, was associated with persistent problems in short-term memory and attention span.[81] Prospective epidemiological studies of infants exposed prenatally to the organophosphate, chlorpyrifos, recorded significant decreases in head circumference and birthweight and slowing of reflexes.[82–84] Small head circumference, a risk factor for neurodevelopmental disorders, was seen only in exposed infants who were born to mothers with low expression of PON1, an esterase involved in organophosphate detoxification.[83] The effect of chlorpyrifos on bodyweight disappeared after introduction of a ban on residential use.[84] Although organophosphates can undoubtedly cause developmental neurotoxicity, the data are insufficient to determine the potential hazard to the developing brain posed by individual compounds among the dozens of organophosphates in use worldwide.

Emerging neurotoxic substances

Documentation of developmental effects in human beings for the other compounds listed in the panel is poor. However, three obvious candidate substances deserve particular attention, including two that have not seemed to cause neurotoxicity in adults.

Manganese

Manganese neurotoxicity in adults has been well documented in occupationally exposed populations; parkinsonism is the classic clinical feature, and subclinical neurotoxicity has also been reported.[85] Concerns about the developmental neurotoxicity of manganese have emerged because the organic manganese compound methylcyclopentadienyl manganese tricarbonyl has been added to petrol as an antiknock agent in Australia and Canada and could be used in the USA and elsewhere in the future. Manganese can also be present in drinking water. In a prospective study of 247 births in Paris, France,[86] high manganese concentrations in cord blood were associated with impaired neurobehavioural development, especially on the Brunet-Lezine scales at age 9 months and the McCarthy scales at 3 years. At age 6, no association was seen but only 100 of the original children participated.[86] Community exposures to manganese released into the environment by combustion of methylcyclopentadienyl manganese tricarbonyl,[87] exposures from a toxic waste site in the USA,[55] and from contaminated drinking water in Bangladesh[88] have been associated with subclinical neurological impairment in children.

Fluoride

Fluoride can cause neurotoxicity in laboratory animals,[89] but is not shown in the panel as a substance proven to be neurotoxic in man. It exists in drinking water as a natural contaminant, but the concentration is dependent on local geological circumstances. In rural communities in China, high fluoride concentrations in well water might cause skeletal abnormalities. In one such community, 222 children aged 8–13 years showed significantly worse IQs than 290 unexposed controls.[90] Parallel results were obtained in a smaller study of 118 children of similar age.[91] Another study of 477 schoolchildren from 22 villages suggested that both increased water fluoride concentrations and very low concentrations were associated with IQ deficits, compared with children exposed to normal concentrations (below 1 mg/L).[92] The reports did not thoroughly consider possible confounders, but do suggest that further in-depth studies be undertaken.

Perchlorate

This chemical is not known as neurotoxic to adults. It is a widespread contaminant of ground water in the USA from the use of ammonium perchlorate as a solid-fuel propellant for rockets and missiles.[93] The thyroid is the primary site of perchlorate toxicity, and iodine uptake by the thyroid is blocked. Abnormal brain development, as a consequence of inhibition of maternal thyroid function,[13,66] is the major potential effect of perchlorate exposure.[93] Because the available evidence is uninformative as to

neurobehavioral toxicity, drinking water standards for perchlorate are set at levels to protect adults and do not include child-protective safety factors.

Effects of developmental neurotoxicity

The five substances recognised as causes of developmental neurotoxicity show similar patterns in the development of scientific documentation of their risks. This pattern of discovery started in each instance with recognition of adult neurotoxicity, typically in people with occupational exposure, and of episodes of acute, high-dose poisoning in children. The next stage was the accumulation of epidemiological evidence of neurobehavioural deficits in children with prenatal exposures at concentrations that are not toxic to adults (figure 1). For lead, methylmercury, and PCBs, widespread subclinical neurotoxicity has been documented internationally, yet the full implications of exposure to arsenic and toluene are unclear. For most substances listed in the panel, only neurotoxicity in adults has been documented.

The combined evidence suggests that neurodevelopmental disorders caused by industrial chemicals has created a silent pandemic in modern society. Although these chemicals might have caused impaired brain development in millions of children worldwide, the profound effects of such a pandemic are not apparent from available health statistics. Additionally, as shown by this Review, only a few chemical causes have been recognised so the full effects of our industrial activities could be substantially greater than recognised at present.

As is shown by the evidence for inorganic lead, globally increased exposures have been responsible for erosion of cognitive skills with subclinical, but permanent, decreases in IQ. Additionally, this neurotoxic chemical produces lifelong changes in behaviour with shortened attention span, increased impulsivity, heightened aggressiveness, slowed motor coordination, and impaired memory and language skills. The consequences are increased likelihood of school failure, diminished economic productivity, and possibly increased risk of antisocial and criminal behaviour.[94] The most striking of these effects occur at the extremes of performance; in highly exposed children, almost none had above average function, whereas the number with obvious deficits increased greatly.[95] The most severely affected individuals will probably need special education and will also be less likely than their peers to pursue productive career options. A study of adults who were exposed to excess lead as children revealed that they were much less successful in life than those from a less exposed comparison group.[96]

The consequences of a pandemic of developmental neurotoxicity extend beyond descriptive data for incidence and prevalence of clinically diagnosed disorders.[1,3] Increased risk of Parkinson's disease[97] or other neurodegenerative diseases[98] is a further potential consequence of the pandemic. Thus, early subclinical chemical injury has been postulated to silently kill a fraction of the cells needed to sustain brain function in later life (eg, in the substantia nigra). These latent impairments cause no symptoms in childhood, but could be unmasked during the natural neuronal attrition associated with ageing.[99,100]

The wide extent of human exposure to pollutants is now becoming apparent after systematic collection of data for the amounts of these substances present in the environment and in human tissues.[101] However, recognition of causal associations could be difficult because exposures vary with time, more than one substance could have an effect, individual vulnerability varies, and other factors can bias epidemiological studies toward the null hypothesis, especially when the outcome might be unrecognised for several years, or even decades.[102]

The population at risk of subclinical neurotoxicity from industrial chemicals is very large. Almost all children born in industrialised countries between 1960 and 1980 were exposed to substantial amounts of lead from petrol that could have reduced the number of children with far above average intelligence (IQ scores above 130 points) by over 50% and might likewise have increased the number with IQ scores below 70.[95] In the USA alone, the aggregate population of children at risk of exposure to airborne lead at that time was about 100 million. In this period, the resulting economic costs are estimated to have ranged from US$110 billion to $319 billion in each year's birth cohort.[103] Most of these costs were related to the diminished economic productivity that resulted over the exposed children's entire lifetimes from wide-scale reductions in intelligence. Today the costs of lead poisoning are estimated to be $43 billion in each birth cohort in the USA,[5] whereas the costs of prenatal methylmercury toxicity are estimated to amount to $8·7 billion yearly (range, $2·2–43·8 billion).[6] Diminished economic productivity remains the main source of these costs. Because of the absence of dose-response associations for other neurotoxic compounds, the total costs are unknown.

The effect of chemical neurotoxicity extends beyond the industrially developed nations. Toxic chemicals, such as highly dangerous pesticides that are banned in industrialised countries, are exported to developing societies, where environmental and occupational standards are often weak or at least poorly enforced.[104] The consequences are largely unreported.

Prevention

A pandemic of neurodevelopmental toxicity caused by industrial chemicals is, in theory, preventable. Testing of new chemicals before allowing them to be marketed is a highly efficient means to prevent toxicity, but has been required only in recent years. Of the thousands of chemicals used in commerce, fewer than half have been subjected to even token laboratory testing for toxicity testing.[24] Nearly 3000 of these substances are produced in quantities of almost 500 000 kg every year, but for nearly

half these high-volume chemicals no basic toxicity data are publicly available, and 80% have no information about developmental or paediatric toxicity.[24] Although new chemicals must be tested more thoroughly, access to these data can be restricted, because they could be claimed to constitute confidential business information. Absence of information about the neurotoxic potential of most industrial chemicals is therefore the main impediment to prevention of developmental disorders induced by neurotoxic pollutants. Accelerated testing of chemicals already in commerce is therefore essential. In the USA, a legal mandate to require testing was established in the Toxic Substances Control Act, but is largely unenforced.[24] In the EU, opportunity exists to require more extensive chemical testing through the REACH programme,[25] although the proposed legislation does not emphasise testing for developmental neurotoxicity as a primary objective.

Toxicity testing protocols for chemicals need to be expanded to include examination of neurobehavioural functions. Present test protocols rely mainly on crude indices, such as brain weight and gross morphology.[105,106] There is a risk that abbreviated protocols used for toxicity screening will overlook neurodevelopmental toxicity, and further testing could erroneously be thought unnecessary. Procedures for functional appraisal are available,[105] and a harmonised protocol for assessment of developmental neurotoxicity was developed under OECD auspices in 1999,[106] although a revision is still under review.

The number of chemicals that can cause neurotoxicity in laboratory studies probably exceeds 1000, which is far more than the estimated 200 that have caused documented human neurotoxicity. However, in the absence of systematic testing,[28] the true extent of the neurotoxic potential of industrial chemicals is unknown. The physiology of brain development[12–14] and experimental evidence[14,26,27] suggest that developmental neurotoxicity is likely for all of them, except perhaps for some of the compounds that require metabolic transformation to become neurotoxic, in which immature metabolism may provide some degree of protection.[19,107] The few substances proven to be toxic to human neurodevelopment should therefore be viewed as the tip of a very large iceberg (figure 2).

Large-scale, prospective epidemiological studies, such as birth cohorts from Europe[108] and the National Children's Study proposed in the USA, will be especially informative about early toxic exposures and neurodevelopmental disorders.[109] Data from these investigations, especially when pooled internationally, will hopefully provide dose-response associations that can guide future disease prevention efforts. This research should move beyond repeated assessments of known neurotoxins to examine chemicals, whose toxicity is just beginning to be recognised. The substances listed in the panel, especially those most prevalent in food, drinking water, and the environment, should provide a useful starting point. Nevertheless, these initiatives could take decades to generate the type of detailed documentation required for chemicals regulation.

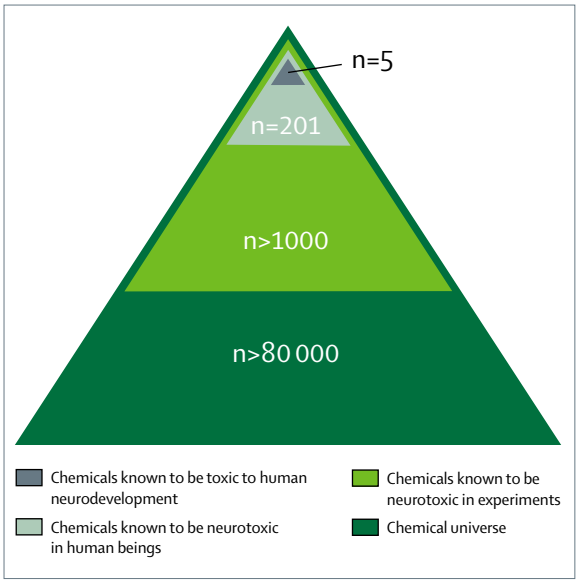

Figure 2: **Diagram of the extent of knowledge of neurotoxic chemicals**
Of the thousands of known chemicals, only a small fraction have been proven to cause developmental neurotoxicity in humans. Although this evidence does not represent the true potential for industrial chemicals to cause neurodevelopmental disorders, assessments of need for preventive measures nonetheless rely on that information.

The Food Quality Protection Act in the USA requires that pesticide standards be set at values that will protect infants against developmental toxicity. If testing data are not available, a child-protective safety factor should be used in standard settings. However, application of this factor has been uneven, and regulatory authorities need to recognise the vulnerability of prenatal brain development.

Prevention of neurodevelopmental disorders of chemical origin will need new approaches to control chemical exposures. The vulnerability of the human nervous system and its special susceptibility during early development suggest that protection of the developing brain should be a paramount goal of public health protection. The high level of proof needed for chemical control legislation has resulted in a slow pace of interventions to prevent exposures to lead and other recognised hazards. Instead, exposure limits for chemicals should be set at values that recognise the unique sensitivity of pregnant women and young children, and they should aim at protecting brain development. This precautionary approach, which is now beginning to be used in the EU, would mean that early indications of a potential for a serious toxic effect, such as developmental neurotoxicity, should lead to strict regulation, which could later be relaxed, should subsequent documentation show less harm than anticipated.[110] As physicians, we should use prudence when counselling our patients, especially pregnant mothers, about avoidance of exposures to chemicals of unknown and untested neurotoxic potential.

Conflict of interest statement

P Grandjean has testified on behalf of the Natural Resources Defense Council in a court case in regard to mercury pollution from a chemical plant in Maine, USA. PJ Landrigan has testified on behalf of the State of Rhode Island, USA, in a lawsuit against the manufacturers of lead-based paint.

Acknowledgments

We thank Prof Katsuyuki Murata for providing and translating literature from Japanese sources, Anna Choi for the translations from Chinese, Jennifer Pintabone-Asetta for the database searches; and for financial support the Danish Medical Research Council, the US National Institute of Environmental Health Sciences (ES07384, ES09584, ES09797, ES11687), and the US Environmental Protection Agency (RD 83171101). These funding sources had no role in preparation of this review, and the contents of this paper are solely the responsibility of the authors and do not represent the official views of the US National Institute of Environmental Health Sciences or any other funding agency.

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