



# Neurobehavioural effects of developmental toxicity

The Harvard community has made this  
article openly available. [Please share](#) how  
this access benefits you. Your story matters

Citation	Grandjean, Philippe, and Philip J Landrigan. 2014. "Neurobehavioural Effects of Developmental Toxicity." <i>The Lancet Neurology</i> 13 (3) (March): 330–338. doi:10.1016/S1474-4422(13)70278-3.
Published Version	doi:10.1016/S1474-4422(13)70278-3
Citable link	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:33087516">http://nrs.harvard.edu/urn-3:HUL.InstRepos:33087516</a>
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP</a>

## **Review**

### **Neurobehavioural impacts of developmental toxicity**

Philippe Grandjean, Philip J Landrigan

Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark, and Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA (P Grandjean, MD) and Department of Preventive Medicine, Mount Sinai School of Medicine, New York, NY; USA (PJ Landrigan, MD)

Full addresses:

Dr Philippe Grandjean, HSPH-EOME, 401 Park Drive 3E-110, Boston, MA 02215, USA.

Dr. Philip J Landrigan, Departments of Preventive Medicine and Pediatrics, Icahn School of Medicine at Mount Sinai, 17 East 102<sup>nd</sup> Street, New York, NY 10029 USA

Correspondence to Dr Philippe Grandjean, E-mail: [pgrand@hsph.harvard.edu](mailto:pgrand@hsph.harvard.edu) or [pgrand@sdu.dk](mailto:pgrand@sdu.dk). Telephone: +1-617-384-8907 or +45-6550-3769.

## **ABSTRACT**

Neurodevelopmental disabilities, including autism, attention deficit/hyperactivity disorder, dyslexia, and other cognitive impairment, affect children worldwide. Some diagnoses appear to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes. In 2006, we conducted a systematic review and identified five industrial chemicals – lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene – as developmental neurotoxicants. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants – manganese, fluoride, chlorpyrifos, DDT/DDE, tetrachloroethylene, and the polybrominated diphenyl ethers (PBDEs). We hypothesize that still more remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed safe to brain development, and chemicals in current use and all new chemicals must therefore be tested for developmental neurotoxicity. To coordinate these efforts and to accelerate translation of science into prevention, we propose the urgent formation of a new international clearinghouse.

## Introduction

Disorders of neurobehavioural development affect 10-15 % of all births,<sup>1</sup> and prevalence rates of autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), appear to be increasing.<sup>2</sup> Subclinical decrements in brain function are even more common. All of these disabilities can have severe consequences.<sup>3</sup> They diminish quality of life, reduce academic achievement, and disturb behaviours, with profound consequences for the welfare and productivity of entire societies.<sup>4</sup>

The root causes of the current global pandemic of neurodevelopmental disorders are only partially understood. Although genetic factors play a role,<sup>5</sup> they cannot explain recent increases in reported prevalence, and none of the genes discovered so far appear to be responsible for more than a few per cent of cases.<sup>5</sup> In the aggregate, genetic factors appear to account for no more than perhaps 30-40% of all cases of neurodevelopmental disorders. Thus, non-genetic, environmental exposures are involved in causation, in some cases likely by interacting with genetically inherited predispositions.

Evidence is strong that industrial chemicals widely disseminated in the environment are important contributors to what we have called the global, silent pandemic of neurodevelopmental toxicity.<sup>6, 7</sup> The developing human brain is exquisitely vulnerable to toxic chemical exposures, and major windows of developmental vulnerability occur *in utero* and during infancy and early childhood.<sup>8</sup> During these sensitive life stages, exposures can cause permanent brain injury at low levels of exposure that would have little or no adverse effect on an adult.

In 2006, we conducted a systematic review of the published clinical and epidemiological literature on the neurotoxicity of industrial chemicals, with a focus on developmental neurotoxicity.<sup>6</sup> We identified five industrial chemicals that could be reliably classified as developmental neurotoxicants - lead, methylmercury, arsenic, PCBs, and toluene. We also located 201 chemicals that had been reported to cause injury to the nervous system in adults, mostly in connection with occupational exposures, poisoning incidents or suicide attempts. In addition, more than 1000 chemicals have been reported to be neurotoxic in laboratory animals.

We observed that recognition of the risks of industrial chemicals to brain development has historically required decades of research and scrutiny, as illustrated in the cases of lead and methylmercury.<sup>9, 10</sup> Discovery began in most cases with clinical diagnosis of poisoning in workers and episodes of high-dose exposure. More sophisticated epidemiological studies were typically initiated only much later. Results from such studies documented developmental neurotoxicity at much lower levels of exposure that had previously been thought to be safe. Thus, recognition of widespread subclinical toxicity typically did not occur until decades after the initial evidence of neurotoxicity. A recurrent theme was that early warnings of subclinical neurotoxicity were often ignored or even glibly dismissed.<sup>11</sup> Dr. David P. Rall, former Director of the US National Institute of Environmental Health Sciences, once observed that "If thalidomide had caused a ten-point loss of IQ instead of obvious birth defects of the limbs, it would probably still be on the market".<sup>12</sup> Many industrial chemicals currently marketed likely cause IQ deficits much less than 10 points and have therefore so far eluded detection, but their combined effects could have enormous consequences.

In our 2006 review, we expressed concern that additional developmental neurotoxicants might lurk undiscovered among the 201 chemicals then known to be neurotoxic to human adults and among the many thousands of pesticides, solvents, and other industrial chemicals in wide use that had never been tested for neurodevelopmental toxicity. Since our previous review, new data have emerged on the vulnerability of the developing brain and on the neurotoxicity of industrial chemicals. Especially important new evidence derives from prospective epidemiological birth cohort studies.

The present review considers recent information on the developmental neurotoxicity of industrial chemicals and updates our previous report.<sup>6</sup> Additionally, we propose strategies to counter this pandemic and to prevent the spread of neurological disease and disability in children worldwide.

### **Exquisite vulnerability of the developing brain**

The foetus is not well protected against industrial chemicals. The placenta does not block the passage of many environmental toxicants from the maternal to the foetal circulation,<sup>13</sup> and over 200 foreign chemicals have been detected in umbilical cord blood.<sup>14</sup> In addition, many environmental chemicals are transferred to the infant via human milk.<sup>13</sup> During foetal life and early infancy, and the blood-brain barrier provides only partial protection against the entry of chemicals into the central nervous system.<sup>15</sup>

Moreover, the developing human brain is uniquely sensitive to injury caused by toxic chemicals,<sup>6</sup> and a number of developmental processes have been shown to be highly vulnerable to chemical toxicity. For example, *in vitro* studies indicate that

neural stem cells are highly sensitive to neurotoxic substances such as methylmercury.<sup>16</sup> Some pesticides inhibit cholinesterase function in the developing brain,<sup>17</sup> thereby affecting the crucial regulatory role of acetylcholine before synaptic formation.<sup>18</sup> Early-life epigenetic changes are also known to affect subsequent gene expression in the brain.<sup>19</sup> In summary, industrial chemicals known or suspected to be neurotoxic to adults are also likely to present risks to the developing brain.

Figure 1 illustrates the unique vulnerability of the brain during early life and indicates how developmental exposures to toxic chemicals are particularly likely to result in functional deficits and disease later in life.

### **New findings on known hazards**

Recent research on well-documented neurotoxicants has generated important new insights into the neurodevelopmental consequences of early exposures to these industrial chemicals.

Lead. Joint analyses that aggregated data on lead-associated IQ deficits from seven international studies<sup>20, 21</sup> support the conclusion that there is no safe level of exposure to lead.<sup>22</sup> Cognitive deficits in adults, who had previously shown lead-associated developmental delays at school age, suggest that the effects of lead neurotoxicity are probably permanent.<sup>23</sup> Brain imaging of young adults who had elevated blood-lead concentrations during childhood revealed exposure-related decreases in brain volume.<sup>24</sup> Lead exposure in early childhood is associated with decreased school performance<sup>25</sup> and with delinquent behaviour in later life.<sup>26, 27</sup>

Methylmercury. Developmental neurotoxicity due to methylmercury occurs at much lower exposures than the levels that affect adult brain function.<sup>28</sup> Deficits at

age 7 years that were linked to low-level prenatal exposures to methylmercury were still detectable at age 14.<sup>29</sup> Some common genetic polymorphisms appear to increase the vulnerability of the developing brain to methylmercury toxicity.<sup>30</sup> Functional MRI studies of subjects exposed prenatally to excess levels of methylmercury showed abnormally expanded activation of brain regions in response to sensory stimulation and motor tasks (Figure 2).<sup>31</sup> Because some adverse effects may be counterbalanced by essential fatty acids from seafood, statistical adjustment for maternal diet during pregnancy results in stronger methylmercury effects.<sup>32, 33</sup>

Arsenic. Prenatal and early postnatal exposures to inorganic arsenic from drinking water are associated with cognitive deficits apparent at school age.<sup>34, 35</sup> Survivors of the Morinaga childhood arsenic poisoning suffer highly elevated risks of neurological disease during adult life.<sup>36</sup>

Other known developmental neurotoxicants. The developmental neurotoxicity of PCBs has been consolidated and strengthened by recent findings.<sup>37</sup>

While little new information has been published on the developmental neurotoxicity of toluene, much has been learned about the developmental neurotoxicity of another common solvent, ethanol, through research on foetal alcohol exposure. Maternal drinking during pregnancy, even in very small quantities, has been linked to a range of neurobehavioural adverse effects in the offspring, including loss of IQ, impaired executive function and social judgement, delinquent behaviour, seizures, other neurological signs, and sensory problems.<sup>38</sup>

## **Newly recognized developmental neurotoxicants**

Prospective epidemiologic birth cohort studies make it possible to measure maternal/foetal exposures in real time during pregnancy as these exposures are actually occurring, thus generating unbiased information on the level and timing of prenatal exposures. Children in these prospective studies are followed longitudinally and examined using age-appropriate tests to reveal delayed or deranged neurobehavioural development. These powerful epidemiologic tools have allowed discovery of additional developmental neurotoxicants.

Manganese. Cross-sectional data from Bangladesh show that exposure to manganese from drinking water is associated with decreased mathematics achievement scores in school children.<sup>39</sup> A study in Quebec found a strong correlation between hair-manganese concentrations and hyperactivity.<sup>40</sup> School-aged children living near manganese mining and processing facilities have shown associations between airborne manganese levels and diminished intellectual function<sup>41</sup> as well as with impairment in motor skills and diminished olfactory function.<sup>42</sup> These results are supported by experimental findings in mice.<sup>43</sup>

Fluoride. A meta-analysis of 27 cross-sectional studies of children exposed to fluoride in drinking water, mainly from China, suggests an average IQ decrement of about 7 points in children exposed to elevated fluoride concentrations.<sup>44</sup> Confounding from other substances seemed unlikely in most of the studies. Further characterisation of the dose-response relationship would be desirable.

Solvents. The occupational health literature<sup>45</sup> suggests that solvents may act as neurotoxicants, but identification of individual responsible compounds is hampered by the complexity of exposures. A French cohort study of 3,000 children

linked maternal occupational solvent exposure during pregnancy to deficits in behavioural assessment at age two years.<sup>46</sup> The data showed dose-related increased risks for attention deficit and aggressive behaviour. One of every five mothers in this cohort reported solvent exposures in common jobs, such as nurse or other hospital employee, chemist, cleaner, hairdresser, and beautician.

In Massachusetts, follow-up of a well-defined population with prenatal and early childhood exposure to the solvent tetrachloroethylene (a.k.a. perchlorethylene) in drinking water showed a tendency toward deficient neurological function and increased risk of psychiatric diagnoses.<sup>47</sup>

Pesticides. Acute pesticide poisoning occurs commonly among children worldwide, and subclinical pesticide toxicity is also widespread. Clinical data suggest that acute pesticide poisoning during childhood may lead to lasting neurobehavioral deficits.<sup>48, 49</sup>

Highly toxic and bioaccumulative pesticides are banned today in Western nations, but are still used in many low and middle income countries. Especially the organochlorine compounds, dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethene (DDE), as well as chlordecone (Kepone), tend to be highly persistent and remain widespread in the environment and in the bodies of people in high-usage regions. Recent studies have documented inverse correlations between serum concentrations of DDT/DDE, which reflect cumulated exposures, and neurodevelopmental performance.<sup>50, 51</sup>

Organophosphate pesticides are eliminated from the human body much more rapidly than organochlorines, and exposure assessment is therefore inherently less precise. Nonetheless, three prospective epidemiological birth cohort studies provide

new evidence that prenatal exposure to organophosphate pesticides may cause developmental neurotoxicity. In these studies, prenatal organophosphate exposure was assessed by measuring maternal urinary excretion of pesticide metabolites during pregnancy. Dose-related correlations were found between maternal exposures to chlorpyrifos or other organophosphates and small head circumference at birth, a reflection of slowed brain growth *in utero*, as well as with neurobehavioural deficits that have persisted to at least to age 7.<sup>52-54</sup> In a subgroup, magnetic resonance imaging of the brain revealed that prenatal chlorpyrifos exposure was associated with structural abnormalities that included thinning of the cerebral cortex.<sup>55</sup>

Herbicides and fungicides may also have neurotoxic potential.<sup>56</sup> Propoxur,<sup>57</sup> a carbamate pesticide, and permethrine,<sup>58</sup> a member of the pyrethroid class of pesticides, have recently been linked to neurodevelopmental deficits in children.

Polybrominated Diphenyl Ethers (PBDEs). This group of compounds is widely used in as flame retardants and are structurally very similar to the PCBs. Experimental evidence now suggests that the PBDEs may also be neurotoxic.<sup>59</sup> Epidemiologic studies in Europe and the US report neurodevelopmental deficits in children with increased prenatal exposures to PBDEs.<sup>60-62</sup> Thus, the PBDEs should be considered hazards to human neurobehavioural development, although attribution of relative toxic potentials to individual congeners is not yet possible.

### **Other suspect developmental neurotoxicants**

A serious difficulty that complicates many epidemiological studies of neurodevelopmental toxicity in children is the problem of mixed exposures. Most

populations are exposed to more than one neurotoxicant at a time, and yet most studies have only limited power and precision in exposure assessment to discern the possible effects of even single neurotoxicants. A further problem in many epidemiological studies of non-persistent toxicants is that imprecise assessment of exposure tends to obscure associations that may, in fact, be present.<sup>63</sup> Guidance from experimental neurotoxicity studies is therefore crucial. In evaluating potential developmental neurotoxicants, we have used a strength of evidence approach similar to that used by the International Agency for Research on Cancer for assessing epidemiological and experimental studies.

Phthalates and Bisphenol A are added to many different types of plastics, cosmetics, and other consumer products. As they are rapidly eliminated in the urine, exposure assessment is complicated, and the imprecision may lead to underestimation of the true risk of neurotoxicity. The best documented effects of early-life exposure to phthalates are the consequence of disruption of endocrine signalling.<sup>64</sup> Thus, prenatal exposures to phthalates have been linked both to neurodevelopmental deficits and behavioural abnormalities characterized by shortened attention span and impaired social interactions.<sup>65</sup> The neurobehavioural toxicity of these compounds appears to be sex-dependent and could therefore relate to endocrine disruption in the developing brain.<sup>66</sup> In regard to Bisphenol A, a prospective study showed that point-estimates of exposure during gestation were linked to abnormalities in behaviour and executive function in the children at age three.<sup>67</sup>

Air pollution. Developmental exposures to air pollution can cause neurodevelopmental delays and disorders of behavioural functions.<sup>68, 69</sup> Among

individual components of air pollution, carbon monoxide is a well-documented neurotoxicant, and indoor exposure to this substance has now been linked to deficient neurobehavioural performance in children.<sup>70</sup> Less clear is the reported contribution of nitrogen oxides to neurodevelopmental deficits,<sup>71</sup> as these compounds commonly co-occur with carbon monoxide as part of complex emissions. Tobacco smoke is a complex mixture of hundreds of chemical compounds and is now a well-documented cause of developmental neurotoxicity.<sup>72</sup> Infants exposed prenatally to polycyclic aromatic hydrocarbons (PAHs) from traffic exhausts at age 5 years showed greater cognitive impairment and reduced IQ.<sup>68</sup>

Perfluorinated compounds, such as perfluorooctanoic acid and perfluorooctane sulfonate, are highly persistent in the environment and in the human body and appear to be neurotoxic.<sup>73</sup> Emerging epidemiological evidence suggests that these compounds may indeed impede neurobehavioural development.<sup>74</sup>

### **Developmental neurotoxicity and clinical neurology**

Exposures in early life to developmental neurotoxicants are now being linked to specific clinical syndromes in children. Thus, an increased risk of ADHD has been linked to prenatal exposures to manganese, organophosphates,<sup>75</sup> and phthalates.<sup>76</sup> Phthalates have also been linked to behaviours that resemble components of autism spectrum disorder (ASD).<sup>77</sup> Prenatal exposure to automotive air pollution in California has been linked to an increased risk for ASD.<sup>78</sup>

The persistent decrements in intelligence documented in children, adolescents, and young adults exposed in early life to neurotoxicants may well

presage later development of neurodegenerative disease. Thus, cumulated lead exposure is associated with cognitive decline in the elderly.<sup>79</sup> Manganese exposure may lead to parkinsonism, and experimental studies have reported Parkinson's Disease (PD) as a result of developmental exposures to the insecticide rotenone, the herbicides paraquat and maneb, and the solvent trichloroethylene.<sup>80</sup> Any environmental exposure that increases risk of neurodegenerative disorders in later life (Figure 1) requires urgent investigation as the world population continues to age.<sup>81</sup>

### **The expanding universe of neurotoxicants**

In our 2006 review,<sup>6</sup> we expressed concern that additional developmental neurotoxicants might lie undiscovered among the 201 chemicals then known to be neurotoxic to human adults, among the approximately 1000 chemicals known to be neurotoxic in animal species, and among the many thousands of industrial chemicals and pesticides that have never been tested for neurotoxicity. Exposure to neurotoxic chemicals is not rare, as almost half of the 201 known human neurotoxicants are considered high-production volume chemicals.

Our updated literature review shows that since 2006 the list of recognized human neurotoxicants has expanded by twelve chemicals from 202 (counting ethanol) to 214 (Table 1 and Appendix table 1), i.e. by about two substances per year. Many of these chemicals are widely used and disseminated extensively in the global environment. Of the newly identified neurodevelopmental toxicants, pesticides constitute the largest group, as was already the case in 2006.

In the same 7-year period, the number of known developmental neurotoxicants has doubled from 6 to 12 (Table 2). While the pace of scientific discovery of new neurodevelopmental hazards is more rapid today than in the past, it is still slower than the recognition of adult neurotoxicants.

The gap that exists between the number of substances known to be toxic to the adult brain and the smaller number known to be toxic to the much more vulnerable developing brain is not likely to close in the near-term future. This discrepancy reflects the fact that toxicity to the adult brain is usually discovered as a result of acute poisoning incidents, typically with a clear and immediate association between causative exposure and adverse effects, as happens in workplace exposures or suicide attempts. By contrast, the recognition of developmental neurotoxicity relies on two sets of evidence collected at two different points in time - exposure data (often obtained from the mother during pregnancy) and data on the child's postnatal neurobehavioural development (often obtained 5-10 years later). Because brain functions develop sequentially, the full impact of early neurotoxic damage may not become apparent until school age or beyond. The most reliable evidence of developmental neurotoxicity is obtained through prospective studies that include real-time recording of information on exposure in early life followed by serial clinical assessments of the child. Such research is inherently slow and is hampered by inherent difficulty of reliably assessing exposures to individual toxicants in complex mixtures.

## **Consequences of developmental neurotoxicity**

Developmental neurotoxicity causes brain damage that is too often untreatable and frequently permanent. The consequence is impaired central nervous system function that lasts a lifetime and may result in diminished intelligence, as expressed in terms of lost IQ points, or disruption in behaviour. A recent study compared the estimated total IQ losses from major paediatric causes and found that the magnitude of losses due to lead, pesticides and other neurotoxicants to be in the same range or even greater than the losses associated with medical events such as preterm birth, traumatic brain injury, brain tumours and congenital heart disease (Table 3).<sup>82</sup>

Loss of cognitive skills reduces children's scholarly and economic attainments and has substantial long-term economic impacts on societies.<sup>4</sup> Thus, each loss of one IQ point has been estimated to decrease average lifetime earnings capacity by about €12,000 or \$18,000, in 2008 currencies.<sup>83</sup> The most recent estimates from the US indicate that the annual costs of childhood lead poisoning are about US\$50 billion and that the annual costs of methylmercury toxicity are approximately US\$5 billion.<sup>84</sup> In the EU, methylmercury exposure is estimated to cause a loss of about 600,000 IQ points every year, corresponding to an annual economic loss of close to €10 billion. In France alone, lead exposure is associated with IQ losses that correspond to annual costs that may exceed €20 billion.<sup>85</sup> Given that IQ losses represent only one aspect of developmental neurotoxicity, the total costs must be even greater.

Evidence from worldwide sources indicates that average national average IQ scores are correlated with gross domestic product (GDP), a correlation that may be

causal in both directions.<sup>86</sup> Thus, poverty can cause low IQ, but the opposite is also true. Given the widespread exposures to lead, pesticides, and other neurotoxicants in developing countries, where chemical controls may be relatively ineffective compared to those in the more highly developed countries,<sup>87, 88</sup> developmental exposures to industrial chemicals may contribute significantly to the observed correlation between IQ and GDP. If this is true, it may take decades for developing countries to emerge from poverty. As pollution abatement may then be delayed, a vicious circle can result.

The antisocial behaviour, criminal behaviour, violence and substance abuse that appear to result from exposures in early life to some neurotoxic chemicals result in increased needs for special educational services, institutionalization and even incarceration. In the United States, the murder rate fell sharply 20 years after the removal of lead from gasoline,<sup>89</sup> a finding consistent with the notion that exposure to lead in early life is a powerful determinant of behaviour decades later. Although poorly quantified to date, such behavioural and social consequences of neurodevelopmental toxicity are potentially very costly.<sup>76</sup>

Prevention of developmental neurotoxicity caused by industrial chemicals is highly cost-effective. A study that quantified the gains resulting from the phase-out of lead additives from petrol reported that in the US alone, the introduction of lead-free petrol has generated an economic benefit of \$200 billion in each annual birth cohort since 1980,<sup>90</sup> an aggregate benefit in the past 30 years of over \$3 trillion. This success has subsequently been repeated in more than 150 countries resulting in vast additional savings. Every \$1 spent to reduce lead hazards is estimated to produce a benefit of \$17 to \$220, a cost-benefit ratio even better than that for

vaccines.<sup>4</sup> Further, the costs associated with late-life consequences of developmental neurotoxicity are enormous, and the benefits from prevention of degenerative brain disorders may be very substantial.

### **New methods to identify developmental neurotoxicants**

New toxicological methods now allow a rational strategy for identification of developmental neurotoxicants based on a multidisciplinary approach.<sup>91</sup> A new guideline has been approved as a standardised approach to identifying developmental neurotoxicants.<sup>92</sup> However, completion of such tests is expensive and requires the use of large numbers of laboratory animals, and reliance on mammals for chemicals testing purposes needs to be reduced.<sup>93</sup> US governmental agencies have established the National Center for Computational Toxicology (NCCT) and an initiative, known as the Tox 21 Program, to promote the evolution of toxicology from a predominantly observational science to a predominantly predictive science.<sup>94</sup>

*In vitro* methods have now reached a level of predictive validity that they can be applied to neurotoxicity testing.<sup>95</sup> Some of these tests are based on neural stem cells. Although these cell systems lack a blood-brain barrier and certain metabolising enzymes, these approaches are highly promising. As a further option, data on protein links and protein-protein interactions can now be used to explore potential neurotoxicity potentials *in silico*,<sup>96</sup> thus suggesting that existing computational tools may predict potential toxic effects.<sup>97</sup>

In summary, using the whole spectrum of approaches along with clinical and epidemiological evidence, when available, should allow for the integration of

information for use in at least a tentative risk assessment. Using these tools, we anticipate that the pace of scientific discovery in developmental neurotoxicology will accelerate further in the years ahead.

## **DISCUSSION**

The updated findings presented in this review confirm and extend our 2006 conclusions.<sup>6</sup> During the 7 years since our previous report, the number of industrial chemicals recognized to be developmental neurotoxicants has doubled. Exposures to these industrial chemicals in the environment contribute to the global pandemic of developmental neurotoxicity.

Two major obstacles impede efforts to control the global pandemic of developmental neurotoxicity. These barriers, which we noted in our previous review,<sup>6</sup> and which were recently highlighted by the US National Research Council<sup>98</sup> are: (1) Large gaps in testing chemicals for developmental neurotoxicity, which results in a paucity of systematic data to guide prevention; and (2) The very high level of proof required for regulation. Thus, very few chemicals have been regulated due to developmental neurotoxicity.

The presumption that new chemicals and technologies are safe until proven otherwise is a fundamental problem.<sup>98</sup> Classic examples of new chemicals that were introduced because they conveyed certain benefits, but later found to cause great harm include several neurotoxicants as well as asbestos, thalidomide, diethylstilboestrol, and the chlorofluorocarbons.<sup>99</sup> A recurrent theme in each of these instances was that commercial introduction and wide dissemination of the chemicals preceded any systematic effort to assess potential toxicity. Especially

absent were advance efforts to examine possible impacts on children's health or potential of exposures in early life to disrupt early development. Similar challenges have been confronted in other public health disasters such as those due to tobacco smoking, alcohol use, and refined foods. These problems have been recently termed industrial epidemics.<sup>100</sup>

To control the global pandemic of developmental neurotoxicity, we propose a coordinated international strategy (see Panel). Mandatory and transparent assessment of evidence for neurotoxicity is the foundation of this strategy. Assessment of toxicity must be followed by governmental regulation and market intervention. Voluntary controls appear to be of little value.<sup>11</sup>

The three pillars of our proposed strategy are (1) legally mandated testing of existing industrial chemicals and pesticides already in commerce, prioritizing those in the widest use, and incorporating new assessment technologies; (2) legally mandated premarket evaluation of new chemicals before they enter markets, using precautionary approaches for chemical testing that recognize the unique vulnerability of the developing brain; and (3) formation of a new clearinghouse for neurotoxicity as a parallel to the International Agency for Research on Cancer (IARC). This new agency will assess industrial chemicals for developmental neurotoxicity using a precautionary approach that emphasizes prevention and does not require absolute proof of toxicity. It will facilitate and coordinate epidemiological and toxicological studies, and it will lead the urgently needed global programmes for prevention.

These new approaches must reverse the dangerous presumption that new chemicals and technologies are safe until proven dangerous. These new approaches

must overcome the current requirement to produce absolute “proof” of toxicity before initiating action to protect children against neurotoxic substances. Precautionary interpretation of data on developmental neurotoxicity must take into account the very great individual and societal costs that result from failure to act on available documentation to prevent disease in children.<sup>101</sup> Academic research has often favoured scepticism and required extensive replication before acceptance of a hypothesis,<sup>101</sup> thereby adding to the inertia in toxicology and environmental health research and the resulting disregard of many other potential neurotoxicants.<sup>102</sup> In addition, the strength of evidence that is required to constitute “proof” must be analysed in a societal perspective, so that the implications of ignoring a developmental neurotoxicant and of failing to act on the basis of available data are also taken into account.

Finally, we emphasise that the total number of neurotoxic substances recognized today almost certainly represents an underestimate of the true number of developmental neurotoxicants that have been released into the global environment. Our very great concern is that children worldwide are exposed today to unrecognized toxic chemicals that are silently eroding intelligence, disrupting behaviours, truncating future achievements and damaging societies, perhaps most seriously in developing countries. A new paradigm of action is required.

### **Contributors**

Both authors undertook the literature review, wrote and revised the manuscript, and approved the final version.

### **Conflicts of interest**

PG has provided paid expert testimony on mercury toxicology for the U.S. Department of Justice. PJL has provided paid expert testimony in cases of childhood lead poisoning. The authors declare that they have no other conflicts of interest.

### **Acknowledgements**

This study was supported by the NIH, National Institute for Environmental Health Sciences (ES09584, ES09797 and ES11687). The funding source had no role in the literature review, interpretation of data, writing of this review, or in the decision to submit the manuscript for publication. The contents of this paper are solely the responsibility of the authors and do not represent the official views of the NIH. We wish to thank Professor Mary S. Wolff, PhD of the Icahn School of Medicine at Mount Sinai, New York, NY, USA and Linda S. Birnbaum, PhD, Director of the US National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA for their critical reading of the manuscript.

## References

1. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2009. *Vital Health Stat* 10. 2010; (247): 1-82.
2. Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environ Health Perspect*. 2012; **120**(7): a258-60.
3. Bellinger DC. Interpreting epidemiologic studies of developmental neurotoxicity: conceptual and analytic issues. *Neurotoxicology and teratology*. 2009; **31**(5): 267-74.
4. Gould E. Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control. *Environ Health Perspect*. 2009; **117**(7): 1162-7.
5. National Research Council. *Scientific frontiers in developmental toxicology and risk assessment*. Washington, DC: National Academy Press; 2000.
6. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*. 2006; **368**(9553): 2167-78.
7. Grandjean P. *Only one chance. How Environmental Pollution Impairs Brain Development – and How to Protect the Brains of the Next Generation*. New York: Oxford University Press; 2013.
8. Rice D, Barone S, Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect*. 2000; **108 Suppl 3**: 511-33.
9. Needleman HL. The removal of lead from gasoline: historical and personal reflections. *Environ Res*. 2000; **84**(1): 20-35.
10. Grandjean P, Satoh H, Murata K, Eto K. Adverse effects of methylmercury: environmental health research implications. *Environ Health Perspect*. 2010; **118**(8): 1137-45.
11. Landrigan PJ, Goldman LR. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Aff (Millwood)*. 2011; **30**(5): 842-50.
12. Weiss B. Food additives and environmental chemicals as sources of childhood behavior disorders. *Journal of the American Academy of Child Psychiatry*. 1982; **21**(2): 144-52.
13. Needham LL, Grandjean P, Heinzow B, Jorgensen PJ, Nielsen F, Patterson DG, Jr., et al. Partition of environmental chemicals between maternal and fetal blood and tissues. *Environ Sci Technol*. 2011; **45**(3): 1121-6.
14. Environmental Working Group. *Body burden - the pollution in newborns*. Washington, DC; 2005.
15. Zheng W, Aschner M, Ghersi-Egea JF. Brain barrier systems: a new frontier in metal neurotoxicological research. *Toxicol Appl Pharmacol*. 2003; **192**(1): 1-11.
16. Bose R, Onishchenko N, Edoff K, Janson Lang AM, Ceccatelli S. Inherited effects of low-dose exposure to methylmercury in neural stem cells. *Toxicological sciences : an official journal of the Society of Toxicology*. 2012; **130**(2): 383-90.
17. Costa LG. Current issues in organophosphate toxicology. *Clinica chimica acta; international journal of clinical chemistry*. 2006; **366**(1-2): 1-13.
18. Augusti-Tocco G, Biagioni S, Tata AM. Acetylcholine and regulation of gene expression in developing systems. *J Mol Neurosci*. 2006; **30**(1-2): 45-8.
19. Roth TL. Epigenetics of neurobiology and behavior during development and adulthood. *Developmental psychobiology*. 2012; **54**(6): 590-7.
20. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect*. 2005; **113**(7): 894-9.
21. Budtz-Jorgensen E, Bellinger D, Lanphear B, Grandjean P. An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children. *Risk Anal*. 2013; **33**(3): 450-61.
22. Grandjean P. Even low-dose lead exposure is hazardous. *Lancet*. 2010; **376**(9744): 855-6.

23. Mazumdar M, Bellinger DC, Gregas M, Abanilla K, Bacic J, Needleman HL. Low-level environmental lead exposure in childhood and adult intellectual function: A follow-up study. *Environmental health : a global access science source*. 2011; **10**: 24.
24. Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, et al. Decreased brain volume in adults with childhood lead exposure. *PLoS Med*. 2008; **5**(5): e112.
25. Zhang N, Baker HW, Tufts M, Raymond RE, Salihu H, Elliott MR. Early childhood lead exposure and academic achievement: evidence from Detroit public schools, 2008-2010. *Am J Public Health*. 2013; **103**(3): e72-7.
26. Fergusson DM, Boden JM, Horwood LJ. Dentine lead levels in childhood and criminal behaviour in late adolescence and early adulthood. *J Epidemiol Community Health*. 2008; **62**(12): 1045-50.
27. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, Lanphear BP, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med*. 2008; **5**(5): e101.
28. Oken E, Bellinger DC. Fish consumption, methylmercury and child neurodevelopment. *Curr Opin Pediatr*. 2008; **20**(2): 178-83.
29. Debes F, Budtz-Jorgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicology and teratology*. 2006; **28**(5): 536-47.
30. Julvez J, DS, G., Golding, J., Ring, S., St. Pourcain, B., Gonzalez, J.R., Grandjean, P. Genetic predisposition to cognitive deficit at age 8 years associated with prenatal methylmercury exposure *Epidemiology*. 2013; **24**(5): 643-50.
31. White RF, Palumbo CL, Yurgelun-Todd DA, Heaton KJ, Weihe P, Debes F, et al. Functional MRI approach to developmental methylmercury and polychlorinated biphenyl neurotoxicity. *Neurotoxicology*. 2011; **32**(6): 975-80.
32. Budtz-Jorgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environ Health Perspect*. 2007; **115**(3): 323-7.
33. Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. *Neurotoxicology*. 2008; **29**(5): 776-82.
34. Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, Kline J, et al. Water arsenic exposure and intellectual function in 6-year-old children in Araihaazar, Bangladesh. *Environ Health Perspect*. 2007; **115**(2): 285-9.
35. Hamadani JD, Tofail F, Nermell B, Gardner R, Shiraji S, Bottai M, et al. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. *Int J Epidemiol*. 2011; **40**(6): 1593-604.
36. Tanaka H, Tsukuma H, Oshima A. Long-Term Prospective Study of 6104 Survivors of Arsenic Poisoning During Infancy Due to Contaminated Milk Powder in 1955. *J Epidemiol*. 2010.
37. Engel SM, Wolff MS. Causal inference considerations for endocrine disruptor research in children's health. *Annual review of public health*. 2013; **34**: 139-58.
38. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychology review*. 2011; **21**(2): 81-101.
39. Khan K, Wasserman GA, Liu X, Ahmed E, Parvez F, Slavkovich V, et al. Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology*. 2012; **33**(1): 91-7.
40. Bouchard M, Laforest F, Vandeland L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. *Environ Health Perspect*. 2007; **115**(1): 122-7.

41. Riojas-Rodriguez H, Solis-Vivanco R, Schilman A, Montes S, Rodriguez S, Rios C, et al. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. *Environ Health Perspect*. 2010; **118**(10): 1465-70.
42. Lucchini RG, Guazzetti S, Zoni S, Donna F, Peter S, Zacco A, et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. *Neurotoxicology*. 2012; **33**(4): 687-96.
43. Moreno JA, Yeomans EC, Streifel KM, Brattin BL, Taylor RJ, Tjalkens RB. Age-dependent susceptibility to manganese-induced neurological dysfunction. *Toxicological sciences : an official journal of the Society of Toxicology*. 2009; **112**(2): 394-404.
44. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect*. 2012; **120**(10): 1362-8.
45. Julvez J, Grandjean P. Neurodevelopmental toxicity risks due to occupational exposure to industrial chemicals during pregnancy. *Industrial health*. 2009; **47**(5): 459-68.
46. Pele F, Muckle G, Costet N, Garlantezec R, Monfort C, Multigner L, et al. Occupational solvent exposure during pregnancy and child behaviour at age 2. *Occup Environ Med*. 2013; **70**(2): 114-9.
47. Janulewicz PA, White RF, Martin BM, Winter MR, Weinberg JM, Vieira V, et al. Adult neuropsychological performance following prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water. *Neurotoxicology and teratology*. 2012; **34**(3): 350-9.
48. Kofman O, Berger A, Massarwa A, Friedman A, Jaffar AA. Motor inhibition and learning impairments in school-aged children following exposure to organophosphate pesticides in infancy. *Pediatr Res*. 2006; **60**(1): 88-92.
49. London L, Beseler C, Bouchard MF, Bellinger DC, Colosio C, Grandjean P, et al. Neurobehavioral and neurodevelopmental effects of pesticide exposures. *Neurotoxicology*. 2012; **33**(4): 887-96.
50. Torres-Sanchez L, Schnaas L, Rothenberg SJ, Cebrian ME, Osorio-Valencia E, Hernandez Mdel C, et al. Prenatal p,p -DDE Exposure and Neurodevelopment among Children 3.5-5 Years of Age. *Environ Health Perspect*. 2013; **121**(2): 263-8.
51. Boucher O, Simard MN, Muckle G, Rouget F, Kadhel P, Bataille H, et al. Exposure to an organochlorine pesticide (chlordecone) and development of 18-month-old infants. *Neurotoxicology*. 2013; **35C**: 162-8.
52. Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, et al. 7-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide. *Environ Health Perspect*. 2011; **119**(8): 1196-201.
53. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, et al. Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year Old Children. *Environ Health Perspect*. 2011; **119**(8): 1189-95.
54. Engel SM, Wetmur J, Chen J, Zhu C, Barr DB, Canfield RL, et al. Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood. *Environ Health Perspect*. 2011; **119**(8): 1182-8.
55. Rauh VA, Perera FP, Horton MK, Whyatt RM, Bansal R, Hao X, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; **109**(20): 7871-6.
56. Bjorling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environmental health : a global access science source*. 2008; **7**: 50.
57. Ostrea EM, Jr., Reyes A, Villanueva-Uy E, Pacifico R, Benitez B, Ramos E, et al. Fetal exposure to propoxur and abnormal child neurodevelopment at 2 years of age. *Neurotoxicology*. 2012; **33**(4): 669-75.

58. Horton MK, Rundle A, Camann DE, Boyd Barr D, Rauh VA, Whyatt RM. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. *Pediatrics*. 2011; **127**(3): e699-706.
59. Dingemans MM, van den Berg M, Westerink RH. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environ Health Perspect*. 2011; **119**(7): 900-7.
60. Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environ Health Perspect*. 2009; **117**(12): 1953-8.
61. Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al. Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect*. 2010; **118**(5): 712-9.
62. Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, et al. In Utero and Childhood Polybrominated Diphenyl Ether (PBDE) Exposures and Neurodevelopment in the CHAMACOS Study. *Environ Health Perspect*. 2013; **121**(2): 257-62.
63. Grandjean P, Budtz-Jorgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. *Pure Appl Chem*. 2010; **82**(2): 383-91.
64. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine reviews*. 2012; **33**(3): 378-455.
65. Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect*. 2010; **118**(4): 565-71.
66. Swan SH, Liu F, Hines M, Kruse RL, Wang C, Redmon JB, et al. Prenatal phthalate exposure and reduced masculine play in boys. *International journal of andrology*. 2010; **33**(2): 259-69.
67. Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics*. 2011; **128**(5): 873-82.
68. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics*. 2009; **124**(2): e195-202.
69. Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. *Brain Cogn*. 2008; **68**(2): 117-27.
70. Dix-Cooper L, Eskenazi B, Romero C, Balmes J, Smith KR. Neurodevelopmental performance among school age children in rural Guatemala is associated with prenatal and postnatal exposure to carbon monoxide, a marker for exposure to woodsmoke. *Neurotoxicology*. 2012; **33**(2): 246-54.
71. Vrijheid M, Martinez D, Aguilera I, Bustamante M, Ballester F, Estarlich M, et al. Indoor air pollution from gas cooking and infant neurodevelopment. *Epidemiology*. 2012; **23**(1): 23-32.
72. Hernandez-Martinez C, Arijia Val V, Escribano Subias J, Canals Sans J. A longitudinal study on the effects of maternal smoking and secondhand smoke exposure during pregnancy on neonatal neurobehavior. *Early Hum Dev*. 2012; **88**(6): 403-8.
73. Mariussen E. Neurotoxic effects of perfluoroalkylated compounds: mechanisms of action and environmental relevance. *Archives of toxicology*. 2012; **86**(9): 1349-67.
74. Gump BB, Wu Q, Dumas AK, Kannan K. Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. *Environ Sci Technol*. 2011; **45**(19): 8151-9.
75. Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC. Update on environmental risk factors for attention-deficit/hyperactivity disorder. *Current psychiatry reports*. 2011; **13**(5): 333-44.
76. Carpenter DO, Nevin R. Environmental causes of violence. *Physiology & behavior*. 2010; **99**(2): 260-8.

77. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. Endocrine disruptors and childhood social impairment. *Neurotoxicology*. 2011; **32**(2): 261-7.
78. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry*. 2013; **70**(1): 71-7.
79. Bandeen-Roche K, Glass TA, Bolla KI, Todd AC, Schwartz BS. Cumulative lead dose and cognitive function in older adults. *Epidemiology*. 2009; **20**(6): 831-9.
80. Lock EA, Zhang J, Checkoway H. Solvents and Parkinson disease: a systematic review of toxicological and epidemiological evidence. *Toxicol Appl Pharmacol*. 2013; **266**(3): 345-55.
81. Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. Early environmental origins of neurodegenerative disease in later life. *Environ Health Perspect*. 2005; **113**(9): 1230-3.
82. Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect*. 2012; **120**(4): 501-7.
83. Bellanger M, Pichery C, Aerts D, Berglund M, Castano A, Cejchanova M, et al. Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention. *Environmental health : a global access science source*. 2013; **12**(1): 3.
84. Trasande L, Liu Y. Reducing the staggering costs of environmental disease in children, estimated at \$76.6 billion in 2008. *Health Aff (Millwood)*. 2011; **30**(5): 863-70.
85. Pichery C, Bellanger M, Zmirou-Navier D, Glorennec P, Hartemann P, Grandjean P. Childhood lead exposure in France: benefit estimation and partial cost-benefit analysis of lead hazard control. *Environmental health : a global access science source*. 2011; **10**: 44.
86. Lynn R, Vanhanen T. *IQ and the wealth of nations*. Westport, CT: Praeger; 2002.
87. Blacksmith Institute. *The world's worst pollution problems: Assessing health risks at hazardous waste sites*. New York: Blacksmith Institute; 2012.
88. Trasande L, Massey RI, DiGangi J, Geiser K, Olanipekun AI, Gallagher L. How developing nations can protect children from hazardous chemical exposures while sustaining economic growth. *Health Aff (Millwood)*. 2011; **30**(12): 2400-9.
89. Nevin R. Understanding international crime trends: the legacy of preschool lead exposure. *Environ Res*. 2007; **104**(3): 315-36.
90. Schwartz J. Societal benefits of reducing lead exposure. *Environ Res*. 1994; **66**(1): 105-24.
91. National Research Council. *Toxicity Testing in the 21st Century: A Vision and a Strategy*. Washington, DC: National Academy Press; 2007.
92. Makris SL, Raffaele K, Allen S, Bowers WJ, Hass U, Alleva E, et al. A retrospective performance assessment of the developmental neurotoxicity study in support of OECD test guideline 426. *Environ Health Perspect*. 2009; **117**(1): 17-25.
93. Rovida C, Longo F, Rabbit RR. How are reproductive toxicity and developmental toxicity addressed in REACH dossiers? *Altex*. 2011; **28**(4): 273-94.
94. Collins FS, Gray GM, Bucher JR. *Toxicology. Transforming environmental health protection*. Science. 2008; **319**(5865): 906-7.
95. Crofton KM, Mundy WR, Lein PJ, Bal-Price A, Coecke S, Seiler AE, et al. Developmental neurotoxicity testing: recommendations for developing alternative methods for the screening and prioritization of chemicals. *Altex*. 2011; **28**(1): 9-15.
96. Audouze K, Grandjean P. Application of computational systems biology to explore environmental toxicity hazards. *Environ Health Perspect*. 2011; **119**(12): 1754-9.
97. Willighagen EL, Jeliakova N, Hardy B, Grafstrom RC, Spjuth O. Computational toxicology using the OpenTox application programming interface and Bioclipse. *BMC Res Notes*. 2011; **4**: 487.
98. National Research Council. *Science and decisions: advancing risk assessment*. Washington, D.C.: National Academy Press; 2009.

99. Late Lessons from Early Warnings: Science, Precaution, Innovation. Copenhagen: European Environment Agency; 2013.
100. Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, Thamarangsi T, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. 2013; **381**(9867): 670-9.
101. Grandjean P. Seven deadly sins of environmental epidemiology and the virtues of precaution. *Epidemiology*. 2008; **19**(1): 158-62.
102. Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: A bibliometric analysis of chemical substances in journal articles. *Environmental health : a global access science source*. 2011; **10**(96): 96.
103. Lauterbach M, Solak E, Kaes J, Wiechelt J, Von Mach MA, Weilemann LS. Epidemiology of hydrogen phosphide exposures in humans reported to the poison center in Mainz, Germany, 1983-2003. *Clin Toxicol (Phila)*. 2005; **43**(6): 575-81.
104. Demarest C, Torgovnick J, Sethi NK, Arsura E, Sethi PK. Acute reversible neurotoxicity associated with inhalation of ethyl chloride: a case report. *Clinical neurology and neurosurgery*. 2011; **113**(10): 909-10.
105. Imamura T, Yanagawa Y, Nishikawa K, Matsumoto N, Sakamoto T. Two cases of acute poisoning with acetamiprid in humans. *Clin Toxicol (Phila)*. 2010; **48**(8): 851-3.
106. Veale DJ, Wium CA, Muller GJ. Amitraz poisoning in South Africa: a two year survey (2008-2009). *Clin Toxicol (Phila)*. 2011; **49**(1): 40-4.
107. Sung YF, Huang CT, Fan CK, Lin CH, Lin SP. Avermectin intoxication with coma, myoclonus, and polyneuropathy. *Clin Toxicol (Phila)*. 2009; **47**(7): 686-8.
108. Yang CC. Acute human toxicity of macrocyclic lactones. *Current pharmaceutical biotechnology*. 2012; **13**(6): 999-1003.
109. Lee SJ, Mulay P, Diebolt-Brown B, Lackovic MJ, Mehler LN, Beckman J, et al. Acute illnesses associated with exposure to fipronil--surveillance data from 11 states in the United States, 2001-2007. *Clin Toxicol (Phila)*. 2010; **48**(7): 737-44.
110. Malhotra RC, Ghia DK, Cordato DJ, Beran RG. Glyphosate-surfactant herbicide-induced reversible encephalopathy. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2010; **17**(11): 1472-3.
111. David D, Prabhakar A, Peter JV, Pichamuthu K. Human poisoning with hexastar: a hexaconazole-containing agrochemical fungicide. *Clin Toxicol (Phila)*. 2008; **46**(7): 692-3.
112. Shadnia S, Moghaddam HH. Fatal intoxication with imidacloprid insecticide. *The American journal of emergency medicine*. 2008; **26**(5): 634 e1-4.
113. Deng X, Li G, Mei R, Sun S. Long term effects of tetramine poisoning: an observational study. *Clin Toxicol (Phila)*. 2012; **50**(3): 172-5.
114. Khalil M, Abudiab M, Ahmed AE. Clinical evaluation of 1,3-butadiene neurotoxicity in humans. *Toxicology and industrial health*. 2007; **23**(3): 141-6.
115. Grandjean P, Pichery C, Bellanger M, Budtz-Jorgensen E. Calculation of mercury's effects on neurodevelopment. *Environ Health Perspect*. 2012; **120**(12): A452; author reply A.

Chemical group	Number known		Identified since 2006
	2006	2013	
Metals/inorganic compounds	25	26	Hydrogen phosphide <sup>103</sup>
Organic solvents	40*	41	Ethyl chloride <sup>104</sup>
Pesticides	91	100	Acetamiprid <sup>105</sup>
			Amitraz <sup>106</sup>
			Avermectin <sup>107</sup>
			Emamectin <sup>108</sup>
			Fipronil (Termidor) <sup>109</sup>
			Glyphosate <sup>110</sup>
			Hexaconazole <sup>111</sup>
Imidacloprid <sup>112</sup>			
			Tetramethylenedisulfotetramine <sup>113</sup>
Other organic compounds	46	47	1,3-Butadiene <sup>114</sup>
Total	202*	214	(12 new substances)

\*Including ethanol

**Table 1: Industrial chemicals known to be toxic to the nervous system in 2006 and 2013**

Chemical group	Known in 2006	Newly identified
Metals/inorganic compounds	Arsenic/arsenic compounds	Fluoride
	Lead	Manganese
	Methyl mercury	
Organic solvents	(Ethanol)	Tetrachloroethylene
	Toluene	
Pesticides		Chlorpyrifos
		DDT/DDE
Other organic compounds	Polychlorinated biphenyls	Brominated diphenyl ethers
	(PCBs)	
Total	6*	6

\*Including ethanol

**Table 2. Industrial chemicals known to cause developmental neurotoxicity in humans in 2006 and 2013**

<b>Risk factor</b>	<b>Number of IQ points lost</b>
<b>Major medical and neurodevelopmental conditions</b>	
Preterm birth	34,031,025
ASDs	7,109,899
Paediatric bipolar disorder	8,164,080
ADHD	16,799,400
Postnatal traumatic brain injury	5,827,300
<b>Environmental chemical exposures</b>	
Lead	22,947,450
Methylmercury	1,590,000*
Organophosphate pesticides	16,899,488
Other neurotoxicants	???

\*From Grandjean et al.<sup>115</sup>

**Table 3: Total losses of IQ points in US children 0-5 years of age associated with major risk factors, including developmental exposure to industrial chemicals that cause neurotoxicity (adapted from Bellinger<sup>82</sup>)**

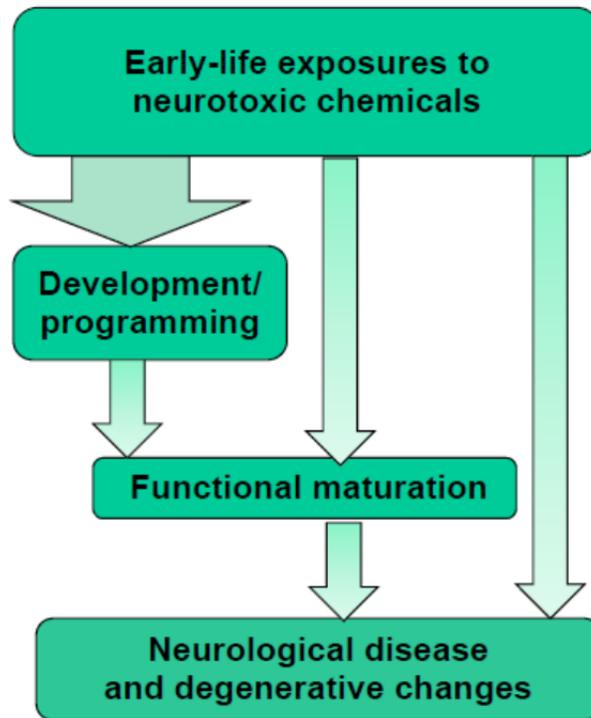
## **Panel: Recommendations for an international clearinghouse on neurotoxicity**

The main purpose of this body would be to promote optimal brain health, not merely avoidance of neurological disease, by inspiring, facilitating, and coordinating research and public policies that aim at protecting brain development during the most sensitive life stages. The main efforts would aim at:

- Screening industrial chemicals present in human exposures for neurotoxic effects so that hazardous substances can be identified for tighter control;
- Stimulating and coordinating new research to understand how toxic chemicals interfere with brain development and how best to prevent long-term dysfunctions and deficits;
- Functioning as a clearinghouse for research data and strategies by collecting and evaluating documentation on brain toxicity and stimulating international collaboration on research and prevention; and
- Promoting policy development aiming at protecting vulnerable populations against brain toxic chemicals without requiring unrealistic levels of scientific proof.

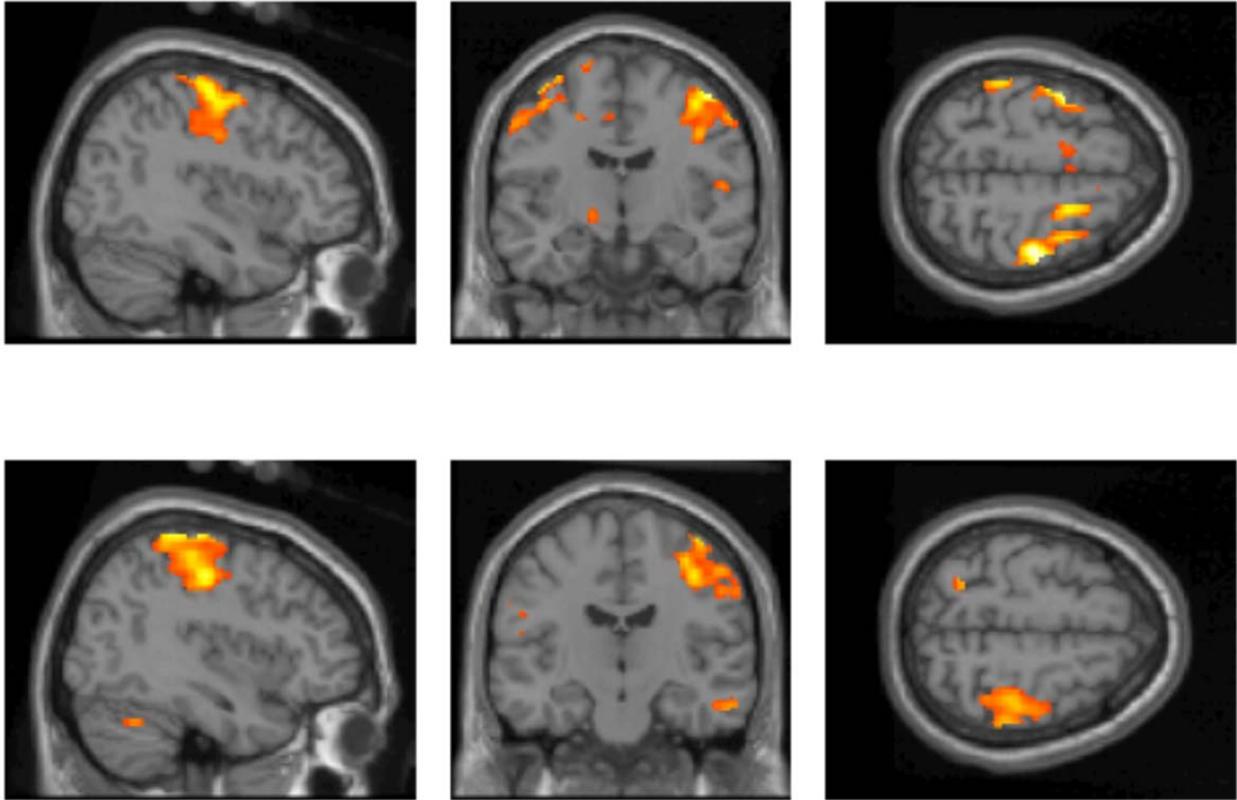
### **Search strategy and selection criteria**

We identified literature published since 2006 on neurotoxic effects of industrial chemicals in humans and by using the search terms "Neurotoxicity Syndromes"[MeSH], "neurotoxic", "neurologic", or "neuro\*" combined with "exposure" and "poisoning" in PubMed. For developmental neurotoxicity, the search terms were "Prenatal Exposure Delayed Effects"[MeSH], "maternal exposure" or "maternal fetal exchange" , "developmental disabilities/chemically induced" and "neurotoxins", all of them with the limiters "All Child: 0-18 years, Human". We also used references cited in the publications retrieved.



**Figure 1: Impact of neurotoxicants during early brain development.**

Exposures in early life to neurotoxic chemicals can produce a wide range of adverse effects on brain development and maturation that can become manifest as functional impairments or disease at any point in the human lifespan from early infancy to extreme old age.



**Figure 2: Functional magnetic resonance scans reveal abnormal activation**

Average activation during finger tapping with the left hand in three adolescents with increased prenatal methylmercury exposure (upper) and three control adolescents (lower). The latter group activates the motor cortex on the right, while exposed subjects activate this area on both sides of the brain.<sup>31</sup>

## Supplementary webappendix

Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity

**Appendix table 1.** Chemicals known to be human neurotoxicants

CAS number	Compound
<i>Metals and inorganic compounds</i>	
7429905	Aluminum
7440382	Arsenic and arsenic compounds
14343692	Azides
7440393	Barium compounds
7440699	Bismuth compounds
630080	Carbon monoxide
57125	Cyanides
17702419	Decaborane
19287457	Diborane
627441	Ethylmercury
16984488	Fluorides
7783064	Hydrogen phosphide
78002	Hydrogen sulfide
7439932	Lead and lead compounds
7439965	Lithium compounds
7439976	Manganese and manganese compounds
22967926	Mercury and mercuric compounds
13463393	Methylmercury
19624227	Nickel carbonyl
7803512	Pentaborane
7723140	Phosphine
7782492	Phosphorus
13494809	Selenium compounds
7440280	Tellurium compounds
7440315	Thallium compounds
7429905	Tin compounds
<i>Organic solvents</i>	
67641	Acetone
71432	Benzene
100516	Benzyl alcohol
106945	1-Bromopropane
75150	Carbon disulfide
67663	Chloroform
110827	Cyclohexane
108930	Cyclohexanol
108941	Cyclohexanone
106934	1,2-Dibromoethane
79436	Dichloroacetic acid

---

75092	Dichloromethane
111466	Diethylene glycol
68122	N,N-Dimethylformamide
64175	Ethanol (Alcohol)
141786	Ethyl acetate
107211	Ethyl chloride
110805	Ethylene glycol
109864	Ethylene glycol ethyl ether (Ethoxyethanol)
111466	Ethylene glycol methyl ether (Methoxyethanol or Methyl cellosolve)
110543	n-Hexane
78591	Isophorone
67630	Isopropyl alcohol
67561	Methanol (Methyl alcohol)
591786	Methyl-n-butyl ketone (2-Hexanone)
96377	Methylcyclopentane
78933	Methyl ethyl ketone
108101	Methyl isobutyl ketone
78820	2-Methylpropanenitrile
98953	Nitrobenzene
79469	2-Nitropropane
71410	1-Pentanol
110861	Pyridine
100425	Styrene
79345	1,1,2,2-Tetrachloroethane
127184	Tetrachloroethylene (Perchloroethylene)
108883	Toluene
71556	1,1,1-Trichloroethane (Methylchloroform)
79016	Trichloroethylene
1330207	Xylenes

---

*Other organic substances*

---

75865	Acetone cyanohydrin (2-Hydroxy-2-methylpropanenitrile)
79061	Acrylamide (2-Propenamide)
107131	Acrylonitrile
107051	Allyl chloride (1-Chloro-2-propene)
62533	Aniline
106503	1,4-Benzenediamine (4-Aminoaniline)
91156	1,2-Benzenedicarbonitrile (1,2-Dicyanobenzene)
100470	Benzonitrile
106990	1,3-Butadiene
220352352	Butylated triphenyl phosphate
105602	Caprolactam (Azepan-2-one)
126998	Chloroprene
98828	Cumene
121824	Cyclonite (RDX)
4074888	Diethylene glycol diacrylate
84742	Di-N-butyl phthalate
77781	Dimethyl sulfate
30260663	Dimethylhydrazine

---

1738256	3-(Dimethylamino)-propanenitrile
25154545	Dinitrobenzene
25321146	Dinitrotoluene
538078	Ethylbis(2-chloroethyl)amine
74851	Ethylene
75218	Ethylene oxide
640197	Fluoroacetamide
144490	Fluoroacetate
70304	Hexachlorophene
302012	Hydrazine
123319	Hydroquinone
74873	Methyl chloride (Chloromethane)
107313	Methyl formate
74884	Methyl iodide
80626	Methyl methacrylate
100016	4-Nitroaniline
108952	Phenol
100630	Phenylhydrazine
67774327	Polybrominated biphenyls (PBBs)
63936561	Polybrominated diphenyl ethers (PBDEs)
1336363	Polychlorinated biphenyls (PCBs)
75569	1,2-Propylene oxide
1746016	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
126738	Tributyl phosphate
78308	Tri-o-cresylphosphate
512561	Trimethyl phosphate
115866	Triphenyl phosphate
555771	Tris(2-chloroethyl)amine (Trichlormethine)
75014	Vinyl chloride (Chloroethene)
<hr/> <i>Pesticides</i> <hr/>	
135410207	Acetamiprid
116063	Aldicarb (Temik)
309002	Aldrin
33089611	Amitraz
65195553	Avermectin
741582	Bensulide
2104963	Bromophos (Brofene)
63252	Carbaryl (Sevin)
1563662	Carbofuran (Furadan)
786196	Carbophenothion (Trithion)
15879933	$\alpha$ -Chloralose
12789036	Chlordane
470906	Chlorfenvinphos
24934916	Chlormephos
500287	Chlorothion
2921882	Chlorpyrifos (Dursban, Lorsban)
56724	Coumaphos
68085858	Cyhalothrin (Karate)

---

947024	Cyolane (Phospholan)
52315078	Cypermethrin
52918635	Deltamethrin (Decamethrin)
919868	Demeton-S-methyl
10311849	Dialifor
333415	Diazinon
97176	Dichlofenthion
96128	1,2-Dibromo-3-chloropropane (DBCP)
50293	Dichlorodiphenyltrichloroethane (DDT)
94757	2,4-Dichlorophenoxyacetic acid (2,4-D)
542756	1,3-Dichloropropene
62737	Dichlorvos (DDVP, Vapona)
60571	Dieldrin
115264	Dimefox
60515	Dimethoate
534521	4,6-Dinitro-o-cresol
88857	Dinoseb
78342	Dioxathion
298044	Disulfoton
17109498	Edifenphos
119791412	Emamectin
115297	Endosulfan (Thiodan)
2778043	Endothion
72208	Endrin
29973135	Ethiofencarb (Croneton)
563122	Ethion
13194484	Ethoprop
2104645	O-Ethyl O-(4-nitrophenyl) phenylphosphonothioate (EPN)
122145	Fenitrothion
115902	Fensulfothion
55389	Fenthion
51630581	Fenvalerate
120068373	Fipronil (Termidor)
944229	Fonofos
2540821	Formothion
1071836	Glyphosate
76448	Heptachlor
23560590	Heptenophos
118741	Hexachlorobenzene
79983714	Hexaconazole
138261413	Imidacloprid
297789	Isobenzan
119380	Isolan
18854018	Isoxathion
143500	Kepone (Chlordecone)
21609905	Leptophos
58899	Lindane ( $\gamma$ -Hexachlorocyclohexane)
150505	Merphos

---

---

108623	Metaldehyde
10265926	Methamidophos
950378	Methidathion (Suprathion)
16752775	Methomyl
74839	Methyl bromide
298000	Methyl parathion (Parathion-methyl)
7786347	Mevinphos
315184	Mexacarbate (Zectran)
371868	Mipafox
2385855	Mirex
6923224	Monocrotophos
300765	Naled
54115	Nicotine
301122	Oxydemeton-methyl
56382	Parathion
87865	Pentachlorophenol
298022	Phorate
13171216	Phosphamidon (Dimecron)
7292162	Propaphos
114261	Propoxur (Baygon)
53558251	Pyriminil (Pyrinuron, Vacor)
107448	Sarin
152169	Schradan
96640	Soman
35400432	Sulprofos
8065483	Systox (Demeton)
96182535	Tebupirimfos
79538322	Tefluthrin
13071799	Terbufos
80126	Tetramethylenedisulfotetramine (Tetramine)
137268	Thiram
8001352	Toxaphene
93765	2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)
52686	Trichlorfon
327980	Trichloronate

---