



## Neurobehavioural effects of developmental toxicity

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Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, we did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants—manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. We postulate that even more neurotoxicants remain undiscovered. To control the pandemic of developmental neurotoxicity, we propose a global prevention strategy. Untested chemicals should not be presumed to be safe to brain development, and chemicals in existing 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 and attention-deficit hyperactivity disorder seem to be increasing worldwide.<sup>2</sup> Subclinical decrements in brain function are even more common than these neurobehavioural developmental disorders. All these disabilities can have severe consequences<sup>3</sup>—they diminish quality of life, reduce academic achievement, and disturb behaviour, with profound consequences for the welfare and productivity of entire societies.<sup>4</sup>

The root causes of the present global pandemic of neurodevelopmental disorders are only partly understood. Although genetic factors have a role,<sup>5</sup> they cannot explain recent increases in reported prevalence, and none of the genes discovered so far seem to be responsible for more than a small proportion of cases.<sup>6</sup> Overall, genetic factors seem 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 probably by interacting with genetically inherited predispositions.

Strong evidence exists that industrial chemicals widely disseminated in the environment are important contributors to what we have called the global, silent pandemic of neurodevelopmental toxicity.<sup>7,8</sup> The developing human brain is uniquely vulnerable to toxic chemical exposures, and major windows of developmental vulnerability occur in utero and during infancy and early childhood.<sup>9</sup> During these sensitive life stages, chemicals can cause permanent brain injury at low levels of exposure that would have little or no adverse effect in an adult.

In 2006, we did a systematic review of the published clinical and epidemiological studies into the neurotoxicity of industrial chemicals, with a focus on developmental neurotoxicity.<sup>7</sup> We identified five industrial chemicals that could be reliably classified as developmental neurotoxicants: lead, methylmercury, arsenic, polychlorinated biphenyls, and toluene. We also noted 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. Additionally, more than 1000 chemicals have been reported to be neurotoxic in animals in laboratory studies.

We noted that recognition of the risks of industrial chemicals to brain development has historically needed decades of research and scrutiny, as shown in the cases of lead and methylmercury.<sup>10–12</sup> In most cases, discovery began with clinical diagnosis of poisoning in workers and episodes of high-dose exposure. More sophisticated epidemiological studies typically began only much later. Results from such studies documented developmental neurotoxicity at much lower exposure levels than had previously been thought to be safe. Thus, recognition of widespread subclinical toxicity often did not occur until decades after the initial evidence of neurotoxicity. A recurring theme was that early warnings of subclinical neurotoxicity were often ignored or even dismissed.<sup>13</sup> David P Rall, former Director of the US National Institute of Environmental Health Sciences, once noted that “if thalidomide had caused a ten-point loss of intelligence quotient (IQ) instead of obvious birth defects of the limbs, it would probably still be on the market”.<sup>14</sup> Many industrial chemicals marketed at present probably cause IQ deficits of far fewer than ten points and have therefore eluded detection so far, but their combined effects could have enormous consequences.

In our 2006 review,<sup>7</sup> we expressed concern that additional developmental neurotoxicants might lurk undiscovered among the 201 chemicals then known to be neurotoxic to adult human beings and among the many thousands of pesticides, solvents, and other industrial chemicals in widespread use that had never been tested for neurodevelopmental toxicity. Since our previous review, new data have emerged about the vulnerability of the developing brain and the neurotoxicity of industrial chemicals. Particularly important new evidence derives from prospective epidemiological birth cohort studies.

In this Review, we consider recent information about the developmental neurotoxicity of industrial chemicals

# Neurobehavioural Effects Of Developmental Toxicity

**Michael Brown**



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