Adverse effects of pollution on mental health: the stress hypothesis

D Lanoix¹, P Plusquellec¹,²*  

glucocorticoids, has been overlooked. Glucocorticoids are able to cross the blood–brain barrier and reach the central structure involved in cognitive functions and emotional/behavioural regulation. Furthermore, studies have revealed that environmental contaminants significantly influence the stress system across a variety of wildlife animals, laboratory animals and recently in humans.  

Introduction  
Environmental contaminants act at very low levels of exposure that are not reflected by high doses. Therefore, public regulation agencies are consistently reducing acceptable blood levels of exposure. For example, clinical management plans for children and elders at risk of toxicity are thus adapted to reflect the novel blood lead action level. Environmental contaminants acting at such low doses were found to be endocrine-disrupting chemicals, and most studies have thus focused on the sexual steroids system. However, the stress system, which produces glucocorticoids, has been overlooked.

Discussion  
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Abstract

Introduction  
Environmental contaminants are ubiquitous. Among the most studied environmental contaminants, lead, mercury, polychlorinated biphenyls and pesticides have been found to impact mental health. In particular, exposure to environmental contaminants has been related to executive functions and emotional/behavioural maladjustment in children, and cognitive variability in elders. We hypothesise that the association between environmental contaminants and mental health, particularly in children and elders, could be explained by a disruption of the stress system.

Discussion  
The hypothesis of the stress system, linking environmental contaminant exposure to adverse mental health effects, needs to be addressed in future research. In addition, in cases of environmental contaminants toxicity, clinicians could recommend the testing of the hypothalamic–pituitary–adrenal axis functioning in order to prevent children and/or the elderly to develop impairments due to its alteration.

Introduction  
Adverse effects of pollution on mental health: the stress hypothesis. This paper discusses the adverse effects of ECs on mental health. This paper discusses the adverse effects of pollution on mental health.
insults^1. Moreover, because some contaminants have been recently banned or restricted, the elderly have been exposed to more contaminants than younger generations.

**Toxic metals**

The best known threats to human health from toxic metals are associated with lead and mercury. These toxic metals have been used in many different areas for thousands of years. Lead is one of the oldest known poisons. It has been used for at least 5000 years, in pipes for transporting water and in pigments for glazing ceramic. In ancient Rome, lead acetate was used to sweeten wine. Therefore, Romans might have ingested as much as a gram of lead per day, leading to the theory that lead poisoning might have contributed to the decline of the Roman Empire. Mercury was also used in the Roman Empire to sore teething pain in infants. More recently (from the 14th to the 18th century), mercury was employed as a cure for syphilis, leading to the myth that Wolfgang Amadeus Mozart died from mercury poisoning in an attempt to cure syphilis. Although adverse health effects of toxic metals have been known for a long time, and their use has been restricted, exposure to toxic metals continues and is even increasing in some areas of the world (see Table 1 for common sources of exposure). For example, mercury is still used in gold mining in Africa and Latin America. In addition, even though lead has been banned as a gasoline additive for on-road vehicles in developed countries, it remains a common additive to gasoline for off-road use, including aircraft, racing cars, farm equipment and marine engines.

**Lead**

Most lead in the environment comes from anthropogenic sources. Humans are, therefore, mainly exposed to lead from air, water and food. Inorganic lead accumulates in the skeleton and is slowly released from this body compartment. Half-life of lead in the skeleton is about 25–30 years. In blood, lead is both free and bound to proteins and sulphhydryl compounds, in the latter case, preventing it to cross the blood–brain barrier. However, the portion of blood-circulating lead that is free of ligand rapidly crosses the blood–brain barrier. The ability of lead to pass through this barrier is due to its ability to substitute for calcium ions. Indeed, lead is directly transported to the brain via the Ca-ATPase pumps. In foetus and infants, the developing blood–brain barrier is more permeable, allowing both free and bound lead to reach the brain. Elders are also more vulnerable to lead exposure because of age-related bone demineralisation, releasing the accumulated lead into the blood.

**Mercury**

Mercury contamination occurs both from anthropogenic and natural sources. Most of the mercury found in the environment is in its inorganic form. However, mercury naturally found in soil, and deposited in soil or water from anthropogenic sources, is transformed into methylmercury through biomethylation. This organic form of mercury is highly toxic. Methylmercury is accumulated in the liver and kidney of animals, and biomagnified through the food chain.

The main source of methylmercury for human beings is found in food, particularly fish and marine mammals. Methylmercury is known to cross the placental and blood–brain barriers, accumulating in the foetus and the brain.

**Persistent organic pollutants**

POPs are organic compounds that are highly resistant to chemical, photolytic or biological degradation. These chemicals have very low water solubility and high lipid solubility. POPs are mostly halogenated, especially with chlorine molecules. The single or multiple halogen elements, such as fluorine, chlorine, bromine or iodine, bound to their structure are responsible for POPs stability to degradation and high lipid solubility (Figure 1). Therefore, POPs are persistent in the environment. They bioaccumulate in human and animal fat tissues, biomagnifies in the food chain and can significantly alter the human health. POPs high lipid solubility enables them to pass through any biological barrier, such as the placental and blood–brain barriers. Virtually, all humans are thought to store POPs in fat tissues. POPs originate almost entirely from anthropogenic sources associated with the manufacture, use and disposal of organic chemicals (see Table 1 for common sources of exposure). POPs were massively produced and used from the 1930s to 1980s. While some POPs have been banned or restricted, others remain.

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**Table 1** Common environmental contaminants and their sources of exposure

<table>
<thead>
<tr>
<th>Environmental toxin</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Smelters, battery plants, mine, lead-based paint, lead-based water pipes, gasoline and electronic waste</td>
</tr>
<tr>
<td>Mercury</td>
<td>Chlor-alkali industry, thermometers, barometers, manometers, sphygmomanometers, fluorescent lamps, amalgam fillings and soil</td>
</tr>
<tr>
<td>PCBs</td>
<td>Contaminated electrical equipment, stabilizer of PVC, food (mainly fish), soil water and air</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Pesticides manufacture, food, air, water, soil, sediments, plants and animals</td>
</tr>
</tbody>
</table>

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Human exposure to compounds that have been banned for more than 40 years continues mostly through the food chain, such as the pesticide dichlorodiphenyltrichloroethane. The traditional legacy POPs comprises polychlorinated biphenyls (PCBs) and several chlorinated pesticides.

**Environmental contaminants and mental health**

In adulthood, significant associations between ECs and mental health are well known even at very low levels of exposure, such as those shown between blood lead levels and depressive symptoms in the US population. In childhood, mental health disorders may be difficult to identify early, therefore, studies have focused mainly on neurobehavioural outcomes. Significant associations that have been revealed are mainly confined to emotional/behavioural adjustments (activity, attention, emotionality) and cognitive abilities (Table 2). More precisely, a comprehensive review of results from prospective PCB cohorts suggested that among the cognitive functions assessed in the different studies, detrimental effects have been more clearly established for executive functions. From a more general perspective, and according to Grandjean and Landrigan, children’s exposure to ECs has even created a pandemic of neurodevelopmental disorders.

In the elderly population, studies have focused mainly on neurodegenerative diseases and exposure to ECs in relation to cognitive variability. Effects of exposure to ECs on impaired learning, memory and cognitive performances in the elderly have been documented (Table 3).

**Dose of exposure and clinical management of contaminant exposure**

In regulatory toxicology, there is a precept stating that higher doses will cause greater effects and conversely that substances considered toxic will be harmless in small doses. It is based on the early observations made by Paracelsus, the founder of toxicology, dating back to the 16th century. It is paraphrased as ‘The dose makes the poison’. However, the validity of the Paracelsus logic has recently been challenged since several epidemiological studies have shown that low dose exposure to ECs are associated with human diseases in disabilities and many chemicals even appear to have greater impact on human development at low doses than at higher doses. For example, the

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Mean level of exposure</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb</td>
<td>3.5 (μg/dl)</td>
<td>↑ inattention</td>
<td>3</td>
</tr>
<tr>
<td>Pb</td>
<td>5.4 (μg/dl)</td>
<td>↑ impulsivity</td>
<td>4</td>
</tr>
<tr>
<td>Pb</td>
<td>5.4 (μg/dl)</td>
<td>↑ irritability</td>
<td>4</td>
</tr>
<tr>
<td>Pb</td>
<td>2.7 (μg/dl)</td>
<td>↑ hyperactivity</td>
<td>5</td>
</tr>
<tr>
<td>Pb</td>
<td>8.1 (μg/dl)</td>
<td>↓ cognitive ability</td>
<td>6</td>
</tr>
<tr>
<td>Hg</td>
<td>21.6 (μg/dl)</td>
<td>↑ inattention</td>
<td>5</td>
</tr>
<tr>
<td>Hg</td>
<td>21.6 (μg/dl)</td>
<td>↑ hyperactivity</td>
<td>5</td>
</tr>
<tr>
<td>Hg</td>
<td>22.9 (μg/dl)</td>
<td>↓ cognitive ability</td>
<td>7</td>
</tr>
<tr>
<td>PCBs</td>
<td>112.3 (ng/g lipids)</td>
<td>↑ inattention</td>
<td>8</td>
</tr>
<tr>
<td>PCBs</td>
<td>120.6 (μg/kg)</td>
<td>↑ impulsivity</td>
<td>4</td>
</tr>
<tr>
<td>PCBs</td>
<td>120.6 (μg/kg)</td>
<td>↑ irritability</td>
<td>4</td>
</tr>
<tr>
<td>Pesticides</td>
<td>13.7 (nmol/l)</td>
<td>↑ inattention</td>
<td>9</td>
</tr>
<tr>
<td>Pesticides</td>
<td>13.7 (nmol/l)</td>
<td>↑ hyperactivity</td>
<td>9</td>
</tr>
<tr>
<td>Pesticides</td>
<td>130 (nmol/l)</td>
<td>↓ cognitive ability</td>
<td>10</td>
</tr>
</tbody>
</table>

Pb, lead; Hg, mercury; PCBs, polychlorinated biphenyls.
Table 3  Some identified endocrine-disrupting chemicals with adverse mental health effects in the elderly

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Mean level of exposure</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb</td>
<td>5.3 (μg/dl)</td>
<td>↓ attention</td>
<td>13</td>
</tr>
<tr>
<td>Pb</td>
<td>27.7 (μg/dl)</td>
<td>↓ verbal memory</td>
<td>14</td>
</tr>
<tr>
<td>Pb</td>
<td>27.7 (μg/dl)</td>
<td>↓ learning</td>
<td>14</td>
</tr>
<tr>
<td>Pb</td>
<td>14 (μg/dl)</td>
<td>↓ executive functions</td>
<td>15</td>
</tr>
<tr>
<td>Hg</td>
<td>500–2000 (μg/l)</td>
<td>↓ attention and reaction time</td>
<td>16</td>
</tr>
<tr>
<td>Hg</td>
<td>500–2000 (μg/l)</td>
<td>↓ memory and learning</td>
<td>16</td>
</tr>
<tr>
<td>Hg</td>
<td>500–2000 (μg/l)</td>
<td>↓ visual memory</td>
<td>16</td>
</tr>
<tr>
<td>PCBs</td>
<td>78.2 (ppb)</td>
<td>↓ attention</td>
<td>17</td>
</tr>
<tr>
<td>PCBs</td>
<td>78.2 (ppb)</td>
<td>↓ visual memory</td>
<td>17</td>
</tr>
<tr>
<td>PCBs</td>
<td>78.2 (ppb)</td>
<td>↓ verbal memory</td>
<td>17</td>
</tr>
<tr>
<td>Pesticides</td>
<td>716 (ng/g lipids)</td>
<td>↓ memory</td>
<td>18</td>
</tr>
<tr>
<td>Pesticides</td>
<td>716 (ng/g lipids)</td>
<td>↓ memory</td>
<td>18</td>
</tr>
<tr>
<td>Pesticides</td>
<td>716 (ng/g lipids)</td>
<td>↓ learning</td>
<td>18</td>
</tr>
</tbody>
</table>

Pb, lead; Hg, mercury; PCBs, polychlorinated biphenyls.

Lead-associated intelligence quotient (IQ) deficits observed in a recent pooled analysis were significantly greater at lower blood lead concentrations. Those chemicals follow a non-monotonic dose–response curve. Their slope reverses from negative to positive or vice-versa, such as biological U-shaped or inverted U-shaped curves. The health implications of non-monotonicity are striking; it means that concentrations of chemicals in the environment are more of concern for human health than current testing conditions. In addition, the complications identified by the epidemiological studies supporting the non-monotonicity of chemicals, such as cancer, obesity, heart disease, IQ and attention deficit hyperactivity disorder, contribute greatly to the steadily increasing burden of human disease and to the escalating health care cost throughout the world. It is thus imperative to revise the 16th century dogma in ways that reflect modern scientific knowledge. Accordingly, the National Academy of Science’s Board on Environmental Studies and Toxicology conjointly with major public regulatory agencies, including the Environmental Protection Agency, the National Institute of Environmental Health Science’s, the Food and Drug Administration and the National Institute of Child and Human Health Development, are preparing a report that will be released in the summer of 2013 about non-monotonic dose–response curves for chemicals. This report will help policy makers determine appropriate testing strategies to capture adverse effects of chemicals following non-monotonic dose–response curves. Public regulatory agencies have already been faced with the problem of low dose effects in the establishment of acceptable exposure levels. Indeed, they consistently decreased the acceptable level of exposure to chemicals as the study designed to evaluate neurodevelopment evolved.

Lead exposure and clinical management

Lead has been the most studied EC, particularly in children. As a consequence, lead exposure in children is the contaminant with the most complete clinical screening and clinical management strategy. This example should be followed for other chemicals as soon as scientific knowledge becomes available. The World Health Organization (WHO) estimates that lead exposure accounts for 1% of the global burden of disease in children. In developing countries, 15%–20% of mental retardations are caused by exposure to lead. Not only is lead poisoning a tragedy for the child and his/her family, but it also carries a significant societal and economic cost. In the USA, burden of disease for lead poisoning in children is 20 times higher than for asthma and 120 times higher than for cancer; it is estimated at $43.4 billion annually. On a population basis, for each 1 μg/dl increase in blood lead level, there is a reduction of 0.87 points in IQ. In addition, the rate of decline in intellectual impairment is greater at blood lead levels below 10 μg/dl than above. In children, prenatal exposure to 10 μg/dl blood lead level compared to 3 μg/dl results in a reduction of 4.8 points in IQ. This is a serious situation because in an entire population, a 5-point reduction in IQ results in a 57% increase in ‘mentally retarded’ people requiring remedial assistance. The societal consequences are clearly enormous. Therefore, it is of critical importance to clinically manage lead exposure in children. As previously evoked, acceptable blood lead levels in children was consistently revised according to...
the increasing knowledge in environmental health. The level of concern for lead in children gradually decreased from 60 μg/dl in 1960, 40 μg/dl in 1973, 30 μg/dl in 1975, 25 μg/dl in 1985, 10 μg/dl in 1991 to 5 μg/dl in 2012, as established by the CDC. The current action level of 5 μg/dl in children may even be evaluated as too high, as suggested by the studies revealing adverse mental health outcome in children at 2.7 and 3.5 μg/dl. In 2006, a study advocated that although no level of exposure to lead is safe, blood lead action level in children should be further reduced from 10 to 2 μg/dl, to prevent population from developmental neurotoxicity. Nevertheless, the CDC established specific intervention recommendations that paediatric health care providers must follow based on the current blood lead action level of 5 μg/dl.

Clinicians have an important role in preventing lead exposure and in managing lead-exposed children, as they are often the primary source of nutritional and lead-risk education received by parents. Therefore, according to the current management recommendations, clinicians should: (1) provide anticipatory guidance about childhood lead poisoning and its prevention to minimise exposure before blood lead testing; (2) assess blood lead levels to identify exposed children, for whom primary prevention has failed; (3) intervene appropriately when clinically indicated; (4) oversee monitoring of children with elevated blood lead levels, defined as a level above the reference value of 5 μg/dl and (5) coordinate efforts with parents as well as local and state authorities to minimise risks to individual children and to assist communities in their primary prevention efforts. The WHO reinforces the importance to screen blood lead level in children because lead poisoning is subclinical, it has nonspecific symptoms and its diagnostic relies exclusively on laboratory screening. Contrary to the past recommendations, when clinicians detect children blood lead level above the reference value (5 μg/dl), they must report it to the parents and public health officials to take action earlier to reduce the child’s future exposure to lead. To manage acute toxicity and reduce the body burden when blood lead levels are between 45 and 70 μg/dl, chelation is advised as a therapy. Chelation partly removes lead from the circulation using succimer as chelating agents. However, chelation is not recommended in children with a blood lead level below 45 μg/dl because of the potential risk of adverse drug events and concerns about remobilised lead. For levels above 70 μg/dl, children must be immediately hospitalised to perform chelation with succimer simultaneously with EDTA.

Although the current blood lead action level is still too high, successful progress was made in the US to reduce lead exposure in children due to the management plan established by public health regulatory agencies over the past four decades. In 1976, 88% of children aged 1–5 years had blood lead levels above 10 μg/dl. This percentage has markedly fallen to 4.4% in 1991 and to 1.6% in 1999. Then, blood lead levels in children substantially declined from 8.6% in 1999 to 2.6% in 2010. The CDC therefore acquiesced that primary prevention is the only practical approach to preventing elevated blood lead levels in children. The American Academy of Paediatrics further advised that ‘childhood lead-poisoning policy should shift from case identification and management to primary prevention, to reach a goal of safe housing for all children’. The current blood lead action levels apply to children, but we could wonder whether it should also apply to elders. Indeed, no such screening recommendations are currently done in ageing people. We thus recommend clinicians to pay attention to the emerging results in the field of environmental health, since researchers start understanding the process by which ECs impact health and it should change clinical management in near future. One plausible process by which lead and other ECs could impact neurodevelopment at very low levels is through their action on hormonal systems.

Endocrine-disrupting chemicals
Early observations of reproductive organ malformations and abnormal sexual behaviours in wildlife first unveiled the ability of ECs to interfere with steroid hormone action and led to their definition as endocrine-disrupting chemicals. The WHO identifies an endocrine-disrupting chemical as ‘an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations’. Furthermore, in a report published earlier in 2013, the WHO states that there is an urgent need for more research on the health outcome of endocrine disruptors. Although the sexual steroids system has been widely studied and will continue to be, another steroids system has been poorly investigated in environmental health—the stress system.

The stress system
Over the past three decades, two major factors have been shown to significantly contribute to the increased inter-individual variability in behaviour and cognitive performance across development. The first factor relates to genetics and the second relates to stress. When individuals are faced with a stressful situation, activation of the hypothalamic–pituitary–adrenal (HPA) axis is induced (Figure 2). Glucocorticoids (GCs; cortisol in humans) are the final secretory products of HPA activation. Given the lipophilic properties of GCs, these adrenal steroid hormones can easily cross the blood–brain barrier and affect the hypothalamus–pituitary–adrenal (HPA) axis. The current blood lead screening recommendations are also applied to elders. Indeed, no such screening recommendations are currently done in ageing people. We thus recommend clinicians to pay attention to the emerging results in the field of environmental health, since researchers start understanding the process by which ECs impact health and it should change clinical management in near future. One plausible process by which lead and other ECs could impact neurodevelopment at very low levels is through their action on hormonal systems.

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barrier and enter the brain, where they can influence brain functions and behaviour by way of binding to different receptor types. Two of the most important brain areas containing GCs receptors are the hippocampus and frontal lobes, which are brain structures known to be involved in cognitive function such as memory and emotional/behavioural maladjustments, such as impulsivity. Interestingly, deficits in HPA functioning has been related to impaired executive functions, emotional/behavioural adjustments in children and adolescents and cognitive impairments such as memory complaints in the elderly.

Endocrine disruptors and the stress system

EGs may disrupt the stress system, and thus have an impact on the release of GCs following a stressful event. In wildlife, impairments in the stress system have been observed in relation to toxic metals exposure (lead, mercury) and environmental organic contaminants (PCBs, solvents, pesticides) in fish, amphibians, birds and large mammals. For example, Oskam et al. stated that the sum of pesticides combined with the sum of PCBs, and their interactions, explained over 25% of the variation in the cortisol concentration. In laboratory studies with rodents, altered function of the system that control GCs has been reported following early exposure to PCBs and toxic metals. Structure-activity relationship studies have shown that some PCBs acted as antagonists at the human GCs receptors, and that dioxin-like PCBs altered GCs biosynthesis in human adrenocortical cells. Moreover, a study has shown that a low-level lead exposure increased GCs responses to acute stress in 9–10-year-old children. A recent study reported a significant association between lead exposure and higher ACTH:CORT ratio in occupationally exposed participants, suggesting a lead-induced alteration of the HPA axis.

The stress system could be the missing link between environmental contaminants and adverse mental health

Taken together, the current literature indicates that through their action on GCs, EGs could significantly impact behaviour and cognition in those who are the most at-risk—children and the elderly (Figure 3). Although research should continue in order to better characterise the mechanism of action of EGs on the stress system, unveiling this mechanism of action could also provide at-risk populations with ways to potentially decrease adverse effects of exposure to EGs. Indeed, psycho-social interventions have started to emerge in the scientific literature, illustrating that biological systems could be re-adapted, and thus leaving the way open for biological resilience.

Critical appraisal of the validity of relevant articles

According to the Levels of Evidence of the Oxford Centre for Evidence-based Medicine, relevant articles cited in this review are from Level II and III. Their validity is therefore acceptable.

Conclusion

Children and ageing adults are more vulnerable to EGs exposure than adults. EGs have been shown to impair behavioural development and cognitive abilities even at low doses of exposure. As shown in this review, the endocrine-disrupting properties of EGs are a plausible mechanism through which these compounds could interfere with the stress system to induce neurobehavioural impairment.

Figure 2: Hypothalamic–pituitary–adrenal (HPA) axis. Experiencing an environmental stressor, as perceived by the brain, results in the activation of the HPA axis. The hypothalamus will thus secrete corticotrophin-releasing hormone (CRH). In the anterior lobe of the pituitary gland, CRH stimulates the secretion of adrenocorticotropic hormone (ACTH). The cortex of the adrenal glands will then produce glucocorticoids (cortisol in humans) in response to ACTH. Cortisol will then generate a stress response.
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**Clinical applicability**

Clinicians should be aware of the potential risks posed by endocrine-disrupting components. They should thus have access to straightforward and accurate health information tools to share with patients. Ultimately, in cases of lead or other chemical toxicity, clinicians could recommend the testing of HPA axis functioning through diurnal cortisol assessment. Altered diurnal cortisol level could thus become a potential indicator of chronic stress in patients at risk of ECs toxicity.

**Acknowledgement**

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**References**

27. CDC. CDC response to Advisory Committee on Childhood Lead Poisoning Prevention recommendations in “Low Level Lead Exposure Harms Children: A Renewed Call of Primary Prevention.” In: Services USDoHaH, editor. Atlanta: CDC; 2012.
carcinoma cells. Chemosphere. 2006 May;63(5):772-84.
