REVIEW ARTICLE

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Chemical exposure early in life and the neurodevelopment of children – an overview of current epidemiological evidence

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Abstract

A number of chemicals have been shown to demonstrate neurotoxic effects either in human or laboratory animal studies. This article aims at evaluating the impact of exposure to several chemicals including: organophosphate, organochlorine pesticides, polychlorinated biphenyls (PCBs), mercury and lead on the neurodevelopment of children by reviewing the most recent published literature, and answer the question whether any progress has been made in the epidemiology of the neurodevelopment of children induced by exposure to those chemicals. The result of the presented studies show that exposure to the above-mentioned chemicals may impair the neurodevelopment of children. Neonates exposed to organophosphate pesticides demonstrated a higher proportion of abnormal reflexes, and young children had more attention problems. Exposure to organochlorine pesticides in children was associated with alertness, quality of alert responsiveness, cost of attention and other potential attention associated measures. The majority of studies indicate the negative impact of lead exposure at the level <10 µg/dl or even <5 µg/dl on the neurodevelopment of children. The results of studies on exposure to PCBs, mercury, and their effect on neurodevelopment are inconsistent. Some suggest that prenatal exposure to PCBs and mercury is related to performance impairments, attention and concentration problems, while other do not present any statistically significant association. The studies were mostly well designed, using prospective cohorts with the exposure assessment based on the biomarker of exposure. Concerning the covariates and confounders affecting the endpoints in most of the presented studies, confounders were included in data analysis. In order to recognize the early cognitive, motor and language outcomes of chemical exposures, well standardized tools were used for evaluating the neurodevelopmental effects and offer an early and fairly comprehensive measure of child development. Because the neurotoxicants may cross the placenta and the fetal brain, exposure consideration regarding the reduction of exposure to those chemicals should be implemented.

Key words

pesticides, PCB, mercury, lead, neurodevelopment, exposure assessment

INTRODUCTION

There is increasing evidence that some chemicals present in the environment can interrupt neurodevelopmental processes during the critical periods of development, resulting in effects on sensory, motor and cognitive function. It is now generally accepted that developmental exposure to chemicals can have adverse effects on the structure or function of the nervous system, and adversely affect neurodevelopmental processes [1].

Neurodevelopmental disorders such as autism, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability [2]. Their causes are mostly unknown. A few industrial chemicals: lead, methylmercury, polychlorinated biphenyls [PCBs], and pesticides are recognized causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early foetal development can cause brain damage at doses much lower than those affecting adult brain function [3]. Evidence has been accumulating over several decades that these chemicals can also cause neurodevelopmental damage. The possibility of a link between chemicals and widespread neurobehavioral changes was first raised by research which showed that lead was toxic to the developing brain [3]. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays [1].

Objective. The aims of this review are to characterize the impact of exposure to organophosphorus pesticides, organochlorine pesticides, polychlorinated biphenyls (PCBs), mercury and lead on the neurodevelopment of children. This review will attempt to answer the question of whether any progress has been made in the epidemiology of the neurodevelopment of children induced by exposure to chemicals, and in particular to find whether any limitations in study design, exposure assessment, and co-nfounders used in the analysis have been overcome.

Selection of studies for review. Epidemiological studies focused on exposure to environmental chemical factors (organophosphate and organochlorine pesticides, polychlorinated biphenyls (PCBs), mercury, lead) and the neurodevelopment of children were identified by a search of the Pubmed, Medline and Ebsco literature databases. The

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presented review is restricted to human studies published in English in peer reviewed journals from the year 2000. Relevant studies were also identified via review of references cited in all published studies. The combination of the following key words was used and referred to the following:

1) exposure: pregnancy, prenatal exposure, postnatal exposure, exposure to organophosphorus pesticides, organochlorine pesticides, polychlorinated biphenyls (PCBs), mercury and lead;
2) outcome: neurodevelopment, neurobehavior, psychomotor development, behavioural problems, cognitive development, mental health, school achievements, learning abilities and IQ.

From each study, the following information was abstracted: study design and population, assessment of neurodevelopment (including neurodevelopmental test used), exposure and methods used for its assessment (including biomarkers) and confounding factors. Finally, in this review were included human studies published in peer reviewed journals from the year 2000.

Altogether, out of total 170 articles identified, 68 met eligibility criteria and were included in the presented review.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Exposure to organophosphate pesticides and children neurodevelopment. Pesticides are used extensively worldwide. Organophosphate pesticides (OPs) are popular because of their broad spectrum of applications, potent toxicity to insects, relatively low cost and decreased likelihood of pest resistance [4]. Young children may also be more susceptible to the potentially neurotoxic effects of pesticides, not only because their organ systems, specifically the brain and central nervous system, are developing rapidly, but also because they have lower levels than adults of detoxifying enzymes (paraoxonase or chlorpyrifos-oxonase) that deactivate OPs [5]. The neurotoxic consequences of acute high-level pesticide exposure are well established. Whether the exposure to moderate levels of pesticides is also neurotoxic is more controversial. OP pesticides at high doses inhibit acetylcholinesterase which may produce biochemical and behavioural effects [6], including adverse effects on sustained attention and an increase in impulsivity [7]. In addition, OPs may operate through a variety of non-cholinergic mechanisms, such as by disruption of various cellular processes: DNA replication and axonal and dendritic growth [8], and by oxidative stress in the developing brain [9].

Several studies have assessed neurodevelopment of neonates and young children after low-level OP pesticide exposure [4, 10, 11, 12, 13, 14, 15, 16, 17]. Most of these studies were performed in United States [11, 12, 13, 14, 15, 16, 17] while two studies were conducted in North Ecuador [10] and China [4]. Two studies were among infants [14, 17], and seven among young children [4, 10, 11, 12, 13, 15, 16] (Tab. 1).

The effect of prenatal exposure to OP and abnormal reflexes among neonates were evaluated in two studies in the United States:

In New York among children from Mount Sinai Children's Environmental Health Cohort Study. In this study conducted among 3-day-old infants, an increasing average prenatal urinary metabolite of organophosphates pesticides levels were associated with both an increase in the number of abnormal reflexes and the proportion of infants with more than three abnormal reflexes [14].

In the second study, prenatal exposures to OP and abnormal neonatal behaviour and/or primitive reflexes was examined. Maternal urine samples were analyzed for six dialkylphosphate metabolities and malathion dicarboxylic acids. Malathion dicarboxylic acids levels above the limit of detection were associated with an increased number of abnormal reflexes [17]. Higher levels of total diethylophosphates and total dialkylophosphates were associated with an increase in abnormal reflexes.

Rauh et al. [12] examined the relationship of maternal blood levels of a diethyl phosphate pesticide, during pregnancy and performance on the Bayley Scales of Infant Development of 254 inner-city children through 3 years of age. Three-year-olds with a high prenatal level of chlorpyrifos (chlorpyrifos levels in umbilical cord plasma of > 6.17 pg/g

Table 1. Exposure to organophosphate pesticides and risk of neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
United States, New York City (Mount Sinai Children's Environmental Health Cohort Study)						
Unites States, California 381 infants ≤ 2 months	cohort	DAPs (DMP and DEP) in urine measured twice during pregnancy (14 and 26 weeks of gestation and one post delivery (7 days postpartum)	Brazelton Neonatal Behavioural Assessment Scale (NBAS)	Age at assessment, smoking, alcohol, method of delivery, interviewer, number of prenatal care visits, poverty level, gender, parity, caffeine use, infant sex	Among the > 3 day old infants increasing average prenatal urinary metabolite levels of organophosphate pesticides were associated with both an increase in the number of abnormal reflexes and proportion of infants with more than abnormal reflexes.	Young 2005 [14]
United States, New York City 311 neonates before hospital discharge	cohort	Maternal urine samples analyzed for six DAPs (DMP, DMTP, DMDTP, DEP, DETP, DEDTP), and malathion dicarboxylic acids. Maternal peripheral blood samples analyzed for polichlorinated biphenyls and 1,1'-dichloro-2,2'-bis(4-chlorophenyl)ethylene	Brazelton Neonatal Behavioural Assessment Scale (NBAS)	Drug use during pregnancy, interviewer, pre-pregnancy BMI, infant age at examination, caffeine consumption during pregnancy, maternal education, smoking during pregnancy	Malathion dicarboxylic acids levels above the limit of detection were associated with increased number of abnormal reflexes: OR= 2.24 95%CI (1.55–3.24). No adverse associations found with polychlorinated biphenyl and any behavior dominants.	Engel 2007 [17]

Table 1 (Continuation). Exposure to organophosphate pesticides and risk of neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
United States, Salinas Valley, California (The Center for the Health Assessment of Mothers and Children of Salinas [CHAMACOS])						
United States, California 396- Children at 6 months 395- children at 12 months 372- children at 24 months	cohort	Six DAP metabolites in maternal and child urine: *a*) three dimethyl phosphate (DM) metabolites (DMP, DMTP, DMDTP), *b*) three diethyl phosphate (DE) metabolites (DEP, DETP, DEDTP)	Bayley Scales of Infant Development (BSID)	Psychometrican, location, age at assessment, gender, breast-feeding duration, HOME, household income above poverty threshold, parity	Pregnancy DAP levels were negatively associated with MDI at 24 months of age. Both prenatal and postnatal DAPs were associated with risk of pervasive developmental disorder.	Eskenazi 2007 [16]
United States, Yuma County, Arizona (The Children Pesticide Survey of southern Arizona)						
United States, Yuma County, Arizona 48 children at 7 years; 25 exposed to OP pesticides and 23 unexposed to OP pesticides according to urine analysis	Cross-sectional	OP metabolites in urine: DMP, DMTP, DMDTP, DEP, DETP, DEDTP	Wisconsin Card Sorting Test (WCST); Wechsler Intelligence Scale for Children (WISC-III) Children's Memory Scale, Trail Making Test A and B, Achenbach Child Behavior Checklist [CBCL]	None	Adverse associations of child urinary DAPs and attention-related performance errors.	Sanchez-Lizzardi 2008 [15]
Unites States, Mississipi and Ohio						
United States, Mississipi and Ohio; 365 children in Mississipi (147 exposed to methyl parathion and 218 unexposed) 287 children in Ohio (104 exposed and 183 unexposed); age: 2–12 years old	Cross-sectional	Urinary para-nitrophenol levels and environmental wipe samples	Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI); Kaufman Brief Intelligence test; Purdue Pegboard tests; Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test (WRAML); Trail Making test; Verbal Cancellation test; Personality Inventory for Children; Vineland Adaptive Behaviour Scales	Income, race, mother's use of chemicals at work, mother had one or more of the following conditions: diabetes or epilepsy before pregnancy, hospitalized, fever, X ray, vaginal bleeding during pregnancy	Exposed children had more difficulties with tasks involving short-term memory and attention. There were no differences in tests for general intelligence, integration of visual and motor skills.	Ruckart 2004 [13]
United States, New York, prospective cohort study of inner-city mothers and their newborn infants						
United States, New York 254 children evaluated through the first 3 years of life (12, 24, 36 months of life)	cohort	Chlorpyrifos levels in umbilical cord plasma	Bayley Scales of Infant Development (BSID); Achenbach Child Behavior Checklist [CBCL]	Prenatal ETS exposure, gender, ethnicity, gestational age at birth, quality of the home care-taking environment, maternal education level, maternal IQ	Highly exposed children scored on average 6.5 points lower on the Bayley PDI and 3.3 points lower on the Bayley MDI at 3 years of age, compared with those with lower levels of exposure.	Rauh 2006 [12]
United States, Oregon, North Carolina						
United States 78 children aged 48–71 months	Cross-sectional	No biomarker	Santa Ana Dexterity, Purdue Pegboard Test	Child's age, mother's education, location, gender	Male children from agricultural area performed significantly worse than the male non-agricultural communities, children on right hand Finger Tapping had significantly longer latencies on the Match-to-Sample test.	Rolhman 2005 [11]
China, Shanghai						
China, Shanghai 301 children aged 23–25 months of age	Cross-sectional	Five DAP metabolites: DMP, DMTP, DEP, DETP, DEDTP	Gesell Developmental Schedules	Child gender, maternal education level, household income	No association found between child urinary levels of OP metabolites and any of the developmental quotients scores.	Goudong 2012 [4]
Northern Ecuador						
Northern Ecuador 79 elementary school children aged 7	Cross-sectional	Recent and current pesticide exposure assessed by erythrocyte acetylocholine esterase activity and urinary excretion of organophosphate metabolites	Santa Ana Dexterity, Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Copying Test, Finger Tapping Test, Simple Reaction Time test	Age, gender, body weight, trauma, other injury, maternal education, maternal race, socio-economic status, maternal smoking and alcohol use during pregnancy	OP metabolite levels was associated with increased reaction time, but not with other domains of neurobehaviour.	Grandjean 2006 [10]

DAPs – dialkyl phosphate metabolites, DMP dimethylphosphate, DMTP dimethylthiophosphate, DMDTP dimethyldithiophosphate, DEP diethylphosphate, DETP diethylthiophosphate, DEDTP diethyldithiophosphate
OP – organophosphate pesticides, ETS – Environmental Tobacco Smoke
OR- odds ratio, CI- confidence interval, MDI-Mental Development Index, PDI-Psychomotor Development Index, HOME- Home Observation for Measurement of the Environment

plasma) showed significantly more delays in psychomotor and mental development, and their mothers reported more attention problems and symptoms of pervasive developmental disorders at 3-years of age [12].

Mental and psychomotor developments were also investigated in a cohort of children of farmworker families living in the Salinas Valley of California [16]. An adverse association of prenatal OP metabolites with mental development and pervasive development problems at 24 months of age was observed.

In a study performed among 6–9-year-old Ecuadoreans attending the two lowest grades of a public school, prenatal pesticide exposure was associated with a lower score for copying designs in the exposed children. Postnatal exposure to OPs, as assessed by the children's urinary dialkyl phosphate (DAP) metabolite levels, was associated with increased reaction time, but not with other domains of neurobehaviour [10].

The result of the study among pre-school children showed poorer neurobehavioural performance of children from agricultural communities exposed to OP, compared to the performance of those from non-agricultural communities, as measured by response speed, number correct and latency. Children from the agricultural area performed significantly worse than children from non-agricultural communities on right hand Finger Tapping. The children from agricultural communities also had significantly longer latencies on the Match-to-Sample test [11].

In a study of 2–12-year-olds living in Mississippi and Ohio, where methyl parathion was illegally sprayed in homes, the children were classified as exposed or unexposed on the basis of urinary para-nitrophenol levels and environmental wipe samples. Exposed children had more difficulties with tasks involving short-term memory and attention. Additionally, parents of exposed children had more behavioural and motor skill problems than did parents of unexposed children [13]. Another study of Hispanic children living in an agricultural community reported adverse associations of child urinary DAPs and attention-related performance errors on the Wisconsin Card Sorting Test [15].

On the other hand, no association was found between child urinary levels of OP metabolites and any of the developmental quotients scores in the study performed among 301 young children from Shanghai [4].

The result of the presented studies show that exposure to organophosphate pesticides is associated with poorer neurodevelopment of children. Neonates demonstrated a higher proportion of abnormal reflexes [14, 17], while young children had more attention problems [12, 13], especially attention-related performance errors [15], symptoms of pervasive developmental disorders at 3 years of age [12], lower score for copying designs [10] at age 6 – 9-years-old, and more difficulties with tasks involving short-term memory [13]. Poorer response speed and number correct and latency were found among children exposed to pesticides from agricultural areas [11]. Only one current cross-sectional study performed in China did not find an association between exposure to pesticides and the neurodevelopment of children [4].

Exposure to organochlorine pesticides and polychlorinated biphenyls and the neurodevelopment of children. Organochlorines, including polychlorinated biphenyls (PCBs) and *p,p*'-dichlorodiphenyl dichloroethene (*p,p*'-DDE), the main degradation product of *p,p*'-dichlorodiphenyl trichloroethane (*p,p*'-DDT). Organochlorine compounds are persistent and ubiquitous environmental contaminants that were intensively used in the past. Although today DDT is banned from use and production in most Western countries, it is still sprayed in some developing countries for disease-vector control [18]. Organochlorine chemicals are resistant to degradation and bioaccumulate in the food chain. Exposure occurs *in utero,* and because of their lipophilicity also via breastfeeding. DDT metabolites directly affect nerve cells and have endocrine disruption effects in the hypothalamic–hypophysis–thyroid axis [19]. Alterations in the central nervous system have been documented concerning the visual–motor and cognitive functions of workers chronically exposed to DDT [20].

Six studies have examined the association between cord PCBs and organochlorine pesticides (*p,p*'-dichlorodiphenyl dichloroethene (DDE)) and the neurodevelopment of children [21, 22, 23, 24, 25, 26] (Tab. 2).

The study which examined the associations between prenatal exposure to p,p-DDE and mental and psychomotor development in children aged 1 year from a rural village in the vicinity of an electrochemical factory (where DDT, hexachlorobenzen and other chlorinated solvents were produced), found that p,p'-DDE cord serum levels were negatively associated with lower psychomotor development at 13 months of age [22]. Long-term breastfeeding was found to be protective against this effect. On the other hand, no such association was found for exposure to hexachlorobenzen. The same authors evaluated the association of cord blood serum level of DDT and its metabolite DDE with neurodevelopment at age 4 years [23]. Children were assessed by using the McCarthy Scales of Children's Abilities. DDT cord serum concentration at birth were inversely associated with verbal, memory, quantitative and perceptual-performance skills at age 4 years.

Torres-Sanchez [24] found that DDE levels during the first trimester of pregnancy were related to significant reduction in psychomotor development index (PDI) but not with mental development index (MDI).

The effects of *in utero* exposure to DDT and DDE on neurodevelopmental was also investigated among Mexican farm workers' children in California. The birth cohort study consisted of 360 singletons with maternal serum measures of p,p'-DDT, o,p'-DDT, and p,p'-DDE. Psychomotor development and mental development were assessed with the Bayley Scales of Infant Development at 6, 12, and 24 months. A 2-point decrease in Psychomotor Developmental Index scores with each 10-fold increase in p,p'-DDT levels at 6 and 12 months (but not 24 months), and p,p'-DDE levels at 6 months only, was found. Breastfeeding was associated positively with the Bayley scale scores [25].

To investigate an association between cord serum polychlorinated biphenyls (PCBs) and *p,p*'-dichlorodiphenyl dichloroethene (DDE) levels and measures of attention, Sagiv et al. in [26] performed a study among 788 infants (5–22 days old) born between 1993–1998 to mothers residing near a PCB-contaminated harbour and Superfund site in New Bedford, Massachusetts, USA [26]. Consistent inverse associations between cord serum PCB and DDE levels, and of alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures, including self-quieting and motor maturity, were observed [26]. However, no association was found between cord blood DDE levels

Table 2. Exposure to organochlrine pesticides and risk of neurodevelopmental effects in children.

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Mexico, State of Morelos						
Mexico, 244 children at 1,3,6 and 12 months of age	cohort	Serum level of DDE before pregnancy and during each trimester of pregnancy	Bayley Scales of Infant Development (BSID)	Birth weight, age at evaluation, breastfeeding, HOME	DDE levels during the first trimester of pregnancy were associated with reduction in PDI, and not associated with MDI.	Torres-Sanches 2007 [24]
United States, Oswego, New York, Ontario Lake (The Oswego Newborn and Infant Development Project)						
United States, North Carolina 230 children tested at 6 months and again 216 children tested at 12-months	cohort	Cord-blood DDE level	Fagan test for Infant Intelligence (FTII)	Based on abstract – no information about confouders	No significant associations between FTII performance and DDE cord blood level.	Darvil 2000 [21]
United States, Salinas Valley, California (The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS))						
United States, California 360 sigletons tested at 6,12, 24 months	cohort	Maternal serum measures of p,p′-DDT, o,p′-DDT and p,p′-DDE	Bayley Scales of Infant Development (BSID)	Psychometrican, gender, maternal years in US, poverty level, season for assessment, maternal education, age, HOME, maternal work status	2-point decrease in PDI scores with each 10-fold increase in p,p′DDT levels at 6 and 12 months and p,p′-DDE levels at 6 months.	Eskenazi 2006 [25]
United States, New Bedford, Massachusetts						
United States, New Bedford, Massachusetts 788 infants (5–22 days) residing near a PCB-contaminated harbor	Cohort	Cord serum level of the 51 individual PCB congeners and two chlorinated pesticides (*p,p′*-DDE, hexachlorobenzen (HCB))	Bazelton Neonatal Behavioural Assessment Scale (NBAS)	Infant's age at examination, birth year, time since last feeding, NBAS examiner, and maternal age, education, breast-feeding, household income	Inverse associations between cord serum PCB and DDE levels and of alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures including self-quieting and motor maturity were observed.	Sagiv 2008 [26]
Spain, Barcelona						
Spain, Barcelona 92 mother-infant pairs 1-year old infants	Birth cohort	Organochlorine compounds: DDE, hexachlorobenzene (HCB) in cord serum	Bayley Scales of Infant Development (BSID); Griffiths Scales of Infant Development	Maternal age, tobacco and alcohol exposure during pregnancy, maternal education, migration, paternal occupation, gender, kindergarden, breastfeeding	DDE cord serum levels negatively associated with both MDI and PDI. HCB had no effect on child neurodevelopment.	Ribas-Fito 2003 [22]
Spain, Barcelona 475 children at age 4 years	Birth cohort	DDT and DDE were measured in cord serum	McCarthy Scales of Children's Abilities (MSCA)	Gender, school trimester of examination, psychologist, breastfeeding, maternal social class, maternal consumption of alcohol and use of tobacco during pregnancy	Children whose DDT concentration in cord serum level were >0.20 ng/ml had mean decreases of 7.86 points in the verbal scale and 10.86 points in the memory scale, compared with children whose concentrations were <0.05 ng/ml.	Ribas-Fito 2006 [23]

MDI – Mental Development Index; PDI – Psychomotor Development Index
DDT – dichlorodiphenyltrichloroethane; DDE – Dichlorodiphenyldichloroethylene; PCB – polychlorinated biphenyls, HOME – Home Observation for Measurement of the Environment

and scores on the Fagan Test of Infant Intelligence at ages 6 or 12 months [21] (Tab. 2).

Despite the relatively large body of literature on potential associations between early-life exposure to PCBs and adverse neurodevelopmental effects, controversy still exists over whether PCBs are in fact neurotoxicants [27]. Mechanisms hypothesized to underlie PCB neurotoxicity have included thyroid disruption [28], interference with sex steroids, either as agonists or antagonists [29], and Ah-receptor activity. Thyroid hormones are critical to neuronal proliferation, migration, synaptogenesis, and brain myelination [19].

The relation between exposure to low levels of polychlorinated biphenyls (PCBs), a class of persistent organic pollutants, and cognitive and motor development in infants and young children, has been examined in many studies, and the results have varied (Tab. 3).

Studies which assess the exposure to PCBs and neurodevelopment in infants were performed in the United States, the Great Lake Region [21, 30] and in Germany [31]. In the Great Lakes Region, the consumption of fish contaminated with PCB from Lake Ontario were examined in relation to infant neurodevelopment [21, 30]. The relationship between prenatal (cord blood) polychlorinated biphenyls (PCBs) and the Neonatal Behavioural Assessment Scale (NBAS) performance in babies at 25–48 h after birth was examined by Stewart et al. in 2000. Results revealed significant relationships between the most heavily chlorinated PCBs and performance impairments [30]. Infants were also examined at conceptual age 67 weeks and again at conceptual age 92 weeks, using the Fagan Test of Infant Intelligence. Analysis of the results revealed a dose-dependent relationship between total umbilical cord-blood PCB levels and poorer performance at the Fagan Test at both ages [21]. In Germany, on the other hand, no associations between exposure and neurological and developmental measures were observed in the study performed in infants 2 weeks and 24 months of age [31].

Studies which assess the impact of exposure to PCBs and neurodevelopment in children have been performed in Japan [32], Slovakia [33], Germany [34], the United States, Ontario Lake [35, 36, 37, 38], Michigan Lake [39], 12 hospitals in United States: Baltimore, Boston, Buffalo, Memphis, Minneapolis, New Orleans, New York (two hospitals), Philadelphia, Portland, Providence and Richmond

Table 3. Exposure to polychlorinated biphenyls and neurodevelopmental effects in children.

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Oswego, New York, Lake Ontario (The Oswego Newborn and Infant Development Project)						
United States, Great Lake Region, Oswego, New York, babies born to women who consumed contaminated Lake Ontario fish (152 women who reported never consuming Lake Ontario fish and 141 women who reported consuming at least 40 PCB-equivalent lbs) at 25–48 h after birth	cohort	Cord blood PCBs, DDE, HCB, Mirex, lead, and hair mercury levels	Neonatal Behavioural Assessment Scale (NBAS)	Socio-economic status, maternal IQ, maternal education, home environment, smoking	Significant linear relationships between the most heavily chlorinated PCBs and performance. Higher prenatal PCB exposure was associated with a non-specific performance impairment.	Stewart 2000 [30]
United States, Great Lake Region, Oswego, New York, babies born to women who consumed contaminated Lake Ontario fish tested at 6 month-230 children and 12-month – 216 children	cohort	Cord blood PCBs level	Fagan Test for Infant Intelligence (FTII)	Based on abstract – no information about confounders	Dose-dependent relationship between total umbilical cord-blood PCB levels and poorer performance at both ages.	Darvill 2000 [21]
United States, Oswego, New York, 189 children at 4.5 years old	cohort	Umbilical cord blood level of PCBs, maternal hair mercury (MeHg), postnatal PB exposure (venous blood)	McCarthy Scales of Children's Abilities (MSCA)	Socio-economic status, maternal IQ, maternal education, home environment, smoking	A dose dependent association between cord blood PCBs and errors of commission.	Stewart 2003 [35]
United States, Oswego, New York: 202 children at 8 years of age and later at 9 ½ years of age	cohort	Umbilical cord blood level of PCBs, postnatal Pb exposure (venous blood), methylmercury (MeHg) in hair	Continuous Performance Test (CPT)	Maternal IQ, maternal sustained attention and maternal response inhibition, socio-economic status, maternal education	Prenatal PCB exposure was associated with increased impulsive responding on CPT.	Stewart 2005 [36]
United States, Oswego, New York, 167 children at 9.5 years of age	cohort	Umbilical cord blood level of PCBs, methylmercury (MeHg) in hair, postnatal Pb exposure (venous blood)	Differential Reinforcement of Low Rates task (DRL)	HOME, socio-economic status, maternal IQ, maternal education, paternal education	Children prenatally exposed to PCBs responded excessively, with significantly lower interresponse time and fewer reinforcers earned across the session.	Stewart 2006 [37]
United States, Oswego, New York: 156 children at 9 years of age	cohort	Placental PCBs level	Wechsler Intelligence Scale for Children (WISC)	HOME, socio-economic status, parental IQ, alcohol/cigarette use, neonatal risk factor	For each 1-ng/g (wet weight) increase in PCBs in placental tissue, Full Scale IQ dropped by three points ($p = 0.02$), and Verbal IQ dropped by four points ($p = 0.003$).	Stewart 2008 [38]
United States (Collaborative Perinatal Project). Children from 12 hospitals: Baltimore, Boston, Buffalo, Memphis, Minneapolis, New Orleans, New York (2 hospitals), Philadelphia, Portland, Providence, Richmond						
United States, 12 hospitals: 1,065 children at 8 months of age	cohort	PCBs measured in maternal serum taken during pregnancy.	Bayley Scales of Infant Development (BSID)	Research Center, mother's education, triglycerides, cholesterol, child first born	No relation between prenatal PCB exposure and children's MDI and PDI.	Daniels 2003 [40]
United States, 12 hospitals: 894 children at the age of 7	cohort	Third trimester serum analyzed for PCBs	Wechsler Intelligence Scale for Children (WISC)	Study Center, triglycerides, cholesterol, maternal age, child gender, race, parity, socio-economic status, smoking, number of day breastfed, presence of meconium	No relation between prenatal PCB exposure and children's MDI and PDI.	Gray 2005 [41]
United States, Michigan, Lake Michigan						
United States, Michigan: 154 children assessed at 4 years of age, 148 children at 11 years	cohort	Umbilical cord serum, maternal serum and milk concentration of PCBs	Continuous Performance Test (CPT), Wisconsin Card Sorting Test, Sternberg Memory Paradigm, Wechsler Intelligence Scale for Children (WISC)	Socio-economic status, mother's age at child's birth, marital status, gender of child, parity, maternal education, HOME, maternal alcohol consumption and smoking during and after pregnancy, delivery complications	Prenatal PCB exposure associated with greater impulsivity, poorer concentration, and poorer verbal, pictorial, and auditory working memory.	Jacobson 2003 [39]

Table 3 (Continuation). Exposure to polychlorinated biphenyls and neurodevelopmental effects in children.

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Europe, Netherlands (The Netherlands Cohort Study)						
The Netherlands, 207 children at age 7,5 ±0.4	cohort	Sum of PCB 118, 138, 153 and 180 in maternal and cord plasma and breast milk	Pre-School Activities Inventory (PSAI)	Maternal age, parental education, parental verbal IQ, HOME	In boys, higher prenatal PCB levels were related with less masculinized play and composite scale, whereas in girls, higher PCB levels were associated with more masculinized play. Higher prenatal dioxin levels were associated with more feminized play in boys as well as girls.	Vreugdenhil 2002 [42]
The Netherlands, 207 children at age 9	cohort	Sum of PCB 118, 138, 153 and 180 in maternal and cord plasma and breast milk	Tower of London (TOL)	Type of feeding, duration of breastfeeding, gender, parity, parental education level, parental verbal IQ, HOME, age at examination	Higher prenatal PCB levels associated with longer response times (RTs), more variation in RTs, and lower scores on the TOL.	Vreugdenhil 2004 [43]
Europe, Germany						
Germany 232 healthy mother-infant pairs recruited between 2000–2002	cohort	Dioxins, dioxin-like PCBs and six indicator PCBs analyzed in maternal blood during pregnancy, and in maternal milk following extraction	Bayley Scales of Infant Development (BSID)	Parental education and occupation, alcohol and smoking during pregnancy, duration of pregnancy, number of pregnancies, mother's BMI before delivery, mother's age at delivery, birth weight, nationality, lead and cadmium in blood, selenium in serum and mercury in urine of the pregnant women, medication during pregnancy (especially iodide and thyroid hormones), diseases of the thyroid gland, Apgar score, neonatal jaundice, duration of breastfeeding, assessment of the child's home environment	No associations between exposure and neurological and developmental measures observed.	Wilhelm 2008 [31]
Germany, 171 healthy mother-infant pairs aged 7, 18, 30, and 42 months	cohort	Prenatal and perinatal PCB exposure in cord blood and maternal milk. At 42 months, PCB concentrations were measured in serum	Bayley Scales of Infant Development (BSID) and the Kaufman Brief Intelligence Test at 42 months	Age at examination, gestational age, alcohol/smoking during pregnancy, Apgar score, delivery, parental education, parental occupation, parity, neonatal illnesses, lead in cord blood, duration of breastfeeding, mother's BMI, maternal verbal intelligence	Negative associations between milk PCB and mental/motor development reported at all ages.	Walkowiak 2001[34]
Europe, Faroese Island						
Faroe Islands, 435 children at the age of 7	cohort	PCBs examined by analysis of cord tissue Cord Blood Hg	Finger Tapping Test, Hand–Eye Coordination Test, Continuous Performance Test, Wechsler Intelligence Scale for Children (WISC), Bender Visual Motor Gestalt Test, California Verbal Learning Test, Boston Naming Test	Gender, age, maternal score on Raven's Progressive Matrices, medical risk for neurobehavioural deficit, maternal and paternal education level, paternal employment, day care	Cord PCB concentration was associated with deficits within the highest tertile of mercury exposure on the Boston Naming Test, the Continuous Performance Test reaction time (p=0.03).	Grandjean 2001 [44]
Europe, Slovakia						
Slovakia, 750 children at 16 months	cohort	Maternal and cord serum samples collected at delivery, and analyzed for PCBs	Bayley Scales of Infant Development (BSID)	District, HOME, child gender	PCBs significantly associated with lower scores on both the psychomotor (PDI) and mental development indices (MDI).	Park 2010 [33]
Japan, Hokkaido (The Hokkaido Study on Environment and Children's Health)						
Japan, 134 6-month-old infants	cohort	Pregnant women's peripheral blood level of PCB and dioxins after the second trimester PCB	Bayley Scales of Infant Development (BSID)	Gestational age, smoking during pregnancy, caffeine intake during pregnancy, blood sampling time	Levels of one polychlorinated PCDD isomer, total PCDDs, and total PCDDs/ PCDFs were significantly negatively associated with MDI, and the levels of two PCDD isomers and three PCDF isomers were significantly negatively associated with the PDI.	Nakajima 2006 [32]
Canada, North Quebec						
Canada, North Quebec: 110 preschool Inuit children aged 4–6 years of age	cohort	Umbilical cord blood PCBs level	Catsys system developed by Danish Product Development The Sway Analysis Test System	HOME, socio-economic status, maternal reproductive history, smoking, use of drugs and alcohol	No association between exposure to PCBs and neuromotor development.	Despres 2005 [45]

DDE – Dichlorodiphenyldichloroethylene; HCB – Hexachlorobenzene; PCBs – Polychlorinated biphenyls; PCB 118 – 2,3',4,4'5-pentachlorobiphenyl; PCB 138 – 2,2',3,4,4',5'-Hexachlorobiphenyl; PCB 153–2,2',4,4',5,5'-Hexachlorobiphenyl; PCB 180 – 2,2',3,4,4',5,5'- Heptachlorobiphenyl; MDI-Mental Development Index; PDI – Psychomotor Development Index; HOME – Home Observation for Measurement of the Environment

[40, 41], the Netherlands [42, 43], Faroe Island [44] and Canada [45].

The associations between the total or individual isomer levels of PCBs and dioxins in peripheral blood of 134 pregnant Japanese women and the mental and motor development of their 6-month-old infants, were evaluated. The levels of one polychlorinated dibenzo-pdioxin (PCDD) isomer, total PCDDs, and total PCDDs/polychlorinated dibenzofurans (PCDFs) were significantly negatively associated with the Mental Development Index (MDI), and the levels of two PCDD isomers and three PCDF isomers were significantly negatively associated with the PDI [32]. In a study performed in Slovakia among children at 16 months, maternal mono-ortho-substituted PCBs were significantly associated with lower scores on both the psychomotor (PDI) and mental development indices (MDI). Also, a significant association between cord mono-ortho-substituted PCBs and reduced PDI was observed, although the association with MDI was marginal (p=0.05) [33]. In a study in Germany, 171 healthy mother-infant pairs were investigated to assess psychomotor development in the newborn infants aged 7, 18, 30, and 42 months. Negative associations between milk PCB and mental/motor development were reported at all ages [34].

Investigators from the Oswego Newborn and Infant Development Project reported associations between prenatal PCBs and errors of commission (false-positive responses) on the Continuous Performance Test at 4.5, 8, and 9.5 years of age, suggesting a potential impairment of response inhibition [35, 36]. This was supported by observed associations of PCBs with poorer performance on the Differential Reinforcement of Low Rates of Response test (in the same cohort at age 9.5 years), which measures the ability to withhold a rewarded response for a specific time delay, another test of response inhibition [37]. The next study by Stewart et al 2008 [38] in the same cohort of children was performed at 9 years of age, where the exposure to PCBs was associated with a decrease in Full Scale IQ (p = 0.02), and Verbal IQ (p=0.003). This association was significant after controlling for many potential confounders, including prenatal exposure to methylmercury, dichlorodiphenyldichloroethylene, hexachlorobenzene, and lead [38].

The Faroe Islands study found association between PCBs and attention measured by a continuous performance test among 7-year-old children only in the context of high mercury exposure, suggesting a potential interaction between these contaminants [44]. A study of children born to Lake Michigan fish consumers reported associations between prenatal PCB exposure and poorer performance on a Digit Cancellation task, which indicates difficulty with focused attention and concentration among 11-year-old children who had not been breast-fed [39].

The effects of exposure to environmental levels of PCBs and dioxins on development which persist until the school age was observed in a Dutch cohort [42]. Negative effects of prenatal PCB and dioxin exposure on cognitive and motor abilities were noticed when parental and home characteristics were less optimal in the case of intellectual stimulation [42]. The same author also evaluated the effects of perinatal exposure to PCBs and dioxins on play behaviour in Dutch children at school age (7.5 years of age). In boys, higher prenatal PCB levels were related to less masculinized play, whereas in girls, higher PCB levels were associated with more masculinized play [42]. The children from this study were then followed and their neuropsychological functioning was assessed at 9 years of age. Higher prenatal PCB levels were associated with longer response times and more variation in the response time; additionally, a longer breast-feeding duration was associated with lower scores on the neurodevelopmental test and with better spatial organizational skills [43].

Whereas in a study performed in 12 hospitals in the United States, the authors did not observe any relations between prenatal PCB exposure and children's mental or psychomotor scores [40]. The children were followed and their neurodevelopment were assessed at the age of 7 years. *In utero* exposure to background levels of PCBs was not associated with lower IQ [41]. Also, no negative effects of PCBs on neuromotor development were observed in 110 pre-school (4–6 years of age) Inuit children from Canada [45].

Summing up, exposure to organochlorine pesticides in infants (5–22 days old) was associated with alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures [26]. Organochlorines exposure negatively affect psychomotor and mental development at 1, 3, 6, 12, and 13 months [22, 24, 25], and later was inversely associated with verbal, memory, quantitative and perceptual-performance skills at age 4 years [23]. One study found no association between cord blood DDE levels and neurodevelopment at ages 6 or 12 months [21].

In the case of exposure to PCBs and the neurodevelopment of children, the results of the presented studies are not consistent. Prenatal exposure to PCBs in neonates (25–48 h after birth) was associated with performance impairments [30]. Poorer Mental and Psychomotor Development Index in children at 6, 7, 16, 18, 30 and 42 months [32, 33, 34] was also noticed. Children exposed to PCBs demonstrated impairment of response inhibition [35, 36, 37], longer response times, and more variation in the response time [43], attention and concentration problems [39, 44], and less masculinized play [42]. In a study performed in Germany, no associations was observed in infants 2 weeks and 24 months of age [31], and in three studies which examined the association between PCBs exposure and neurodevelopment in children [40, 41, 45].

In some of the studies mentioned, the effect of breast-feeding was also investigated. Long-term breastfeeding was found to be protective against the effect of organochlorine pesticides exposure [22]; on the other hand, longer breast-feeding duration was also associated with lower scores on the neurodevelopmental test, and with better spatial organizational skills in the case of prenatal exposure to PCB [43].

Exposure to mercury and neurodevelopment of children. Mercury is found in various chemical forms: elemental Hg, inorganic Hg and organic Hg (ethyl-, methyl-, alkyl- or phenyl-Hg). The chemistry of Hg modulates its toxicity and metabolism: inorganic Hg acts mainly on the kidneys, voliate metallic Hg and especially methylmercury (MeHg) affects the central nervous system [46]. Methylmercury absorbed by the mother in pregnancy, easily cross the placenta and accumulates in the foetus in high concentrations [47]. The vulnerability of the developing human brain is the most important window for harmful Hg compounds [46].

Mercury (Hg) is a neurodevelopmental toxicant commonly encountered as dietary methylmercury, which adversely affects enzymes, cellular membrane function, and neurotransmitter levels [48]. Mercury causes oxidative

stress, lipid peroxidation, and mitochondrial dysfunction, and disrupts synaptic transmission, microtubule formation, amino acid transport, and cellular migration in the developing brain [49]. The principal source of human exposure to organic mercury is fish consumption. This form of mercury is monomethyl mercury (MeHg). Sea mammals and shellfish also carry variable concentrations of MeHg in their tissues. Mercury is such a highly reactive toxic agent that it is difficult to identify its specific mechanism of damage, and much remains unknown about the mechanism [50].

Epidemiological studies have been conducted within variable fish-eating populations in order to examine the consequences of chronic exposure to low doses of methylmercury on the neurodevelopment of children. The results of those studies are inconsistent (Tab. 4). Several birth cohort studies conducted in the Faroe Islands [51, 52], Boston, Massachusetts (USA) [53, 54], Tohoku (Japan) [55], Kraków (Poland) [56, 57], Seychelles [58, 59, 60, 61] and New York (USA) [62] reported an inverse association between the neurodevelopment of children and prenatal mercury exposure.

The results in the Faroe cohort study showed an association between prenatal exposure to mercury and its effects on motor speed, attention, and language at ages 7 and 14 years [51]. In the same cohort, the adverse effects on visual information processing and attention functioning in children aged 14 years was observed [52]. In the study performed in Boston in the United States among infants 6 months of age, an increase of 1 ppm in mercury was associated with a decrement in visual recognition memory scores. Those scores were the highest among the infants of women who consumed > 2 weekly fish servings, but had mercury levels of ≤ 1.2 ppm [53]. Higher mercury levels (≥4.5 ng/g) were associated with poorer child cognitive test performance in the same Boston cohort among children 3 years of age [54]. In Japan, prenatal exposure to methylmercury adversely affected neonatal neurobehavioural function [55].

The aim of the study performed in Poland was to assess the cognitive and psychomotor status of 233 1-year-old children whose mothers were exposed to low, but varying, amounts of mercury during pregnancy [56]. The relative risk for delayed performance increased if the cord blood mercury level was greater than 0.80 μg/L. The risk for delayed performance in the group of infants with greater maternal mercury levels (>0.50 μg/L) was also significantly greater, compared with children whose mothers had mercury levels less than 0.50 μg/L [56]. The same author assessed the neurodevelopment at 12, 24 and 36 months in a bigger group of 374 children [57]. An inverse association found between mercury exposure and both MDI and PDI scores at 12 months of age. Subsequent testing at 24 and 36 months did not confirm a significant association between exposure and cognitive or psychomotor function [57]. In the studies performed in the Seychelles, a 10-fold increase in cord blood mercury concentration was associated with decreased neurologic optimality scores (p=0.03) among infants 2 weeks after birth [58]. In the same cohort of children, an adverse association was observed between MeHg and PDI at 30 months among children periodically evaluated to the age of 9 and 30 months [59]. The same author continued the study and assessed the children's neurodevelopment at the age of 10.7 years [60]. An adverse association was found between methylmercury exposure and Reproduction Task scores (p=0.04), but no association was found with Copying Task scores [60]. Two of 21 neurodevelopmental endopints (decreased performance in the grooved pegboard test, using the non-dominant hand in males and improved scores in the hyperactivity index of the

Table 4. Exposure to mercury and neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
United States, Boston, Massachusetts (Viva Project)						
United States, Boston, Massachusetts 135 mother-infant pair age 6 months	cohort	Hair sample at 6–8 months of pregnancy	Visual Recognition Memory (VRM)	Maternal age, race, education, marital status, infant sex, gestational age, birth weight at gestational age, breast-feeding duration, age at testing	An increase of 1 ppm in mercury was associated with a decrement in VRM score of 7.5 95% CI (-13.7 to -1.2) points. VRM scores were highest among infants of women who consumed > 2 weekly fish servings but had mercury levels </= 1.2 ppm.	Oken 2005 [53]
United States, Boston, Massachusetts 341 mother-infant pair age 3 years	cohort	Blood mercury level at second trimester of pregnancy	The Purdue Pegboard Test, The Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test	Child sex, age at testing, fetal growth, gestational length, breastfeeding duration, birth order, primary language, maternal: Peabody Picture Vocabulary Test score, age, prepregnancy BMI, race, education, marital status, alcohol consumption, smoking during pregnancy, paternal education	Higher mercury levels were associated with poorer child cognitive test performance.	Oken 2008 [54]
United States, New York						
United States, New York 194 children assessed at 36 and 54 months	cohort	Cord blood mercury level	Bayley Scales of Infant Development (BSID), Wechsler Intelligence Scale for Children (WISC)	Race, maternal IQ, per capita family income, child gender, gestational age at birth, maternal age, prenatal ETS exposure, marital status, education, maternal hardship, age at testing	Inverse association with psychomotor scores at 36 months and performance, verbal and full IQ scores at 48 months.	Lederman 2008 [62]

Table 4 (Continuation). Exposure to mercury and neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Japan, Tohoku						
Japan 498 mother-neonate pairs 3 days after birth	cohort	Level of mercury in maternal hair at parturition, PCB level in cord blood	Neonatal Behavioral Assessment Scale (NBAS)	Maternal age, birth weight, parity, PCBs, maternal seafood intake	A negative relationship between the hair mercury level and the motor cluster of NBAS was observed.	Suzuki 2010 [55]
Canada, Quebec						
Canada, Quebec 110 children at age 5 years	cohort	Umbilical cord blood mercury level	Bayley Scales of Infant Development (BSID)	Child age, child gender, testing location, breast-feeding status, maternal binge drinking during pregnancy, haemoglobin status, cord Pb	No association between exposure to mercury and child behaviour.	Plusquellec 2010 [69]
Brazil, Porto Velho						
Brazil, 100 women and newborns at 6 months of age	cohort	Maternal hair Hg, infant hair Hg, maternal tissues Hg	Gesell Developmental Schedules	Socioeconomic status, tissue Hg	No association between exposure to Hg and children neurodevelopment.	Marques 2007 [65]
Europe, Poland						
Poland 233 infants 12 months of age	cohort	Mercury levels in cord and maternal blood at delivery	Bayley Scales of Infant Development (BSID)	Gender of the child, gestational age, maternal age, maternal education	Delayed performance (RR = 3.58 95% CI (1.40–9.14)) if cord blood mercury level was greater than 0.80 mg/L was observed. Risk for delayed performance in the group of infants with greater maternal mercury levels (>0.50 mg/L) also was significantly greater (RR = 2.82 95% CI (1.17–6.79)) compared with children whose mothers had mercury levels less than 0.50 mg/L.	Jędrychowski 2006 [56]
Poland, 374 children at 12, 24 and 36 months of age	cohort	Total mercury level in cord blood	Bayley Scales of Infant Development (BSID)	Gender of the child, maternal education, number of siblings, prenatal ETS exposure	An inverse association between mercury exposure and both MDI (p=0.01) and PDI scores (p=0.04) at 12 months of age. No association between exposure and cognitive or psychomotor function at 24 and 36 months.	Jędrychowski 2007 [57]
Europe, Great Britain						
Great Britain, 7421 British children born in 1991–1992 at 15 and 18 months of age	cohort	Mercury measured in umbilical cord tissue	MacArthur Communicative Development Inventory at 15 months of age and the Denver Developmental Screening Test at 18 months of age	Based on abstract- no information about confounders	Total mercury concentrations were not associated with neurodevelopment.	Daniels 2004 [64]
Europe, Spain Cohort the INMA (Environment and Childhood)						
Spain 1,683 children at 14 months of age	Cohort	Cord blood total mercury level	Bayley Scales of Infant Development (BSID)	Season of delivery, maternal education level, country of birth, maternal employment situation during pregnancy, total fish intake during pregnancy, calorie intake	Doubling in total mercury levels did not show an association with MDI or PDI, however, stratified findings by sex suggest a negative association between prenatal exposure to total mercury and psychomotor development among female infants.	Liop 2012 [70]
Spain, Cohort from Granada						
Spain, 72 children at 4 years of age	Cohort	Children's hair mercury level	McCarthy Scales of Children's Abilities (MSCA)	School term of evaluation, psychologist, place of residence, maternal age, parity, mother's educational level, occupational status	Total mercury level was associated with decrements in the general cognitive, memory, and verbal scores.	Freire 2010 [63]
Europe, Faroe Islands						
Faroe Islands 878 children at 14 years of age	cohort	Cord blood, cord tissue and maternal hair mercury level	Continuous Performance Test (CPT), The Catsys® equipment, Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Copying Test	Age, sex, residence in town/ village, school grade, maternal and paternal employment, time of day, language, and computer experience	An association between prenatal exposure to mercury and effect on speed, attention, language at ages 7 and 14 years.	Debesa 2006 [51]

Table 4 (Continuation). Exposure to mercury and neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Faroe Islands 878 children at 14 years of age	cohort	Cord blood, cord tissue and maternal hair mercury level	The Continuous Performance Test	Age, sex, school grade, maternal and paternal employment, time of day, language, hand dominance, computer experience	Adverse effects on visual information processing and attention functioning were observed.	Julvez 2010 [52]
Republic of Seychelles						
Republic of Seychelles, 182 newborns 2 weeks after birth	cohort	Maternal hair, cord whole blood and serum	The Neurological Examination of the Full-Term Newborn Infant	Socioeconomicstatus, maternal intelligence, maternal age, birth weight, child gender, both parents living with the child	10-fold increase of the cord blood mercury concentration was associated with a decreased neurologic optimality scores (p=0.03) among infants 2 weeks after birth.	Steuerwald 2000 [58]
Republic of Seychelles, 229 children periodically evaluated to the age of 30 months (9, 30 months)	cohort	Maternal hair during pregnancy	Bayley Scales of Infant Development (BSID)	Socioeconomicstatus, maternal intelligence, maternal age, birth weight, child gender, both parents living with the child	An adverse association between MeHg and PDI at 30 months.	Davidson 2008 [59]
Republic of Seychelles, 711 mother-child pairs aged 5.5	cohort	Prenatal- maternal hair during pregnancy Postnatal-mercury in children hair	McCarthy Scales of Children's Abilities (MSCA)	Child gender, birth weight, maternal age, socioeconomic status, HOME, care giver IQ, Child's medical history	No association between MeHg exposure and performance.	Palumbo 2000 [66]
Republic of Seychelles, 87 children at age 9 years	cohort	Prenatal MeHg exposure was determined from maternal hair growing during pregnancy, postnatal- children hair	Wechsler Intelligence Scale for Children (WISC),The California Verbal Learning Test (CVLT), The Boston Naming Test (BNT), Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), The Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test (WRAML), The Purdue Pegboard Test, Trailmaking The Finger Tapping Test	Socioeconomic status, maternal age, maternal history of alcohol consumption during pregnancy, gender, post enrollment disabilities, family crises that could compromise development	No adverse association between maternal MeHg exposure and any developmental outcome measure.	Davidson 2000 [67]
Republic of Seychelles 613 children 5–11 years of age	cohort	Prenatal- Maternal hair during pregnancy Postnatal-mercury in children hair	The Bender Visual Motor Gestalt Test	Maternal age, age at testing, tester, HOME, socioeconomic status, child gender	The adverse association between methylmercury exposure and Reproduction Task scores (p=0.04).	Davidson 2008 [60]
Republic of Seychelles, 643 children at age 9 years	cohort	Prenatal MeHg exposure was determined from maternal hair growing during pregnancy, postnatal- children hair	Wechsler Intelligence Scale for Children (WISC), Woodcock-Johnson Test of Achievement, California Verbal Learning Test, The Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test (WRAML), Finger Tapping Test, Trailmaking, The Purdue Pegboard Test, Bruininks-Oseretsky Test of motor Proficiency, Boston Naming Test, Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), Test of Haptic Matching, Continuous Performance Test	Caregiver IQ, maternal IQ, child's age, HOME, socioeconomic status	Increased exposure was associated with decreased performance in the Grooved Pegboard using the non-dominant hand in males and improved scores in the hyperactivity index of the Conner's scale.	Myers 2003 [61]
Republic of Seychelles, 215 children	cohort	Prenatal MeHg exposure was determined from maternal hair growing during pregnancy, postnatal- children hair	Test was carried out by the Southern and Eastern African Consortium for Monitoring Educational Quality (SACMEQ)	Caregiver IQ, maternal IQ, child's age, HOME, socioeconomic status	No association between prenatal or postnatal exposure and adverse educational measures of scholastic achievements.	Davidson 2010 [68]

PCBs-polychlorinated biphenyls, Hg- mercury, MeHg- methylmercury, ETS-Environmental Tobacco Smoke
MDI- Mental Development Index, PDI-psychomotor Development Index
OR- odds ratio, CI- confidence interval, RR – relative risk
HOME- Home Observation for Measurement of the Environment

Conner's teacher rating scale) were associated with prenatal methylmercury exposure and developmental outcomes at 9 years of age [61] in the same cohort of children.

The study in New York City aimed to determine whether prenatal mercury exposure, including potential release from the World Trade Center disaster, affected the neurodevelopment of children [62]. Higher cord blood mercury (>5.58μg/L) was associated with reductions in developmental scores at 36 and 48 months of age [62].

Only one study in Spain (Granada Cohort) assessed the exposure to mercury postnatally in the hair of children 4 years of age. Total mercury (≥ 1 μg/g) was associated with decrements in the general cognitive (-6.6 points), memory (-8.4 points), and verbal (-7.5 points) scores. [63]. However, another birth cohort study conducted in Bristol (UK) [64], Porto Velho (Brazil) [65], Republic of Seychelles [66, 67, 68], Quebec (Canada) [69] and in Spain [70] did not find association between exposure to mercury and the neurodevelopment of children.

The association between maternal fish intake during pregnancy and offspring's early development of language and communication skills in a cohort of 7,421 British children [64] aged 15–18 months of age was assessed. Total mercury concentrations were low and not associated with neurodevelopment. Fish intake by the mother during pregnancy, and by the infant postnatally, was associated with higher mean developmental scores [64]. Also, no association was found between exposure to fish-Hg during pregnancy, lactation and the neurodevelopment of children at 6 months in Porto Velho, Basil [65].

The cohort of children from the Republic of Seychelles found no association between MeHg exposure and performance on the MacCarthy Scales of Children's Abilities General Cognitive Index among children 5.5 years old [66]. 87 children from the same cohort were evaluated at 9 years of age. The results indicated no adverse association between maternal MeHg exposure and any developmental outcome measure. For three endpoints (Boston Naming Test and two tests of visual motor coordination), enhanced performance in males was associated with increasing prenatal MeHg exposure [67]. A subsequent study was carried out to assess the school achievement of children in the Seychelles Cohort at 9 and 17 years of age [68]. Prenatal methylmercury exposure at a dosage consumed by mothers on a diet rich in fish was not associated with adverse educational measures of scholastic achievements [68]. In the study performed in Quebec (Canada), no association between exposure to mercury and child behaviour at 5 years of age was observed [69]. A study in Spain (Spain Cohort, the INMA – Environment and Childhood)) aimed to evaluate whether cord blood total mercury levels may have a negative effect on both mental and psychomotor development in a maternal-birth cohort from moderate-high fish consumption areas. In multivariate analysis, a doubling in total mercury levels did not show an association with mental or psychomotor developmental delay in children at 14 months of age; however, stratified findings by gender suggest a negative association between prenatal exposure to total mercury and psychomotor development among female infants [70].

The results obtained from review studies suggest that the evidence of adverse effects of prenatal mercury exposure on the neurodevelopment of children are inconclusive. In some studies, exposure to mercury was associated with poorer motor speed, attention, and language at ages 7 and 14 years [51], visual information processing and attention functioning in children 14 years of age [52], and visual recognition memory score at 6 months [53]. An inverse association between mercury exposure and both MDI and PDI [54, 56, 57], decreased neurologic optimality [58], decreased performance [61], Reproduction Task scores [60] decrements in the general cognitive [62, 63] and memory [62] were also observed.

Whereas no association between exposure to mercury and children neurodevelopment was noticed in several studies [64, 65, 66, 68, 69, 70].

The lack of homogeneity in the results should be studied in depth, as well as possible modifying factors that could be influencing the effect of mercury exposure on the neurodevelopment of children. Fish and other seafood may contain beneficial nutrients, such as n-3 fatty acids as well as harmful contaminants, such as mercury. The dietary recommendation for pregnant women should therefore incorporate the nutritional benefits as well as the risk from high fish intake.

Exposure to lead and the neurodevelopment of children. Despite remarkable success in the reduction of the prevalence of elevated blood lead level (BLL) in children, exposure to this heavy metal still remains an important paediatric environmental health problem. Thanks to the public health and regulatory activities limiting the lead content of paint, and the use of tetraethyl lead as a petrol addictive, the BLL decreased in preschool children in the USA, from 15 μg/dl noted in 1970s to the 1.9 μg/dl at the beginning of this century [71]. Although the magnitude of racial and socio-economic disparities has declined, higher blood lead levels are still noted more frequently in a minority children, primarily children in low-income families and those living in older houses [71]. The majority of studies confirmed the neurodevelopmental effect on blood level > 10 μg/dl. These include lowered intelligence, behavioural problems and diminished school performance [72, 73]. As the magnitude of exposure to this heavy metal decreased and the US Center for Disease Control and Prevention lowered its level of concern to 10 μg/dl, recently conducted research has focused on the cognitive developmental effects of lead below this guideline level [74]. Many of these studies also confirmed the existence of adverse effect below that level, and additionally indicate that the rate of decline in IQ scores might be greater at BLL below 10 μg/dl than it is at levels above 10 μg/dl. The pooled analysis performed by Lanphear et al. [72] on data collected from 1,333 children from population-based longitudinal cohort studies indicated that the estimated IQ point decrements associated with an increase in BLL from 2.4–10 μg/dl was 3.9 (95% CI 2.4–5.3), from 10–20 μg/dl 1.9 (95% CI 1.2–2.6) and 20–30 μg/dl 1.1 (95% CI 0.7–1.5).

The mechanism of lead neurodevelopmental effect has been widely studied. Lead has been implicated in diverse process, such as mitochondrial dysfunction, oxidative stress, deregulation of protein turnover, brain inflammation, decreased cellular energy metabolism, lipid peroxidation, altered activity of first and second messenger systems, abnormal neurotrophic factor expression, and altered regulation of gene transmission [71, 75].

Sixteen studies evaluating the impact of lead pre and/or postnatal exposure on child neurodevelopment were identified since 2000 [73, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90] (Tab. 5).

Table 5. Exposure to lead and neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
Europe, Poland (Krakow cohort)						
Krakow, Poland 452 infants at 6 months of age	cohort	Cord BLL	Fagan Test of Infant Intelligence (FTII)	Child gender, maternal education, parity	The mean cord BLL 1.4 µg /dl (95% CI: 1.4–1.5). Visual recognition memory scores were inversely related to cord BLL (β=-0.2; p=0.007). The infants scored lower by 1.5 points with an increase by 1 µ/dl of cord BLL. The mean Fagan score in the lower exposed infants (≤1.7 µg/dl) was 61.0 (95% CI: 60.3–61.7) and in the higher exposed group (>1.7 µ/dl) was 58.4 (95% CI: 57.3–59.7). The estimated risk of scoring the high-risk group of developmental delay due to higher BLL was two-fold greater (OR=2.3; 95% CI: 1.3–4.1) than for lower BLL.	Jedrychowski 2008 [76]
Krakow, Poland 457children at 12, 24 and 36 months of age born to non-smoking women			Bayley Scales of Infant Development (BSID)	Child gender, maternal education, parity, breastfeeding, prenatal and postnatal environmental tobacco smoke	The median cord BLL 1.2 µg/dL (range 0.4–4.6 µg/dL). MDI scores over 3-year follow-up were inversely correlated with cord BLL (cord BLL 1.7 µg/dL vs. <1 µg/dL β=-3.0; 95%CI: -5.2 to -0.7). The effects of prenatal lead exposure on mental score in girls were not significant at any time point of follow-up. At 36 months, prenatal lead exposure was inversely and significantly associated with cognitive function in boys (β=-0.2, p<0.001) and the interaction between BLL and male gender was significant (β=-4.5; 95%CI: -8.3 to -0.6). MDI deficit in boys at 36 months confirmed negative impact of prenatal lead exposure (BLL>1.7 µg/dL vs. BBL <1 µg/dL; β=-6.2, p=0.002).	Jedrychowski 2009 [77]
Krakow, Poland 444 children at 12, 24 and 36 months of age					The median cord BBL 1.2 µg/dl (range 0.4–6.9 µg/dl). An adverse effect of prenatal lead exposure on MDI scores at 12 months (β = −5.4; 95% CI: −11.2 to 0.4), at 24 months of age (β = −7.7; 95% CI: −14.7 to −0.6) at 36 months of age (β = −6.7; 95% CI: −12.5 to −0.9). The average deficit in the cognitive development attributable to lead exposure over 3 years β = −6.6; 95% CI: −1.5 to −1.7.	Jedrychowski 2009 [78]
Kosovo, Yugoslavia						
Kosovo, Yugoslavia 442 children at 3, 4, 5, 7 years of age from smelter town and non-lead-exposed town	cohort	BLL at mid-pregnancy, cord BLL, child BLL	McCarthy Scales of Children's Abilities (MSCA), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC)	HOME, ethnicity, birthweight, maternal age, IQ, education, child gender, number of prior live births, assessment age	Prenatal and postnatal BLL were associated with decrements in children's intelligence (prenatal BLL β=-6.1; p<0.001; postnatal increase relative to prenatal BLL β=-2.7; p<0.05).	Wasserman 2000 [79]
United States						
United States 172 children at 6, 12, 18, 24, 36, 48, and 60 months of age	cohort	BLL in children	Stanford-Binet Intelligence Scale at the ages of 3 and 5 years	Child gender, birth weight, and iron status, mother's IQ, years of education, race, tobacco use during pregnancy, yearly household income, and HOME	Each increase of 10 µg/dL in the lifetime average BLL was associated with a 4.6-point decrease in IQ (p=0.004). For the children whose maximal BLL remained below 10 µg/dL, the change in IQ associated with a given change in lead concentration was greater. IQ declined by 7.4 points as lifetime BLL increased from 1 to 10 µg/dL.	Canfield 2003[80]
United States 79 children at 7 months of age	cohort	Maternal BLL less than 5 µg/dL	Fagan Test of Infant Intelligence (FTII)	Gestational age, age at time of test, birth weight, mother's education	The mean BLL 0.7 µg/dL (range 0.05–3.3 µg/dL). Infants who scored in the upper 5th or 15th percentile of novelty preference scores had lower lead values than those scoring in the lower 5th or 15th percentile. No infant who scored in the upper percentile range was ever classified as having high maternal BLL.	Emory 2003 [81]
United States 246 children at 7.5 years of age	cohort	BLL in children	Wechsler Intelligence Scale for Children (WISC), Wisconsin Card Sorting Task, The Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test (WRAML), The Grooved Pegboard Test	Alcohol and drug use, socioeconomic status, age, marital status, education, child gender, parity, number of children in the household, HOME, primary caregiver's vocabulary, caregiver's level of depression, crowded living conditions, disruption in caregiving, caregiver psychological symptoms, verity of personality disorder, family function, life stress (child and caregiver), domestic violence experienced by the mother, the age of the child, the examiner.	The study show neurobehavioral deficits in relation to low levels of lead in the areas of intelligence, reaction time, visual–motor integration, fine motor skills, attention, including executive function, off-task behaviors, and teacher-reported withdrawn behaviors. Visual inspection of nonparametric regression plots suggested a gradual linear dose–response relation for most endpoints. No threshold discontinuity was evident. Regression analyses in which lead exposure was dichotomized at 10 µg/dl were no more likely to be significant than analyses dichotomizing exposure at 5 µg/dl.	Chiodo 2004 [82]

Table 5 (Continuation). Exposure to lead and neurodevelopmental effects in children

Study population	Type of study	Definition of exposure	Test used	Confounders	Results	References
United States 780 children treated for elevated BLL (20–40µg/dl) at 2 years of age and followed until 7 years of age	Prospective data set from Clinical trial of lead poisoning treatment	BLL in children	Bayley Scales of Infant Development (BSID),Wechsler Intelligence Scale for Children (WISC)	Clinic center, race, sex, language, parent's education, parent's employment, single parent, caregiver's IQ, exact age at both blood measurements	The stronger relationship between BLL at 7 years and IQ at 7 years was found than between IQ at 7 years and the higher 2-year-old BLL; the association of BLL at 5 years and IQ at 5 years was also stronger than that between IQ at 5 years and BLL at 2 years. The strength of the association increases over time (from 2 years of age to 5–7 years of age), despite lower BLL in older children.	Chen 2005 [83]
United States Boston, Massachusetts, Farmington 534 children at 6–10 years of age	New England Children's Amalgam Trial (NECAT)	BLL in children	Wechsler Intelligence Scale for Children (WISC)	Age, race, SES, primary caregiver IQ	Children with 5–10 µg/dL had 5.0 (S.D. 2.3) points lower IQ scores compared to children with blood lead levels of 1–2 µg/dL (p=0.03). Children with levels of 5–10 µg/dL scored 7.8 (S.D. 2.4) and 6.9 (S.D. 2.2) points lower on reading and math composite scores, respectively, compared to children with levels of 1–2 µg/dL (p<0.01). Finally, levels of 5–10 µg /dL were associated with decreased attention and working memory.	Surkan 2007 [84]
United States 194 children at 6, 12, 18, 24, 36,48, 60 and 72 months of age	cohort	BLL in children	Wechsler Intelligence Scale for Children (WISC) at 6 years of age	Child gender, birth weight, transferrin saturation; mother's race, IQ, and education level; HOME, family income, maternal prenatal smoking.	Lifetime average BLL (mean = 7.2 µg/dL) was inversely associated with Full-Scale IQ (p = 0.006) and Performance IQ scores (p = 0.002). Compared with children who had lifetime BLL < 5 µg/dL, children with BLL between 5 and 9.9 µg/dL scored 4.9 points lower on Full-Scale IQ (91.3 vs. 86.4, p = 0.03).	Jusko 2008 [85]
United States New York, Ohio 462 children that were followed from infancy to 6 years of age	cohort	BLL measured at least annually from 1 through 6 years of age	Wechsler Intelligence Scale for Children (WISC-III),	Site average childhood BLL, HOME, birthweight, maternal IQ, maternal education	The ratio of BLL at 6 years to the BLL at 2 years showed a strong effect on IQ (p < 0.001). IQ decreased by 7.0 points for children whose BLL at 6 years of age was 50% greater than that at 2 years compared with children whose 6-year BLL was 50% less than their 2-year BLL.	Hornung 2009 [86]
Mexico						
Mexico Mexico City 294 children at 12 and 24 months of age	cohort	BLL in children	Bayley Scales of Infant Development (BSID)	Child gender, age, birthweight, mother;s IQ,	The mean BLL 4.3 µg/dL (SD 2.2 µg/dL). BLL at 24 months was associated with MDI (β=-4.7; p<0.01) and PDI (β=-5.4; p<0.01) at 24 months. BLL at 12 months was not associated with MDI or PDI scores at 12 months and with MDI at 24 months. For MDI and PDI at 24 months the coefficients that were associated with current BLL were significantly larger among children with BLL <10 µg/dL than it was among children with levels > 10 µg/dL.	Tellez-Rojo 2006 [87]
Mexico Mexico City 146 mother-infant pairs	Cohort	BLL at each trimester of pregnancy, cord BLL, BLL at 12 and 24 months of age	Bayley Scales of Infant Development (BSID)	Current BLL, sex, height-for-age Z-score, current weight, mother's IQ, mother's age	Both maternal plasma and whole BLL during the first trimester (but not in the second or third trimester) were significant predictors (p < 0.05) of poorer MDI scores. A 1-SD change in first-trimester plasma lead was associated with a reduction in MDI score of 3.5 points. Postnatal BLLs in the offspring were less strongly correlated with MDI scores.	Hu 2006 [88]
Egypt						
Egypt Cairo 100 children at 6–12 years of age	Cross-sectional	BLL in children	Wechsler Intelligence Scale for Children (WISC-III) adopted to Arabic norms	Based on abstract- no information about confouders	Median BLL 9 µg /dL (3–28 µg /dL). 43% of children had BLL ≥10 µg /dL, of whom 90% were living in high-risk areas for lead pollution. Children with cognitive dysfunction had significantly higher BLL and lower hemoglobin than those without (p < 0.001).	Mostafa 2009 [89]
Saudi Arabia						
Saudi Arabia 653 children at 6,12,18 and 24 months of age	cohort	cord BLL	Bayley Scales of Infant Development (BSID)	Variety of confounding variables	Prenatal lead exposure was found to be significantly associated with the standardized MDI and PDI scores at the age of 6 months (p=0.02). A borderline significant effect of prenatal lead exposure was also seen on standardized PDI scores at the age of 24 months (p = 0.09). No relationship was seen between postnatal BLL and concurrent cognitive development scores.	Al-Saleh 2009 [90]
India						
India Chennai 74 children at 4–14 years of age	Cross-sectional	BLL in children	The Binet-Kamath IQ test and teachers completed the Connor's Behavioral Rating Scale.	Based on abstract- no information about confouders	Mean BLL 11.1 µg /dL (2.5–38.3). IQ was inversely related to BLL with effect size of approximately 6 points decline for 10 µg/dl increase in blood lead. Children in highest and lowest blood lead quartiles head mean IQ of 95.6 ± 13.3 and 102.0 ± 22.5 respectively.	Bellinger 2005 [73]

MDI – mental development index; PDI – psychomotor development index;
BLL blood lead level
HOME- Home Observation for Measurement of the Environment

The majority of the studies indicate the negative impact of lead exposure at the level <10 μg/dl or even <5 μg/dl on the neurodevelopment of children. An analysis of the Rochester Longitudinal Study indicated decrement of 7 points in IQ at 5 years of age, associated with an increase in mean child BLL from 1–10 μg/dl [80]. A more recent update of this cohort found that 6-year-old children with BLL <5 μg/dl scored 5 IQ points higher than children with BLL between 5–9.9 μg/dl (91.3 vs 86.4; p=0.03) [85]. An updated analysis of the Boston (USA) cohort found similar results among children with maximum BLL <10 μg/dl [91]. A small birth cohort study in Atlanta (USA) reported an inverse association between Fagan intelligence scores at 7 months of age and low prenatal BLL (<5 μg/dl) [81].

Some of the studies aimed at determining the age of greatest susceptibility to lead exposure. A study of the effects of lead on IQ by Wasserman et al. [79] addressed the problem of serial correlation of BLL measurements. They examined pre- and postnatal lead exposure in a Yugoslavian cohort of lead-exposed children. The results indicated that elevations in both prenatal and postnatal BLL were associated with decrements in children's intelligence, and that early childhood BLL were most strongly related to decrements in IQ, but elevated BLL in late childhood were also associated with IQ decrements. Another analysis performed on 146 mother–infant pairs from Mexico city indicated that both maternal plasma and whole blood lead during the first trimester (but not in the second or third trimester) were significant predictors of poorer Mental Development Index (MDI) scores and that postnatal BLL were less strongly correlated with MDI scores [88].

In an analysis of data from a clinical trial of lead poisoning treatment in children with BLL between 20 – 44 μg/dL, Chen et al. [83] attempted to determine whether BLL measured in early or late childhood were more strongly related to IQ scores. The authors concluded that BLL measured at 7 years of age was more strongly related to IQ measured at 7 years than the higher BLL measured at 2 years of age. The same conclusion was made by Hornung et al. [86]. He analyzed two cohorts of children who were followed from infancy to 6 years of age, and concluded that 6-year BLL was more strongly associated with cognitive development than BLL measured in early childhood: IQ decreased by 7 points for children whose BLL at age 6 years of age was 50% greater than that at 2 years, compared to children whose 6-year BLL was 50% less than 2-year BLL.

A series of analyses about the impact of lead exposure on child mental development were performed in Poland (Kraków Cohort) [76, 77, 78]. On average, the mental function of girls was significantly higher than that of boys, and the initial gap between the MDI scores observed between boys and girls at 12 months persisted and even became a little wider by the age of 24 months [77]. The cognitive gap between boys and girls might reflect different rates in cognitive development in both genders in early childhood, or result from different effects of escalating socio-cultural challenges to children's cognitive ability with age. The cognitive gap might also reflect a possible delay in the distinct manifestation of the cognitive deficit recognizable by BSIDII test, or the persisting functional brain damage in boys in the sphere of cognitive function.

Gender differences in exposure to toxic metals have been well documented in the literature. It is thought that gender differences in susceptibility to a toxic environment may result from the already well-documented fact that specific areas of the brain develop differently in males and females under the influence of a disproportionate number of genes present in the X and Y chromosomes and sex hormones. It is understood that estrogen plays an important role in regulating neural structure and brain function, and there is a distinct anatomical difference in the distribution and density of estrogen receptors in the brain between males and females. As males generally have fewer estrogen receptors throughout the CNS, compared to females, it is thought that the consequences of neurotoxicant exposure and the gender differences in the response to toxic exposure can partially depend on the protective effects of estrogen. Moreover, the CNS maturation is accompanied by extensive pruning and competitive eliminations, leading to restructuring and reorganization of brain function. This in turn may lead to more distinct and permanent gender-related differences in the various neurotransmitter systems in both health and disease. These differences may be manifested in early cognitive responses to xenobiotics in childhood.

In conclusion, the weight of evidence suggests that adverse effects on cognitive development are associated with BLL <10 μg/dl.

SUMMARY

The results of the presented studies show that exposure to industrial chemicals (organophosporous pesticides, organochlorine pesticides, PCBs, mercury and lead) may impair the neurodevelopment of children. Studies on exposure to organophosphate, organochlorine pesticides and lead found an inverse effect of those exposures on neurodevelopment, whereas the studies on exposure to PCBs and mercury did not reach a final conclusion (Tab. 6).

Neonates exposed to organophoparus pesticides demonstrated a higher proportion of abnormal reflexes [14, 17], young children had more attention problems [12, 13], especially attention-related performance errors [15], symptoms of pervasive developmental disorders at 3 years of age [12], lower score for copying designs [10], and more difficulties with tasks involving short-term memory [13]. Only one current cross-sectional study performed in China did not find an association between exposure to pesticides and the neurodevelopment of children [4] (Tab. 6).

Exposure to organochlorine pesticides in infants was associated with alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures [26]. Organochlorines exposure was associated with lower psychomotor development in children at 1, 3, 6, 12, 13 months [22, 24, 25], and later at age 4 years, were inversely related to verbal, memory, quantitative and perceptual-performance skills [23]. One study found no association between cord blood DDE levels and the neurodevelopment of children at ages 6 or 12 months [21].

The results of the studies on exposure to PCBs and the neurodevelopment of children are inconsistent. Some suggest that prenatal exposure to PCBs was associated with performance impairments [21, 30] impairment of response inhibition [35, 36, 37], longer response times, more variation in response time [43], attention and concentration problems [39, 44] and less masculinized play [42]. Several studies did not found an association between exposure to PCBs and the neurodevelopment of children [31, 40, 41, 45] (Tab. 6).

Table 6. Neurodevelopmental effect of exposure to chemicals

Neurodevelopmental effects of exposure to chemicals	OP pesticides	Organochorine pesticides	PCB	Hg	Lead
MDI	– (Goudong 2012) [4] + (Rauh 2006, Eskenazi 2007) [12,16]	-(Dravill 2000) [21] + (Ribas-Fito 2003) [22]	-(Wilhelm 2008, Daniels 2003, Gray 2005, Despres 2005) [31,40,41,45] + (Nakajima 2006, Park 2010, Walkowiak 2001) [32,33,34]	+ (Oken 2008, Jędrychowski 2007, Lederman 2008, Freire 2010) [54,57,62,63] -(Daniels 2004, Marques 2007, Davidson 2000, Plusquellec 2010, Liop 2012) [64,65,67,69,70]	+ (Jedrychowski 2009a,b, Al-Saleh 2009, Tellez-Rojo 2006, Hu 2006, Emory 2003, Mostafa 2009) [77,78, 90,87,88,81,89]
PDI	-(Goudong 2012) [4] + (Rauh 2006) [12]	+ (Ribas-Fito 2003, Torres-Sanchez 2007, Eskanazi 2006) [22,24,25] -(Dravill 2000) [21]	-(Wilhelm 2008, Daniels 2003, Gray 2005, Despres 2005) [31,40,41,45] + (Nakajima 2006, Park 2010, Walkowiak 2001) [32,33,34]	+ (Suzuki 2010, Davidson 2008, Lederman 2008) [55,59,62] -(Jędrychowski 2007, Daniels 2004, Marques 2007, Davidson 2000, Plusquellec 2010, Liop 2012) [57,64,65,67,70]	+ (Al-Saleh 2009, Tellez-Rojo 2006) [90,87]
Increased number of abnormal reflexes	+ (Young 2005, Engel 2007) [14,17]				
Prevasive developmental disorders	+ (Rauh 2006, Eskanzai 2007) [12,16]				
Attention problems	+ (Rauh 2006, Ruckart 2004, Sanchez-Lizzardi 2008) [12,13,15]	+ (Sagiv 2008) [26]	+ (Grandjean 2001) [44]	+ (Debes 2006, Juvlez 2010) [51,52]	+ (Chiodo 2004) [82]
Poorer memory	+ (Ruckart 2004) [13]	+ (Ribas-Fito 2006) [23]	+ (Jacobson 2003) [39]	+ (Lederman 2008, Oken 2005) [62,53]	+ (Jędrychowski 2008 Emory 2003) [76,81]
Increased reaction time	+ (Grandjean 2006) [10]				+ (Chiodo 2004) [82]
Quality of alertness		+ (Sagiv 2008) [26]			
Quality of alert responsiveness		+ (Sagiv 2008) [26]			
Problems with responding (longer response time, more variation in response time, impairment of response inhibition, impulsive responding)			+ (Verugdenhil 2004, Stewart 2003, 2005, 2006) [43, 35,36,37]		
Poorer concentration			+ (Jacobson 2003) [39]		
Performance impairment			+ (Stewart 2000, Dravill 2000) [30,21]	+ (Jędrychowski 2006, Myers 2003) [56,61] -(Palumbo 2000) [66]	
Less masculinized play			+ (Verugdenhil 2002) [42]		
Decrease in IQ scores			+ (Stewart 2008) [38]		+ (Canfield 2003, Surkan 2007, Bellinger 2005, Jusko 2008, Chen 2005, Wasserman 2000, Chiodo 2004, Hornung 2009) [80,84,73,85,83,79,82,86]
Greater Impulsivity			+ (Jacobson 2003) [39]		
Scholastic achievements				-(Davidson 2010) [68]	

MDI – mental development index; PDI – psychomotor development index;

At present, there is insufficient evidence of the possible neurotoxic effects of prenatal mercury exposure and more research is needed. Some studies suggest that exposure to mercury was not associated with poorer neurodevelopment of children [64, 65, 66, 68, 69, 70]. On the other hand, some studies have found significant associations with poorer motor speed, attention, language [51], visual information processing and attention functioning [52], visual recognition memory score [53], and poorer child cognitive test performance [54, 61, 62, 63]. An inverse association between mercury exposure and both MDI and PDI [56, 57], decreased neurologic optimality [58], and memory [62], has also been observed (Tab. 6). It is therefore advisable to continue evaluating children to ascertain whether exposure to mercury may impair neurodevelopment.

In the case of studies on exposure to lead (BLL <10 μg/dl), the weight of evidence suggests adverse effects on Mental Development Index (MDI) [77, 78, 87, 90], Psychomotor Development Index (PDI) [87, 90] and IQ [73, 79, 80, 83, 84, 85] (Tab. 6).

Differences in the results between studies. There are possibly numerous factors contributing to the divergent results between studies. The various developmental endpoints used may be a possible explanation for the different results. The use of different biomarkers to ascertain prenatal exposure may have some bearing on the statistical association. Studies have used a variety of biomarkers, such as maternal hair, maternal blood, umbilical cord blood, meconium, children's blood, children's hair, breast milk for exposure assessment [57]. The choice of covariates for statistical models may also impact on the results. A further issue is the possibility of concomitant exposure to other neurotoxicants. Other potential explanations for the differences among studies

include the type and timing of exposure, dose, measurement of the exposure or the outcome. The same exposure at different points in development could result in an adverse effect on motor systems versus memory or executive functions. Similarly, exposures at different concentrations or for different lengths of time could potentially produce differential effects. Therefore, the constellation of observed effects should not be expected to be the same in different children exposed to the same neurotoxic agent [92].

Studying neurodevelopmental vulnerabilities in children is very difficult. Varying definitions of end points, non-specific end points caused by multiple factors, lack of exposure and effect surveillance data, confounders and effect modifiers, and long latency periods between exposures and outcomes, complicate attempts to reach definitive conclusions through epidemiologic studies.

Assessment of exposure in the studies. The exposure assessment in most of the studies mentioned is based on the biomarker of exposure. In the case of organophosphate pesticides, maternal or child urine was analyzed, based on the dialkylphosphate pesticide metabolites (DAPs) [4, 13, 14, 15, 16, 17], the level of chlorpyrifos was also analyzed in the cord plasma [12], as well as erythrocyte acetylcholine esterase activity [10], which is the best biomarker of exposure to OP pesticides. No biomarker of exposure was used only in one study [11] where the exposure was assessed on residence in an agricultural area. DAP metabolites are limited as biomarkers of exposure. Recent studies suggest that urinary metabolite levels may reflect exposure, not only to OP parent compounds, but also to the potentially less toxic ambient metabolites [93]. The exposure to OPs varies considerably from day-to-day, therefore the DAPs from one urine spot sample may not represent the average exposure over time [16]. The organochlorine pesticides and PCBs were measured in blood, serum, cord blood and cord serum [21, 22, 23, 24, 25, 26, 30, 32, 33, 35, 36, 37, 38, 39, 40, 41, 45]. In the case of PCBs exposure, assessment of breast milk was also used [31, 34, 42, 43]. The level of mercury in the umbilical cord and maternal blood [51, 52, 54, 56, 57, 62, 64, 69, 70] is frequently assessed, but maternal or foetal hair are also used [53, 55, 58, 59, 60, 61, 63, 65, 66, 67, 68]. Hair strands are the best integratory of past mercury exposure [65]. Whereas detailed comparison of various prenatal exposure indices within one cohort has shown that the cord blood concentration is consistently the most precise predictor of nervous system deficits determined during postnatal follow up [94]. Studies evaluating the health consequences of lead exposure measure such a metal level in the blood. The majority of studies focused on the BLL below 10 μg/dl or even below 5 μg/dl. For the prenatal exposure assessment, the studies measured maternal BLL (in the pregnancy period) and/or cord BLL [76, 77, 78, 79, 81, 88, 90], whereas for exposure assessment within the first years of life, the series analysis of BLL in children are performed [73, 79, 80, 82, 83, 84, 85, 86, 87, 89].

Confounders. Early childhood is a period of dramatic development of mental and psychomotor functions of a child, where many environmental factors concurrently play very important roles. One of these factors is certainly the maternal education which appears to be so crucial in the mental development of the child [57]. In some neurotoxic epidemiological studies, the effects of exposure to these compounds on child development are also seen to be related to socio-economic risk factors. Children from lower social economic backgrounds were more vulnerable to the negative cognitive effects of prenatal exposure to lead than children in more advantaged families [3]; it is therefore recommended that the study results should be adjusted for this factor. Also, a very important confounder is the child's gender, as the neuro-developmental test used in the study may be designed to assess areas of development, such as motor coordination and visuo-spatial orientation, that develop differently in the two genders. Variables, which are difficult to measure, such as: subtle parent-child intercation aspects or ascpects related to self-esteem and emotional development may also have an impact on the results [42].

Concerning the covariates and confounders affecting the endpoints in most of the presented studies, confounders were included in data analysis, such as maternal age, birth weight, education, race, gender, exposure to different neurotoxicants.

Tests used in the studies assessing the neurodevelopment of children. Extensive literature exists on the use and interpretation of neurodevelopmental tests that serve as outcome measures in population studies examining effects of environmental exposures.

Among the problems that interfere with a more complete understanding of the incidence and etiology of neuro-developmental disorders are learning-related disorders that may be isolated as mild and specific, or associated with severe mental retardation. This test should be sensitive enough to detect the different chemical effect, if they are present. The tests used in reviewed studies are presented in Table 7.

To assess infant neurodevelopment, the Brazelton Neonatal Behavioural Assessment Scale and Fagan Test of Infant Intelligence were used [14, 17, 21, 30, 76, 81]. In evaluating the neurodevelopment of children the most often used test is: the Bayley Scales of Infant Development [12, 16, 22, 24, 25, 31, 32, 33, 34, 40, 56, 57, 59, 62, 69, 70, 77, 78, 83, 87, 88, 90], the Wechsler Intelligence Scale for Children [12, 16, 22, 24, 25, 31, 32, 33, 34, 40, 51, 55, 56, 62, 70, 79, 82, 83, 84, 85, 86, 89], and the McCarthy Scales of Infant Development [23, 35, 63, 66, 79]. In most of the studies mentioned in the presented review, a change in a few points on the neurodevelopmental scales was observed. This may seem clinically unimportant for an individual child. However, beginning with studies from the population level, it can be predicted that a slight shift in the mean performance in the adverse direction can result in a substantial increase in the number of children who are in the subnormal range in the clinical setting [95].

Study design. Most of the studies on exposure to organochlorine and organophosphate pesticides, PCBs, mercury and lead, used a prospective cohort design. A cross-sectional design was used in studying the exposure to organophosphate pesticides [4, 10, 11, 13, 15] and to lead [89, 73]. Also, in the case of assessment of lead exposure on the neurodevelopment of children, data from clinical trials were used (New England Children's Amalgam Trial and Clinical trial of lead poisoning treatment) [83, 84]. In cross-sectional studies, behavioural functions are measured in exposed subjects at one point in time, and typically related to concurrent exposure, either relative to unexposed, but otherwise comparable subjects, or relative to one continuous exposure variable using regression models. In prospective studies, associations are established between changes in

Table 7. Test used in assessment of neurodevelopmental effects in children

Test used	What measures?	Chemical of interests, author, year
The Brazelton Neonatal Behavioural Assessment Scale (NBAS)	Infant behaviour is divided in seven domains: – habituation – ability to respond to and inhibit discrete stimuli while asleep – orientation – attention to visual and auditory stimuli and quality of overall alertness – motor – motor performance and quality of movement and tone – range of state – measure of infant arousal and state ability – regulation of state – ability to regulate state in the face of increasing levels of stimulation – automatic stability – signs of stress related to homeostatic adjustment of the central nervous system – number and type of abnormal primitive reflexes.	Organophospate pesticides [Young 2005, Engel 2007] [14,17], organochlorine pesticides [Sagiv 2008] [26], PCB [Stewart 2000] [30], Hg [Suzuki 2010] [55]
Fagan Test of Infant Intelligence (FTII)	Test that relies on an infant's memory as the main measure of intelligence. In the test, the infant is presented with a series of visual images. After a period of time, he/she is presented with the same images again and the length of his/her gaze is measured to determine how many of them he/she remembers.	Organochlorine pesticides [Darvill 2000] [21], PCB [Darvill 2000] [21], Pb [Jędrychowski 2008, Emory2003] [76,81]
The Neurological Examination of the Full-Term Newborn Infant	Assess functional abilities, most reflexes and responses, and the stability of behavioural status during the examination.	Hg [Steuerwald 2000] [58]
Bayley Scales of Infant Development (BSID)	BSID is a standard series of measurements to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers. It consists of two scales: Mental Development Index (MDI) variety of cognitive abilities, Psychomotor Development Index (PDI) characterizes large muscle and fine motor coordination.	Organophosphate pesticides [Rauh 2006, Eskenazi 2007] [12,16] organochlorine pesticides [Ribas-Fito 2003, Eskenazi 2006,Torres-Sanchez 2007] [23,24,25], PCB [Park 2010, Nakajima 2006, Daniels 2003] [32,33,40], Hg [Jędrychowski 2006, Jędrychowski 2007, Lederman 2008, Davidson 2008, Plusqellec 2010, Llop 2012] [56,57,62,67,69, 70] Pb [Jędrychowski 2009a,b, Chen 2005, Tellez-Rojo 2006, Hu 2006, Al-Saleh 2009] [77,78,83,87,88,90]
Gesell Developmental Schedules	Test evaluate the physical, emotional, and behavioral development of children. Describes typical behavior at specified ages in the following areas: ability to adapt, motor functioning, use of language and social interaction.	Organophosphate pesticides [Goudond 2012] [4], Hg [Marques 2007] [65]
Wechsler Intelligence Scale for Children (WISC)	It provides subtest and composite scores that represent intellectual functioning in verbal and performance cognitive domains, as well as providing a composite score that represents a child's general intellectual ability.	Organophospate pesticides [Grandjean 2006, Sanchez-Lizardi 2008] [10,15], PCB [Stewart 2008, Jacobson 2003, Gray 2005, Grandjean 2001] [38,39,41,44], Hg [Debes 2006, Myers 2003, Lederman 2008, Davidson 2000,] [51,61,62,67], Pb [Wasserman 2000, Chiodo 2004, Chen 2005, Surkan 2007, Jusko 2008, Hamoung 2009, Mostafa 2009] [79,82,83,84,85,86,89]
McCarthy Scales of Children's Abilities (MSCA)	MSCA is used to assess the abilities of preschool children. The test consists of different scales: general cognitive, verbal, perceptual-performance, quantitative, memory and motor.	Organochlorine pesticides [Ribas-Fito 2003] [22], PCB [Stewart 2003] [35], Hg [Freire 2010, Palumbo 2000] [63,66], Pb [Wasserman 2000] [79]
Griffiths Scales of Infant Development	The test cover five areas of infant development: locomotion, personal-social, hearing and language, eye-hand coordination, performance.	Organochlorine pesticides [Ribas-Fito 2003] [22]
Children's Memory Scale	Comprehensive learning and memory test for children ages five to 16 which compares memory and learning to ability, attention, and achievement.	Organophosphate pesticides [Sanchez-Lizardi 2008] [15]
The Trail-Making test- Part A and Part B	Test assess the multistep processing involving more than one cognitive function area (visual perception, motor speed, sequential skills and symbol recognition).	organophosphate pesticides [Ruckart 2004, Sanchez-Lizardi 2008] [13,15], Hg [Myers 2003, Davidson 2000] [61,67]
Achenbach Child Behavior Checklist [CBCL]	The test by which parents or other individuals who know the child well rate a child's problem behaviors and competencies.	organophosphate pesticides [Rauh 2006, Sanchez-Lizardi 2008] [12,15]
The Continuous Performance Test (CPT)	CPT is a neuropsychological test which measures a person's sustained and selective attention and impulsivity.	PCB [Stewart 2005,Jacobson 2003, Grand jean 2001] [36,39,44], Hg [Debes 2006, Juvlez 2010, Myers 2003] [51,52,61]
Connor's Behavioral Rating Scale	An assessment tool that prompts the teacher to provide valuable information about the child's behavior in a classroom setting.	Pb [Bellinger 2005] [73]
Wisconsin Card Sorting Test (WCST)	WCST provides a measure of deductive reasoning and an estimate of the subject's ability to shift to a new strategy (or response set) when reinforcement contingencies change. It provide measures of perseverative responding and impulsivity.	Organophosphate pesticides [Sanchez-Lizardi 2008] [15], PCB [Jacobson 2003] [39], Pb [Chiodo 2004] [82]
Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)	Test measures the integration of visual and motor skills.	Organophosphate pesticides [Ruckart 2004] [13], Hg [Myers 2003, Davidson 2000] [61,67]
The Kaufman Brief Intelligence Test	Test measures general intelligence, verbal ability and nonverbal reasoning.	Organophosphate pesticides [Ruckart 2004] [13], PCB [Walkowiak 2001] [34]
The Purdue Pegboard Test	Test measures visual-motor coordination, manual dexterity and motor speed.	Organophosphate pesticides [Rolhman 2005, Ruckart 2004] [11,13], Hg [Oken 2008, Myers 2003,Davidson 2000] [54,61,67], Pb [Chiodo 2004] [82]
The Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning test (WRAML)	Assess memory functions in children. The screening version of this test consisted of four subtests that examine picture, design, story memory and verbal learning.	Organophosphate pesticides [Ruckart 2004] [13], Hg [Oken 2008, Davidson 2000, Myers 2003] [54,61,67], Pb [Chiodo 2004] [82]

Table 7 (Continuation). Test used in assessment of neurodevelopmental effects in children

Test used	What measures?	Chemical of interests, author, year
The Verbal Cancellation Test	Test measures sustained selective attention.	Organophosphate pesticides [Ruckart 2004] [13]
The Personality Inventory for Children	Test assessed the child's behavior and cognitive status.	Organophosphate pesticides [Ruckart 2004] [13]
The Vineland Adaptive Behavior Scales	Test measures communication, daily living skills (eating and dressing, household tasks), time and money skills, socialization and motor skills.	Organophosphate pesticides [Ruckart 2004] [13]
Santa Ana Dexterity	Test of motor coordination.	Organophosphate pesticides [Grandjean 2006, Rohlman 2001] [10,11]
Stanford-Binet Copying Test	Test of copying of visual designs and assesses visuospatial and visuoconstructional function.	Organophosphate pesticides [Grandjean 2006] [10], Hg [Debes 2006] [51], Pb [Canfield 2003] [80]
Finger Tapping Test	Test of motor speed and coordination.	Organophosphate pesticides [Grandjean 2006] [10], PCB [Grand jean 2001] [44], Hg [Davidson 2000, Myers 2003] [61,67]
Simple Reaction Time Test	Test reaction time after visual and auditory stimulus.	Organophosphate pesticides [Grandjean 2006] [10]
Differential Reinforcement of Low Rates task (DRL)	A schedule in which a minimum amount of time must elapse between responses in order for reinforcement to occur.	PCB [Stewart 2006] [37]
Sternberg Memory Paradigm	Test measures of working memory.	PCB [Jacobson 2003] [39]
Pre-School Activities Inventory (PSAI)	Test designed to discriminate play behaviour both within and between the sexes.	PCB [Vreugdenhil 2002] [42]
Tower of London (TOL)	Test measures higher order problem-solving ability.	PCB [Vreugdenhil 2004] [43]
Hand–Eye Coordination Test	Test assess the hand eye coordination skill.	PCB [Grand jean 2001] [44]
Boston Naming Test (BNT)	Neuropsychological assessment tool to measure confrontational word retrieval in individuals with aphasia or other language disturbance.	PCB [Grandjean 2001] [44], Hg [Davidson 2000, Myers 2003] [61,67]
Bender Visual Motor Gestalt Test	Psychological assessment used to evaluate visual-motor functioning, visual-perceptual skills, neurological impairment, and emotional disturbances.	PCB [Grandjean 2001] [44], Hg [Davidson 2008] [60]
California Verbal Learning Test (CVLT)	Neuropsychological test which assess an individual's verbal memory abilities.	PCB [Grandjean 2001] [44], Hg [Davidson 2000, Myers 2003] [61,67]
The Catsys system developed by Danish Product Development	Test used to record postural hand tremor, reaction time and postural sway.	PCB [Despres 2005] [45], Hg [Debes 2006] [51]
MacArthur Communicative Development Inventory	Parent report forms for assessing language and communication skills in infants and young children.	Hg [Daniels 2004] [64]
The Denver Developmental Screening Test	Test for screening cognitive and behavioural problems in preschool children.	Hg [Daniels 2004] [64]
Visual Recognition Memory (VRM)	Test assess the health and cognitive functioning of infants during the first year of life.	Hg [Oken 2005] [53]
School achievements- Test was carried out by the Southern and Eastern African Consortium for Monitoring Educational Quality (SACMEQ)	Test assess children for educational achievement in Reading Comprehension and Mathematics.	Hg [Davidson 2010] [68]
Woodcock-Johnson test of achievement	Test assess learning and achievement.	Hg [Myers 2003] [61]
Bruininks-Oseretsky Test of Motor Proficiency	Test assess motor functions.	Hg [Myers 2003] [61]
Haptic Matching	Test assess visual-motor integration.	Hg [Myers 2003] [61]
Children's Category Test	Test measures the complex intellectual functioning of higher-order cognitive abilities.	Hg [Debes 2006] [51]

neuro-behavioural functions relative to natural exposure history. This approach offers an opportunity to identify critical periods of exposure and to clarify whether the observed effects are reversible or not [96]. The longitudinal design has potential to provide important information on the long-term impacts of early exposures, as well as on introductions among chemical exposures, social and behavioural factors, and genetically determined susceptibility to xenobiotic. The longitudinal character of the studies made it possible to obtain sufficient information concerning maternal and child characteristics that may affect maternal and psychomotor development, as well as those that may act as confounders of exposure. Because the study population was followed-up over time, it was possible to detect changes in certain variables, such as smoking, which may affect the cognitive development of children.

CONCLUSIONS

The results from the reviewed studies suggest that exposure to organophospate pesticides, organochlorine, PCBs, mercury and lead, may affect the neurodevelopment of children. Studies on exposure to organophosphate and organochlorine pesticides and lead found an inverse effect of such exposure on neurodevelopment, whereas the studies on exposure to PCBs and mercury did not reach a conclusion. The studies were mostly well designed, using prospective cohorts (a cross-sectional design was used in studying the exposure to organophosphate pesticides and lead), and the exposure assessment was based on the biomarker of exposure. Concerning the covariates and confounders affecting the endpoints, in most of the studies mentioned, confounders were included in data analysis, such as, maternal age, birth

weight, education, race, gender, and exposure to different neurotoxicants. In order to ascertain the early cognitive, motor and language outcomes of chemical exposures, the Brazelton Neonatal Behavioural Assessment Scale and Fagan Test of Infant Intelligence was used in the case of infants, and the Bayley Scales of Infant Development, Wechsler Intelligence Scale for Children and the McCarthy Scales of Infant Development were most frequently used for children. These are well standardized and the most common tools used for evaluating the neurodevelopmental effects, and offer an early and fairly comprehensive measure of the development of a child.

Because the neurotoxicants may readily cross the placenta, and because the foetal brain must be regarded as particularly sensitive to neurotoxicant exposure, consideration regarding the reduction of exposure should be implemented. The knowledge that a chemical is neurotoxic should prompt efforts to restrict its use and control exposure. Previous evidence-based programmes of exposure prevention, such as those directed against the exposure of children to lead, have been highly successful, although they were initiated only after substantial delay [2].

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