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The impact of air pollution to central nervous system in children and adults

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Abstract

The aim of this paper was to review studies analyzing the associations between air pollution and neurodevelopment in children as well as the effect on adult population. Effect of prenatal exposure to polycyclic aromatic hydrocarbons (PAHs, benzo[a] pyrene, B[a]P) were already studied on cohorts from New York, Poland, China, and Spain. All results indicate changes of child behavior and neurodevelopment at the age of 3–9 years, decrease of IQ, increase of Attention Deficit Hyperactivity Disorder (ADHD), decrease of brain-derived neurotrophic factor (BDNF), reduction of left hemisphere white matter.

Effect of traffic-related air pollution (TRAP) to neurobehavioral development in children, measured as PM2.5 (particulate matter <2.5 μm), PM10, elemental carbon (EC), black smoke (BC), NO_2, NOx, were studied in USA, Spain, Italy, and South Korea. Increased concentrations of TRAP were associated with the increase of ADHD, autism, affected cognitive development; PM2.5 decreased the expression of BDNF in placenta.

Increased concentrations of PM2.5 affected adults cognition (episodic memory), increased major depressive disorders. Increased concentrations of NO_2 were associated with dementia, NOx with Parkinson's disease.

Increased concentrations of PAHs, PM2.5 and NO_2 in polluted air significantly affect central nervous system in children and adults and represent a significant risk factor for human health.

STUDIES IN CHILDREN

Environmental factors affecting behavioral function

Behavioral function may be affected in two ways:

1. through exposure to pollutants during neonatal development or by
2. affecting gametes and transmitting induced changes to progeny.

First experimental data were obtained several decades ago, indicating that behavioral changes induced by air pollution may be a new problem.

The effect of air pollutants on behavioral alterations was studied by Singh (1986, 1988 and 1989). Pregnant mice were exposed during the 7th–18th day of pregnancy. Exposure to SO_2, NO_2 and CO increased the time required for the righting reflex

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and aerial righting score, which indicate significant functional deficits in the progeny of mice. The effect of mutagens was studied as male mediated effects. Male rats were treated for 15 days by cyclophosphamide and mated 100 days after treatment with virgin females. The learning deficits were observed in the F1, F2 as well as F3 generations (Auroux *et al.* 1990). Following acute NO exposure to paternal rats, the offspring demonstrated delays in developmental indices and neuroendocrine responses (Friedler and Meadows 1987). Widespread environmental mutagen in polluted air is benzo[a] pyrene (B[a]P). Recently Meier *et al.* (2017) proved that exposure to B[a]P to pregnant mice significantly increased mutation frequency in brain, bone marrow, liver, and sperm, higher proportion of mosaicism particularly in brain.

Environmental mutagens and other pollution factors may significantly affect brain development. This may occur during the critical and sensitive periods of CNS development as well as during the third trimester, when induced changes may correspond to various behavioral defects – patterns varying from learning ability and IQ to various other forms of minimal brain dysfunction as well as expressed mental illness. Based on the results obtained in mammals, we can assume that mutations in gametes can accumulate from generation to generation. Behavioral changes induced in the parental generation may be potentiated, if environmental pollution simultaneously affects the development of their children. In a longterm, this means that this type of injury may potentiate in time, resulting in decreasing IQ and various behavioral dysfunction.

The comparison of the morbidity of children 7–15 years old in the industrially polluted region of Northern Bohemia with the morbidity in the Czech Republic suggested that there are approximately twice as many mentally ill and retarded children in these polluted regions. Therefore Sram (1991) hypothesized that in utero exposure of the fetus to air pollutants may cause functional changes in the nervous system expressed later as developmental disorders or neurobehavioral impairment. Later neurobehavioral studies in the mining district Teplice showed evidence of the higher prevalence of learning disabilities in 2nd- and 4th-grade children from the highly polluted mining district as teachers reported significantly more children for the clinical assessment of learning or behavioral problems (27% in exposed vs. 13% in control districts) (Sram *et al.* 1996).

Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAH) on neurodevelopment

New York cohort. Federica Perera was a pioneer of this topic, based in the Columbia Universty of New York. She has studied the cohort of nonsmoking African-American and Dominican mothers and children to evaluate the role of prenatal exposure to urban pollutants. First results indicated that exposure to PAH air pollutants during pregnancy produced DNA damage and impaired fetal growth (Perera *et al.* 2003).

At the age of 3, child behavior and neurodevelopment was evaluated by the Bayley Scales of Infant Development-Revised (BSID-II) to assess cognitive and psychomotoric development at 12, 24, and 36 months of age (Bayley 1993). Prenatal exposure to 3.49 ng PAH/m^3 affected mental development index. Results suggest that more exposed children are potentially at risk of performance deficits (language, reading, and math) in the early school years. It was the first study proving that environmental PAHs levels in New York may adversely affect cognitive development in children (Perera *et al.* 2006).

At the age of 5 years intelligence was assessed by using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (N=249). High prenatal PAH exposure (above the median 2.26 ng/m^3) affected full-scale and verbal IQ (intelligence quotient) score (Perera *et al.* 2009). It was the first epidemiological study of the effects of prenatal PAH exposure on child IQ.

Later, Lovasi *et al.* (2014) evaluated the same cohort (N=277) at the age of 5 years scores on WPPSI-R the impact of prenatal PAH exposure and neighborhood context variables as poverty, low educational attainment, low English language proficiency, and inadequate plumbing. Higher prenatal PAH exposure (above the median 2.26 ng/m^3) predicted lower total and verbal score at age 5 years. Neighborhood limited English language proficiency was associated with lower WPPSI-R total, verbal, and performance IQ scores, low neighborhood-level educational attainment was associated with lower performance IQ scores. These findings suggest that early life exposure to neighborhood social disadvantages is associated with lower test scores at age 5.

At the age of 6–7, children´s behavior was examined using Child Behavior Checklist (CBCL, derived from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., DSM-IV), scoring anxious/depressed and attention problems (N=253). Children of mothers with higher PAH exposure (above the median 2.26 ng/m^3) had significantly more symptoms of anxious/depressed and attention problems. Similar results were confirmed when exposure was evaluated using PAH-DNA adducts in the cord blood. These results provide additional evidence that air pollution by PAH in New York can adversely affect child behavior (Perera *et al.* 2011, 2012).

At the age of 7 years (Vishnevetsky *et al.* 2015) studied the effect of prenatal exposure of PAHs (determined as PAH-DNA adducts in cord blood), maternal hardship on child IQ (N=273). Maternal hardship prenatally, at child age 6 months, and 1, 2, 3, and 5 years was assessed by asking about affordance of food, a place to stay, gas/electricity, clothing. Child IQ at age 7 years assessed by the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). DNA adducts were significantly associated with full scale IQ, perceptual

reasoning and working memory only within the high hardship group. This report indicates that socioeconomic disadvantage can increase the adverse effects of air pollutants; associations between high DNA adducts in cord blood and reduced IQ were significant only among the group of children whose mothers reported high material hardship.

At the age of 9 years Perera *et al.* (2014) assessed Attention Deficit Hyperactivity Disorder behavior problems (ADHD) (N=250) by CBCL. High maternal DNA adducts were insignificantly associated with DSM-oriented Attention Deficit Hyperactivity Disorder behavior problems scale on the CBCL. Authors interpreted their results that they suggest that air pollution by PAH in New York may play a role in childhood Attention Deficit Hyperactivity Disorder behavior problems (Perera *et al.* 2014).

Later Perera *et al.* (2015) studied on this cohort (N=450) the associations between prenatal PAH exposure, PAH/DNA adducts and brain derived neurotrophic factor (BDNF, a protein involved in neuronal growth) concentrations in the cord blood, and neurodevelopment at age 2 years, using Bayley Scales of Infant Development Mental Development Index (MDI). PAH-DNA adducts by ^{32}P-postlabeling was a significant predictor of lower BDNF concentrations as well as lower MDI scores. The obtained data suggest that prenatal exposure to PAH may adversely affect MDI outcomes at ages 2 and 3 years as well as the levels of BDNF in the fetus.

Abid *et al.* (2014) studied the relationship between childhood PAH exposure in urine and prevalence of ADHD, learning disability (LD), and special education (SE) in the U.S. representative sample of 1 257 children 6–15 years of age. Multivariate logistic regression was used to determine the association between PAH metabolites and ADHD, LD, and SE. All characteristics were affected by maternal smoking during pregnancy and smokers in household. Children exposed to higher levels of fluorine metabolites had increased use of special education services. But no other developmental disorders as ADHD or LD were associated with urinary PAH metabolites.

Peterson *et al.* (2015) studied the impact of prenatal exposure to PAHs on brain white matter and cognitive and behavioral functions in 40 children at 7–9 years of age using magnetic resonance imaging (MRI) (20 children with exposure to PAHs above median 8.2±7.6 ng/m^3, 20 children below median 2.1±0.9 ng/m^3). Neurodevelopmental outcomes were measured by CBCL and WISC-IV. Authors detected dose-response relationship between prenatal PAH exposure and subsequent reduction of the white matter surface, almost exclusively to the left hemisphere of the brain. Reduced left hemisphere white matter was associated with slower information processing speed during intelligence testing, white matter reductions was also associated with attention problems and ADHD. Results indicate that prenatal exposure to PAH air pollutants contributes to slower processing speed, ADHD symptoms, and externalizing problems in urban youth by disrupting development of left hemisphere white matter.

Polish cohort. Another prospective cohort of Caucasian mothers and children were followed in Krakow, Poland (Jedrychowski *et al.* 2004). At the age of 5, children (N=214) were assessed for their nonverbal reasoning activity by Raven Colored Progressive Matrices (RCPM). Prenatal exposure to PAH higher than median 17.96 ng/m^3 decreased RCPM scores (Edwards *et al.* 2010). Transplacental exposures to PAHs have been linked to decrements in head circumference, birth weight and birth length. These decrements have potential long-term implications for producing lower cognitive functioning and poorer school performance in childhood (Hack *et al.* 1991).

At the age of 7 years, children (N=170) were assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R). The risk of depressed verbal IQ index (DepVIQ) was increased by prenatal as well as postnatal PAH exposure. Long-term breastfeeding (at least 6 months) showed a protective effect. It was the first epidemiological study showing that prenatal PAH exposure measured by cord blood PAH-DNA adducts is associated with cognitive dysfunction (DepVIQ) Jedrychowski *et al.* 2015).

Chinese cohort. In 2002, a study from Tongliang, China, was assessing the impact of prenatal exposure to PAHs according cord blood PAH-DNA adducts (N=110) to developmental quotients (DQs) in motor, adaptive, language, and social area. Increased adduct levels were associated with decreased motor area DQ, language area DQ, and average DQ Tang *et al.* 2008).

The same cohort was studied in 2005, one year after a coal-fired power plant was shut down. Child development was assessed by the Gesell Developmental Schedule (GDS) at 2 years of age. Significant associations seen in 2002 between elevated DNA adducts and decreased motor area DQ and average DQ were not observed in the 2005 cohort. The results indicate that an intervention to eliminate emissions from a polluting coal-burning power plant was effective in improving developmental outcomes among children living in Tongliang (Perera *et al.* 2008).

Tang *et al.* (2014) further studied in both cohorts their cord blood the level of BDNF. Child neurodevelopment was evaluated using GDS. The plasma level of BDNF was significantly higher in the 2005 cohort as compared to the 2002 cohort (1266.56 pg/ml vs. 752.87 pg/ml, $p<0.05$). Also, the mean birth head circumference of the 2005 infants was greater than of the 2002 cohort 34.1 cm vs. 33.7, $p<0.05$). Authors hypothesized that reduction in BDNF levels as a result of prenatal PAH exposure may have contributed to the adverse neurocognitive effects in the 2002 cohort.

Barcelona cohort. Mortamais *et al.* (2017) investigated the effects of PAHs on basal ganglia and ADHD symptoms in 242 school children aged 8–12 years in the city of Barcelona using magnetic resonance imaging (MRI) one year after PAHs measurement. Results revealed a negative relationship between B[a]P levels (approx. 0.1 ng/m^3) and caudate nucleus volume (CNV), this reduction corresponded to 2% of the mean CNV. But this reduction was subclinical, not significantly associated with ADHD symptoms. Trends for associations between B[a]P exposure and higher ADHD scores and inattentiveness were not statistically significant. Observed B[a]P exposure is very low.

Traffic-related pollution exposure and chilhood cognition

Newman *et al.* (2013) explored the association between early-life exposure to traffic-related air pollution (TRAP) in the first year of life, expressed as the concentration of elemental carbon attributed to traffic (ECAT) and ADHD symptoms at 7 years of age in children from Cincinnati, Ohio (N=576). The child behavior was assessed by the Behavioral Assessment Systems for Children, Parent Rating Scale, 2nd Edition (BASC-2) (Reynolds and Kamphaus 2004). The highest tertile of ECAT (>0.40 μg/m^3) during the child's first year of life was associated with hyperactivity scores, limited to mothers with higher education. Children with high ECAT exposure were 70% more likely to have a high hyperactivity score.

Volk *et al.* (2013) examined the relationship between TRAP and autism on 279 autism cases and 245 matching controls in California. Children diagnosis was evaluated using Autism Diagnostic Observation Schedules (ADOS), and Social Communication Questionnare (SCQ), parents were administered Autism Diagnostic Interview-Revised (ADI-R). Increased autism risk was associated with exposure to TRAP (higher levels of exposure to PM2.5, PM10, and NO_2) during the first year of life. E.g. PM2.5 increase 8.7 μg/m^3 during the first year of life, children were 2.12 times more likely to have autism. Increases were also present for all pregnancy and trimester-specific estimates of PM2.5 and NO_2.

Becerra *et al.* (2013) studied the influence of TRAP during pregnancy on the development of autism in Los Angeles County, California, using data from air monitoring stations and land use regression (LUR). Autistic disorder was diagnosed by DSM-IV-R, participated 7 603 children with autism and 10 controls per case matched by sex. Per interquartile range, 4.68 μg/m^3 PM2.5 was estimated 15% increase of autism. Data suggest association between autism and prenatal air pollution exposure, mostly related to TRAP.

Raz *et al.* (2015) explored the association between maternal exposure to PM2.5 and autism spectrum disorder (ASD) in the Nurses´ Health Study II Cohort, in children born 1990–2002, with ASD (N=245) and children without ASD (N=1 522). PM2.5 exposure during pregnancy was associated with increased risk of ASD, odds ratio (OR) per interquartile range higher PM2.5 (4.42 mg/m^3) (OR=1.57; 95% CI: 1.22, 2.03). Higher maternal exposure to PM2.5 during pregnancy, particularly in the third trimester, was associated with greater risk of child having ASD.

Associations of exposure to TRAP on behavioral development of schoolchildren, 7–11 years of age, was investigated on 2 897 children from 39 schools in Barcelona, Spain (Forns *et al.* 2016). TRAP levels were measured as elemental carbon (EC), black carbon (BC) and NO_2. Behavioral development was assessed using the Strengths and Difficulties Questionnaire (SDQ), ADHD was reported by teachers filling out (ADHD-DSM-IV) list. Higher levels of TRAP were generally associated with higher SDQ total difficulties scores. The results suggest that higher levels of TRAP (EC, BC, NO_2) at school are associated with worse general behavioral development in schoolchildren.

On the same cohort of 2 715 children in Barcelona, Sunyer *et al.* (2015) studied association between long-term TRAP in schools and cognitive development in primary school children. Children were tested four times within 12 months via computerized tests (n-back task). TRAP was characterized by the concentrations of EC, NO_2, and UFP (ultrafine particle number, 10–700 nm). Cognitive development was assessed as working memory, superior working memory, and inattentiveness. Children attending schools with higher level of EC (1.82 vs. 1.13 μg/m^3), NO_2 (56.1 vs. 40.5 μg/m^3), and UFP (28 745 vs. 18 043 number/cm^3) experienced substantially smaller growth in all the cognitive measurements, e.g. a change from the first to the fourth quartile in indoor EC reduced the gain in working memory by 13%. EC comes almost exclusively from diesel vehicles in Barcelona. This study suggests that traffic related air pollution in schools negatively affects cognitive development.

Sunyer *et al.* (2017) later examined on the same cohort of 2687 schoolchildren in Barcelona the association between daily variation in traffic-related air pollution and attention. Cognitive development over 12 months were assessed each 3 months using child attention network test (ANT), calculating inattentiveness by the hit reaction time as well as working memory functions.. Short-term exposures were measured as the daily concentrations of NO_2 (indoor 22.8 μg/m^3, outdoor 24.7 μg/m^3) and EC (indoor 1.24 μg/m^3, outdoor 1.13 μg/m^3). Daily ambient levels of both NO_2 and EC were associated with impaired attention function (i.e. increased hit reaction time, SE of hit reaction time, omissions, and commissions). Interquartile increase in daily levels of NO_2 were associated with increase of hit reaction time or a higher number of missing answers (omissions). There was not observed any associations with working memory. Daily variations in attention process were associated with daily levels of TRAP. Children´s performance was slower and less consistent throughout the test on days with higher levels of ambi-

ent traffic-related air pollution, NO_2 and EC had acute associations with inattentiveness. These results add to the evidence that air pollution may have potential harmful effects on neurodevelopment.

Bassagana *et al.* (2016) analyzed in the same cohort of 2 618 schoolchildren in Barcelona the role of PM2.5 from different emission sources on cognitive development over one year. Average concentrations of PM2.5 were outdoor 28.1 μg/m^3, indoor 35.6 μg/m^3. An interquartile range increase in indoor traffic-related PM2.5 was associated with reductions in cognitive growth equivalent to 22% of the annual change in working memory, 30% of the annual change in superior working memory, and 11% of the annual change in the inattentiveness scale. None of the other PM2.5 sources was associated with adverse effects on cognitive development. Therefore Bassagana *et al.* (2016) concluded that traffic was the only source of fine particles associated with a reduction in cognitive development.

Sentis *et al.* (2017) evaluated the association between prenatal and postnatal exposure to NO_2 and attentional function in children 4–5 years of age, using Kiddie-Conners Continuous Performance Test (K-CPT). Children from four Spanish regions, N=1298, showed that prenatal exposure to NO_2, increase for 10 μg/m^3, increased the hit reaction time and omissions error. Higher exposure to NO_2 during pregnancy is associated with impaired attentional function in children at 4–5 years old.

Porta *et al.* (2016) analyzed associations between TRAP and cognitive function in a prospective birth cohort in Rome, Italy. At age of 7 years 474 children were assessed by the Wechsler Intelligence Scala for Children-III for IQ composite scores. Exposure to NO_2 and PM2.5 at birth was assessed using land use regression models and traffic intensity. A 10 μg/m^3 higher NO_2 exposure during pregnancy was associated with 1.4 fewer points of verbal IQ, and 1.4 fewer points of verbal comprehension IQ. Similar associations were found for traffic intensity in a 100 m buffer around home.

The birth cohort study in South Korea was investigated for association between concentrations of PM10 and NO_2 during pregnancy and neurodevelopment at ages 6, 12 and 24 months, using Korean Bailey Scale of Infant Development II. There were significant effects of prenatal NO_2 and PM10 exposure to mental development index and psychomotor development index at 6 months (Kim *et al.* 2014).

Harris *et al.* (2015) studied 1 109 children from eastern Massachusetts, USA, for prenatal TRAP exposure and childhood cognition at 8 years, measured verbal and nonverbal intelligence, visual motor abilities, and visual memory. BC exposure during the third trimester was 0.69±0.23 μg/m^3, PM2.5 exposure 12.3±2.6 μg/m^3, similar low concentrations of BC and PM2.5 were over their childhood. Prenatal and childhood near-residence traffic density, BC, and PM2.5 did not display consistent patterns of association with child cognition.

Saenen *et al.* (2015) investigated the association between *in utero* exposure to PM2.5 and placental expression of genes implicated in neural development in samples of placenta from 247 mothers. PM2.5 exposure during pregnancy was 15.8±6.6 – 18.7±6.0 μg/m^3. A 5 μg/m^3 increase in residential PM2.5 exposure during the first trimester of pregnancy was associated with 15.9% decrease in expression of placental *BDNF* (brain derived neurotrophic factor) and 24.3% decrease of *SYN1* (synapsin 1) at birth. These results are the first molecular epidemiological evidence concerning association between in utero exposure to PM2.5 and the expression of genes that may influence neurodevelopmental process.

STUDIES IN ADULTS

Wang *et al.* (2014) estimated association between TRAP and presence of depressive symptoms among 732 Boston-area adults (78.1±5.5 years). Depressive symptoms were assessed by the Revised Center for Epidemiological Studies Depression Scale (CESD-R), exposure to TRAP was evaluated as BC exposure (0.37±0.12 μg/m^3). This study did not observe any evidence suggesting a positive association between depressive symptoms and long-term exposure to TRAP or short-term changes in pollutants levels.

Allshire and Crimmins (2014) used Health and Retirement Study of US adults aged 50 years, sample consisted from 13 996 participants. Cognitive function was evaluated by the Telephone Interview for Cognitive Status (72% face-to-face interview). Exposure to PM2.5 ranged from 4.5 to 20.7 μg/m^3; effect was divided into quartiles. Data indicate that living in areas with annual PM2.5 concentrations that exceeds EPA air quality standards (12 μg/m^3) is harmful to older adults´ cognition, especially to episodic memory component of cognitive function.

Kim *et al.* (2016) determined the association between long-term PM2.5 exposure and major depressive disorders (MDD) in 27 270 participants aged 15–79 years from Seoul, Republic of Korea, in the period 2002 and 2010. MDD was defined as a diagnosis of depressive episodes (ICD-10 code F32.x). Average PM2.5 concentration between 2007 and 2010 was 26.7 μg/m^3. The risk increased with an increase of 10 μg/m^3 in the PM2.5 concentrations between 2007 and 2010 (hazard ratio, HR=1.47; 95% CI: 1.14, 1.90). When stratified for chronic disease, the association between PM2.5 exposure and MDD was grater in participants with diabetes mellitus (HR=1.83; 95% CI: 1.26, 2.64), then without it (HR=1.27, 95% CI: 0.98, 1.64). Similar associations were identified for cardiovascular disease and chronic obstructive pulmonary disease. Long-term PM2.5 exposure increased the risk of MDD among the general population; individuals with chrnic diseases are more vulnerable to long-term PM2.5 exposure.

Long-term exposure to TRAP and dementia incidence in Umea, Northern Sweden, were obtained over 15-year period from the longitudinal Betula study (Oudin *et al.* 2016). TRAP was expressed according to NOx (nitrogen oxides) concentrations. Dementia was assessed by DSM-IV core criteria for dementia. In study was included 1 806 participants, 191 were diagnosed with Alzheimer disease, 111 were diagnosed with vascular dementia. Participants in the group with the highest exposure (>26 μg/m^3 NOx) were more likely than those in the group with lowest exposure (4.8–9 mg/m^3 NOx) to be diagnosed with dementia (Alzheimer's disease or vascular dementia) with HR=1.43 (95% CI; 0.99, 2.08). TRAP might be an important risk factor for vascular dementia and Alzheimer's disease.

TRAP and Parkinson's disease (PD) was studied in Denmark, comparing 1 696 PD patients and 1 800 population controls, NO_2 concentrations were in Copenhagen 16.83 μg/m^3, in provincial cities 12.63 μg/m^3, rural regions 12.11 μg/m^3. Ambient air pollution from traffic sources is associated with 9% increased risk of PD (95% CI: 3, 16) per interquartile range increase (2.97 mg/m^3) in modeled NO_2. Association was observed in Copenhagen residents, OR=1.21 (95% CI: 1.11, 1.31), no association was seen in rural residents. TRAP increase the risk of PD in populations with high or increasing exposures (Ritz *et al.* 2016).

DISCUSSION

Experimental data indicate that neonatal exposure to B[a]P induce oxidative stress in five days old male Wistar rats (Patel *et al.* 2016). Behavioral analysis showed anxiolytic-like behavior. Using cytomorphometry of hippocampus showed that the number of neurons and glia in B[a]P treated group were significantly reduced. B[a]P induced acute neurotoxicity by oxidative stress has been explained by experiment on F-344 rats, after a single oral dose, analyzing activity of several antioxidant enzymes and levels of malondialdehyde (Saunders *et al.* 2006). B[a]P caused inhibition of the activity of superoxide dismutase and glutathione peroxidase, enhancement in catalase and lipid peroxidation in the striatum and hippocampus. These finding suggest that B[a]P-induced acute neurobehavioral toxicity may occur through oxidative stress due to inhibition of the brain antioxidant scavenging system.

Chepelev *et al.* (2015) suggested that neurotoxic endpoints are more sensitive than cancer endpoints for health risk associated with B[a]P exposure. Using already published papers on this topic, they proposed mode of action (MOA) to explain B[a]P-induced neurotoxicity in rodents. The MOA includes: 1) B[a]P binding to the aryl hydrocarbon receptor (AHR); 2) AHR-dependent modulation of transcription of N-methyl-D-aspartate glutamate receptor (NMDAR) subunits; 3) NMDAR-mediated loss of neuronal activity and decreased long-term potentiation; 4) compromised learning and memory.

Reviewed papers indicate a significant effect of prenatal exposure to airborne PAHs on neurodevelopment in four ethnically different cohorts in New York, Poland, China, and Spain. Perera *et al.* (2006) observed in the New York cohort adverse effect already in 3 years of age, at 5 years effect on IQ scores (Perera *et al.* 2009), at the age 6–7 years also anxious/depressed and attention problems, at the age of 9 years also ADHD (Perera *et al.* 2014). Decrease of BDNF concentrations in cord blood was related to the decrease of mental development index at age 2 years (Perera *et al.* 2015). MRI study on 7–9 years old children showed reduced left hemisphere white matter, associated with attention problems and ADHD (Peterson *et al.* 2015).

Prenatal concentration of PAHs in the New York cohort were 2.26 ng/m^3 (median), which is <1 ng B[a]P/m^3.

Polish cohort was exposed to 17.96 ng/m^3 PAHs (median) (corresponding approx. to 4–5 ng B[a]P/m^3). These concentrations affected nonverbal reasoning activity at the age of 5 years (Edwards *et al.* 2010), at the age of 7 years was decreased IQ (Jedrychowski *et al.* 2015).

In the Chinese cohort was exposure evaluated according to the level of DNA adducts in the cord blood (Tang *et al.* 2008, Perera *et al.* 2008).

In the Barcelona cohort Mortamais *et al.* (2017) observed, using MRI, the reduction of caudate nucleus volume in children aged 8–12 years, when exposure to B[a]P in polluted air corresponded to 0.1 ng/m^3.

These results should be of a great interest in the Czech Republic. Recent study by Ambroz *et al.* (2016) on the impact of air pollution to oxidative damage in newborns indicate in winter 2014 exposure to B[a]P in the polluted district of Karvina 5.36±3.64 ng/m^3, in the control district of Ceske Budejovice 1.45±1.19 ng/m^3. Concentrations of B[a]P in Karvina are certainly significantly higher than in New York or Barcelona, probably similar to Krakow, surprisingly also in Ceske Budejovice higher than in New York or Barcelona. It means that contemporary B[a]P air pollution in both locations in the Czech Republic may significantly affect neurodevelopment in these children. This knowledge have a significant impact for all country, as more than 50% of total population is exposed in air to concentrations of B[a]P >1 ng/m^3 (EU standard).

Traffic-related air pollution studies analyzed impact of different pollutants to neurobehavioral changes in children.

Increased levels of elemental carbon (EC) during the first year of life increased ADHD symptoms at 7 years old children in Cincinnati (Newman *et al.* 2013).

Increase of PM2.5 concentration during pregnancy increased autism in California (Volk *et al.* 2013; Becerra *et al.* 2013) as well as in children of mothers from the Nurses' Health Study II Cohort (Raz *et al.* 2015). In the

Barcelona cohort, the increase of PM2.5 concentrations was associated with adverse effect of cognitive development (Bassagna *et al.* 2016). Saenen *et al.* (2015) observed that the increase of PM2.5 concentrations decrease the level of *BNDF* in placenta.

Effect of NO_2 to behavioral and cognitive development in schoolchildren was observed in Barcelona (Forns *et al.* 2016, Sunyer *et al.* 2015, Sunyer *et al.* 2017), in four Spanish regions (Sentis *et al.* 2017), in children in Rome (Porta *et al.* 2016) as well as in South Korea (Kim *et al.* 2014).

Increased TRAP exposure also affected mental health in adults: Allshire and Crimmins (2014) postulates that PM2.5 concentrations >12 μg/m^3 deteriorate cognitive functions, especially episodic memory. Increased concentrations of PM2.5 increased major depressive disorders in Seoul (Kim *et al.* 2016). Study in Sweden found the effect of NOx to increase the incidence of dementia (Oudin *et al.* 2016). Higher NO_2 concentrations in Denmark increased risk of Parkinson´s disease (Ritz *et al.* 2016).

Toxicological studies support the neurotoxic effect of motor exhaust particles, especially from diesel exhaust (Grahame *et al.* 2014).

Summing up the present knowledge about the impact of air pollution to central nervous system:

1. Perinatal exposure to airborne PAHs significantly affect neurodevelopment in children, decreasing IQ, affecting cognitive functions and behavior, increasing ADHD.
2. Perinatal exposure to PM2.5 increase the risk of autism.
3. TRAP (expressed as EC, BC, NO_2) affects cognitive and behavioral development in children.
4. TRAP affects in adults cognitive functions, increase major depressive disorders, dementia and Parkinson disease.

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