ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 11, pp. 21665-21672, November, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

THE ROLE OF PESTICIDES IN THE DEVELOPMENT OF AUTISM SPECTRUM DISORDER

Ewelina Soroka., Urszula Fałkowska., Dorota Adamczyk., Katarzyna Adamczyk and Marcin Olajossy

Department of Psychiatry and Psychiatric Rehabilitation, Medical University of Lublin, Poland

DOI: http://dx.doi.org/10.24327/ijrsr.2017.0811.1117

ARTICLE INFO

Article History:

Received 10th August, 2017
Received in revised form 14th September, 2017
Accepted 08th October, 2017
Published online 28th November, 2017

Key Words:

ASD, pesticides, environmental factors, neurotransmission

ABSTRACT

Diseases with the autistic symptoms belong to a common group called autism spectrum disorders (ASD). The individuals with ASD have the difficulties with communication, behavior and social interactions. There are some genetic and environmental reasons of ASD. Environmental aspects comprise pre and postnatal factors. It is claimed that up to 40% of ASD's cases have environmental causes. The pesticides play a significant role in causing disturbances in homeostasis. There are synthetic or natural substances used to eliminate noxious or undesired organisms. They are widely used in horticulture and agriculture as plant protection products. Pesticides can exert influence on the nervous system. Depending on the structure, they have effect on GABA and glutamatergic neurotransmission. Changes in neurotransmission can cause cognitive dysfunctions, automatisms and memory deficits.
This article is review about the potential role of pesticides in the development of ASD.

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogenous neurodevelopmental disorder with various degrees of intensity, diverse clinical manifestations and resulting from the combination of genetic and environmental factors. The diagnosis is usually made during early childhood and persists throughout adult life, with the type of autism likely being modified by influence of the experience, education and rehabilitation [1]. According to DSM-5 criteria, autism spectrum disorders are characterized by:

- persistent problems in social communication and interactions across multiple contexts manifesting as: deficits in social-emotional reciprocity - ranging from aberrant social relations to inability to initiate or respond to any interaction; deficits in non-verbal communication and in establishing, maintaining and understanding relations.
- restricted and stereotyped patterns of behavior, interests and activities as manifested by at least two of the following groups of symptoms, currently or by history (stereotyped or repetitive motor movements, use of objects or speech elements, insistence on sameness, adherence to routines or ritualized patterns of verbal and non-verbal behavior, extremely limited interests of abnormal intensity, increased or decreased reactivity to sensory input or unusual interest in sensory aspects to the environment).
- symptom onset in the early developmental period
- symptoms cause clinically significant impairment in social, professional and other important aspects of functioning
- presence of the aforementioned disturbances cannot be explained by intellectual disability (intellectual developmental disorder) or global developmental delay [2].

Current epidemiological data indicate growing prevalence of ASD [3,4,5], however, this phenomenon cannot be fully explained with changes in diagnostic criteria [6]. This epidemiological evidence gave rise to the suspicion of possible effects of the harmful environmental factors on the evolution of such developmental disturbances [7]. It is commonly accepted, that the development of autistic disorders is influenced by multifactorial threats resulting from the interactions between genetic and environmental factors. Environmental aspects comprise pre and postnatal factors. Some authors claim that even 40% of ASD have environmental causes [7,8]. Millions of tons of chemical compounds produced annually are emitted to the surrounding environment. Nevison declares that from approximately 80 thousand new chemical substances synthesized within last 50 years, merely 20% were tested for

Corresponding author:* **Ewelina Soroka
Department of Psychiatry and Psychiatric Rehabilitation, Medical University of Lublin, Poland

possible influence on neurodevelopmental processes [8,9]. Their harmful impact on brain development, including cellular divisions and differentiation, synaptic formation, apoptosis and neurotransmitter levels, were experimentally proven [10].

The fact is that increasing numbers of children diagnosed with autism have been recorded over a few past decades. Therefore, the extent to which this neurological disorder might be correlated with civilization progress and growing environmental contamination should be investigated [14].

Humans are exposed to environmental substances, including pesticides. To protect from the harmful effects they exert, mechanisms of their action on the organism must be understood with respect to prenatal and early postnatal periods, during which the nervous system develops and shows particular sensitivity to homeostasis disturbances [11].

What are pesticides?

Pesticides (lat. *pestis,* disease, plague; *caedo,* kill) are synthetic or natural substances used to eliminate noxious or undesired organisms. They are essentially applied for means of protection of plants, forests, water reservoirs, as well as animals and alimentary products, or to combat living organisms considered detrimental within inventory and residential buildings, hospitals or magazines. First natural pesticides, in the form of tobacco infusion, were used as long as 200 years ago to combat aphids. First synthetic pesticide (dinitroorthocresol) was introduced in 1892. Since the beginning of 1940s and until 1960s, DDT was a commonly used pesticide later proven to be severely harmful to the natural environment. Due to the aforementioned reasons, DDT had been removed from the market and its use became prohibited, regardless of the favorable outcomes in eliminating infectious diseases. In the agricultural and forest economy, the employment of pesticides resulted in significantly increased yields from the edible crop plants, reduced epidemic disease occurrence among livestock animals and poultry, as well as improved food production and supply. The use of pesticides has led to substantial reduction of epidemic disease occurrence, especially within developing countries. In addition, it has contributed to better life hygiene, thereby decreasing mortality rates.

Pesticides were also applied in the field of post-production food industry - as measures employed to protect crops from pests at the time of storage and transportation. Moreover, these substances extend the quality of industrial products (paper, textiles) and prolong exploitation times of roads, tracks and airports by preventing growth of the devastating weeds.

The effects of pesticides are not limited exclusively to noxious organisms; they destroy every single (useful) organism existing in certain area. Based on the chemical composition, there may be distinguished i.a. organophosphate insecticides, polychloride insecticides, carbamates, dithiocarbametes, aryl-alkane carboxylic acid derivatives, triazine derivatives, nitrophenol derivatives, urea derivatives, uracil derivatives, organomercurial compounds, compounds containing tin and copper, pyrethroids. Acute poisonings are most commonly evoked by pesticides from either organophosphate insecticide or organomercurial fungicide groups. Chronic intoxication may regard individuals exposed to pesticides at work. However, the whole human population is exposed to the chronic poisoning due to common global use of pesticides, resulting in their accumulation in the alimentary products, soil, water and air. Pesticides accumulated in the organism influence (initiate or promote) oncogenic processes, are neurotoxic, disturb hormonal and enzymatic regulation [12,13].

According to their chemical structure, pesticides are divided into inorganic and organic. The examples are as follows:

- zoocides
- insecticides (DDT, dieldrin, chlordan)
- acaricides, rodenticides, molluscicides
- herbicides (atrazine)
- fungicides
- plant growth regulators
- synergists
- desiccants
- desflorants

In Poland, organic insecticides take the lead in terms of production and application. They comprise:

- chlorinated hydrocarbons
- organophosphates (endosulfan, chlorpyrifos, diazinon)
- carbamic acid derrivatives
- pyrethroids.

Pesticides are characterized by: selective toxicity, mobility, bioacummulative ability and environment durability, the latter being the elementary criterion to get certified to apply specific compound. Based on their environmental degradation rates, pesticides were classified into four categories:

- highly persistent - soil half-lives of dozens of years
- persistent - 2-5 years
- moderately persistent - 1-18 months
- non-persistent - 1-12 weeks.

Lethal dose and the onset of action are the most important criteria determining pesticide toxicity. Several ways exist through which pesticides penetrate into pests' organisms: upon direct contact to the central nervous system, through gastrointestinal tract or airways of the pest, via conduction system and into the tissues on plants.

The mobility of pesticides is largely problematic for the environment. Pesticides are the example of the area source of pollution, i.e. agricultural terrain, non-agricultural terrain (traffic routes) or precipitations. They may as well be translocated by wind or water. Infiltration of pesticides or their degradation products into soil, water, air or alimentary products and fodder poses serious hazard to humans. To date, not only presently-applied pesticides, but also those used back in the day circulate in the environment.

There exists a list of 201 industrial chemical agents which are perceived as neurotoxic for humans. They may cause autism, and ADHD, as well as mental retardation along with cerebral palsy. These chemicals had been divided into 4 categories: metals and inorganic compounds (comprising 25 agents), organic solvents (43 agents), other organic substances (93 agents), pesticides (40 agents). Out of these 201 substances, 5 are considered to induce substantial developmental neurotoxicity in humans. These comprise: methylmercury, lead, arsenic, polychlorinated biphenyls and toluene [11,14].

Hormonally active agents (polychlorinated biphenyls, dioxins and pesticides) which are present in the surrounding environment, undoubtedly affect developmental processes and plasticity of the central nervous system, which, in turn, may result in decreased levels of endogenous hormones, impaired function of GnRH neurons and dopaminergic or serotonergic pathway dysfunction [8,11].

In rats it was shown that prenatal exposition to polychlorinated biphenyl PCB 153 generates postnatal changes in dopamine and serotonin levels within hippocampus and hypothalamus. Several studies have indicated that pesticides, i.e. organic phosphates and DDT severely impair dopaminergic neurotransmission, which in animals is manifested by, for example, disturbed motor activity. Low doses of pesticides are thought to increase, whereas high doses seem to reduce aforementioned activity, along with evoking neurodegeneration such as Parkinson's or Alzheimer's disease. Studies indicate that administering DDT pesticide to pregnant mice results in the occurrence of sex-linked depressive disorders in their offspring [11].

The toxicity of mercury should primarily be attributed to its methylated derivative, not the metallic element itself [16]. Mercury poses the greatest risk to developing organisms. The blood-brain barrier is easily penetrated by this metal, in young mammals in particular [17]. The methylmercury concentration within fetal red blood cells may even exceed levels found in women who were exposed to this compound during pregnancy. Research shows that mercury might be present in the breast milk of women who consumed fish or bread contaminated with methylmercury or methylmercury fungicides, respectively [18]. Epidemic mercury intoxications were observed more frequently just after mercury-rich agents became broadly used as bactericides and fungicides (since 1950s) [19]. What is interesting is that the term „childhood autism" had been introduced to medical terminology at the same time. Behavioral aspects of mercury intoxication include: lability, anxiety, fearfulness, irritability, aggression, hysteria, inactivity, obsessive-compulsive behaviors and impairments in social interaction. Sensory distortions (hypersensitivity to noise, increased or decreased pain sensation) and motor impairment are the farther consequences of mercury poisoning. In addition, the function of dopamine, serotonin and acetylcholine neurotransmitters is altered. Analogous alterations are found in children with autism. Exposition to mercury results in destruction of immunologic system and increased vulnerability to viral infections. Chronic viral infections are observed in some sick children. Furthermore, mercury compounds may alter functioning of the gastrointestinal system. Numerous autistic children encounter such problems, including difficulties in digestion of specific products [15]. The prenatal studies in rats have indicated that the exposure of developing dopaminergic system to MeHg results in altered locomotor activity of males, not females. It is also known, that the prevalence of autism is significantly higher in boys than girls [20].

Household indoor pesticide exposure is of particular concern for infants and young children, as they spend most of their time within their homes. Chlorpyrifos, which is an organophosphate, is the most commonly detected pesticide in American homes. High doses of this substance cause inhibition of the enzyme acetylcholinesterase, resulting in the spectrum of cholinergic symptoms [23]. Cholinergic transmission is a subject of interest to psychiatrists due to the role acetylcholine plays in neurophysiological conditioning of the cognitive processes. For instance, altered cholinergic transmission is found in autistic children [14,21].

Reeler mouse is the example of a mutant species employed in neurological research concerning i.e. cerebral development in mammals [46]. The exact mouse mutants had been environmentally exposed to chlorpyrifos, which by inhibiting acetylcholinesterase, had led to paradoxic improvement of behavior in homozygous reeler mice, along with partial response of the heterozygous subpopulation [47]. This gives evidence for the complexity of the problem, which is the influence of environmental factors on the X chromosome. The research may indicate further direction for epidemiological observations on the gender-dependent development of autism [48].

Apart from chlorpyrifos, the other commonly used „indoor pesticides" listed among 201 substances neurotoxic to humans are: chlordane, dieldrin, diazinone and dichlorvos [11].

Research conducted in 2003-2004 by National Health and Nutrition Examination Survey (NHANES) revealed the presence of the organophosphate metabolite dimethyl thiophosphatem (DMPT) in urine samples of 83% of the US pregnant population. The geometric mean concentration of the aforementioned substance in urine samples equaled 2.43 mg/L [26].

Furthermore, the majority of organic chlorinated pesticides exhibit xenoestrogenic activity. They mimic natural hormones by binding with estrogen receptors, and thus may exert negative effects on human health. The examples of such xenoestrogenes comprise insecticide dichlorodiphenyltrichloroethene (DDT) or acaricide endosulfan [14,22].

GABA and Ach

In 2003, Rubenstein and Merzenich introduced the model of autism. According to their hypothesis, combination of genetic and environmental factors impinge on GABA and glutamate neurotransmission resulting in the emergence of „noise" in neural connections. In their study, cortical networks responsible for linguistic and social-behavioral abilities were distorted with increasing stimulation, leading to diffuse neuronal hypersensitivity [49].

Most of the pesticides are acetylcholinesterase inhibitors. These include the OPs chlorpyrifos, diazinon and CBs, which are the most broadly applied pesticides in the world. Other commonly used pesticides comprise the insecticides modulating either voltage-gated sodium channels (i.e. DDT or pyrethroid), nicotinic ACh receptors (imidacloprid) or GABA-A receptors (OC and fipronil) [50]. The activity of sodium channels, which are necessary for healthy pre and postnatal development, might be altered by their mechanism of action. Likewise, they may upset the balance between excitatory and inhibitory neurotransmitters within the brain [51].

GABA is essential for proper development and regulation of neurotransmission [52]. The gamma-aminobutyric acid plays

role in proliferation, differentiation, migration and elongation of the neural stem cells. In addition, GABA activates two major receptor groups in mammalian brains: 1) GABA-A and GABA-C which form a chloride channel, and 2) GABA-B which is a G protein-coupled metabotropic receptor. Because of the increased chloride ion inflow and membrane hyperpolarization, activation of GABA-A in adults leads to decreased neuronal excitability. However, due to chloride gradient reversal during fetal development, activation of GABA-A results in chloride-ion outflow and increased neuronal excitability (Watanabe *et al*., 2002) [53]. Neural network pattern and activity may therefore be determined by localization of GABA receptors. The upregulationGABA-A subunit isoforms takes place during perinatal period. This in turn evokes differences in their pharmacologic and biophysical properties [55,56].

DeLorey *et al*. noticed that mice lacking Beta3 gene for GABA-A receptor exhibit deficits in social behavior [54]. Numerous studies indicate the relationship between distortion of GABA signaling and autism. The post-mortem brain examinations of autistic individuals revealed decreased relative numbers of GABA-A receptors in 4 out of 8 specimen. The expression of GABA-B was altered in 5 out of 7 samples [57]. Moreover, a connection was established between decreased GABA-A expression and *MECP2* gene alterations, which occur in brain structures of the individuals suffering from autism, Rett or Angelman syndrome [58].

Prenatal exposition of rats to the OC pesticides dieldrin and lindane results in reduced binding ability of GABA-A receptors within brainstem [59]. In humans, decreased capacity of GABA binding contributes to reduced muscle tension in more than 50% of the autistic patients, as well as provokes seizure-like excitability [60].

In the past, polychlorinated biphenyls were widely used in industry. They were added to paints, glues, insecticides, impregnates, synthetic materials and many others [61]. However, approximately 40 years ago, the aforementioned substances became prohibited from use after their cancerogenic properties had been discovered back in 1960s. Although their production has been restrained, the exposition to PCB unfortunately still remains largely problematic. This is due to slow decomposition of PCB with creation of dioxin-like derivatives that result in hard-to-remove soil and water contamination. The largest amounts of PCB are absorbed by human organisms with food, significantly less with air and water. In vitro studies in rats and primates revealed deregulating effects of polychlorinated biphenyls on the equilibrium between stimulation and inhibition of neurotransmission within critical regions responsible for speech development, social cognition and seizures. Recent evidence suggests that extensive prenatal exposition to mono-ortho PCB contribute to lower mental (MDI) and psychomotor (PDI) developmental indices in infants [62].

Cholinergic neurotransmission plays the key role in the development of both central and peripheral nervous systems. Apart from affecting brain plasticity, acetylcholine influences the reward/punishment system. In addition, acetylcholine takes part in regulating: muscle contraction, learning and memory processes, as well as shaping cognitive functions. It stimulates reward centers of the brain and promotes associative learning by generating neural priming effect within neocortex and hippocampus [63].

Presence of certain cholinergic dysfunctions have been observed in autistic individuals. Post-mortem examination of the brain specimen revealed decreased binding ability of nAChR within frontal and parietal cortex in 7 out of 10 cases [64]. Localization of these receptors might be of particular importance, as frontal lobe houses centers associated with planning, thinking, memory, volition, decision-making, emotion and situational assessment, muscle memory i.e. dancing, habits, specific behavioral patterns, facial expression, predicting the consequences of actions, social conformity and tact; whereas the centers involved in understanding symbols, abstract and geometric thinking as well as divisibility of attention are situated within parietal cortex.

Furthermore, studies of autopsied brains of autistic individuals indicated decreased binding ability of M1 muscarinic receptors localized within parietal lobe and increasedconcentration of BDNF protein critical to the development and function of cholinergic and dopaminergic neurons. Both studies compared 5 autistic subjects with 5 healthy controls. In spite of limited investigation group, distortions in cholinergic transmission may be suspected to represent the spectrum of symptoms in autistic patients [64].

OPs are irreversible inhibitors of AChE active site. They are toxic to human organism at concentrations lower than inhibitory levels [38,65,88]. Individuals who are slow metabolizers of PON1, the enzyme responsible for hydrolysing OPs, are the ones most susceptible to their noxious action. The OPs exert neurotoxic effects [66], which include: oxidative stress, altered Ca^{2+} and K+ concentrations, decreased nAChR and serotonin receptor levels and changes in cellular density [67-69, 87].

Research have shown that in animals the aftermaths of OP exposure are sex-dependent. Compared to male rats, female subjects that were postnatally exposed to chlorpyrifos (1 mg/kg/day) performed less activity failures and presented better memory capacity [70]. Maintenance of symptoms through adulthood had confirmed the long-term consequences of the exposure. The sex-dependent effects of pesticides were also observed by Levin in 2009. Male rats exposed to low doses of OP had greater deficits in spacial orientation and short-term memory than female representatives. Therefore it may be suspected that the consequences of early exposure to pesticides depend on gender (at least in animals).

Mitochondrial Defect And Oxidative Stress

Mitochondrion is the organelle that generates ATP, the chemical energy carrier employed in processes such as i.e. biosynthesis, cell division, in oxidative reaction. The symptoms of mitochondrial dysfunction are particularly visible in high metabolic rate tissues like skeletal muscles and nervous system, leading to myopathy, encephalopathy and neuropathy [27].

Oxidative stress is the underlying reason of mitochondrial defects, that is to say, inhibition of oxidative phosphorylation and ATP deficiency. It is a state of imbalance between formation and anti-oxidation of the reactive oxygen species (ROS). The excessive levels of ROS generate tissue injury through oxidation of polyunsaturated fatty acids within

phospholipids, and thus altering physical properties of the cell membranes [32]. Additionally, ROS inactivate enzymes, as well as lead to chromosome breakdown, DNA split, adduct formation and single base modifications [31].

That is the oxidative stress induction and free radical accumulation that pesticide toxicity should be attributed to [31]. The exposure to organophosphate, organochlorine and carbamate (CB) pesticides results in the aforementioned mitochondrial dysfunctions and biochemical shifts, which further lead to the development of autism [28-30,33], neurodegenerative and neoplastic diseases, as well as infertility [31].

Although the exact role of mitochondrial dysfunction in the development of autism has not been elucidated yet, it is worth noting that mitochondrial defects occur in nearly 8% of patients with ASD, compared to merely 0.05% of general population [34].

The EXAMPLES of mitochondrial defects possibly evoked by pesticides are as follows:

In low concentrations, organophosphate pesticides and malathion, which were used to spray fruits of the Mediterranean basin back in 1980s, and more recently, to prevent expansion of the Mosquito vectors of the West Nile virus, cause hepatic mitochondrial dysfunction, whereas in higher concentrations they exert cytotoxic effects [34].

Methoxychlor and methoxy-DDT generate mitochondrial, therefore as well oxidative distortions in mice ovary [35] and brain, where it induced additional dopaminergic alterations [36].

It has also been proved that low concentrations of the OP dichlorvos induce mitochondrial deficiency in rat brain, cytochrome C associated neuronal cell apoptosis and activation of cascade 3 [37]. In zebrafish (*Danio rerio*), prenatal exposure to OP dichlorvos results in persistent decrease of dopamine levels during adulthood [38]. Analogous deviations in dopaminergic system of autistic patients therefore seem worthy of attention [39].

The toxicity of pyrethroid insecticides results from dysregulation of cytoplasmic calcium signaling and induction of the oxidative stress [40-44].

Due to prohibition of use, organophosphates were substituted with other insecticides, i.e. pyrethroids, fipronil and phenylpyrazole. The results of studies on rat cells indicate that, although being less toxic than chlorpyrifos, fipronil induces greater oxidative stress [45].

Immunologic Toxicity

Prenatal developmental disorders of the immunologic system may manifest as e.g. allergy, atopy or autoimmunologic reactions [71]. Studies by Diamond *et al*. proved the considerable role of immunologic system in the development of nervous system [72,73].
In addition, central nervous system modulates immunologic response through substances acting as transmitters [72]. Hence, both of the systems are closely correlated.

Autistic children were noticed to have immune system aberrations. They comprise i.a. low lymphocyte count, altered cytokine levels, presence of antinuclear antibodies or central nervous inflammation and reduced IgG and IgM immunoglobulin concentrations [74,75].

Exposure to various pesticides manifests through different symptoms, starting with poor immunologic capacity, through hypersensitivity, ending with autoimmune reactions [76]. Exposure to OPs is particularly hazardous. In addition to being highly immunotoxic, they inhibit the function of NK cells and cytotoxic lymphocytes, weaken FasL/Fas pathways and induce apoptosis of immune cells [77,78].

Research by Rooney led to observations that the exposure of pregnant rats to atrazine resulted in immunosuppressive effects (delayed hypersensitivity reaction and antibody production) in male offspring. However, exposition of pregnant rats to subtoxic, yet environmentally important, concentrations of atrazine impairs social behaviors in the offspring [79,80].

Post-mortem investigation of the autopsied brains of autistic individuals in a wide age range revealed presence of the inflammatory changes [81-83]. The negative effects of pesticides, i.e. chlorpyrifos and cyfluthrin, on functioning of the nervous system had also been noticed. Both chemical compounds are hazardous to fetal astrocytes due to their toxicogenomic properties. Additionally, cyfluthrin leads to upregulation of the insulin genes and genes engaged in the proinflammatory IFN-gamma pathway, including those encoding proinflmmatory IL-6 cytokine receptor. Chlorpyrifos and cyfluthrin promote inflammatory activation of the astrocytes. Mense, in his study, confirmed the danger associated with elevated insulin concentrations and inflammation generated by the aforesaid compounds. These two conditions may lead to chronic brain inflammation which severely impairs its development and proper functioning [84].
In conclusion, the exposure of pregnant individuals to pesticides may result in both behavioral and immune alterations. These impairments are, perhaps, the result of the same pathomechanism as both systems (nervous and immune) are mutually related [85]. Whether immunologic phenomena are the underlying reasons, effects or adverse effects in autistic individuals has not been elucidated until present. However, many incline towards hypothesis that immunologic anomalies play a key role not only in the pathogenesis of autism, but also schizophrenia or major depressive disorder [86].

CONCLUSIONS

According to epidemiological reviews from the ”Environmental Impact Assessment Review” concerning the environmental and health issues within only Eastern and Middle European countries, more than 100 locations have been identified where a strong relationship had been documented between the exposure to toxic environmental contamination and the occurrence of particular diseases including developmental disorders in children, among neoplastic and respiratory problems [14,24]. The risk of ASD incidence after pesticide exposure is immensely hard to assess due to their presence in the communal air, water and food. The omnipresence of pesticides makes designating the the individual dose for pregnant women impossible. Experimental research confirms the adverse effects that pesticides exert on the immune and hormonal systems, as well as behavioral sphere. Although the direct influence of pesticides on the

development of autistic changes has not been proved yet [25], extensive data from the studies on animals, in particular, suggest their possible toxicity on the structure and function of the central nervous system.

References

1. James Morrison "DSM-5 bez tajemnic, praktyczny przewodnik dla klinicystów", wydawnictwo Uniwersytetu Jagiellońskiego, Wydanie 1, Kraków, 2016.
2. Kryteria diagnostyczne z DSM-5 desk reference, American Psychiatric Association, 2013
3. Bryson SE:Brief Report : Epidemiology of autysm. J. Autism and Developmental Disorders 1996; 26: 165-167
4. Deisher TA, Doan NV, OmayieA *et al*: Impact of environmental factors on the prevalence of autistic disorder after 1979. *J Public Health and Epidemiol*. 2014: 6(9) 271-284
5. FombonneE.: The Epidemiology of autism: a review. *Psychol Med* 1999; 29(4):769-786
6. Bittker S: Infant Eksposure to Excessive Vitamin D: Arisk factor for autism. *Autism* 2014; 4:1, 1-7
7. Gerhant A, Olajossy M, Olajossy-Hilkesberger L: Neuroanatomiczne, genetyczne i neurochemiczne aspekty autyzmu dziecięcego. *Psychiatria* Pol 2013, 47(6)1101-1111
8. Langauer-Lewowicka H, Rudkowski Z, Pawlas K:Autyzm - środowiskowe czynniki ryzyka, Medycyna środowiskowa - *Environmental Medicine* 2016, Vol19 No 2, 19-23
9. Nevison CD: Acomparison of temporal trends in United States autism prevalence to trends in suspected environmental factors Envir Health 2014;13, 73:1-16
10. Schetter T: Developmental Disabilities - Impairment of Childrens Brain Development and Function: The role of Environmental factors. *Environm Health Perspectives* 2001, Dec 109, Suppl6: 813-816.
11. Kajta M. "W jaki sposób występujące w środowisku substancje hormonalnie czynne wpływają na mózg?" Wszechświat t.113 nr 1-3/2012
12. Witold Seńczuk red.: *Toksykologia. Podręcznik dla studentów, lekarzy i farmaceutów* Wydanie IV. *Warszawa: Wydawnictwo Lekarskie PZWL, 2002*
13. *S. Deshpande:*Handbook of Food Toxicology. *Marcel Dekker, Inc., 2002, s. 826.*
14. Borgis - Nowa Pediatria 3/2008, s. 50-57Joanna Kałużna-Czaplińska, Wioletta Grys, Jacek Rynkowski" Czynniki neurotoksyczne w środowisku życia dzieci przyczyną zaburzeń rozwojowych w aspekcie autyzmu"
15. Bernard S *et al*.: Autism: a novel form of mercury poisoning. *Med Hypotheses* 2001; 56: 462-71
16. Namieśnik J, Łukasiak J, Jamrógiewicz Z: Pobieranie próbek środowiskowych do analizy. Warszawa: PWN; 1995. s. 21
17. Durczok A *et al*.: Effect of organic mercury exposure during early stage of ontogenic development on the central dopaminergic system in adult rats. *Pol J Environ Stud* 2002; 11: 307-14.
18. Rejmer P: Podstawy ekotoksykologii. Lublin: Ekoinżynieria; 1997. s. 145.
19. Kabata-Pendias A, Pendias H: Pierwiastki śladowe w środowisku biologicznym. Warszawa: Wydawnictwa Geologiczne; 1979. s.143-144.
20. Castololi AF *et al*.: Neurotoxicity and molecular effects of methylomercury. Brain Res Bull 2001; 55: 197-203.
21. Wierzbiński P *et al*.: Zaburzenia ośrodkowej neurotransmisji w przebiegu autyzmu dziecięcego. *Postępy Psychiatr Neurol* 2005; 14: 57-63.
22. Fernandez MF *et al*.: Biomonitoring of environmental estrogens in human tissues. *Inter J Hyg Environ Health* 2007; 210: 429-32
23. Berkowitz GS *et al.:* The rationale for a national prospective cohort study of environmental exposure and childhood development. *Environ Res Section* A 2001; 85: 59-68.
24. Hancock T: Health and sustainability in the urban environment. *Environ Impact Assess Rev* 1996; 16: 259-77
25. Rossignol DAGenuis SJFrey RE: Environmental toxicants and autism spectrum disorders: a systematic review. *Transnational Psychiatry* 2014;4, 1-23
26. Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. *Environ Health Perspect* 119:878-885.
27. Rossignol DA, Frye RE. Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. *Mol Psychiatry*. 2012; 17(3): 290-314.
28. Franco R, Sanchez-Olea R, Reyes-Reyes EM, Panayiotidis MI. Environmental toxicity, oxidative stress and apoptosis: menage a trois. *Mutat Res*. 2009; 674(1-2): 3-22.
29. Karami-Mohajeri S, Abdollahi M. Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: a systematic review. *Hum Exp Toxicol*. 2011; 30(9): 1119-1140.
30. Rohlman DS, Anger WK, Lein PJ. Correlating neurobehavioral performance with biomarkers of organophosphorous pesticide exposure. *Neurotoxicology*. 2010; 32(2): 268-276.
31. Grosicka-Maciąg E. Biological consequences of oxidative stress induced by pesticides. *Postepy Hig Med Dosw*. 2011; 65: 357-366
32. Łuszczewski A, Matyska-Piekarska E, Trefler J, Wawer I, Łącki J, Śliwińska-Stańczyk P. Reaktywne formy tlenu - znaczenie w fizjologii i stanach patologii organizmu. *Reumatologia*. 2007; 45,(5): 284-289
33. Deth R, Muratore C, Benzecry J, Power-Charnitsky VA, Waly M. How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis. *Neurotoxicology*. 2008; 29(1): 190-201.
34. Moore PD, Yedjou CG, Tchounwou PB. Malathion-induced oxidative stress, cytotoxicity, and genotoxicity in human liver carcinoma (HepG2) cells. *Environmental toxicology*. 2010; 25(3): 221-226.
35. Gupta RK, Schuh RA, Fiskum G, Flaws JA. Methoxychlor causes mitochondrial dysfunction and oxidative damage in the mouse ovary. *Toxicol Appl Pharmacol.* 2006; 216(3): 436-445.

36. Schuh RA, Richardson JR, Gupta RK, Flaws JA, Fiskum G. Effects of the organochlorine pesticide methoxychlor on dopamine metabolites and transporters in the mouse brain. *Neurotoxicology* 2009; 30(2): 274-280.
37. Kaur P, Radotra B, Minz RW, Gill KD. Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (OP) exposure in rat brain. *Neurotoxicology*. 2007; 28(6): 1208-1219.
38. Eddins D, Cerutti D, Williams P, Linney E, Levin ED. Zebrafish provide a sensitive model of persisting neurobehavioral effects of developmental chlorpyrifos exposure: comparison with nicotine and pilocarpine effects and relationship to dopamine deficits. *Neurotoxicol Teratol* 2010; 32(1): 99-108.
39. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004; 113(5): e472-e486
40. Cao Z, Shafer TJ, Murray TF. Mechanisms of pyrethroid insecticide-induced stimulation of calcium influx in neocortical neurons. *J Pharmacol Exp Ther*. 2010; 336(1): 197-205.
41. Kale M, Rathore N, John S, Bhatnagar D. Lipid peroxidative damage on pyrethroid exposure and alterations in antioxidant status in rat erythrocytes: a possible involvement of reactive oxygen species. *Toxicol Lett*. 1999; 105(3): 197-205.
42. Soderlund DM. Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. *Arch Toxicol.* 2012; 86(2): 165-181.
43. Yan Y, Yang Y, You J, Yang G, Xu Y, Huang N, *et al*. Permethrin modulates cholinergic mini-synaptic currents by partially blocking the calcium channel. *Toxicol Lett* 2011; 201(3): 258-263.
44. Zhang X, Daugherty SL, de Groat WC. Activation of CaMKII and ERK1/2 contributes to the time-dependent potentiation of Ca2+ response elicited by repeated application of capsaicin in rat DRG neurons. *Am J Physiol Regul Integr Comp Physiol* 2010; 300(3): R644-R654.
45. Lassiter TL, MacKillop EA, Ryde IT, Seidler FJ, Slotkin TA. Is fipronil safer than chlorpyrifos? Comparative developmental neurotoxicity modeled in PC12 cells. *Brain Res Bull.* 2009; 78(6): 313-322.
46. Laviola G, Ognibene E, Romano E, Adriani W, Keller F. Gene-environment interaction during early development in the heterozygous reeler mouse: clues for modelling of major neurobehavioral syndromes. *Neurosci Biobehav Rev*. 2009; 33(4): 560-572.
47. Laviola G, Adriani W, Gaudino C, Marino R, Keller F. Paradoxical effects of prenatal acetylcholinesterase blockade on neurobehavioral development and drug-induced stereotypies in reeler mutant mice. *Psychopharmacology* 2006; 187(3): 331-344.
48. Halladay AK, Amaral D, Aschner M, Bolivar VJ, Bowman A, DiCicco-Bloom E, *et al*. Animal models of autism spectrum disorders: information for neurotoxicologists. *Neurotoxicology* 2009; 30(5): 811-821.
49. Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav*. 2003; 2(5):255-267.
50. Casida JE. Pest toxicology: the primary mechanisms of pesticide action. *Chem Res Toxicol*. 2009; 22(4):609-619.
51. Belmonte MK, Bourgeron T. Fragile X syndrome and autism at the intersection of genetic and neural networks. *Nat Neurosci*. 2006; 9(10):1221-1225.
52. Campbell NA. Biology. 4th ed. Menlo Park, CA:Benjamin/Cummings Publishing Company. 1996
53. Watanabe M, Maemura K, Kanbara K, Tamayama T, Hayasaki H. GABA and GABA receptors in the central nervous system and other organs. *Int Rev Cytol.* 2002; 213:1-47.
54. DeLorey TM, Sahbaie P, Hashemi E, Homanics GE, Clark JD. Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: a potential model of autism spectrum disorder. *Behav Brain Res*. 2008; 187(2):207-220.
55. Cossart R, Bernard C, Ben-Ari Y. Multiple facets of GABAergic neurons and synapses: multiple fates of GABA signalling in epilepsies. *Trends Neurosci*. 2005; 28(2):108-115.
56. Stafstrom CE, Hagerman PJ, Pessah IN. Epilepsy in autism spectrum disorders. *Epilepsia*. 2010; 51(supp 5):78.
57. Fatemi SH, Folsom TD, Reutiman TJ, Thuras PD. Expression of $GABA_B$ receptors is altered in brains of subjects with autism. *Cerebellum*. 2009a; 8(1):64-69.
58. Samaco RC, Hogart A, LaSalle JM. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Hum Mol Genet*. 2005; 14(4):483-492.
59. Brannen KC, Devaud LL, Liu J, Lauder JM. Prenatal exposure to neurotoxicants dieldrin or lindane alters *tert*-butylbicyclophosphorothionate binding to $GABA_A$ receptors in fetal rat brainstem. *Dev Neurosci*. 1998; 20(1):34-41.
60. Ming X, Brimacombe M, Wagner GC. Prevalence of motor impairment in autism spectrum disorders. *Brain Dev*. 2007; 29(9):565-570.
61. U.S. Environmental Protection Agency. 2011. Basic Information about Polychlorinated Biphenyls (PCBs) in Drinking Water. Available:http://water.epa.gov/drink/contaminants/ basicinformation/polychlorinated-biphenyls.cfm [access: 2012.01.03].
62. Park HY, Hertz-Picciotto I, Sovcikova E, Kocan A, Drobna B, Trnovec T. 2010. Neurodevelopmental toxicity of prenatal polychlorinated biphenyls (PCBs) by chemical structure and activity: a birth cohort study. *Environ Health* 9:51; doi:10.1186/1476-069X-9-51 (access: 2010.08.23)
63. Brown DA. Muscarinic acetylcholine receptors (mAChRs) in the nervous system: some functions and mechanisms. *J Mol Neurosci*, 2010; 41(3):340-346.
64. Scharf ME. 2003. Neurological effects of insecticides. In: Encyclopedia of Pest Management. New York:Marcel-Dekker, Inc.
65. eutsch SI, Urbano MR, Neumann SA, Burket JA, Katz E. Cholinergic abnormalities in autism: is there a

rationale for selective nicotinic agonist interventions? *Clin Neuropharmacol*. 2010; 33(3):114-120.
66. Levin ED, Chrysanthis E, Yacisin K, Linney E. Chlorpyrifos exposure of developing zebrafish: effects on survival and long-term effects on response latency and spatial discrimination. *Neurotoxicol Teratol*. 2003; 25(1):51-57.
67. Costa LG, Cole TB, Vitalone A, Furlong CE. Measurement of paraoxonase (PON1) status as a potential biomarker of susceptibility to organophosphate toxicity. *Clin Chim Acta*. 2005; 352(1-2):37-47.
68. Levin ED, Timofeeva OA, Yang L, Petro A, Ryde IT, Wrench N, *et al*. Early postnatal parathion exposure in rats causes sex-selective cognitive impairment and neurotransmitter defects which emerge in aging. *Behav Brain Res*. 2010; 208(2):319-327.
69. Harrison PK, Falugi C, Angelini C, Whitaker MJ. Muscarinic signalling affects intracellular calcium concentration during the first cell cycle of sea urchin embryos. *Cell Calcium*. 2002; 31(6):289-297.
70. Aluigi MG, Angelini C, Falugi C, Fossa R, Genever P, Gallus L, *et al*. Interaction between organophosphate compounds and cholinergic functions during development. *Chem Biol Interact*. 2005; 157-158:305-316.
71. Levin ED, Addy N, Nakajima A, Christopher NC, Seidler FJ, Slotkin TA. Persistent behavioral consequences of neonatal chlorpyrifos exposure in rats. *Dev Brain Res*. 2001; 130(1):83-89.
72. Hertz-Picciotto I, Park HY, Dostal M, Kocan A, Trnovec T, Sram R. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. *Basic Clin Pharmacol Toxicol.* 2008; 102(2):146-154.
73. Diamond B, Huerta PT, Tracey K, Volpe BT. It takes guts to grow a brain: Increasing evidence of the important role of the intestinal microflora in neuro- and immune-modulatory functions during development and adulthood. *Bioessays*. 2011; 33(8):588-591.
74.] Heijtz RD, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, *et al*.. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci* USA. 2011; 108(7): 3047-3052.
75. Ashwood P, Wills S, Van de Water J. The immune response in autism: a new frontier for autism research. *J Leukoc Biol.* 2006; 80(1):1-15.
76. Goines P, Van de Water J. The immune system's role in the biology of autism. *Curr Opin Neurol*. 2010; 23(2):111-117.
77. Corsini E, Liesivuori J, Vergieva T, Van Loveren H, Colosio C. Effects of pesticide exposure on the human immune system. *Hum Exp Toxicol*. 2008; 27(9):671-680.
78. Galloway T, Handy R. Immunotoxicity of organophosphorous pesticides. *Ecotoxicology*. 2003; 12(1-4):345-363
79. Li Q. New mechanism of organophosphorus pesticideinduced immunotoxicity. *J Nippon Med Sch*. 2007; 74(2):92-105
80. Rooney AA, Matulka RA, Luebke RW. Developmental atrazine exposure suppresses immune function in male, but not female Sprague-Dawley rats. *Toxicol Sci*. 2003; 76(2):366-375.
81. Belloni V, Dessi-Fulgheri F, Zaccaroni M, Di Consiglio E, De Angelis G, Testai E, *et al*. Early exposure to low doses of atrazine affects behavior in juvenile and adult CD1 mice. *Toxicology*. 2011; 279(1-3):19-26
82. Li X, Chauhan A, Sheikh AM, Patil S, Chauhan V, Li XM, *et al*. Elevated immune response in the brain of autistic patients. *J Neuroimmunol*. 2009; 207(1-2):111-116.
83. Morgan JT, Chana G, Pardo CA, Achim C, Semendeferi K, Buckwalter J, *et al*. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol Psychiatry*. 2010; 68(4):368-376.
84. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA.. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol*. 2005; 57(1):67-81.
85. Mense SM, Sengupta A, Lan C, Zhou M, Bentsman G, Volsky DJ, *et al*. The common insecticides cyfluthrin and chlorpyrifos alter the expression of a subset of genes with diverse functions in primary human astrocytes. *Toxicol Sci*. 2006; 93(1):125-135.
86. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. *Brain Behav Immun*. 2012; 26(3):383-392.
87. Patterson PH. Brain-Immune Connections in Autism, Schizophrenia, and Depression. In: Infectious Behavior. Cambridge, MA:MIT Press, 2011. 9-28.
88. Murgia A, Zanardi I, Basso M, Deplano S, Falugi C, Prestipino G. Electrophysyological and immunohistochemical studies of a organophospate pesticide on neuron K^+ channels modulated by muscarinic receptor [Abstract]; In: Proceedings of the Meeting Società Italiana Biofisica applicata (SIBPA).2004 September 23-25; Pisa, Italy.
89. Slotkin TA, Bodwell BE, Levin ED, Seidler FJ. Neonatal exposure to low doses of diazinon: long-term effects on neural cell development and acetylcholine systems. *Environ Health Perspect*. 2008; 116:340-34

How to cite this article:

Ewelina Soroka *et al*.2017, The Role of Pesticides In The Development of Autism Spectrum Disorder. *Int J Recent Sci Res*. 8(11), pp. 21665-21672. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0811.1117

****