NEURODEVELOPMENTAL AND NEUROBEHAVIORAL EFFECTS OF ORGANOPHOSPHATE PESTICIDES EXPOSURE IN NEWBORNS AND CHILDREN

CRISTINA FLORIAN[1], ALINA FARCAS[1], ANDREEA VALCEANU MATEI[2], AND GHEORGHE COMAN[1]
[1] *Transilvania University of Braso,*
29 Eroilor Bdv., 500036 – Brasov, Romania
[2] *Emergency County Hospital of Brasov*
25-27 Calea Bucuresti 500326 Brasov, Romania

Correspondence Contact: gh.coman@unitbv.ro

Abstract. Pesticide use is an integral part of our modern society, whether we consider the developed or the developing nations, and their impact on human health is an important research subject. We chose to focus on the organophosphate (OP) pesticides because of their continued use and also because they are potent toxicants and neurological disruptors. Children and the newborn are more susceptible to the toxic effects of pesticides than the adult population. This paper summarizes the findings about neurodevelopmental and neurobehavioral effects of OP pesticides exposure in children from birth up to seven years old. The major problems identified in the literature as the result of long term or sustained pesticide exposure of children pre- and postnatally are the presence of abnormal reflexes in newborns, mental and developmental delays, as well as the impact on behavior, memory and intelligence quotient (IQ) in older children and suggest the existence of a dose dependent inverse correlation between these effects and OP pesticide toxicity. It is important to understand and consider the seriousness of the pesticide problem in our society in order to find ways to mitigate and combat it.

Keywords: Organophosphate, Pesticides, Exposure, Newborns, Children, Neurodevelopmental, Neurobehavioral

L.Simeonov, F. Macaev and B. Simeonova (eds.), *Environmental Security Assessment and Management of Obsolete Pesticides in Southeast Europe,*

1. Introduction

One of the most important public health problems in the prenatal and early life is the exposure to disruptive environmental agents with teratogenic and toxic effects. Some of the most prevalent disruptive agents are pesticides due to their continued use in agriculture, public health and medicine, these being the reasons why we can find them in appreciable quantities in water, air, soil and biota. From all of the different pesticide classes we chose to focus on the OP pesticides for their use as a substitute for the more toxic organochlorine pesticides and also because of the emerging evidence that they are, in their turn, potent toxins and neuroendocrine disruptors (McKinlay et al., 2008; Garry, 2004; Miodovnik et al., 2010).

Humans become victims of these agents, but children are the most vulnerable to their hazardous effects because they are exposed both directly via the food and water they ingest and the air they breathe and indirectly, through their parents (Figure 1), and because of the particularities of their metabolism. It has been shown that younger organisms have lower rates of metabolism for the enzymatic systems that handle toxins in general and pesticides in particular. It is believed that this is due to an age dependent variation in the maturation of these enzymatic systems, whether we look at the cytochromes, paraoxonase or carboxylesterase enzymes, which are the systems most active in OP pesticides metabolism (Costa, 2006).

The main mechanism of action of OP consists in the inhibition of acetylcholinesterase enzyme (hydrolase), leading to accumulation of acetylcholine in the synaptic cleft and the subsequent cholinergic syndrome (Tahara et al., 2005). Increasing new evidence suggests however, that there are other mechanisms that act on other enzyme systems that could be responsible for the neurodevelopmental and neurobehavioral effects of these compounds. The literature mainly refers to the activity of the biotransformation enzymes - cytochrome P and paraoxonase enzymes. These are responsible for the in vivo detoxification or activation of the various organophosphate pesticide substrates. Based on their level of expression and enzymatic efficiency, we can encounter degrees of organic manifestation in human children (Costa, 2006; Garry, 2004).

In this review we will discuss the neurodevelopmental and neurobehavioral implications of OP pesticides exposure in children and newborns. We aim to emphasize the seriousness and magnitude of this problem, the neurological effects of organophosphate pesticides poisoning in children being an important public health concern.

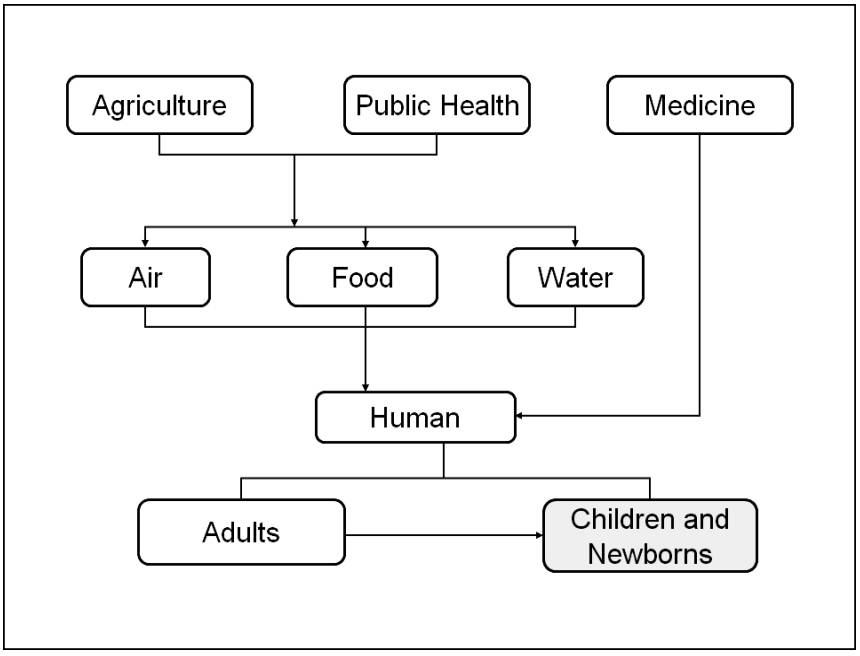

Figure 1. Different pathways of children exposed

2. Findings and Results

In the studies that we considered, the characterization of the neurodevelopmental and neurobehavioral effects of OP pesticides (London et al., 2012) can be done according to at least three criteria:

- the age at exposure – pre - and postnatal (Eskenazi et al., 2007);
- the level of exposure – low, chronic, acute or occupational (Costa, 2006; Rauh et al., 2006);
- the age (from birth up to seven years old) at which the effects are quantified (Young et al., 2005; Rauh et al., 2011).

Pesticides exposure was quantified by measuring either the concentrations of the pesticide itself (for example chlorpyrifos (CFP) as a model for OP pesticides), or the concentration of dialkyl phosphate (DAP) which is a metabolite and general biomarker for OP pesticide exposure, in blood or urine specimens (Slotkin, 2004; Eskenazi et al., 2007).

When considering the route of exposure or the environment that conditions this exposure, children of agricultural workers in particular have an increased risk of secondary pesticides exposure, during pesticides pulverization periods

(Suarez-Lopez et al., 2012), and longer cohabitation with agricultural workers who handle organophosphate pesticides may be associated with lower acetylcholinesterase activity measured in maternal or children's blood, which may induce some neuropathological states in children or fetuses (Vera et al., 2012). At the same time just as perilous has been proven to be the exposure that children face in urban environments, where the uses of OP pesticides for pest control significantly alters the air quality.

In these cases OP or OP residues may be presents in placental blood, children's blood or mother's milk, as circulating compounds.

The quantification of the effects of OP pesticides in children varies according to the age at which the evaluation is done, the level of exposure identified and the nature of the effect under investigation (Table 1). The findings suggest the existence of a dose dependent inverse correlation between OP pesticides exposure of children or their mothers as quantified by measurements of the chemicals in blood samples or of their metabolites in urine, and the indices for mental, psychomotor and neurobehavioral development (Rauh et al., 2006; Wolff and Engel, 2008; Marks et al., 2010).

Young et al. demonstrated that newborns (less than 2 months old) exposed to OP pesticides in utero and postnatally exhibited abnormal reflexes (clinically relevant) on the Brazelton Neonatal Behavioral Assesment Scale (Young et al., 2005). These children were born to mothers from an agricultural community and exposure was quantified by urinary levels of DAP, dimethylphosphate and diethylphosphate metabolites. Also, according to other authors, children exposed in utero to indoor OP pesticides (New York City) exhibited abnormal reflexes on the same Brazelton Neonatal Behavioral Assesment Scale (Engel et al., 2007). The exposure was quantified by analyzing maternal urine samples, and the higher levels of diethylphosphate and its metabolites were found to be correlated with a higher incidence of abnormal reflexes in newborns.

The neurological reflexes of newborn children characterize their current neurological status and indicate the direction of their future neurological development, hence, it is very important to discover early the existence and identify the causes of these abnormal reflexes (absent or diminished reflexes) in order to minimize the impact that OP pesticide toxicity has on them.

For children aged 6 – 12 months there are some existing studies but they didn't find statistically significant correlations between OP pesticides exposure and the appearance of neurodevelopmental and neurobehavioral symptoms (Eskenazi et al., 2007; Rauh et al., 2006)

In regards to older children, at 24 months, a study on farm-worker families found a negative association of prenatal exposure to OP pesticides with mental developmental delays and pervasive developmental disorder. They used Bayley

Scales of Infant Development (Mental Development indices) and measured six DAP metabolites in maternal and child urine (Eskenazi et al., 2007).

TABLE 1. Neurodevelopmental and neurobehavioral effects of OP pesticides on children at different ages and exposures

Age*	Occupational Exposure	Low-level Chronic Exposure
≤ 2 months	Absent or diminished reflexes	Absent or diminished reflexes
6 months 12 months	No statistically significant correlations	No statistically significant correlations
24 months	Mental development delays (which may be associated with PON1$_{_108T}$** genotype) Increased risk of PDD***	Mental development delays
36 months	ADHD**** Attention problems by maternal report	Mental development delays Psychomotor development delays PDD Attention problems ADHD problems
5 years	ADHD Attention problems by maternal report; Especially in boys	No study/ no results
7 years	No study/ no results	Lower IQ Poorer working memory (cognitive deficit)

* Age of evaluation;
** 108T allele - paraoxonase 1 enzyme
*** Pervasive Developmental Disorder
**** Attention deficit hyperactivity disorder

In a more recent study researchers reported that the negative associations between DAP and mental development indices was strongest in children with PON1$_{_108T}$ (108T allele - paraoxonase 1 enzyme). It has been identified in the literature that the enzymatic systems responsible for pesticide detoxification present a certain genetic polymorphism. Based on these findings, the effects of pesticide exposure have been quantified, and the observation was made that certain alleles render the carrier more or less susceptible to the toxic effects of

OP pesticides. The presence of variant of PON1$_{_108T}$ the paraoxonase enzyme has been linked to an increased susceptibility of children to these effects and a higher incidence of mental, developmental and behavioural problems (Eskenazi et al., 2010).

According to Rauh, children at 36 months had an association between CPF (chlorpyrifos) levels in umbilical cord plasma and the following neurodevelopmental and neurobehavioral problems: mental development delays, psychomotor development delays, pervasive developmental disorder, attention problems, ADHD (Attention deficit hyperactivity disorder) problems. They reported that the higher the level of CPF measured in umbilical cord plasma the more important were the neurological symptoms identified. Measurements were made using the Bayley Scale of Infant Development II and the Child Behavioral Checklist. The same article also found an association between CPF burden and mental developmental delays in 24 month old children (Rauh et al., 2006).

One of the most important aspects for children in the 2-3 years old group is the continued remodeling of their neurological pathways. This process, which has started in utero and continues through childhood and adolescence, is at risk in the presence of neurotoxins such as OP pesticides. The continued exposure of children to these chemicals leads to an impaired modeling of the neuronal structure, which is reflected in the mental and behavioral development described. These children are therefore at risk for early school failure and more serious behavioral problems which can lead to an altered social and professional integration.

Another recent study of subjects in an agricultural area investigated the correlation between urinary DAP metabolites measured in mothers and in their children, and attention problems and ADHD symptoms in these children. Children tested positive using Conners'Kiddie Continous Performance scale at 3.5 and 5 years old; also, for the same age ranges, there were maternal reports of attention problems (especially in boys) measured using the Child Behavior Checklist (Marks et al., 2010).

ADHD is a more and more pervasive problem in the child population in the recent years. It is important for preschool aged children who could be suffering from ADHD to be identified and treated properly in order to mitigate its lifelong effects. In order to forestall the appearance of learning and behavioral problems, to insure an appropriate social integration and a healthy parent-child relationship, families of these children need to receive parenting advice and support (Harpin, 2005).

In terms of school-aged children at 7 years old, there was evidence of a positive association between prenatal CPF exposure from air pollution and a measurable decline in IQ and deficits in working memory (cognitive deficits).

Researchers used the Weshsler Intelligence Scale and the CPF toxicity was quantified by testing the umbilical cord blood plasma (Rauh et al., 2011).

These problems (IQ and working memory deficits) have an important negative influence on children's life, conditioning their scholar achievements and professional future on one hand, as well as impacting their family and social lives.

3. Conclusions

The main route of exposure was ingestion of contaminated food and water for children in all of the studied environments. There were also significant contributions to intoxication from the quality of the air inhaled (indoor or outdoor), whether in agricultural settings where pesticides are used regularly or in urban environments where they are used as part of the disease prevention strategies.

The presence of pesticides in children's bodies alters their normal development at the mental, psychomotor and behavioral levels, depending on quantity of OP pesticides, method of exposure (directly, indirectly), period of exposure, ages of exposure (exposure time) etc. compromising their proper functioning and integration in society.

It is important to consider these and other similar findings as a warning signal for the seriousness of the pesticide problem in our society. This highlights the need for the dissemination of information regarding this issue and of implementing strategies for prevention and treatment.

Further research is needed in this area in order to verify the correlations described by these studies, to strengthen the statistical significance of some of the trends that emerged as well as to further characterize the mechanisms and causalities that underline these phenomena.

References

Costa, L.G., 2006, Current issues in organophosphate toxicity, Clinica Chimica Acta, 366, 1-13.

Engel, S.M., Berkowitz, G.S., Barr, D.B., Teitelbaum, S.L., Siskind, J., Meisel, S.J., Wetmur, J.G., Wolff, M.S., 2007, Prenatal Organophosphate Metabolite and Organoclorine Levels and Performance on the Brazelton Neonatal Behavioral Assessment Scale in a Multiethnic Pregnancy Cohort, American Journal of Epidemiology, 165, 1497-1404.

Eskenazi, B., Huen, K., Marks, A., Harley, K.G., Brandam, A., Barr, D.B., Holland, N., 2010, PON1 and Neurodevelopment in Children from the Chamacos Study Exposed to Organophosphate Pesticides in Utero, Environmental Health Perspectives, 118, 1775-1781.

Eskenazi, B., Marks, A.R., Bradman, A., Harley, K., Barr, D.B., Johnson, C., Morga, N., Jewell, N.P., 2007, Organophosphate Pesticide Exposure and Neurodevelopment in Young Mexican-American Children, Environmental Health Perspectives, 115, 792-798.

Garry, V.F., 2004, Pesticides and children, Toxicology and Applied Pharmacology, 198, 152-163.

Harpin, V.A., 2005, The effect of ADHD on the life of an individual, their family,and community from preschool to adult life, Arch Dis Child, 90, 12-17.

London, L, Beseler, L, Bouchard M.F., Bellinger D.C., Colosio C, Grandjean P, Harari R, Kootbodien T, Kromhout H, Little F, Meijster, T, Moretto A, Rohlman D.S., Stallones L., 2012, Neurobehavioral and neurodevelopmental effects of pesticide exposures, NeuroToxicology, 1338, ***-*** (in press).

Marks, A.R., Harley, K., Bradman, A., Kogut, K., Barr, D.B., Johnson, C., Calderon, N., Eskenazi, B., 2010, Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study, Environmental Health Perspectives, 118, 1768-1774.

McKinlay, R., Plant, J.A., Bell, J.N.B., Voulvoulis, N., 2008, Calculating human exposure to endocrine disrupting pesticides via agricultural and non-agricultural exposure routes, Science Of The Total Environment, 398, 1–12.

Miodovnik, A., Engel, S.M., Zhu, C., Ye, X., Soorya, L.V., Silva, M.J., Calafat, A.M., Wolff, M.S., 2010, Endocrine disruptors and childhood social impairment, NeuroToxicology, 32, 261-267.

Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., Whyatt, R., 2011, Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide, Environmental Health Perspetives, 119, 1196-1201.

Rauh, V.A., Garfinkel, R., Perera, F.P., Andrews, H.F., Hoepner, L., Barr, D.B., Whitehead, R., Tang, D., Whyatt, R.W., 2006, Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children, Pedriatrics, 118(6), 1845-1859.

Slotkin, T.A., 2004, Guidelines for developmental neurotoxicity and their impact on Organophosphate pesticides, NeuroToxicology, 25, 631-640.

Suarez-Lopez, J.R., Jacobs, D.R., Himes, J.H., Alexander, B.H., Lazovich, D.A., Gunnar, M., 2012, Lower acetylcholinesterase activity among children with flower plantation workers, Environmental Research, 114, 53-39.

Tahara, M., Kubota, R., Nakazava, H., Tokunaga, H., Nishimura, T., 2005, Use of cholinesterase activity as an indicator for the effects of combinations of organophosphorus pesticides in water from environmental sources, Water Research, 39, 5112-5118.

Vera, B., Cruz, S.S., Magnarelli, G., 2012, Plasma cholinesterase and carboxylesterase activities and nuclear and mitochondrial lipid composition of human placenta associated with maternal exposure to pesticides, Reproductive Toxicology (in press).

Wolff, M., Engel, S., 2008, In utero exposure to pesticides and child neurodevelopment in a New York City cohort, Neurotoxicology and Teratology, 30, 243–259.

Young, J.G., Eskenazi, B., Gladstone, E.A., Bradman, A., Pedersen, L., Johnson, C., Barr, D.B., Furlong, C.E., Holland, N.T., 2005, Association Between In Utero Organophosphate Pesticide Exposure and Abnormal Reflexes in Neonates, NeuroToxicology, 26, 199–209.