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Toxicology of Organochlorines: Implications of Presence in Breast Milk

Pérez Ezequiel[1], Gulayin Miguel[1], H Marín Gustavo[1] and Mestorino Nora[2*]

[1]Department of Pharmacology, Faculty of Medical Sciences, National University of La Plata, 60 y 120, (1900) La Plata, Buenos Aires, Argentina.
[2]Laboratory of Pharmacology and Toxicology Studies, (LEFyT), Faculty of Veterinary Sciences, National University of La Plata, 60 y 118, (1900) La Plata, Buenos Aires, Argentina.

Authors' contributions

This work was carried out in collaboration between all authors. Authors PE, GM and MN managed literature search, analyzed the study, wrote and compiled the draft of the manuscript. MGH wrote the first English version of the manuscript and contributed to edition. MN designed the study; wrote the protocol, and supervised the work. All authors read and approved the final manuscript.

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ABSTRACT

Background: Organochlorine pesticides (OCPs) are compounds that have been widely used in agriculture to control pests and also in the field of public health to control of paludism dissemination and other vectors. Currently, they are banned in most countries because they constitute a great threat to human health and ecosystems. The high affinity for adipose tissue and its slow metabolism place OCPs in the group of bioacumulative substances. Hence, OCPs passage into breast milk is high and involves a severe risk for infants.
Objective: Analyze the toxicity including toxicodynamic and toxicokinetic of organochlorine (OC) and evaluate perinatal and infant toxicity after its exposure through breast milk.
Methods: A desk top systematic literature research was carried out to explore the toxicity of OCPs. We conducted an extensive literature review using databases such as Web of Knowledge, Google

**Corresponding author: Email: noram@fcv.unlp.edu.ar, nmestorino@yahoo.com;*

search engine, Science Direct, Medline, Scopus, Lilacs databases and involved observational studies on low-dose exposure in humans.
Results: 1) OCPs constitute a real threat to ecosystems and public health. 2) They are concentrated in breast milk and breastfeeding contributes to worsen this exposure during the lactation period. 3) They have severe effects on CNS and the immune system, inducing mutagenesis, carcinogenesis, teratogenesis, metabolic and reproductive abnormalities 3) The human fetus and infant exposure to OCPs cause learning disabilities, low intelligence quotient, attention deficit and hyperactivity.
Conclusions: For children, the best way to determine the risk of OC exposure is the analysis of breast milk samples and milk producing animals.

Keywords: Organochlorine pesticides; toxicodynamic; toxicokinetics; toxicity; breastfeeding.

1. INTRODUCTION

Persistent organic pollutants (POPs) are substances that persist in degradation processes and have the ability to transport over long distances in the environment. POPs accumulation become harmful to biota and humans. Due to their transportation characteristics, POPs have been detected in places where they had never been used [1]. Currently, organochlorinated pollutants are one of the most important environmental issues as a consequence of exposure to POPs, such as organochlorine pesticides (OCPs) resulting in a variety of toxic and adverse health effects, including carcinogenesis, immunological and reproductive disorders in living organisms including humans and wildlife. In the past OCPs were indiscriminately used in agriculture for pest control and for eradication of endemic diseases by eliminating vectors (malaria, typhoid, dengue, etc.) [2]. Based on its accessibility and low cost, they were the agents of choice for decades [3], however they have been replaced by less persistent and less toxic compounds such as organophosphates and pyrethroids agents. Unfortunately some developing sub-Saharan African and Southeast Asian countries still apply them, since malaria is a major cause of morbidity and mortality [3].

Despite its limitation in use, the OCPs can still be detected in different biological samples due to its high affinity for adipose tissue, its bioaccumulation (span of waste over time), its difficulties to be eliminated from the body and the phenomenon of biomagnifications (concentration and accumulation through the different levels of the food chain) [4,5].

Organochlorine compounds constitute a real threat to ecosystems and public health since they have severe detrimental effects on the immune system, inducing mutagenesis, carcinogenesis, teratogenesis, metabolic and reproductive abnormalities [6]. Hence, they are substances especially toxic for fetus and infants during gestation and lactation periods. This situation is also associated with poor growth and development that reduce the quality of life of children and their families [6].

This paper analyzes the toxicity including toxicodynamic and toxicokinetic properties of OC, as well as its applicability and finally evaluates perinatal and infant toxicity after OC exposure.

Organochlorine concentration in human milk becomes a good indicator of current environmental pollution since breastfeeding involves continuous mobilization of these substances from adipose tissue into breast milk of mothers living in exposed areas [6]. Therefore, controlling OC levels in breast milk samples becomes crucially not only because its individual toxicity but also for its impact public health. This revision is part of the research project entitled "Breastfeeding in Argentina: influence of cultural, economic, educational and health in the evolution of infants in their first year of life" (M138) accredited by the National University of La Plata.

2. SEARCH METHODS

A desk top systematic literature research was carried out to explore the toxicity of OCPs. This review was conducted by three independent reviewers who retrieved potentially relevant articles and extracted data. The reviewers solved their discrepancies reaching a consensus expressed on final results.

2.1 Search Strategy

We conducted an extensive literature review using databases such as Web of Knowledge,

Google search engine, Science Direct, Medline, Scopus, Lilacs databases and involved observational studies on low-dose exposure in humans.

These databases were selected to allow the identification of not only journal articles but also reports, and gray literature. Hand-searching of key journals and books was carried out in the university library (UNLP), in order to identify articles not indexed in electronic databases or not easily identifiable in electronic databases.

Terms were limited to the title and abstract field. No date or language restrictions were applied to the searches.

2.2 Inclusion Criteria

Information was considered eligible for inclusion in the data extraction of this review if the objective was the development of a search filter that could generally be used for retrieving articles with data on toxicity from an electronic database.

2.3 Data Extraction

Information was extracted about the database and interface with a search filter that was devised to focus on the type of adverse effects or toxicity.

3. RESULTS

3.1 Organochlorine Classification and Chemical Structure

Organochlorine insecticides are organic molecules composed of carbon, hydrogen and chlorine. Its cyclic structure and its high molecular weight are chemically very similar to chlorinated hydrocarbons used as solvents [7].

They have low solubility in water and high solubility in most organic solvents, which significantly increases when the temperature is higher [8]. These compounds have the property of accumulating in soil and groundwater [7,8] and could be detected in earth by several years. One of the most known organochloride for its insecticidal properties, the dichlorodiphenyltrichloroethane **(DDT)** has a rate of decomposition in the environment estimated in 20-30 years [4,5,9].

The OC can be divided into four main categories according to their molecular structure. In the first group, called dichloro diphenyl ethane or diphenyl aliphatics (Fig. 1), are DDT (dichlorodiphenyltrichloroethane), dichlorodiphenyldichloroethane (DDD), dicofol, ethylan, chlorobenzilate and methoxychlor. The second group is cyclodienes containing chlordane, aldrin, dieldrin, heptachlor, endrin, dodecachloropentacyclo decane (mirex), and endosulfan (cyclic ester of sulphuric acid) [7,8,9]. The third group called cyclohexanes includes lindane and the last chlorinated camphenes group contains toxaphene and chlordecone [9].

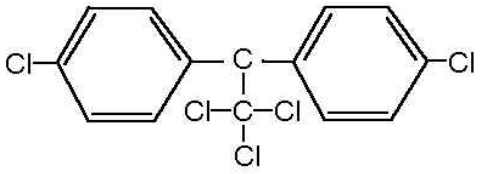

Fig. 1. Chemical structure of an aliphatic diphenyl (DDT)

3.2 Current Status of Organochlorine use in Argentina

The global situation of OC differs according to countries location. DDT is still used in Asian and African countries where malaria is a real problem, claiming thousands of victims annually. In these regions, the World Health Organization endorses the indoor use of chlorinated pesticides, while for the control of mosquito larvae are preferred pyrethroids or phosphorus compounds [10].

In Argentina the OC compounds were widely used from the 1940s both in agriculture and in the field of public health. The application of DDT was supported by policies to fight against malaria. Its widespread use has allowed an efficient control of the disease, at a level close to eradication of the vectors [11]. However, due to deleterious effects on man and the environment, the application of DDT and other OC has been restricted in Argentina to be completely banned nowadays.

The list of banned pesticides in Argentina either for import, processing, commercialization and use can be obtained from the "Regional Workshop on Pesticide Poisoning and Harmonization in the Collection of Information" of the Ministry of Health of Argentina, November 2003 [12]. However, the banning processes not always have the ideal coordination. For example imports of endosulfan was banned by Argentinean's authorities in July 2012, but it use was banned one year after [13]. Table 1 shows

acute pesticide poisoning according to the type of compound.

Note that acute poisoning with OC compounds is negligible with respect to other pesticides because of the great restrictions on its use. However it should be noted that because the bioaccumulation, biomagnification and high lipid solubility, these substances they can accumulate in tissues causing chronic conditions. This phenomenon is crucial during pregnancy, since which these compounds may pass across the placenta reaching the fetus, forming the initial burden of neonatal OC [14,15]. Breastfeeding contributes to worsen this exposure during the lactation period. [16]. It is estimated that infants incorporate these compounds 20 times more than adults, accumulating during the first three months of life 6% of all that accrue during the rest of his life [17]. These early exposures have been linked directly with harmful effects on the developing fetus and child. As mentioned, the detection of OCPs in breast milk reflects the environmental pollution. In a recent study performed in Buenos Aires, Argentina, 23 kinds of OC were analyzed in human milk and it found that in all samples tested (n = 248) had at least a chlorinated compound. The most frequently OC encountered was pp'DDE: 86.7% (95% CI 82-90) at a concentration of 8.98 ng/ml, followed by hexachlorobenzene: 26.6% (95% CI 21.5-32) at 1.50 ng/ml; heptachlor epoxide: 25.4% (95% 10-31) at 1.27 ng/ml, b-hexachlorocyclohexane: 23.0% (95% CI 18-28) at 4.32 ng/ml and chlordane: 15.7% (95% CI 11.7-20.8) at a concentration of 1.49 ng/ml [6]. These findings demonstrate the phenomenon of bioaccumulation of chlorinated substances through the food chain. As discussed in the section on toxicokinetics, the fact that pp 'DDE has been the OC most frequently found demonstrates a predominance of a chronic exposure to DDT. The agricultural pesticides that frequently cause poisoning are listed in Table 2.

3.3 Toxicokinetic of OC

Organochlorines pesticides are highly lipophilic compounds. Its kinetics is determined by this property and by inefficient metabolic pathways against several of them, which affects their bioaccumulation. They have good absorption by oral and inhalation route, and its variable by healthy skin. The transcutaneous passage is low in the case of DDT and higher for dieldrin [18]. This passage may increase if the OC preparations are prepared in lipid solvents.

The main entrance of OC in humans is via inhalation or consumption of contaminated animal origin foodstuffs [19]. However, given its high passage into breast milk, breastfeeding becomes the most important via to be consider in lactating mothers [9,20,21]. The OC are distributed in all tissues (high volume of distribution), having high affinity for the CNS, liver and adipose tissue, where they are deposited [9]. Logically, the milk fat of mammals, including human milk, is not an exception to this phenomenon. Therefore, infants who consume substantial quantities of contaminated milk may reach or exceed the acceptable daily intake of OC [6] (Table 3). The diffusion of the compounds accumulated in the fat milk during lactation depends on its molecular size, protein binding percentage, degree of ionization and lipophilic ability (which facilitates passage through cell membranes) and also of the blood flow between others variables [6].

Organochlorines compounds may also be concentrated on other neutral fat-rich tissues such as adrenal gland [22]. After exposure OC, DDT and DDE are present in adipose tissue steadily, while methoxychlor accumulates in minimum amount. The different isomers of hexachlorocyclohexane (HCH) accumulate very unevenly, beta shows high deposit while gamma HCH has few chances to reach high concentrations. Dieldrin largely deposited while its isomer endrin is effectively removed [22].

This kinetic behavior explains why in certain situations of accelerated lipolysis increased levels of OC can be find in serum. It has been estimated that each 1 ppb of DDT found in serum samples, brain, liver and fat cells contains 5-10 ppb, 47 ppb, and 100-300 ppb respectively [9].

Table 1. Exhibitions-poisoning by type of pesticide

Pesticide type	N	%
Pesticide for domestic use	3561	91.75
Pesticide for agriculture use	287	7.40
No agrochemical pesticide	33	0.85
Total	3881	100.00

Table 2. Pesticide causing poisoning

Pesticide for agricultural use	N	%
Herbicides	77	26.83
Phosphoric insecticide	70	24.39
Carbamate insecticides	34	11.85
Pyrethroid insecticides	34	11.85
Fungicides	28	9.76
Other unidentified	18	6.27
Other unclassified	12	4.18
Other rodenticides	6	2.09
Chlorinated insecticides	3	1.05
Mix of Drugs	3	1.05
Phosphides	2	0.7
Total	287	100

Table 3. WHO extraneous maximum residues limits (EMRL) by OC in raw milk

Pesticide	EMRL (mg/kg)
(α+β)-HCH	0.1
Lindane	0.01
Aldrin+Dieldrin	0.006
Heptachloro + epoxide	0.006
Endrin	0.0008
Total DDT	0.05

Organochlorines biotransformation is performed by hepatic cytochrome P_{450} enzymes. It is a slow process that may be modified by inducers [23]. The metabolism of these pesticides results derived either by glucuronide conjugates (dieldrin), sulphur (endosulfan) and phenolic (lindane) that are eliminated through urine, bile, feces, and breast milk. So when these compounds enter the body of livestock, they will return to the environment though all its routes of excretion. Even aldrin is converted to dieldrin by animals, insects, bacteria and by the action of sunlight [22, 24], while dieldrin also can lead to another toxic compound called aldrin-transdiol [25]. The biotransformation of DDT expressed by the presence of pp'DDE (intermediate metabolite of DDT) in serum indicates a long-term exposure to DDT. The relationship between the concentrations of DDT and DDE (DDE / DDT) allow describing the features of the exposure to OC, because when this ratio is greater than 1, it reflects no recent exposure to DDT [26]. Fig. 2 shows the scheme of DDT metabolites.

Detoxification processes differ according the chemical family. Some of them such as DDT are transformed to lipophilic toxic metabolites (DDE, DDD and DDA-2,2-bis (p-chlorophenyl) acetic acid), which are accumulated, while chlorobenzene derivatives gives more soluble products that can be easily eliminated by urine.

Lindane sub-products become more toxic epoxide compounds before hydroxylated, like cyclohexane derivatives. Lindane and other hexachlorocyclohexane isomers also produce 2,4,6-trichlorophenol as the major product of oxidation [22,27,28]. Heptachlor and fotoaldrín isodrin are as well substrates of microsomal epoxidase activity.

Obviously, by their physicochemical and affinity for fat cells characteristics, OCPs elimination half-lives are very extend, persisting in the body for long time. DDT and DDE are the most abundant OC compounds [29]. Once in the human body DDT is metabolized to DDE in a span of 6 months. A study in volunteers receiving DDT showed that once the dosing ended, a slow decrease in DDT concentration deposited in adipose tissue was observed. The values found after 25.5 months of recovery varied between 32% and 35% of the maximum recorded in the deposits of those who received 35 mg/man/day, but were 66% in those who only received 3.5 mg/man/day, indicating a slower loss when the accumulated concentration is smaller [27]. A fundamental property of the OC insecticides is their ability to induce liver enzymes involved in drug biotransformation (anticoagulants, barbiturates, analgesics, antiinflammatory drugs) and endogenous substances such as steroid hormone. This phenomenon contributes to the anti-estrogenic effect described for chronic

exposure to OC. Among the induced systems are the mixed function oxidases and transferases. Not only DDT but also its biotransformation products DDD, DDE and DDA are potent enzyme inducers [29].

3.4 Mechanism of Toxicity

The OC compounds are mainly neurotoxic. The group of diphenyl-aliphatic and its analogs (DDT, DDD, DDE, dicofol, ethylan, chlorobenzilate and methoxychlor) reduces transport of K^+ and promotes the entry of Na^+ inside the cell. The mechanism is related to its binding capacity to Na^+ activated by voltage channels of axonal membrane, which delays the inactivation gates. This series of events trigger muscle twitching, convulsions and eventually death in both insects and mammals [7,9,30], and these effects is characteristic of acute poisoning.

In contrast to the previous group, cyclodienes (chlordane, aldrin, dieldrin, heptachlor, endrin, mirex, endosulfan and chlordecone), interact with the GABA neurotransmitter receptor, preventing its binding and therefore hindering Cl^- entry. Blockade of the inhibitory stimulus generates hyper abnormal CNS excitability [7].

Other CNS alterations like neuro-endocrine dysfunctions [31,32], deficits in learning and memory, as well as locomotives and behavior [33] disorders are also associated to OC exposure.

3.4.1 Toxicity in relation to the hormone system

Johnson et al, in 1992 [34] demonstrated the estrogenicity of methoxychlor, DDT and derivatives. Later, other authors confirmed the same toxicity for dieldrin, endosulfan and lindane [35]. The estrogenic effects have been attributed to the agonist action of OC on alpha and beta estrogenic receptors (ERα and ERβ). Some pesticides, such as DDT and methoxychlor interact with receptor 30 G-protein coupled (GPR30), which is widely distributed in the brain at the intracellular level [36]. Some OC (eg dieldrin and endosulfan) stimulate phosphorylation of different kinases (ERK1/2 and AKt), enhance Ca^{+2} entry and release of prolactin in different cell lines [37, 38].

Organochlorine pesticides among their various actions can activate gene expression mediated by the retinoic acid receptor and the pregnane PXR [39] and also inhibit the activation of the androgen receptor and progesterone [40]. In addition, after a chronic exposure to OC compounds, levels of estrogen receptors may be altered [41].

3.4.2 Toxicity in relation with CNS

Chronic exposure to OC pesticides alter large number of proteins, including, antioxidant enzymes, receptors and transporters of certain neurotransmitters [42]. Various metabolic enzymes, such as acetylcholinesterase, ion channels or pumps, Mg^{+2}, Na^+/K^+ and Ca^{+2} ATPase in the plasma and mitochondrial membrane [43] are also affected.

In 1993 Naqvi and Vaishnavi [44] reported that the levels of certain monoaminergic neurotransmitters, such as serotonin, dopamine and norepinephrine, are altered by the action of OC pesticides. Subsequently based on the findings of Fleming et al. in 1994 [45], it was found that dieldrin exhibits selective toxicity on mesencephalic dopaminergic neurons, so the chronic exposure to the pesticide might be linked with the development of Parkinson's disease [46]. Later it was found that the production of free radicals and activation of caspases (enzymes that execute apoptosis) caused by dieldrin, endosulfan and lindane, play a decisive role [47], which added to the proteolytic degradation of PKCδ would unleash DNA fragmentation. Dieldrin also affects the dopamine release and the modulation of its transporters mechanisms [47]. The expression of serotonin receptors is also modified by chronic exposure to pesticides OC, as well as alteration of the differentiation and maturation of serotonergic neurons [48].

Similarly the aminoacidergic neurotransmission may be altered by chronic exposure to OC pesticides; dieldrin alters the expression of some subunits of GABA [49] receptor. Also OC reduce functionality of glutaminergic cerebellar neurons and expression level of N-methyl-D-aspartate receptors (NMDA) on their membranes [31].

3.5 Organochlorines Association to Immunotoxicity Process

The immune system can be the target of many chemicals, with potentially severe adverse effects on the host's health.

Organochlorines may initiate, facilitate or exacerbate pathological immune processes, resulting in immunotoxicity by induction of mutations in genes coding for immunoregulatory factors, modifying immune tolerance and activation pathways.

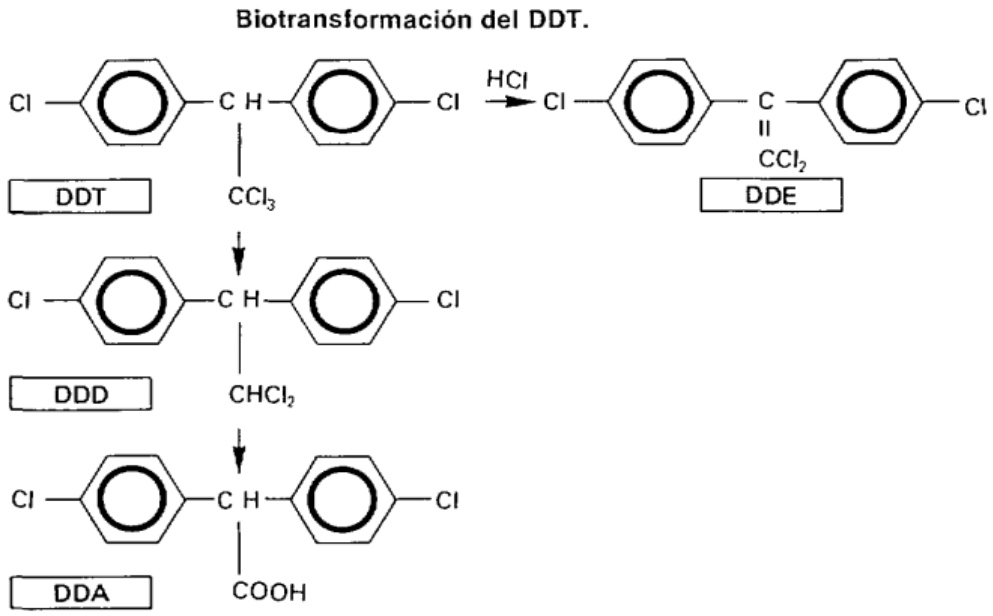

Fig. 2. Scheme of DDT biotransformation

DDT: Dichlorodiphenyltrichloroethane, DDT, DDE: dichlorodiphenyldichloroethane, DDA: dichloro diphenyl acetic

Even if experimental data as well as sporadic human studies indicate that some pesticides can affect the immune system, overall, existing epidemiological studies are inadequate to raise conclusions on the immunotoxic risk associated to pesticide exposure [50].

According to Phillips [51], environmental exposure to pesticides may cause immunotoxic effects in children, thus rendering them susceptible to infections and other immune mediated disorders. Interestingly, all the 25 lindane exposed subjects of Phillips's cohort showed some abnormalities in cytokines associated with hematopoiesis. Additionally, elevations in pro-inflammatory cytokines and neuropeptides indicated a state of generalized and neurogenic inflammation accompanied with some evidence of stimulation of the humoral immune system, as indicated by elevated IL-5 concentrations and clinical allergy. The degree of immune deregulation in the exposed children was found to be quite marked when compared to similar studies performed on age-matched controls. Duramad et al. [52] reviewed the evidence of effects of environmental exposures to pesticides during prenatal and early postnatal development. A possible association with several childhood diseases, including allergic disorders and leukemia, was observed. Apart for children, the existing evidence of possible immune effects related to human exposure to pesticides involves also general population and workers, the latter usually showing exposure levels higher than those involving the general population. Furthermore, it should be taken in due account that consequences of pesticide-induced immunotoxicity may be also particularly relevant in developing countries, where, compared to industrialized world, much larger fractions of the population still live in the countryside and work on the farm. Compounds that have been banned or restricted in industrialized countries are still in use. Together with weak pesticide regulations, lack of training and equipment to safely handle pesticides, makes health risk in developing countries higher.

Cooper et al. [53] showed that increasing plasma levels of DDE correlate with decreased IgG levels in African-American male farmers. In the same study, no association was found with IgA, while the prevalence of antinuclear antibodies was somewhat elevated, although not statistically significant, in the highest category of DDE exposure.

3.6 Clinical Manifestations of OC Exposure

The OC compounds are capable of producing acute, subacute and chronic toxicity. The acute toxic effect is less than in the case of organophosphate insecticides or carbamates, but the chronic effects are higher [54].

Acute poisoning occurs in most cases by accidental or intentional ingestion of household insecticides, especially in children [18,54]. Between 30 minutes and 6 hours after exposure, the individual has anxiety, gastrointestinal disturbances such as nausea, vomiting and oropharyngeal burning symptoms [9,18]. The clinical presentation of acute exposure also includes pallor, dizziness, headache and seizures, often the latter being the reason for consultation [9]. Insecticides with more chances to cause seizures are lindane, dieldrin, endrin, chlordane, heptachlor, toxaphene and strobane [54].

An acute poisoning may also be the cause of severe aplastic anemia, with thrombus and granulocytopaenia.

In the liver, low doses cause an increase in transaminase enzymes levels, whereas a higher dose leads to lobular necrosis. Due to the induction of cytochrome 1A and 2B, the increases of free radicals production and reduction of glutathione levels are causes of the oxidative damage associated with OC [28,54,55].

After poison contact through the airway, respiratory symptoms appear including cough, dyspnea, crackles, and cyanosis [54]. The cardiovascular system does not avoid the toxic effects of OC pesticides. Myocardial arrhythmias, myocarditis, or even episodes of ventricular fibrillation may also occur [18].

The LD50 of the most representative OC compounds can be viewed in Table 4 [54].

Although acute toxicities are associates to all the consequences described in the preceding paragraphs, are in fact the chronic exposures responsible for the most severe damage. The clinical features are dominated by the presence of gradual neurological symptoms such as numbness or limbs paresis, which demonstrate peripheral neuropathy [56]. Tremors and ataxia are manifestations of cerebella abnormalities and nigrostriatal pathway disorder. Moreover, electromyographic studies shows decrease in nerve conduction impulse and dysfunction in muscle contraction [42,43,44]. It is important to note that given the complexity of neurological symptoms it is extremely difficult for the physician to make the diagnosis of OC poisoning [56].

Liver function is impaired, showing an increased of enzymatic markers [27,28,55,57], due to the inducing action.

The effect on reproductive system after OC chronic exposure is well established by experimental methods. Long term exposures at doses from 0.35 to 39 mg/kg/day caused decreased fertility in rodents. This effect may be due to both oestrogenic and anti-androgenic effects [58,59]. In addition, the induction of cytochrome P450 group by OC molecules increases the metabolism of the estrogenic and androgenic hormones, reducing their serum levels. Besides affecting hormonal function, DDE has been associated with multiple qualitative and quantitative abnormalities in semen. Dieldrin cause severe damage of Leydig cells, reducing the production of testosterone and favoring the development of male infertility [9, 59, 60]. At the level of the female reproductive system, some studies indicate that exposure to OC, especially DDT and its metabolites, may reduce the fertile stage triggering early menopause in women affected [9,60]; hence OC are known as "endocrine disruptors".

The endocrine disorders are not just limited to reproductive hormones. The OCPs are associated with thyroid disorders (hypothyroidism) and increased risk of developing type 2 diabetes [7].

Referring to the oncogenic potential effect associated to OC chronic exposure data remains controversial and evidence is still irrelevant [60]. A study from Argentina showed that the OC deposited in the breast fat tissue generate an estrogenic microenvironment which may contribute to the development of hormone-dependent breast cancer. However it exist data demonstrating an association between high levels of OC in breast adipose tissue and breast cancer [60,61].

Chlorinated pesticides such as dieldrin and DDT, increases the risk of lung cancer, non-Hodgkin lymphoma, pancreatic cancer, liver carcinoma and testicular germ cell tumors. Hexachlorobenzene, increases the chances of developing connective tumors (sarcomas) and thyroid neoplasm [9,57].

3.7 Perinatal and Infant Toxicity after oc Exposure through Breast Milk Intake

It is well known since 1951 [62] that OC may contaminate breast milk. However, only few years ago researchers understood the potential effects on infant health and its consequences for child development.

The perinatal period is defined as the time interval extending from the end of the stage of organogenesis to the end of neonatal period (from the 28th week of gestation through the first 4 weeks postpartum) [61, 63]. At such times, the direct action of OC pesticides or their metabolites may interfere negatively with the proper development of the embryo, fetus or neonate. Fetal and neonatal susceptibility to pesticides is greater than in adults, since enzymatic metabolism and elimination systems are not fully developed. In addition during organogenesis, the action of an external substance can leave irreversible consequences for the child [63, 64].

The practice of exclusive breastfeeding (EBF) during first semester of life has proved beneficial for the health of mothers and children when compared with other types of food, including breast feeding mother combined with other foods [65].

Some of the reasons to promote such practice are:

Benefits for the child: Children fed with EBF have lower incidence of respiratory, gastrointestinal, acute otitis media when compared to children fed otherwise. Exclusive breastfeeding for the first six months of life can prevent up to 13% of deaths of children under five years old in developing countries [66].

Benefits for Mother: Mothers that offers their children EBF have lower risk of breast cancer [67].

However, even if nobody questions the benefits of breastfeeding, it is necessary to emphasize that exposure to breast milk with OC is linked to severe health problems [68]. Infants are then not exempt from suffering the acute and chronic toxic effects of OC. There is sufficient evidence to be considered a real threat to the endocrine and nervous systems, when these molecules are present in concentrations above acceptable limit in breast milk [11]. Prenatal or during lactation exposure have been associated with increased risk of: preterm birth [11], early puberty [61], hormonal disorders, especially thyroid and increased risk of type 2 diabetes [14,69], children obesity [70], increased incidence of otitis media [61], and testicular cancer and lymphomas [9, 11]. Since normal development of the brain requires a cascade of processes ranging from cell proliferation to apoptosis during late pregnancy and neonatal period, it is particularly vulnerable to exposure to chemical contaminants over those periods [71,72].

Rogan in 1987 established a correlation between neonatal hypotonia and hyporeflexia and higher levels of OC in umbilical cord blood and breast milk [73].

Duration of breastfeeding, age and parity were related to OC milk levels. The older mothers had high levels of OC pesticides, a situation linked to a longer contact with the environment. The area of residence influences according to the proximity to agricultural or industrial sites [74]. Smoking mothers as tobacco plantations were treated with pesticides in the past and even the new plants are still exposed to those harmful events [75].

The World Health Organization, in 1984 established the level of acceptable daily intake for DDT (ADI), which is 20µg/kg/day. This value can be extrapolated to human milk (acceptable concentrations in breast milk) by the following formula [76]:

$$\frac{\text{ADI µg/kg day}}{\text{Kg milk/day x fat/milk x weight (kg)}}$$

Infants, in some regions, especially those where DDT continues to be marketed for the control and eradication of vectors, may be ingesting greater amounts than the allowed by the WHO. However, as mentioned, given the irreplaceable benefits of breastfeeding for the proper growth and development of children, the suspension of the act of breastfeeding for fear of exposure to excessive amounts of DDT and other OC [14] is not recommended. This paradox demands to have a monitoring method of breast milk and

Table 4. LD_{50} for OC compounds

2-20	mg/kg	Endrin
20-50	mg/kg	Dieldrin, Aldrin
50-100	mg/kg	Tetrachlothiophen
100-300	mg/kg	Toxaphen, Chlordano
300- 500	mg/kg	DDT
500- 1000	mg/kg	Chlordane

baby food OC detection in order to implement appropriate measures to prevent the action of these compounds in the child development. Villaamil Lepori et al. [77] analyzed 50 samples of baby milk and 51 samples of yoghurts and desserts available in the market, finding that only 10% of them were free of dangerous pesticides.

Since infants and children consume more calories per unit of body weight than adults, and even worse, they eat a very limited variety of foods; breast milk or infant formula becomes the main source of nutrition until 6 months old. Children older than six months begin to consume mixed diets, milk and other dairy products such as yogurt made of cow's milk. Then, considering that cow and breast milk are privileged elimination paths of OC pesticides [78], is reasonable to expect becomes a public health problem and is one of the reason that explains why babies and children are exposed 10 to 20 times more than adults to OC effects.

4. DISCUSSION AND CONCLUSION

The indiscriminate use of OC agents still constitutes a real threat to the health of people and ecosystems. Given their kinetic characteristics (lipid solubility and extremely difficult metabolization), the OC tend to accumulate in the fatty tissue of living organisms. Moreover, they are extremely stable in the environment and accumulate in soils and groundwater. Contamination of aquatic and terrestrial ecosystems by OC compounds was reported more than 40 years ago, when the contamination of marine mammals in the Arctic with OC pesticides were found. The first record of the presence of derivatives of hexachlorocyclohexane (HCH's) in Arctic air dates from 1979 when Tatsukawa and Tanabe [79] found a concentration of 1000 pg/m in the Bering Sea. Detection of this contamination in those latitudes, where nobody used these products, shows OC mobilization and proves that they may be present in all environments and climates of the Earth [79,80]. The OC can be emitted to the atmosphere as gaseous products, in liquid or solid particles. Some may degrade in the atmosphere or may be deposited in places far from the emission source, even thousands of miles. Agricultural use until a few decades ago has generated extremely undesirable accumulation phenomena. It should be understood that while in a pasture concentration of pesticides OC can be very low (to the point of being now almost undetectable) when grass is ingested by a ruminant, the OC will concentrate in adipose tissue and milk. Subsequently, when this milk will be industrialized, for example for the production of creams, desserts, cheese, butter (all products of high fat content), the initial levels of CO present in the raw materials will increase rapidly due to concentration processes carried out in the processing of milk products. In Mexico, it has been describe concentrations of DDE and DDT in bovine milk of 44 ppb and 159 ppb respectively [78].

In Spain [81], the presence of OC compounds in milk produced from different farms of the peninsula was monitored weekly throughout a whole year (1987). Authors found that all samples tested (N=460) were contaminated with one or more OC pesticides, although mostly at levels below the maximum allowable limits. These findings are always detected even if is demonstrated that animals were not exposed directly to these compounds.

Altough OC pesticides were banned long ago in Argentina; they are still "appearing" in animal products, especially in dairy, as milk replacers, yoghurts and desserts consumed mainly by infants and children. Let us remember studies performed by toxicologists at the Faculty of Pharmacy and Biochemistry, National University of Buenos Aires, in milk replacers, yoghurts and desserts samples commercially available finding that only 10% were free of OC [77]. These researchers found more frequently heptachlor and heptachlor epoxide metabolite (in 57.4% of samples), but also found other persistent substances such as hexachlorocyclohexane (53.3%); DDT and aldrin-dieldrin (31.7%); chlordane (28.7%); endrin (18.8%); endosulfan and hexachlorobenzene (9.9%) [77]. Subsequently, Ruiz et al. [80] performed in Jujuy, Argentina, track usage of OC pesticides in agricultural and livestock farms of that province, confirming its irrational use: 77% of farmers used 42 different agrochemicals in their fields; as well confirmed the illegal marketing of raw milk (without pasteurization) directly from the farms. After analyzing by gas chromatography the obtained milk samples, they found concentrations above allowable levels for trans-chlordane (4.8 ppb vs 2 ppb). In the case of endrin level, it was the maximum allowed (0.74 ppb vs 0.8 ppb); while HCH, lindane, DDT and its metabolites were at concentrations below the permitted levels. In all samples it was found β-HCH, which can be applied to indicate that, both α and β-HCH were present, since both are

metabolized in living organisms to β-HCH. Dieldrin and heptachlor epoxide also were found, which may be due to the direct application of these compounds or by metabolizing heptachlor aldrin previously applied. In daily farm it was determined the DDE / DDT ratio which was 2.34; this corresponds to uses not very distant in time; however, in another daily the ratio was 0.104 corroborating a recent application of DDT (banned for use in Argentina over 14 years ago). In addition, lindane and endosulfan were in other dairy farm, near a plantation of tobacco. This situation also must be considered when evaluating the chemical quality of milk of smoking mothers [75]. Ultimately these findings confirm the long persistence of these compounds OC, and the irresponsibility or ignorance of these dangers by the agricultural-livestock producers and health authorities.

Data provided in this paper leads us to conclude that organochlorines levels found in bovine milk are alarming, and the fact that those levels are higher in dairy products consumed by mothers or in their breast milk, makes the situation even worse than expected [82].

For animals or nursing mothers living in an environment where the OC compounds have been used to control insects and plant diseases, it is expected that food and breast milk will be contaminated in different degrees with these pesticides. In Argentina during the 90´s there were found OC values above 990 ppb. If we consider that the milk is used for cheese production, final concentration of OC can achieve remarkably higher values (DDE: 1380 ppb, DDT total: 1420 ppb) [78]. These results show that these OC may bio-concentrate more than 31 times in the case of DDE [83]. In Venezuela, studies demonstrated the presence of residues of OC in raw, pasteurized and powdered milk, cheese, butter, vegetable oils, infant formulas and firm yogurt, finding in some cases concentrations exceeding the recommendation given by the Organization for Food and Agriculture Organization and the World Health Organization (FAO / WHO) [84,85,86,87].

It is important to raise public awareness to agricultural and livestock producers, industry and health personnel (pediatricians, obstetricians, clinical), about the danger of these substances to the general public and to future generations. It should be understood that OC substances are deleterious to health, classified by WHO as persistent organic hazardous substances, and its use should be restricted taking appropriate measures to control its use. The finding of elevated levels of OC in biological samples reveals irregularities in the marketing, so it is important that health authorities in each country strengthen and disseminate their control strategies.

The available studies on the effects of OCPs on human especially in children have several limitations including poor indication on exposure levels, multiple chemical exposures, heterogeneity of the approach, and difficulty in giving a prognostic significance to the slight changes often observed. Further studies are necessary, and they should be preferably carried out through comparison of pre and post-exposure findings in the same group of subjects with a matched control group.

Attempt should be made to define the prognostic significance of slight changes often observed. Animal and in vitro studies are also important and necessary to scientifically support epidemiological evidences on pesticide-induced immunotoxicity.

For children, the best way to determine the risk of OC exposure is the analysis of breast milk samples and milk producing animals (cattle, goats, and sheep). This noninvasive method might provide a good measure of potential toxicity to infants and child. Today with the advancement in analytical technology and current knowledge is possible to rapidly determinate the presence of these compounds and other toxins in breast milk. These measurements might provide important information to deal with this problem.

We believe that solutions exist in the case of infants up to six months, in which WHO recommends just this type of feeding. In order to collaborate to this goal, our group initiated a program to quantify levels of OC present in milk samples obtained from lactating horticultural belt inhabitants of the city of La Plata and also to promote workshops that expose this situation to vulnerable population. Right now we have about 400 human milk samples obtained from volunteer mothers' breastfeeding. The results obtained so far enable us to strengthen the commitment to raise awareness, legalize, regulate and develop mechanisms for the promotion and protection of the breastfeeding during the first 6 months of life.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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