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Lactational Exposure to Pesticides: A Review

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Abstract

The aim of this study is to review the reports of pesticides have been detected in human breast milk in worldwide. Contamination levels of pesticides such as organochlorine pesticides (OCPs), organophosphorus pesticides (OPPs), carbamates and pyrethroids in human breast milk were found to be varied in different countries. The chemical properties of chemicals such as lack of ionization, small molecular weight, low volume of distribution, low maternal serum protein binding, and high lipid solubility, facilitate compound excretion into human milk. Since exposure to pesticides during the early postnatal stages may disturb the normal development of the newborn, such studies may shed light on the wide variety of pesticides that have been detected in human breast milk.

Keywords: Breast-feeding; Anatomy; Lactational; Suckling; Exposure; Neonatal; Risk; Toxic; Transfer; Pesticides; Transfer mechanism

Introduction

Lactation is the production and secretion of milk by the mammary glands occurring in female mammals after giving birth. Breast milk provides the ideal nutrition for infants. It contains everything baby needs to grow such as vitamins, protein and fat. It is also containing antibodies the help infants fight off viruses and bacteria. American Academy of Pediatrics [1], concluded that breastfeeding and the use of human milk confer unique nutritional and non-nutritional benefits to the infant and the mother and, in turn, optimize infant and adult health as well as child growth and development. Human milk is uniquely suited to the human infant, both in its nutritional composition and in the non-nutritive bioactive factors that promote survival and healthy development [2]. Human milk provides varied bioactive factors, which include cells, anti-infectious and anti-inflammatory agents, growth factors, and prebiotics [3]. The human milk components derive from different sources, the nutrients of milk originate by synthesis in the lactocyte, some are dietary in origin, and some originate from maternal stores. Breast milk is the almost ideally formulated to suit all nutritional needs of neonates in every mammalian species.

The mammary gland is highly perfused with blood. Lipophilic compounds are passively transported from blood to the lipid in mammary cell which is subsequently secreted as milk lipid [4]. As important as the lipid portion of milk is to the elimination of lipophilic xenobiotic, it should be pointed out that milk is a mixture of proteins and lipids in an aqueous medium. As such, milk may contain virtually any compound, which is in solution in the mother's body water, adsorbed onto her blood proteins, or in solution in her blood lipids.

A wide variety of pesticides and chemical contaminants have been detected in human breast milk and there is a growing concern that exposure to pesticides during the early postnatal stages may disturb the normal development of the newborn. On the other hand, several studies have been carried out on the lactational transfer of pesticides in animal as a model. Different toxic chemicals can be transferred from the body stores and/or from the blood into the breast milk of a nursing mother and thus the suckling infants can expose to chemicals that may pose a health hazard [5]. At high exposure levels of certain chemicals, there is a risk of an adverse effect on the lactation process and on the content of nutrients in the milk [6]. The presence of environmental contaminants in human breast milk has gained increased attention from the regulatory agencies and groups advocating women's and children's health. As the published literature on chemicals in breast milk has grown, there remains a paucity of data on parameters related to infant exposure via breast-feeding, particularly those with a time-dependent nature LaKind [7]. The parameters needed to conduct realistic exposure assessments for breast-fed infants are the level of chemical substance in the mother's milk and the transfer kinetics of the chemical substance from the mother during breast-feeding Fang [8] reviewed the spatial and temporal trends of the Stockholm Convention POPs in mothers' milk and the collected data evident that the concentrations in mothers' milk depend on the use of pesticides and industrial chemicals defined as POPs. They reviewed that polychlorinated biphenyls (PCBs) and dioxins were higher in the more industrialized areas, Europe and Northern America, whereas pesticides were higher in Africa and Asia and polybrominated diphenyl ethers (PBDEs) were reported in higher concentrations in the USA. Pirsaheb et al. [9]. In their systematic review on organochlorine pesticides residue in breast milk, indicated the presence of two or more organochlorine pesticides in the collected samples of breast milk. Dichlorodiphenyltrichloroethane (DDT) had the highest level of concentration in the collected samples of breast milk. Moreover, there was a statistically significant positive correlation between mother's age, her multiparty and concentration of chlorinated pesticides in breast milk. The objective of the study is to provide a review of the literature on the detection of pesticides in human breast milk and other mammals and human health effects that have been associated with lactational exposure to these pesticides.

Methods

Methods for data retrieval on pesticides in mothers' milk were conducted based on the national international peer-reviewed articles and texts extracted from the following virtual databases: Google Scholar, Scopus, Science Direct, Index Medicus /WHO/EMdR, Elsiver,

Directory of Open Access Journal and PubMed. Articles and texts were collected based on the following key words: organochlorine, organophosphorus, pyrethroids, carbamate pesticides, residue, and breast milk.

Results

Lactational exposure to pesticides

The purpose of using pesticides is to control insect and animal vectors of human diseases and to increase agricultural productivity. In using pesticides, the benefits must be weighed against their effects on human health, biological interactions with non-target species, pesticide resistance, and alterations to and/or accumulation of pesticide in the environment. Many pesticides can be grouped into chemical families. Prominent pesticide families include chlorinated hydrocarbons, organophosphorus compounds, carbamates and synthetic pyrethroids. Table 1 summarized the chemical name of different pesticides mentioned in the text.

Compound	Chemical Name
DDT	1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane
DDE	1,1-bis-(4-chlorophenyl)-2,2-dichloroethane
Dieldrin	(1aR,2R,2aS,3S,6R,6aR,7S,7aS)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphtho[2,3-b]oxirene
Heptachlor	1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene
HCB	Hexachlorobenzene
HCH	β-1,2,3,4,5,6-hexachlorocyclohexane
Malathion	Diethyl 2-[(dimethoxyphosphorothioyl)sulfanyl]butanedioate
Chlorpyrifos	O,O-Diethyl O-3,5,6-trichloropyridin-2-yl phosphorothioate
Chlorpyrifos-methyl	O,O-Dimethyl 0-3,5,6-trichloro-2-pyridyl phosphorothioate
Methyl-parathion	O,O-dimethyl O-4-nitrophenyl phosphorothioate
Ethion	O,O,O′,O′-Tetraethyl S,S′-methylene bis(phosphorodithioate)
Dimethoate	O,O-dimethyl S-[2-(methylamino)-2-oxoethyl] dithiophosphate
Profenofos	O-4-bromo-2-chlorophenyl O-ethyl S-propyl phosphorothioate
Monocrotophos	Dimethyl (E)-1-methyl-2-(methylcarbamoyl)vinyl phosphate
Phosalone	6-chloro-3-(diethoxyphosphinothioylsulfanylmethyl)-1,3-benzoxazol-2-one
Phosfolan	N-diethoxyphosphoryl-1,3-dithiolan-2-imine
Mephosfolan	diethyl[(EZ)-4-methyl-1,3-dithiolan-2-ylidene]phosphoramidate
Profenofos	O-4-bromo-2-chlorophenyl O-ethyl S-propyl phosphorothioate
Methamidophos	O,S-Dimethyl phosphoramidothioate
Acephate	N-(Methoxy-methylsulfanylphosphoryl)acetamide
Propoxure	2-Isopropoxyphenyl N-methylcarbamate
Carbofuran	2,2-Dimethyl-2,3-dihydro-1-benzofuran-7-yl methylcarbamate
Permethrin	3-Phenoxybenzyl (1RS)-cis,trans-3-(2,2-dichlorovinyl) -2,2-dimethylcyclopropanecarboxylate
Cyfluthrin	[(R)-cyano-[4-fluoro-3-(phenoxy)phenyl]methyl] (1R,3R)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
Cypermethrin	[Cyano-(3-phenoxyphenyl)methyl]3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
Deltamethrin	[(S)-Cyano-(3-phenoxyphenyl)-methyl] (1R,3R)-3-(2,2-dibromoethenyl)-2,2-dimethyl-cyclopropane-1-carboxylate
Cyhalothrin	3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyano(3-phenoxyphenyl)methyl cyclopropanecarboxylate
Fenvalerate	(RS)-alpha-Cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate

Lambda-cyhalothrin	1:1 mixture of (S)-α-cyano-3-phenoxybenzyl-(Z)-(1R,3R)-3-(2- chloro-3,3,3-trifluoroprop-1-enyl) -2,2-dimethylcyclopropane carboxylate and(R)-α-cyano-3-phenoxybenzyl (Z)-(1S,3S)-3-(2- chloro-3,3,3-trifluoroprop-1-enyl) -2,2-dimethylcyclopropane carboxylate

Table 1: Chemical name of pesticides mentioned in the text.

Lactational exposure of these toxicants, therefore, may be of significance and need to be discussed in detail. These chemicals may be evaluated by special efforts toward identifying groups of women exposed occupationally or through heavy intake in consumer preparations of food, water, or air. Thus different pesticides may be transport through human breast milk during the early postnatal stages and may disturb the normal development of the newborn. Therefore, screening lactational exposure hazards should include the entire range of neonatal responses, including the risk trend for their breastfed newborns ingesting these compounds.

Fundamental principles of breast milk excretion are used to construct a pharmacokinetic approach useful for the study of most drugs. An infant-modulated 3-compartment open model is proposed for drug distribution and elimination in the breast feeding woman. Milk/plasma drug concentration ratios are projected on the basis of pH partitioning. While some studies confirm these projections, other studies demonstrate a need to consider additional factors such as lipid solubility and protein binding characteristics of a drug in milk. Data are lacking for most drugs and hence dosing via milk or risk to the infant remains speculative. Very few pharmacokinetic studies of both milk and infant plasma were found. A review of selected drug classes cites available information as a basis for future studies. Few drugs are contraindicated in breast feeding women, but supportive data for either proscriptions or permissive statements are often lacking. A neglected but potentially serious infant risk--impaired behavior and development--is discussed from the standpoint of emerging animal data. Conceptually valid and comprehensive studies on drug excretion in breast milk are needed if this valuable nutrient for infants is to be made available safely Wilson et al. [10]. Physiological pharmacokinetic modeling of plasma to milk transfer of compounds has been proposed by [11]. To enable the prediction of milk to plasma (M/P) ratio. They indicated that the most accurate in prospective performance is the log-transformed phase distribution model. This model developed by stepwise multiple linear regression analysis, also assists in the understanding of the relative contribution of the various physiological factors involved in the distribution of drugs into milk.

Organochlorine pesticides (OCPs)

Organochlorine pesticides (OCPs) are well known for their long persistence in the environment and living organisms due to their high lipophilicity, bioaccumulation and biomagnifying through the food chain. OCPs can be stored in the mother's body and then transferred postnatally from breast milk to the suckling infants, especially when the mother has significant ongoing exposures or has accumulated an unusually high body burden of persistent chemicals [12]. The levels of OCPs in human breast milk have been declined in countries where these chemicals have been banned or otherwise regulated [13]. In this respect, Harris et al. [14] determined OCPs residues in 168 samples of human breast milk in the United Kingdom collected between 1997 and 1998. They found that the median concentration levels of p,p'-DDT, p,p'-DDE, dieldrin, HCB, β –HCH and γ –HCH were 25, 283, 25, 25, 50 and 25 ng/g milk lipid, respectively. In another study, Kalantzi et al. [15] collected milk samples from 54 United Kingdom resident mothers between late 2001 and early 2003. p,p′-DDT and its metabolites were found to be ranged from 24-2,300 ng/g milk lipid; HCB ranged from non-detectable levels to 180 ng/g milk lipid, and ∑HCHs levels ranged from 1.2 to 1,500 ng/g milk lipid. Nagayama et al. [16] examined the frequency of sister chromatid exchanges (SCEs) in cultured lymphocyte obtained from Japanese infants postnatal of around ten months to evaluate the genotoxic or clastogenic potency of lactational exposures to some OCPs. They reported that the median concentrations of HCHs, DDT and chlordane were 341, 272, and 69 μg/g milk lipid, respectively. In Poland [17], determined the levels of p,p'-DDT and its metabolites, HCB, HCHs isomers, chlordanes and their metabolites in human milk collected from 22 mothers living in the Wielkopolska region. They indicated that p,p'-DDT and its major metabolite, p,p'-DDE, together with HCB, were found in all milk samples and the median concentration of p,p'-DDE in milk was 634 ng/g milk lipid. Sudaryanto et al. [18] analyzed the levels of OCPs in human breast milk among Indonesians populations. They reported that OCPs concentrations are varied between locations and individuals where DDTs levels were higher in suburban and rural areas than urban localities. These findings may be due to the differences in food habits and sources between the individuals and locations. Data from Surakarta site indicated continuing DDT exposure, which may confirm recent usage of DDT in Indonesia. A positive correlation was observed between concentration of OCPs in human milk and age of mothers, primiparas women having higher OCPs than multiparas, suggesting that these parameters play an important role influencing the OCPs burdens in lactating women. Some individuals accumulated DDTs and HCHs in breast milk close to or even higher than the tolerable daily intake (TDI) guidelines proposed by Health Canada. DDT was also determined in breast-milk collected from three towns in KwaZulu-Natal, South Africa, one of which had no need for DDT for malaria control. Primiparae from one town had the highest mean of DDT level (238.23 μg/l whole milk) Bouwman et al. [19] In another study, Sereda et al. [20] indicated that the presence of OCPs in human breast milk in malaria control areas is of major concern where DDT is used as indoor residual spray (IRS). The levels of DDT in breast milk from northern KwaZulu-Natal in South Africa was determined in both reference and exposed mothers used the same market food. The median DDT levels in the exposed mothers was 10 μg/g milk fat, while in the reference mothers it was 1.3 μg/g milk fat. This difference in residue levels indicates uptake from IRS-applied DDT, most likely via air and skin contact. Pesticide residue analysis of breast milk of lactating mothers residing in the state of Lower Saxony in Germany was carried out over a time of 8 years (1999-2006) Zietz et al. [21]. The median values of DDT, β-HCH, and HCB were found to be 81.5, 11.6 and 22.9 ng/g milk lipid, respectively. A clear downward trend of OCPs median values was observed in all participants and also in different selected subgroups. The amounts of pesticides declined between 40.9% and 47.1% compared to the year 1999. They also indicated that the median concentrations of pesticides enhanced with increasing the age of mothers. Mueller et al. [22] indicated that human milk has been used as a surrogate for the assessment of body burden and exposure to persistent lipophilic OCPs. They also reported that the use of OCPs has been banned in Australia

since the 1980s. The decline of human body burden of OCPs following their ban in many industrialized countries is well recorded worldwide from the 1970s until the 1990s though little is known on whether these trends are continuing. They collected 157 human milk samples during 2002 and 2003 as well as 24 samples in 1993 for OCPs residue analysis. OCPs were detected in all pooled human milk samples from 2002/03 typically with highest concentrations of p,p'-DDE (311 ng/g lipid) followed by γ-HCH (80 ng/g lipid) . Other OCPs consistently detected included dieldrin (16 ng/g lipid), HCB (18 ng/g lipid), transnonachlor (11 ng/g lipid) and p,p'-DDT (9 ng/g lipid). The use of multivariate statistics indicated some regional trends with slightly higher levels of the broadly used insecticides DDT and HCH in both historic and recent samples from Melbourne, whereas sample pools collected from mothers that lived in rural Queensland and New South Wales as well as Adelaide and Sydney showed comparatively higher levels of heptachlor and dieldrin – both of which have been used for termite treatment. These results indicated that even 20 years after the discontinuation of usage, historical use of OCPs rather than exposure via global transport of OCPs is responsible for continuous low exposure in Australia. The distribution and time trend of OCPs levels in human milk samples from Croatia collected in 1981–2003 was investigated by Krauthacker et al. [23]. They indicated that between 1981/1982 and 1987/1989, the concentrations of HCB, β-HCH and DDE decreased about 50%, while for the last decade, the concentrations have been decreasing very slowly. In 2002/2003 the range of OCPs was from below the limit of determination to 332 ng/g milk lipid. Pan et al. [24] indicated that the growth of infants exposed to persistent organic pollutants (POPs) and environmental endocrine disruptors such as p,p'-DDT and p,p'-DDE through breast feeding may be influenced. Human milk samples from women residing in the agricultural region of Salinas and the urban San Francisco Bay Area in California were collected from 2002-2007 for pesticide residue analysis Weldon et al. [25]. The median concentrations of OCPs among urban and agricultural women were 0.191 and 0.223 ng/g milk lipid for HCB, 0.220 and 0.443 ng/g milk lipid for β-HCH, 0.0366 and 0.0624 ng/g milk lipid for o,p'-DDT, 0.107 and 0.102 ng/g milk lipid for p,p'-DDT, 0.0057 and 0.0052 ng/g milk lipid for o,p'-DDE and 3.170 and 3.490 ng/g milk lipid for p,p'-DDE, respectively. The occurrence and levels of OCPs in human breast milk in Bangladesh was studied by Bergkvist et al. [26] p,p′-DDT, o,p′-DDT, p,p′-DDE, p,p′-DDD (ΣDDT), HCB, α-, β- and γ-HCH, trans-chlordane, cis-chlordane, oxy-chlordane, trans-nonachlor, cis-nonachlor and mirex were analyzed in breast milk collected in 2002 from 72 first-time mothers (median age 20 years) living in the rural area Matlab, Bangladesh. They found that the concentrations of many of these pesticides were low, while the concentrations of p,p′-DDT and its metabolite p,p′-DDE were high (median 349 and 1645 ng/g milk lipid, respectively) in comparison with other countries. The median value of ΣDDT was 2123 ng/g milk lipid. The estimated daily exposure to p,p′-DDT, p,p′-DDE and ΣDDTs was 10, 30 and 42 μg/kg body weight, respectively, in 3 months old infants. The p,p′-DDE/p,p′-DDT ratio ranged from 1 to 23, where 58% of the mothers had a ratio below 5 indicating recent or ongoing DDT exposure. Analysis of pesticide residues in human breast milk samples collected from Punjab state in India by Bedi et al. [27] revealed the presence of β-, γ-HCH, p,p' DDD, p,p' DDE, p,p' DDT and ending with mean concentration of 97.9, 101.7, 239.8, 1574.1, 100.3 and 90.7 ng/g milk lipid, respectively. With increase in parity, HCH and DDT residue burden in donor's milk decreased. Although levels of HCH and DDT residues in breast milk samples have decreased significantly, yet estimated daily intake values for DDT are higher than the FAO/WHO permissible tolerable daily intake values for few infants. The largest population of study carried out by Vukavic et al. [28] for monitoring the pesticide residues in human milk for 27 years (1982-2009) in South Backa, Voyvodina, Serbia. Concentrations of DDT and HCH had general decreasing trend from 1982 to 2009. The latest estimated daily intake of DDT and HCH was below the EU upper limit for pesticides in food intended for infants and small children.

On the other hand, many investigators have been studied the lactational transfer of OCPs in animal as a model. The transfer of chemicals to milk was determined by its pharmacokinetic properties, such as volume of distribution, protein binding, lipid solubility, pKa and molecular weight. Vrecl et al. [29] studied that the transfer of OCPs from blood to milk and to suckling infants in sheep. The transfer coefficients of HCB and DDE between milk and blood were monitored for eight weeks in sheep previously administered with these compounds by intramuscular injection. The milk/blood ratio on a fat basis was nearly 1 for HCB and more than 1 for DDE. It is speculated that the deviation from the ratio 1 results from the interactions of OCPs with lipoproteins in blood and/or milk. In milk, the enrichment of DDE was observed. The distribution of ingested HCB in dams and their transfer to fetuses and suckling's were investigated in rats by Nakashima et al. [30]. On day 16 after parturition, HCB concentrations in the blood and subcutaneous and perirenal fat of nursing rats fed the HCB diet during pregnancy and lactation were approximately 1/3.5, 1/15 and 1/2.8, respectively, those of pregnant rats fed the HCB diet only during pregnancy. On the other hand, the HCB concentrations in the blood, and subcutaneous and perirenal fat of suckling were approximately 6, 29 and 15 times higher than those of their dams. Therefore, a large amount of HCB apparently was transferred from dams to suckling pups through the milk. Miranda Filho et al. [31] studied the lactational transfer of OCPs in pups of southern elephant seals (Mirounga leonina) from Antarctica. They found that the mean concentrations of OCPs in milk samples collected from 7 dams of southern elephant from a breeding population on Elephant Island (Antarctica) during the 1999–2000 breeding season as the followings: HCB, 4.75 ng/g lipid; ΣHCH, 0.43; Σchlordane, 2.25; heptachlor epoxide, 8.79; dieldrin, 4.14; ΣDDT, 78.05 ng/g lipid. Table 2 summarized the OCPs detected in human breast milk in different countries.

Organophosphorus pesticides

Organophosphorus pesticides (OPPs) are known as organic ester of phosphoric or thiophosphoric acid. OPPs are poisonous and used primarily in pest control as an alternative to OCPs that persist in the environment. OPPs are powerful as acetylcholinesterase inhibitors and used as insecticides. Dordevic et al. [32] screened the morbidity in newborns exposed to OPPs and concluded that morbidity is three times greater, often in combination with some disorders of the central nervous system, and the relative risk for its appearance is eight time greater in newborns exposed to OPPs. Thus, the presence of OPPs in blood and breast milk has negative effects on newborns. In India, Sanghi et al. [33] monitored the occurrence of some OPPs such as malathion, chlorpyrifos, and methyl-parathion in human milk samples collected from Bhopal, Madhya Pradesh. Through breast milk, infants consumed 4.1 times more malathion than the average daily intake levels recommended by the World Health Organization. A correlation analysis (r values) between mothers' age and the content of the chemicals accumulated in breast milk indicated a substantial degree of correlation for malathion (r=0.5). The other chemicals showed low to negligible correlation with donor age. In another study, sample of human breast milk were collected from rural region of Faizabad

district, Uttar Pradesh and separately screened for OPPs Srivastava et al. [34]. Frequency percentage (N%) of organophosphates analyzed was highest for ethion (23.1% or 6/26) in colostrum and chlorpyrifos (50% or 4/8) in mature milk samples. Frequency percentage in colostrum was 19.2% (5/26) for chlorpyrifos and 3.8% (1/26) for dimethoate; 25.0% (2/8) mature milk samples carried dimethoate and 12.5% (1/8) carried ethion. The median concentrations of dimethoate, ethion and chlorpyrifos were 85.888, 48.000 and 4.003 ng/g milk lipid in colostrum, respectively. These values were 26.752, 744.925 and 37.274 ng/g milk lipid in mature milk, respectively. None of the samples exceeded acceptable daily intake standards set by Joint Meeting on Pesticide Residues (JMPR). Chlorpyrifos present in milk has been reported first time in India by Bedi and his associates Bedi et al. [6] An another study by Sharma et al. [35] determined that the concentrations of OPPs in human breast milk from the same region Punjab, India. Profenophos, chlorpyriphos, monocrotophos, and phosalone were detected with the mean levels of 2.66, 1.91, 1.63 and 0.29 ng/g milk lipid, respectively. It was observed that the residue levels were decreasing with increase in parity and age of mother. In Sri Lanka, Samarawickrema et al. [36] detected dimethoate in sample collected from human breast milk in a rural farming community during spray season. The median concentration of dimetoate in milk was >50 µg/l. In USA, human milk samples from women residing in the agricultural region of Salinas and the urban San Francisco Bay Area in California were collected from 2002-2007 for pesticide residue analysis Weldon et al. [25]. The median concentrations of chlorpyrifos and chlorpyrifos-methyl were 24.5 and 4.02 pg/g milk lipid, respectively among urban women. However, the median level of chlorpyrifos in agricultural women was 28 pg/g milk lipid.

Compounds	Country	Amounts and Reference
	Japan	272 µg/g milk lipid Nagayama et al. [16]
	South Africa	238.23 µg/l Bouwman et al. [19], 10 µg/g milk fat Sereda et al. [20]
	Germany	0.0815 µg/g milk lipid Zietz et al. [21]
	Bangladesh	2123 ng/g milk lipid Bergkvist et al. [26], 349 ng/g milk lipid Bergkvist et al. [26]
	India	100.3 ng/g milk lipid Bedi et al. [27]
	Australia	9 ng/g lipid Mueller et al. [22]
	USA	107-102 pg/g milk lipid Weldon et al. [25]
DDT	UK	0.025 µg/g milk lipid Harris et al. [14]
p,p′-DDT and its metabolites	UK	24 -2,300 ng/g milk lipid Kalantzi et al. [15]
o,p'-DDT	USA	36.6-62.4 pg/g milk lipid Weldon et al. [25]
	Poland	634 ng/g milk lipid Jaraczewska et al. [17]
	UK	0.283 µg/g milk lipid, Harris et al. [14]
	Australia	311 ng/g lipid Mueller et al. [22]
	USA	3.17-3.49 µg/g milk lipid Weldon et al. [25]
	India	1574.1 ng/g milk lipid Bedi et al. [27]
p,p'-DDE	Bangladesh	1645 ng/g milk lipid Bergkvist et al. [26]
o,p'-DDE	USA	5.65-5.17 pg/g milk lipid Weldon et al. [25]
p,p'-DDD	India	239.8 ng/g milk lipid Bedi et al. [27]
	Australia	16 ng/g lipid Mueller et al. [22]
Dieldrin	UK	0.025 µg/g milk lipid Harris et al. [14]
Endrin	India	90.7 ng/g milk lipid Bedi et al. [27]
	Australia	18 ng/g lipid Mueller et al. [22]
	UK	0.025 µg/g milk lipid Harris et al. [14], nondetected-180 ng/g milk lipid Kalantzi et al. [15]
	USA	191-223 pg/g milk lipid, Weldon et al. [25]
HCB	Germany	0.0229 µg/g milk lipid, Zietz et al. [21]
HCH	UK	1.2-1,500 ng/g milk lipid, Kalantzi et al. [15]

	Japan	341 µg/g milk lipid, Nagayama et al. [16]
	USA	220-443 pg/g milk lipid, Weldon et al. [25]
	UK	0.050 µg/g milk lipid, Harris et al. [14]
	Germany	0.0116 µg/g milk lipid, Zietz et al. [21]
β-HCH	India	97.9 ng/g milk lipid, Bedi et al. [27]
	India	101.7 ng/g milk lipid, Bedi et al. [27]
	UK	0.025 µg/g milk lipid, Harris et al. [14]
γ –HCH	Australia	80 ng/g lipid, Mueller et al. [22]
Chlordane	Japan	69 µg/g milk lipid, Nagayama et al. [16]
Transnonachlor	Australia	11 ng/g lipid, Mueller et al. [22]

Table 2: Organochlorine Pesticides (OCPs) detected in human breast milk.

On the other hand, many investigators have been studied the lactational transfer of organophosphorus compounds in animal as a model. Bakry et al. [37] studied the milk transfer of phosfolan and mephosfolan in mice. They found that 7.30 and 3.86% of the applied dose of phosfolan and mephosfolan were transferred to suckling pups following 18 and 12 h, respectively. In another study Bakry et al. [38] studied the lactational transfer of some OPPs and they found that chlorpyrifos (10.55% of dose) and profenofos (1.95% of dose) were transferred via mother's milk in mice after 6.0 and 1.0 h, respectively. [39] Investigated the milk transfer of dimethoate in nursing mice to suckling pups. They indicated that exposure to sublethal doses of dimethoate during prenatal as well as postnatal life induced substantial maternal and developmental toxicity. Salama et al. [40] found that 1.89% of the applied dose of 14C-methamidophos to nursing Sprague Dawley rat was transferred to suckling pups after 48 h. In another study, they found 0.96% of the applied dose of 14C-acephate was transferred from nursing mothers to suckling pups via milk after 48 h Salama et al. [41] Mansour and Mossa [42] evaluated the oxidative damage, biochemical and histopathological alterations in sucking rats whose mothers were exposed to the chlorpyrifos. Exposure of the mothers to the insecticide caused increase in lipid peroxidation and decrease in superoxide dismutase and glutathione-s-transferase in lactating pups. The results suggested that the transfer of CPF intoxication through the mother's milk has resulted in oxidative stress and biochemical and histopathological alterations in the suckling pups. Table 3 summarized the OPPs detected in human breast milk.

Compounds	Country	Amounts and Reference
Chlorpyrifos	India	24.5-28.0 pg/g milk lipid in urban women, Weldon et al. [25]
		1.91 ng/g milk, Bedi et al. [27], 4.003 ng/g milk lipid, Srivastava et al. [34]
Chlorpyrifos-methyl	USA	4.02 pg/g milk lipid in urban women, Weldon et al. [25]
Ethion	India	48.000 ng/g milk lipid, Srivastava et al. [34]
Dimethoate	India	85.888 ng/g milk lipid, Srivastava et al. [34]
	Sri Lanka	>50 µg/l milk, Samarawickrema et al. [36]
Profenophos	India	2.66 ng/g milk, Bedi et al. [27]
Monocrotophos	India	1.63 ng/g milk, Bedi et al. [27]
Phosalone	India	0.29 ng/g milk, Bedi et al. [27]

Table 3: Organophosphorus Pesticides (OPPs) detected in human breast milk.

Carbamates compounds

Carbamates (N-methyl carbamate insecticides) have been widely used throughout the world. In agricultural applications, the use of the carbamate insecticides has replaced by synthetic pyrethroids and other insecticides. Carbamates do not persist in the environment and have a low potential for bioaccumulation. Some other types of carbamates, thiocarbamates and dithiocarbamates, are used as herbicides and fungicides. Human milk samples from women residing in the urban region of San Francisco Bay Area in California were collected from 2002-2007 for pesticide residue analysis Weldon et al. [25]. The median concentration of the carbamate insecticide propoxur was found to be 4.32 pg/g milk lipid.

On the other hand, Pant et al. [24] found that male offspring of adult females treated with 0.2 or 0.4 mg/kg during the lactation period

induced testicular and spermato toxic effects in rats. These may be due to the transfer of carbofuran or its metabolites through mother's milk.

Synthetic pyrethroids

Pyrethroids are a group of man-made pesticides similar to the natural pesticide pyrethrum, which is produced by Chrysanthemum flowers. Pyrethroids constitute the majority of commercial household insecticides. There is an assumption that pyrethroid pesticides are converted to non-toxic metabolites by hydrolysis in mammals. However, some recent works have shown their bioaccumulation in human breast milk. Bouwman et al. [43] determined that the residues of pyrethroids found in 152 breast-milk samples at KwaZulu-Natal in South Africa. The mean concentrations of permethrin, cyfluthrin, cypermethrin, deltamethrin and Sigmapyrethroid were found to be 14.51, 41.74, 4.24, 8.39 and 31.5 µg/l in most likely derived from agriculture. The ADI for pyrethroids was not exceeded by infants. In another study by Bouwman determined the levels of pyrethroids in human breast milk collected from KwaZulu-Natal (KZN), a province in South Africa. The median concentrations were 42.0, 8.4, 57.0 µg/l whole milk for cyfluthrin, deltamethrin and permethrin, respectively. Similarly, Sereda et al. [20] also determined that pyrethroids levels in breast milk collected from northern KwaZulu-Natal in South Africa. They found that the median concentration of permethrin was ranging from 1.1 to 1.6 µg/g milk lipid. It was probably derived from home garden and indoor use. Cypermethrin and cyfluthrin were also detected but at lower concentrations which may probably derived from food and agricultural exposure. Human milk samples from women residing in the agricultural region of Salinas and the urban San Francisco Bay Area in California were collected from 2002-2007 for pyrethroids residue analysis Weldon et al. [25]. The median concentrations of cis-permethrin and trans-permethrin were observed 0.082 and 0.093 ng/g milk lipid among urban women and 0.103 and 0.176 ng/g milk lipid among agricultural women, respectively. In a study carried out by Corcellas et al. [44] thirteen pyrethroids have been analyzed in human breast milk samples coming from areas without pyrethroid use for malaria control, such as Brazil, Colombia and Spain. They observed that concentrations of pyrethroids ranged from 1.45 to 24.2 ng/g milk lipid and cypermethrin, λ-cyhalothrin, permethrin and esfenvalerate/fenvalerate were present in all the studied samples. Additionally, they reported that estimated daily intakes for nursing infants were below the acceptable daily intake levels, nevertheless the detected concentrations of certain samples were very close to the maximum acceptable levels. The presence of pyrethroid insecticides in human breast milk collected during 2002 from Southern Africa subtropical area (Manhiça, Mozambique) was investigated by Feo et al. [45]. Pyrethroids were widely used as insecticides for mosquito bed nets in Mozambique for malaria control. The median concentration value of total pyrethroids ranged between 87 and 1200 ng/g milk lipid, with λ-cyhalothrin being the most predominant pyrethroid in human breast milk contributing for 35% of the total amount. The study from India, Bedi et al. [27] revealed that the presence of cypermethrin in human breast milk. Recently, Sharma et al. [35] conducted very similar study in same region, Punjab, India. They analyzed 127 breast milk samples and detected 25% of tested samples contain pyrethroids residues. Residues of cyfluthrin, fenvalerate and cypermethrin were detected with mean levels of 63.04, 11.69 and 3.63 ng/g milk lipid, respectively. Table 4 summarized the pyrethroid and carbamate compounds detected in human breast milk.

Compounds	Country	Amounts and Reference
Pyrethroids		
Permethrin	South Africa	14.51 µg/l, Bouwman et al. [19] 57.0 µg/l, Sereda et al. [20] and 1.1-1.6 µg/g milk lipid Sereda et al. [20]
cis-Permethrin	USA	81.9- 103 pg/g milk lipid, Weldon et al. [25]
trans-Permethrin	USA	93.1-176 pg/g milk lipid, Weldon et al. [25]
Cyfluthrin	South Africa	Bouwman et al. [19], Sereda et al. [20], Bedi et al. [27], Sharma et al. [35]
Cypermethrin	South Africa	4.24 µg/l, Bouwman et al. [19]
	India	3.63 ng/g milk lipid, Sharma et al. [35]
Deltamethrin	South Africa	8.39 µg/l, Bouwman et al. [19], 8.4 µg/l, Sereda et al. [20]
Cyfluthrin	South Africa	41.74 µg/l, Bouwman et al. [19], 42.0 µg/l, Sereda et al. [20]
	India	63.04 ng/g milk lipid, Sharma et al. [35]
Fenvalerate	India	11.69 ng/g milk lipid, Sharma et al. [35]
Sigmapyrethroid	South africa	31.5 µg/l, Bouwman et al. [19]
Carbamate		
Propoxure	USA	4.32 pg/g milk lipid, Weldon et al. [25]

Table 4: Pyrethroids compounds & carbamate detected in human breast milk.

Discussion

The passage of chemical substances through breast milk from nursing mothers to suckling pups depends on several factors, such as physical and chemical properties of substances, maternal physiology and transfer kinetics [46]. These biological processes are time-dependent and concentration-dependent, and therefore the neonate dose depends not only on the exposure of the suckling but also on the level of the chemical substance in the mother's milk. In general, chemical properties of a compound, such as lack of ionization, small molecular weight, low volume of distribution, low maternal serum protein binding, and high lipid solubility (lipophilicity), facilitate compound excretion into human milk. Chemicals with long half-lives are more likely to accumulate in human milk, and compounds with high oral bioavailability are more easily absorbed by the infant [47]. Physiologically based pharmacokinetic (PBPK) models can aid in the prediction of infant exposure via breast milk. This modeling is also useful in predicting maternal and neonatal distribution of toxic compounds. Benefits of these quantitative models include the ability to account for changing maternal physiology and transfer kinetics, as well as the chemical-specific characteristics, in order to produce more accurate estimates of neonatal risk. Recently, Mead [48] pointed out that persistent organic pollutants (POPs), pesticides, heavy metals, and other contaminants have the tendency to accumulate in human milk.

Different chemicals may undergo lactational transfer that involves different mechanisms. These mechanisms depend on a number of factors related to the mother, the milk itself, and the infant Wilson et al. [10]. The possible mechanisms by which substances transport from blood to breast milk may be considered as passive diffusion, active transport, or apocrine secretion (reversed pinocytosis). Passive diffusion is the transport of chemical from the blood, region of higher concentrations to the breast milk, region of lower concentrations, down concentration gradient until equilibrium is reached. Active transport involves participation of cellular pumps of the membrane in the transfer of chemical molecules. This type of transport mechanism is associated with moving molecules against the concentration gradient, from a region of low concentration to a region of high concentration. Thus substance transfers opposite an electrochemical gradient and requires the expenditure of metabolic energy. Transfer from plasma to milk without an equilibrium state being reached as in the passive process [49]. Active transport is generally a one-way process in which energy is expended by the work involved in carrying the drug molecules across membranes. Apocrine secretion is a process in which larger chemical molecules and proteins may be transported actively into the alveolar cell by pinocytosis and released into the milk. Some chemicals may also enter directly into milk through spaces between alveolar cells [50], and bypass the alveolar structures completely from capillary to interstitial space to intercellular cleft and directly into milk.

Conclusion

This article helps to aware the knowledge about reported pesticides values in breast milk. These chemicals may be evaluated by special efforts toward identifying groups of women exposed occupationally or through heavy intake in consumer preparations of food, water, or air. Thus different pesticides may be transport through human breast milk during the early postnatal stages and may disturb the normal development of the newborn. Exposures to pesticides via breast-feeding assume that they do disturb the normal development of the newborn. Human breast milk volume and fat content may adversely have affected by the presently encountered pesticide levels. Our studies showed that breast feeding counteracts the adverse developmental effects of pesticides. Such studies may shed light on the wide variety of pesticides that have been detected in human breast milk and the risk of that exposure during the early postnatal stages.

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