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REVIEW ARTICLE

TERATOGENICITY AND EMBRYOTOXICITY OF ORGANOPHOSPHORUS COMPOUNDS IN ANIMAL MODELS - A SHORT REVIEW

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Summary

Organophosphorus compounds (OPCs) are a wide group of compounds both structurally and functionally. Each OPC has a unique toxicological profile. The exposure to this type of poison is not limited only to certain occupationally exposed people but also to children, women, pregnant women; all have chances to be exposed to this poison. During the recent past years it has been reported in many poison epidemiological studies and case reports that exposure of OPCs during pregnancy caused malformed fetuses, neural tube defect (NTD) and shortening of pregnancy. The literature for animal models reveals inconclusive evidence. The generalized view is that they are neither teratogenic nor embryotoxic. But it is not true. There is a lack of systematic study and scarcity of reports on the topic. The present study was undertaken to investigate the teratogenicity induced by organophosphorus compounds in different animal models by literature review. Literature was searched by Toxicology Data NetWork (TOXNET), Developmental and Reproductive Toxicology Database (DART), Toxicology Literature Online (TOXLINE), Hazardous Substances Data Bank (HSDB), Pubmed Central, Entrez-Pubmed, Science Direct, Directory Of Open Access Journal (DOAJ), Google Scholar and International Program on Chemical Safety (IPCS-INCHEM), Embase. The terms for literature search were teratogenicity, organophosphorus compounds; fetal toxicity, organophosphorus compounds; organophosphorus poisoning and pregnancy; organophosphorus poisoning and growth restriction; organophosphorus poisoning and IUGR; organophosphorus poisoning and reproduction; organophosphates and reproduction; pregnancy and organophosphates. The outcome of the study concludes that the work on teratogenicity induced by organophosphorus compounds was completely neglected, inconclusive, and only carried out on less than half of the OPCs available in the market. A more comprehensive and systemic study on the subject is clearly needed and its importance should not be ignored because more positive cases are being reported on the teratogenicity and embryotoxicity of OPCs.

Key words: IUGR; fetotoxicity; teratogenicity; Resorption; organophosphorus compound (OPC); embryotoxicity; organophosphates.

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INTRODUCTION

Over hundred different OPCs are available in the market as insecticides, pesticides, miticides, acaricides etc. and to a smaller extent herbicides and fungicides [1]. These are the most commonly used

compounds all over the world in houses, farm houses and agriculture fields. Over the last 100 years, the use of organophosphorus compounds has dramatically increased with new applications still being developed. OP pesticides are used for public health purposes to control disease vectors. Human food contamination by organophosphates mostly occurs to farmers and agriculture workers [2]. Studies have shown an increased exposure to pesticides by women and children and suggest an association between environmental exposure to certain agricultural pesticides like OPCs and adverse reproductive outcomes in men and women working on or living near farms [3]. Many studies have shown that working in agriculture increases the risk of neural tube defect (NTD). Elevated risks of NTDs and anencephaly or spina bifida subtypes were also associated with exposures to organophosphorus pesticides. These results suggest that ambient exposure to certain categories of agricultural pesticides may increase the risk of NTDs [4,5]. The exposure of organophosphorus compounds and other toxicants to pregnancy is an important entity because of its effect on two organisms – a mother and a fetus.

Briefly, all sections of population, including women, children and even developing fetuses are unknowingly and unintentionally exposed to lethal and sub lethal doses of OPCs and other toxicants. Organophosphates (OP) have shown the ability to penetrate the placental barrier and thus could potentially affect the developing fetus. Pesticides like OP have been detected in amniotic fluid, umbilicord blood, (Umbilical cord blood is blood that remains in the placenta and in the attached umbilical cord after childbirth. It is a reservoir of stem cells which can be used to treat hematopoietic and genetic disorders), meconium and infant urine, indicating exposure of the human fetus to pesticides [6-9].

During the past few years, a good number of epidemiological studies have been conducted to show the exposure of OPCs and other compounds to pregnant women and their consequences but there is paucity of literature on animal models for the effect of OPCs during different stages of pregnancy. Eskenazi et al. [10] suggested that high OP pesticides level might adversely affect duration of gestation. Peiris-John et al. [11] found the evidence of impairment of fetal growth and development brought about by prenatal exposure to OPCs. Similar effect was noted with parathion [12, 13].

The present study was carried out to investigate the available evidences of organophosphorus acetylcholinesterase (AChE) inhibitor induced teratogenicity in an animal model. It is obvious that over hundreds of different kinds of OPCs are available in the market but there is no clear evidence of teratogenicity and embryotoxicity of *all or almost all* OPCs. Concern related to this issue is addressed in this short review.

Table 1. Key words for search and results on different search engines.

Key words for search		DART	HSBD	TOXLINE	Academic Search complete	Entrez Pubmed	Science Direct
Teratogenicity, organophosphorus compounds	Total retrieved	0	0	0	0	7	332
	related	0	0	0	0	1	20
Fetal toxicity, organophosphorus compounds	Total retrieved	0	0	0	0	7	1123
	related	0	0	0	0	1	20
Organophosphorus poisoning and pregnancy	Total retrieved	6	77	28	423	23	482
	related	3	40	7	3	0	3
Organophosphorus poisoning and growth restriction	Total retrieved	0	24	1	18	0	279
	related	0	12	0	0	0	0
Organophosphorus poisoning and IUGR	Total retrieved	0	4	0	1	0	9
	related	0	0	0	0	0	0
Teratogenic organophosphorus compounds	Total retrieved	27	163	97	54	261	549
	related	11	93	24	4	66	20
Pregnancy and organophosphates	Total retrieved	181	124	315	158	75	1670
	related	20	38	33	0	8	20/1000

Note: For each key search word, the first row shows the total retrieved and the second row reveals the related literature found. However, it is noteworthy that further screening of related literature reduced the number of relevant literature and it is not more than thirty in any maximum retrieval.

Table 2. List of OPCs and reported teratogenic effect.

S.No.	Chemical	Class	uses	Reference	Model	Result
1	Acephate	III	insecticide	[4,28], HSDB	mice,rats	*Conflicting*
2	Azinphos ethyl	IB	insecticide	INCHEM	rats and rabbits	Negative
3	Azinphos methyl	IB	insecticide	[34], HSDB, INCHEM	rats and rabbits	Negative
4	Bromophos	OB	Insecticide acaricides	INCHEM	rabbit	Negative
5	Carbophenothion	NA	Insecticide acaricide	HSDB	NA	*Conflicting*
6	Caumophos	II	insecticide	HSDB	cattle	Negative
7	Chlorophos	NA	Pesticide	[35]	rats	positive
8	Chlorpyriphos	II	insecticide	[36-41], HSDB	rat, mice	*Conflicting*
9	Chlorphoxim	OB	insecticide	INCHEM	rats	Negative
10	Chlorpyriphos- methyl	III	insecticide	HSDB, INCHEM	rats	Negative
11	Demeton	OB	Insecticide Acaricide	INCHEM	mice	Positive
12	Demeton-S-methyl	IB	insecticide	HSDB, INCHEM	rabbits	Negative
13	DFP	NA	insecticide	HSDB	rats	Negative
14	Diazinon	II	insecticide	[42,43], HSDB, INCHEM	rabbit, hamster	Negative
15	Diclorvos (DDVP)	IB	insecticide	[44]	rat, rabbit	Negative
16	Dicrotophos	IB	insecticide	[45-49], HSDB	mice, birds, chick	*Conflicting*
17	Dimethoate	II	Insecticide	[50-56], HSDB,INCHEM	mice, rat	Negative
18	Disulfoton	IA	insecticide	HSDB, INCHEM	mice, rats, rabbit	Positive
19	EPN	IA	insecticide	[52], HSDB	mice, duck, mallard	*Conflicting*
20	Ethephon	III	PGR	[57]	mice	Positive
21	Ethoprop	IA	insecticide	HSDB, INCHEM	rats	*Conflicting*
22	Ethion	II	insecticide	HSDB	fowl	Negative
23	Fenamiphos	IB	Nematocide	[34,56,58], HSDB, INCHEM	rats, rabbit	*conflicting*
24	Fenthion	II	insecticide	INCHEM		*conflicting*
25	Fenchlorphos	OB	Insecticide	[59]	rabbit	Positive
26	Fenitrothion	II	insecticide	[60], HSDB, INCHEM	rabbit	Negative
27	Fensulfothion	OB	Insecticide nematicide	HSDB, INCHEM	mice, rabbit	Negative
28	Flupyrazofos	OB	Insecticide fungicides	[61]	mice	Positive
29	Isofenfos	OB	insecticide	[34]	rats, rabbits	Negative
30	Isosystox	IB	insecticide	HSDB	mice	Positive
31	Jodfenfos	OB	insecticide	HSDB. INCHEM	rats	Negative
32	Leptophos	OB	insecticide	INCHEM	rabbits	Negative
33	Malathion	III	insecticide	[62-65], INCHEM	rats	*Conflicting*
34	Methamidophos	IB	insecticide	[66], HSDB	rats, mice	*Conflicting*
35	Mevinfos	IB	Insecticide acaricide	HSDB	rabbit	*Negative*
36	Monocrotophos	IB	insecticide	[67]	rats	Negative
37	Naled	II	insecticide	HSDB, INCHEM	rats	Negative
38	Oxydemeton-methyl	IB	Insecticide acaricide	[34,68]	chick ,rats	Negative
39	Parathion	IA	Insecticide acaricide	[48,69],HSDB	qual, chick	Positive
40	Parathion-methyl	IA	Insecticide acaricide	[70-75], HSDB, INCHEM	rats, mice, chick	Positive
41	Phorate	IA	Insecticide acaricide	HSDB, INCHEM	rats, mice	*conflicting*
42	Phosmet	IA	Insecticide	HSDB	rodents	*conflicting*
43	Phosphamidon	IA	Insecticide Nematicide	[76,77]	mice	Positive
44	Primiphos-methyl	II	Insecticide acaricide	INCHEM	rabbits, rats, chick	*conflicting*
45	Quinalphos	II	Insecticide acaricide	[78]	rats	Negative
46	Sarin	NA	Nerve agent	[79,80]	rats	Negative
47	Tabun	NA	Nerve agent	[80]	rabbits	Negative
48	Terbufos	IB	Insecticide Nematicide	HSDB	rats, rabbits	Negative
49	Temephos	III	Insecticide Larvicide	HSDB, INCHEM	rats, hen	Negative
50	Thiometon	IB	Insecticide acaricide	INCHEM	rabbits	Negative
51	Triazofos	OB	Insecticide Acaricide Nematicide	HSDB	rats	*Conflicting*
52	Trichorfon	II	Insecticide	[27,35,82-85]	rats	*Conflicting*

Note: The above mentioned list of OPC anti-ChE does not include the metabolic or active forms like paraoxon, malaoxon etc. Any information available in other language than English was not included. MSDS of the compounds was not selected because it does not contain an independent research citation. Over one hundred and twenty compounds were screened.
NA stands for not available.

MATERIALS AND METHODS

To review the teratogenic and embryo toxic risk associated with the exposure of OPCs in animal models, a systematic review of literature was carried out. TOXNET, DART, TOXLINE, HSDB, Pubmed Central, Entrez-Pubmed, Science Direct, DOAJ, Google Scholar and IPCS-INCHEM databases were used to search the predefined key words (table 1). Year was not specified, therefore the search included all the possible literature available on the databases and in most cases it included literature from 1966 to 2011. Then further search was also done on the retrieved papers. Mostly abstracts or papers published and available in English were included in the review. Papers in other languages such as Russian, Polish or French were low in numbers and their exclusion will not change the scenario of our topic. About hundred and twenty organophosphorus compounds were screened. In addition to the search engine listed in table 1, toxipedia (free toxicology encyclopedia), Extension Toxicology Network (EXTOXNET) and different resources were checked on the internet. When a result is described as negative, it means that there was no reported teratogenicity or embryotoxicity; positive means that there is a report about the effect, and conflicting stands for no clear evidence or that both positive and negative reports were found in the search. The result is outlined in table 2. The term teratogenicity is referred to as the malformations produced in the offspring of animal models. Intra uterine growth retardation (IUGR) including the reduced/increased body weight of the pups/dams after treatment in comparison to untreated control was also included in the term. Developmental effect was also included in the study under teratogenesis. The term embryotoxicity included effect on implantation, fetal death, litter size, abortion, and reduced gestation period.

Table 3. WHO's classification scheme

Class	Category	LD_{50} for the rat (mg/Kg body weight)			
		Oral		Dermal	
		Solids	Liquids	Solids	Liquids
IA	Extremely hazardous	5 or less	20 or less	10 or less	40 or less
IB	Highly hazardous	5-50	20-200	10-100	40-400
II	Moderately hazardous	50-500	200-2000	100-1000	400-4000
III	Slightly hazardous	Over 500	Over 2000	Over 1000	Over 4000

RESULTS

The teratogenic and embryotoxic risk associated with the exposure of OPCs in animal models was investigated. Systematic review of literature was carried out according to the procedure described in materials and methods and shown in table 1. Table 2 shows the list of those OP pesticides whose teratogenicity/embryotoxicity information was available. Over one hundred and twenty OPCs were screened but reports on only fifty two compounds were found which is listed in table 2. Table 3 provides the basis of WHOs classification of pesticides.

The INCHEM database revealed the teratogenicity information about twenty seven OPCs out of over one hundred. The total number of related articles on TOXNET including DART, HSDB, and TOXLINE was 281 but further screening reduced the number to twenty four. and is not different from INCHEM. The further analysis of table 2 shows that there are ten teratogenic positive results and fifteen conflicting results which included both positive and negative reports. It means that totally twenty five cases out of fifty four (47%) may be considered to be a concern regarding teratogenicity. Among the 53% (29/54) of negative results, 15 (26%) have no independent research reference or have very old references. During the last twelve years (2000 to 2011) only twelve papers were found where five of them were on chlorpyrifos, all showing teratogenic and embryotoxic effect, two on dimethoate; one positive and the other one negative, and five on different OPCs; four positive and one negative. It is noteworthy that most literature showed teratogenic potential in OPCs during this period.

DISCUSSION

The exposure of OPCs to pregnancy is an important factor because it effects two organism, a mother and a fetus. Abu-Qare et al. [9,14-15] conducted pharmacokinetic studies on the placental transfer of methyl parathion in rats and reported that the placenta is a poor barrier against methyl parathion. This results in a rapid and extensive placental transfer and the concentration was found to be the highest in the placenta followed by the concentration in rat fetuses. According to the authors, there is a reduction of several metabolizing enzymes and xenobiotic-binding proteins during pregnancy which may influence the toxicity of methyl parathion. Abu-Qare et al. [14, 15] found that a single dose of diazinon and methyl parathion has an easy access into maternal and fetal tissues resulting in inhibition of cholinesterase (ChE) enzymes, however the fetuses were found to faster recover ChE enzymes.

Exposure of rodent dams to certain OP pesticides such as chlorpyrifos, dimethoate, quianalphos and trichlorfon[16-19] during pregnancy has been associated with decrement in fetal weight in some studies. Other studies of the same pesticides [20] and other organophosphates [21,22] have shown no association with fetal growth. There have been conflicting results in literature regarding fetal and embryotoxicity of OPCs. For example parathion, diazinon, malathion and dichlorvos induce maternal toxicity but there is no evidence of teratogenicity [23-26]. However dipterex has shown to cause teratogenic effect at high concentration [26] and acephate was found to cause developmental toxicity at maternal toxic dose to mice [27]. Similarly, Chung et al. [29] reported that flupyrazofos, a new OP, causes fetal growth retardation at maternal toxic doses in rats. Ambali et al. [30] reported that chlorpyrifos affected conception and pre-implantation losses in dose dependent manner in Swiss albino mice.

Exposure to chemicals during different stages of development like pre and peri-conception, fetal, perinatal, peripubertal and adult has a different impact on health. Numerous animal studies have shown that in utero or early exposure to OP pesticides affect neurodevelopment as reviewed by Eskenazi et al. [10].These studies have shown that both fetuses and infants may be more susceptible to developmental effects.

Secondly, a transfer of compounds to fetuses through placenta [9, 14] and a higher sensitivity of the young ones [86] also makes the topic critical. Moreover, the role of ChE during organogenesis [87] and anti-ChE activity of OPCs should not be ignored. The history of OPCs and anti-ChE activity is more than a century old but the study on this topic seems to be highly neglected. The scanty literature on the subject and consistent reports of harmful effects on humans [3, 4] is contradictory.

The importance of AChE in the function of the nervous system has been recognized for a long time, yet its role in development remains mysterious [31]. AChE is transiently expressed during discrete periods of neural development of the thalamocortical pathways, and transient AChE activity correlates with the specific growth of thalamic axons into the cortex and synaptogenesis with cortical neurons [32]. In addition, significant sequence similarity exists between AChE and cell adhesion proteins that function in morphogenic phenomena. These observations have led to the hypothesis that AChE may play key roles in neural development. Albeit, no clear physiological function has yet been assigned to BChE, Mack and Robitzki [33] reported a functional role of BChE in regulation of cell proliferation and the onset of differentiation during early neuronal development which was independent of its enzymatic activity.

The present study reviewed over one hundred OPCs for their teratogenic and embryotoxic effect in an animal model. The generalized view is that organophosphorus is non teratogenic or non embryotoxic in nature. According to one hypothesis where teratogenicity is taken to mean an induction of malformations in live offspring without a decrease in a number of births (i.e., no embryotoxicity), no adverse effects of organophosphates on pre- or postpartum mortality have been reported for the vast majority of organophosphorus pesticides, nor have embryonic defects been proved, except at doses that significantly retarded growth in the mother [88]. It was noted in the review that there is no similarity in the design of all the papers, particularly in a selection of dosages. Majority of the OP application was found to be between gestation days (GD) 6 to 15. Of course, logically it is a good time selection to observe teratogenesis but investigations have revealed that repeated injections of an OP does not necessarily produce the teratological effect. Secondly, very low, non toxic dose was tested for its effect but it is believed and reported that a non toxic dose for mother is also a non toxic dose for dams. Lassiter et al. [89] concluded in their result that dosages of the AChE inhibitor that were not maternally toxic also produced no embryotoxicity or teratogenicity. For instance, fetal brain Cholinesterase (ChE) has been

found to be less inhibited than maternal brain, maybe due to placental and fetal detoxification of anti-ChE [90,91] with a few exceptions where we find the opposite [92,93]. It is also important to mention that for a given dosage of many OPCs, brain ChE is much more inhibited in young and postnatal animals than in the adults [94-96] but this age related differences to anti-ChE do not apply to fetuses [88-91]. It means OPCs may be teratogenic or embryotoxic at maternal toxic doses. Gomes et al. [97] found congenital malformations when mice were treated with formulations of organophosphates.

If we look at the comparison of multiple dosages vs. a single dose, we find that maternal and fetal brain ChE is comparable in multiple dosages but in case of single high dosage, inhibition was found to be much higher in a fetal brain than in a maternal brain [88]. Similarly, Kimbrough & Gaines [98] found the deaths and resorption was increased in pregnant rats when they were given a single high dose of parathion or diazinon on the 11th day of gestation. Abou-Qare and Abou Donia [14] reported that a single cutenous dose of methyl parathion significantly inhibited maternal and fetal brain AChE and plasma butyrylcholinesterase (BuChE) in rats.

In brief, the question which initiated this short review is whether there is sufficient evidence in literature. Short answer to the question after going through all searches is *NO*. There is a complete scarcity of literature on the subject which is evident from the table 2. Secondly, the references were very old or the information given in toxic compound databases like INCHEM or HSDB are either without references or with one or two old references. Moreover, information on less than 50% of OPCs is available. No review article on the topic could be retrieved from research publications. Designs of studies were not uniform. During the last twelve years, (2000-2011) only twelve papers could be retrieved on different OPCs and interestingly, most of the papers reported teratogenic and embryotoxic effect of studied compounds in comparison to the old studies which mostly showed OPs as safe compounds. There are many discrepancies and limitations in the studies.

SUMMARY

1. Less attention to the subject may be due to a generalized hypothesis that OPCs are safer and do not cause teratogenic effect. But the unique and diversified toxicological profile of different OPCs do not fit in the hypothesis and need proper attention from scientific community.
2. A comprehensive multicentre study on the teratogenicity and embryotoxicity by OPCs is warranted.
3. Threshold dose (Threshold of Teratological Concern; TTC) for the effect should be determined for all OPCs.
4. No uniformity in the study design was found. There must be one standard procedure to declare a compound as teratogenic and embryotoxic.
5. Multiple doses vs. single sub toxic dose and high dose vs No Observable Effect level (NOEL) dose should be checked for all OPCs.
6. Different time course application like early or late gestation, organogenesis period, pre-implantation and peri-implantation period should be screened for all OPCs.
7. Since most of the results presented during the last twelve years showed teratological effect of OPC, all the compounds should be re-screened.
8. In the undertaken study, a maternal toxic dose was noted to be embryotoxic and teratological.
9. A maternal toxic dose or a minimum toxic dose (for instance LD_{01}) of all OPCs should also be checked for the teratological and embryotoxic effect.
10. Relationship of ChE inhibition and teratogenesis study also need attention.
11. For the registration of each compound to a concerned authority, submission of teratological data should be made compulsory.
12. Which animal model is appropriate for teratogenic study is also a question.

CONCLUSION

Study on teratology and embryotoxicity by organophosphorus compounds has been neglected. The results are conflicting showing both effect and no effect. Study procedure should be standardized for all OPCs and a comprehensive multicentre study should be undertaken with a uniform standard procedure. The conflicting situation may be due to non systemic and non uniform studies.

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