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MORBIDITY OF ORGANOPHOSPHORUS COMPOUNDS – A CRITICAL ANALYSIS

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ABSTRACT **Background:** Organophosphorus compounds are used as pesticides in agricultures. But, its effects are not only limiting to pets also affects to human being. Here, we have analyzed the published articles with respect to author's contribution using some bibliometrics parameters.

Materials and Methods: The published articles on organophorphorus were retrieved from SCOPUS database from the year 2012 to 2016 for this study and analyze the documents published with respect to year, source title, types of documents, subject of documents and degree of collaboration etc. All the statistical analysis was carried out with the help of MS excel spreadsheet.

Results: On analysis of all articles with Organophosphorus compounds, it was revealed that the highest number of articles was published in the year 2014 and least in the year 2016. Among all articles 197 documents are under Medicine, 118 documents are under Chemistry and 101 documents are listed under Pharmacology, Toxicology and Therapeutics. This study found that the degree of collaboration "C" is 0.95 with 395 numbers of documents are more than single author.

Discussion and Conclusion: Indian publications on Organophosphorus compound during the year 2012 to 2016 showed not much more. In this study it was revealed that less work of single authors in comparison to the multiple authors. So the collaboration work plays more important to success the research work.

KEYWORDS : Organophosphorus pesticides, Acute and chronic toxicity of Organophosphorus compounds, Environmental exposure, Fetal toxicity of Organophosphorus compounds

Introduction:

Organophosphorus compounds are extensively used in agriculture as pesticides especially in developing countries, because they are cheap, easily available and highly effective against agricultural pests. The use of Organophosphorus compounds as pesticides have boosted agriculture productivity, which has lead to an explosive rise in agriculture produce, often referred to as – "The Green Revolution" in various countries in the world.

The toxicity of the Organophosphorus compounds is however not limited to pests only, they are as toxic to human beings as well. More than 100 different Organophosphorus compounds are in use and both intentional and unintentional poisoning occurs due to these chemicals and the unintentional poisoning disproportionately affect infants and children [1].

Acute Toxicity of Organophosphorus compounds:

The Organophosphorus compounds are shown to have both acute as well as chronic toxicity. The Organophosphorus compounds reveals acute systemic toxicity due to inhibit the enzyme "Acetyl cholinesterase" by phosphorylation. The inhibition of this enzyme by the Organophosphorus compounds causes the neurotransmitter "acetylcholine" to accumulate at nerve endings, resulting in manifestation of common signs of Organophosphorus compound intoxication. The manifestation of acute Organophosphorus compound poisoning includes – an acute cholinergic crisis, an intermediate syndrome consisting of paralysis of neck, proximal limb and respiratory muscles, 24 to 96 hours after the cholinergic crisis and finally a delayed onset of distal polyneuropathy 2 – 3 weeks after acute poisoning.

Animal studies have shown that the fetus and very young are more susceptible to damage by acute exposure to Organophosphorus compound than the adult. The probable reason being their immature microsomal enzyme system and greater permeability of the blood – brain barrier in the fetus and the very young is, however teratogenic effects seen to be rare [2,3].

Chronic Toxicity of Organophosphorus compound:

The deleterious effects of chronic exposure to Organophosphorus compound, is a subject of ongoing research. The data available from research on chronic toxicity of Organophosphorus compound, through limited, shows some interesting findings. Available evidence, suggests that, there is every possibility of adverse effects occurring below Organophosphorus compound concentration that are generally considered to be safe, based on measurements of ChE inhibition. The effects seen in those conditions are not clearly related to the inhibition of cholinesterases [4-7]

Non-specific, self reported symptoms attributed to chronic exposure of Organophosphorus compound, in agricultural workers, who handle, store and use Organophosphorus compound have been documented. These symptoms include burning or prickling of skin, tingling or numbness of hands and face, muscular twitching or cramps in the face, neck, arms and legs; respiratory symptoms, including chest pain, cough, runny nose, wheezing, shortness of breath, irritation of the throat, excessive sweating, nausea, vomiting, diarrhea, excessive salivation, abdominal pain, lacrimation and irritation of eyes, restlessness, difficulty in falling asleep, trembling of hands and irritability [4,8]. An increased prevalence of symptoms was found at ChE activities generally considered to be non-adverse [8]. Various studies also show evidence of chronic toxicity of Organophosphorus compound, not only among the farmers who directly handle / spray Organophosphorus compound, but also among those employed in inland fisheries, living within a 25 km radius of the cultivated land, which are not directly exposed.

Neurobehavioral effects in chronic Toxicity:

Epidemiological studies [9] have demonstrated impaired neurobehavioural performance with chronic exposure to Organophosphorus compound. The neuropsychiatric disorders resulting from chronic exposure to Organophosphorus compound occurs without cholinergic symptoms and these effects appear not dependent on AChE inhibition, though the underlying mechanisms are unclear [10,11,12]. The clinical manifestations in these cases include

anxiety disorder, depression, psychotic symptoms, dysthymic disorder (DSM – III - R) problems with short term memory, learning, attention, information processing, eye hand coordination and reaction time, autonomic dysfunction and enduring extra-pyramidal symptoms [4, 13].

Mechanism of chronic Toxicity:

The mechanisms of chronic toxicity of Organophosphorus compound remain unclear. However chronic toxicity of Organophosphorus compound may have some relation to the speed at which pesticide metabolites are hydrolyzed and eliminated from body. The enzymatic hydrolysis status as to whether "slow" or "fast" seems to be determined by gene polymorphisms of hydrolases such as paraoxonase [14].

A poor correlation between evidence of toxicity and the degree of AChE inhibition in chronic exposure to Organophosphorus compound occurs in some situation [7,10]. It could be so that toxicity in this situation of chronic exposure to Organophosphorus compound may well be mediated by other mechanism such as oxidative stress through Organophosphorus compound- induced generation of free oxygen radicals leading to lipid peroxidation [15, 16] rather than inhibition of AChE. The basic aim of this study is to discuss about the morbidity of Organophosphorus compounds with the year wise contribution of Indian research output. Apart from this, we analyze the authorship pattern of published articles, the individual authorship of Indian researchers, about the publication of documents in various journals, about the documents published in different subjects, about the degree of collaboration of authors with respect to the topic Organophosphorus compound.

Methodology

Bibliometric analysis is a common method used in the field of pure science research. It is the practice of patterns, frequency and some other bibliometric measures in articles. This study discusses on the influence of Organophosphorus compound and contribution of Indian researchers indexed in SCOPUS database. All the relevant data were retrieved from SCOPUS database with a limit to 2012 – 2016 for this study and to analyze the documents published in different year, source title, types of documents, subject of documents and degree of collaboration etc. Finally, all the relevant data were sorted, tabulated and comprehended in a rational manner to draw assumptions for this present study using MS-Excel spread sheet and some statistical measure.

Result

Probable Symptoms and signs of organophosphate poisoning are collected and documented with several literatures with both national and international (Table 1). Symptoms and signs of organophosphate poisoning based on time of manifestation also recorded according several authors (Table 2). This study found the highest number of publication (24.58%) in the year 2014 and less is in the year 2016 (Table 3). Out of 415 papers, the number of single authored paper is only 20 and the number of more than four author paper is 123 (Table 4). Types of document are very important in the field of research. It is found from this study that a total of 380 are published as original papers and other 35 documents are listed under review, letter, conference paper, book chapter etc. (Table 5). The published documents are indexed under different subject areas, where 197 documents are under Medicine, 118 documents are under Chemistry and 101 documents are listed under Pharmacology, Toxicology and Therapeutics (Table 6). The journal "Medico-Legal Update" published 18 documents during this period of study and followed by "Indian Journal of Forensic Medicine and Toxicology" and " Journal of Indian Academy of Forensic Medicine" with 13 and 8 number of documents respectively (Table 7). This study found that the degree of collaboration "C" is 0.95 with 395 numbers of documents are more than single author (Table 8). P. S. Rajini of CSIR-Central Food Technological Research Institute, Food Protestants and Infestation Control Department, Mysore, Karnataka has the highest number of publications (10) and T. Das of Bhabha Atomic Research Centre, Mumbai is in second position with 7 documents (Table 9,10). Degree of collaboration is a measurement of the prominent area of inquiry in scientific studies indicating the trend in patterns of single and joint authorship. It is examined in this study of the Indian publications on Organophosphorus compound during this five year period study, as shown in Table-6. The degree of collaboration "C" is 0.95 which means there is less work of single authors in comparison to the multiple authors.

The extent of collaboration in research can be measured with the help of the formula:

$$C = \frac{N_M}{N_M + N_S}$$

Where, C= Degree of Collaboration
N_M = Number of multiple authors
N_S = Number of single authors

In five year study, a total number of 415 papers were published in India and indexed in SCOPUS database. The number of authors was varied from article to article. A comparative study between single author and more than one author was taken and it was found that statistically significant at p = 0.00001 in t test (Table 6).

Discussion:

Acute poisoning remains a major public health problem in worldwide and pesticide poisoning remains the most important poison. However, cases of medicinal drug poisoning have recently dramatically increased. Youth in these rural communities remain very vulnerable to acute poisoning and the problem is so common that school-based primary prevention programs may be worthwhile [17]. Many authors throughout India were worked on organophophorous poisoning and published many article.

Organophosphate (OP) compounds are commonly used as suicidal agents and produce characteristic toxic effects. Cardiac arrhythmias are often observed in the acute phase of toxicity; late onset polymorphic ventricular tachycardia preceded by prolonged QT interval on the EKG is also known to occur. However, there are no reports of late onset, prolonged asystole without preceding arrhythmias and after acute toxicity had abated [18]. Organophosphate exposure produces clinical manifestations of cholinergic excess. Cardiac complications commonly occur in association with poisoning and are described primarily as a result of OP exposure [19]. Accidental cases are also reported by other researchers where the clinical features stated were salivation, lacrimation, emesis, GI cramping, bronchorrhea, muscle fasciculations, depression of respiratory center, etc [20]. In our study, we had found the similar clinical features that are mainly caused due to the accumulation of acetylcholine (ACh) as organophosphate is an anticholinesterase compound. Patients who were exposed to acute OP poisoning in 2010 visited MGM Hospital showed typical manifestations of OP poisoning. It is notable that 12 patients have QTc prolongation that has recently started to be considered as one of the targets of abnormalities in ECG because of prolonged QTc interval in the heterogeneous ion channel disease that can cause sudden death by lethal arrhythmia. The acquired form of the long QT syndrome has been associated with the use of QT prolonging medications (e.g., quinidine, erythromycin) and in part modified by electrolytes abnormalities. This has also suggested that the high susceptibility of ventricular arrhythmia on drug-induced QTc prolongations exists in some individuals with latent ion channel abnormalities, female sexuality, or CYP enzyme polymorphism [21-24]. The QT prolongation causes catastrophic polymorphic ventricular arrhythmia or ventricular fibrillation without affecting cardiac pump function. Adrenaline, premature complexes, and QT/T-wave alternans are known to trigger these catastrophic cardiac malfunctions. Such lethal arrhythmia has individual differences and depends on the type of the ion channels with abnormality. The QT prolongation and repetitive ventricular tachyarrhythmia after OP poisoning was first described by Luzhnikov et al. [25] and precisely documented by Ludomirsky et al. (1982) [26, 27]. Apart from QTc prolongation, we have also found nonspecific

ST-T changes like ST segment elevation ([0.2 mV) and inverted T waves. Although the nonspecific ST-T change has generally been recognized as being not directly related to any cardiac diseases, it has been observed before starting the ST elevation caused by coronary spasm [28]. Thus, the non-specific ST-T change has a considerable clinical meaning for the patient of OP poisoning. Lower T wave with prolonged QT is similar to congenital long QT syndrome type 2, which is inward rectifier potassium ion channel (I Kr) abnormality [29]. It is reported that OP directly disturbed the function of the ion channel in rat cardiac muscle [30]. ECG change caused by OP was also reported by Kiss and Fazekas (1979): five cases with a transient picture of

myocardial infarction were observed among 168 cases of OP poisoning [20]. Saadeh et al. (1997) described ST-T change along with prolonged QT after exposure to OP [17]. In our study, almost all the reported cases were large dose acute OP poisoning by suicidal use. In sharp contrast, patients studied in this report were the patients who were intentionally exposed to OP compounds consumed for suicidal attempt, due to their personal problems. It is notable that as a background to this study 4, patients had been repeatedly exposed to OP poisoning. Additionally, contaminants in organophosphorus compounds might more or less contribute to the observed symptoms. Due to organophosphate and nicotinic poisoning, hypertension and sinus tachycardia and cholinergic manifestations reveals [30]. Although bradycardia is thought to dominate in the early cholinergic phase of the poisoning, sinus tachycardia was a more frequent finding in our study. The same observation has also been made by others [32,31]. Bradycardia develops secondary to augmented vagal influence that shortens the effective refractive period of atrial myocytes and increases the refractive period and conduction time of the SA and AV mode [33]. Some investigators consider the presence of hypertension and sinus tachycardia to be manifestations of severe poisoning [34]. Indian publications on Organophosphorus compound during the year 2012 to 2016 showed not much more. The degree of collaboration "C" is 0.95 which means there is less work of single authors in comparison to the multiple authors.

Conclusion:

Organophosphorus compound present a grave threat to the health status of the population, especially those that are engaged in agricultural work in developing countries owing to its acute and chronic toxicity. While the acute toxicity resulting from Organophosphorus compound are somewhat well documented and therefore amiable to proper treatment. Chronic toxicity is matter of concern as these chronic effects are insidious and because of the fact that the fetus and the very young are very vulnerable to it. More intensive research is the need of the hour, so as to combat the chronic toxicity of this widely used Organophosphorus compound.

Table 1 Probable Symptoms and signs of organophosphate poisoning

Type of receptor	Receptor sub-type	Action on	manifestation
Nicotinic receptor stimulation	N1 (Nm) receptors	Neuromuscular junction	Weakness, fasciculations, cramps, paralysis
	N2 (Nn) receptors	Autonomic ganglia Adrenal medulla	Tachycardia, hypertension
Muscarinic receptor stimulation	M1-M5*	Central nervous system	Anxiety, restlessness, ataxia, convulsions, insomnia, Dysarthria, tremors, coma, respiratory depression, circulatory collapse
	M2 receptor	Heart	Bradycardia, hypotension
	M3, M2 receptor*	Pupils	Blurred vision, miosis
	M3, M2 receptors*	Exocrine glands	Respiratory-rhinorrhea, bronchorrhea, Gastrointestinal-increased salivation, diarrhea Ocular-increased lacrimation, Others-excessive sweating
	M3, M2 receptors*	Smooth muscles	Bronchospasm, abdominal pain, urinary incontinence

M1 receptors play a critical role in cognitive function. M3 receptor effect predominates in the pupils, airway smooth muscles and mucuc glands. Nicotinic receptors are sub-typed as N1 or Nm receptors and N2 or Nn receptors. Muscarinic receptors are sub-typed from M1 to M5.

Table 2 Symptoms and signs of organophosphate poisoning based on time of manifestation

Time of manifestation	Mechanism	Manifestation
Acute(minutes to 24 hours)	Nicotinic receptor action	Weakness, fasciculations, cramps, paralysis
	Muscarinic receptor action	Salivation, lacrimation, urination, defecation, gastric cramps, emesis, bradycardia, hypotension, miosis, bronchospasm
	Central receptors	Anxiety, restlessness, convulsions, respiratory depression
Delayed (24 hours to 2 weeks)	Nicotinic receptor action	Intermediate syndrome
	Muscarinic receptor action	Cholinergic symptoms-bradycardia, miosis, salivation
	Central receptors	Coma, extra-pyramidal manifestations
Late(beyond 2 weeks)	Peripheral-neuropathy target esterase	Peripheral neuropathic process

Table 3 Year wise percentile distribution of documents

Year	No. of Article	Percentage	Cumulative Percentage
2016	63	15.18	
2015	84	20.24	15.18
2014	102	24.58	35.42
2013	72	17.35	60.00
2012	94	22.65	77.35
Total	**415**	**100.00**	**100.00**

Table 4 Authorship pattern of the published documents

Year	Single Author	Double Author	Triple Author	Four Authors	More than four Authors	Total
2012	4	20	25	15	30	**94**
2013	4	6	23	18	21	**72**
2014	2	25	25	27	23	**102**
2015	5	16	12	24	27	**84**
2016	5	14	6	16	22	**63**
Grand Total	**20**	**81**	**91**	**100**	**123**	**415**

Table – 4(a)

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
2012	5	94	18.8	99.7
2013	5	72	14.4	77.3
2014	5	102	20.4	107.8
2015	5	84	16.8	79.7
2016	5	63	12.6	50.8
Single Author	5	20	4	1.5
Double Author	5	81	16.2	50.2
Triple Author	5	91	18.2	75.7
Four Authors	5	100	20	27.5
Five Authors	5	123	24.6	14.3

Table – 4(b) ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Rows	200.8	4	50.2	1.687395	0.2019558	3.00692
Columns	1185.2	4	296.3	9.959664	0.0003048	3.00692
Error	476	16	29.75			
Total	1862	24				

Table 5 – Distribution of published documents into different types

Type	No. of Document	Percentage	Cumulative Percentage
Article	380	91.57	
Review	15	3.61	91.57
Letter	8	1.93	95.18
Conference Paper	5	1.20	97.11
Book Chapter	4	0.96	98.32
Article in Press	2	0.48	99.28
Editorial	1	0.24	99.76
Total	**415**	**100.00**	**100.00**

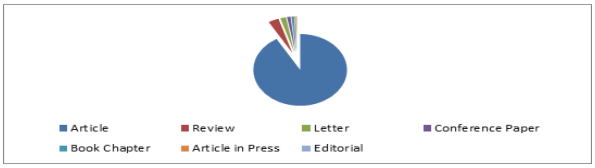

Fig 1 – Different types of organophosp horus documents

Table 6 – Distribution of documents in different subject

Name of the Subject	No of Article	Percentage	Cumulative Percentage
Medicine	197	25.13	
Chemistry	118	15.05	25.13
Pharmacology, Toxicology and Pharmaceutics	101	12.88	40.18
Biochemistry, Genetics and Molecular Biology	95	12.12	53.06
Environmental Science	83	10.59	65.18
Agricultural and Biological Sciences	35	4.46	75.77
Chemical Engineering	33	4.21	80.23
Physics and Astronomy	22	2.81	84.44
Materials Science	20	2.55	87.25
Immunology and Microbiology	18	2.30	89.80
Social Sciences	16	2.04	92.09
Engineering	13	1.66	94.14
Energy	12	1.53	95.79
Neuroscience	6	0.77	97.32
Earth and Planetary Sciences, Mathematics	8	1.02	98.09
Computer Science	3	0.38	99.11
Arts and Humanities, Health Professions, Psychology, Veterinary	4	0.51	99.49
Total	**784**	**100.00**	**100.00**

Table 7 – Documents published in different Journals

Sl. No	Name of the Journals	Number	Cumulative Number	Percentage	Cumulative Percentage
1	Medico-Legal Update	18		4.34	
2	Indian Journal of Forensic Medicine and Toxicology	13	18	3.13	4.34
3	Journal of Indian Academy of Forensic Medicine	8	31	1.93	7.47
4	Environmental Monitoring and Assessment	7	39	1.69	9.40
	Indian Journal of Critical Care Medicine	7	46	1.69	11.09
	International Journal of Pharma and Bio Sciences	7	53	1.69	12.77
5	Chemico-Biological Interactions	6	60	1.45	14.46
	PLoS ONE	6	66	1.45	15.91
6	**5** Journals published	25	72	6.02	17.35
7	**11** Journals published	44	97	10.60	23.38
8	**10** Journals published	30	141	7.23	33.98
9	**37** Journals published	74	171	17.83	41.21
10	**170** Journals published	170	245	40.96	59.04
Total	**241 Journals**	**415**	**415**	**100.00**	**100.00**

Table 8– Degree of Collaboration

Year	Single Author Paper NS	Multiple Author Paper NM	NM + NS	Degree of Collaboration (C)
2012	4	90	94	0.96
2013	4	68	72	0.94
2014	2	100	102	0.98
2015	5	79	84	0.94
2016	5	58	63	0.92
Grand Total	**20**	**395**	**415**	**0.95**

Table 9 – Authors Productivity

Sl. No	Name	No. of Document	Percentage
1	Rajini, P.S.	10	2.41
2	Das, T.	7	1.69
3	Hooda, V.	6	1.45
4	Abraham, J.	5	1.20
5	Acharya, J.	5	1.20
6	Banerjee, S.	5	1.20
7	Dhull, V.	5	1.20
8	Ganguly, B.	5	1.20
9	Kaushik, M.P.	5	1.20
10	6 authors having 4 documents each	24	5.78
11	26 authors having 3 documents each	78	18.80
12	114 authors having 2 documents each	228	54.94
13	32 authors having 1 document each	32	7.71
Total	**187 Authors**	**415**	**100.00**

Table 10 – Authors affiliation into different organizations

Sl. No	Name of the Organization	No. of Document	Percentage
1	Bhabha Atomic Research Centre	21	5.06
2	Defence Research & Development Establishment India	11	2.65
3	All India Institute of Medical Sciences	10	2.41
4	Sri Venkateswara University	8	1.93
5	Jiwaji University	8	1.93
6	Vellore Institute of Technology	8	1.93
7	Sri Krishnadevaraya University India	8	1.93
8	Central Food Technological Research Institute India	7	1.69
9	University of Hyderabad	7	1.69
10	Maharshi Dayanand University	6	1.45
11	Central Salt and Marine Chemicals Research Institute India	6	1.45
12	6 organizations	30	7.23
13	7 organizations	28	6.75
14	32 organizations	96	23.13
15	51 organizations	102	24.58

16	59 organizations	59	14.22
Total	**166 organizations**	**415**	**100.00**

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