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Health Problem Caused by Long-Term Organophosphorus Pesticides Exposure - Study in China

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1. Introduction

Organophosphorus pesticides (OPs), one of the most popular classes of pesticides, are widely used all over the world especially in developing countries, such as China. There are many OPs, with thousands of trade names such as dimethoate, parathion and omethoate, most of which have been used for insect control in residential and agriculture settings. The acute toxicity of OPs are believed to be due primarily to the inhibition of acetylcholinesterase (AChE) resulting in an accumulation of acetylcholine (Ach) with a sustained overstimulation of Ach receptors in the clefts of central and peripheral neuron synapses. They can cause a progression of toxic signs, including hypersecretions, convulsions, respiratory distress, coma and death. However, the heavy usage of OPs has given rise to wide public concern on their chronic toxicity. Generally, long-tem exposure to OPs can be divided into occupational exposure and non-occupational exposure. The former often involves farming population and workers employed in pesticide-related industries. And the latter is more for general population potentially exposed to OPs via a number of different routes including dietary, lifestyle or medicinal.

China is a large country with large demand of pesticides. This means that there are much more Chinese people, both occupational and non-occupational population, whose health are under the threat of OPs exposure. The presence of common and specific metabolites of OPs in urine samples taken from the general population has demonstrated the widespread exposure to OPs in China. Moreover, workers engaged in OPs production are at high risk from OPs exposure, as confirmed by higher levels of OPs metabolites in biological samples compared to those present in individuals from non-agricultural communities. Therefore, a great deal of research has been conducted by Chinese scientists to understand the adverse effects of long-term, low-level exposure to OPs in both general and occupational population.

2. OPs exposure assessment - biolocial monitoring

OPs exposure in both occupational and general population can be assessed by measurement of esterase activity and by direct measurement of urinary OPs metabolites.

2.1 Esterase activity

The activity of esterases including butyrylcholinesterase (BChE), erythrocyte acetyl cholinesterase (AChE), carboxylesterase (CarbE) and paraoxonase (PonE) can be inhibited

by OPs. However, the sensitivity of these four kinds of esterases to inhibition differs. We previously conducted a cross-sectional study among 241 workers from a pesticide plant as directly exposed group, 161 service persons in the same pesticide plant as indirectly exposed group and 150 workers without any records of pesticide exposure in another plant as control group. We measured the esterase activity of all these subjects. The results showed that the CarbE, BChE and PonE activity of subjects in exposed group was significantly lower than subjects in control group (Table 1). The inhibition of AChE activity was related to the type of workshop and work process whereas the inhibition of AChE and BChE activity does not necessarily correlate closely with exposure time and level (Table 2~4). Besides, there was a dose-response relationship between the external exposure dose and CarbE activity (Table 5).

Goup	Number	CarbE	BchE	PON
Direct Exposure	241	513.44±184.59*	39.52±17.84*	142.75±70.49*
Indirect Exposure	161	480.75±115.8#	38.67±15.34#	147.96±93.21
Control	150	615.90±149.55	44.05±12.28	167.97±112.04
p value		0.000	0.004	0.021

*: the esterase activity of subjects in exposed group are significantly lower than those in Control ($p<0.01$).
#: the esterase activity of subjects in Indirectly exposed group are significantly lower than those in C ($p<0.01$).

Table 1. Esterase activity (nmol·ml^{-1}·min^{-1}) of subjects in different groups

Esterase	Type of Workshops			*p* value
	Methamidophos (n=87)	Dimethoate (n=83)	Other OPs (n=71)	
CarbE	508.36±194.62	39.21±22.52	488.14±186.19	0.205
BChE	38.65±13.55	137.11±69.62	40.96±16.40	0.710
PonE	150.72±75.91	126.33±9.83	139.57±64.43	0.411
AChE	127.21±8.13	126.33±9.83	139.57±64.43	**0.003**

Table 2. Esterase activity (nmol·ml^{-1}·min^{-1}) of subjects in different workshops

Esterase	Type of Processes			*p* value
	Packers (n=70)	Operators (n=136)	Inspectors (n=35)	
CarbE	475.23±183.92	526.89±189.88	537.68±156.23	0.115
BChE	39.15±13.61	39.01±14.82	42.26±31.48	0.620
PonE	144.21±68.67	142.84±73.84	139.48±61.95	0.949
AChE	123.31±9.80	126.01±9.23	127.91±7.35	**0.034**

Table 3. Esterase activity (nmol·ml^{-1}·min^{-1}) of workers with different jobs in directly exposed group

Esterase	Working time (years)				*F* value	*p* value
	1~5 (n=9)	5~10 (n=48)	10~20 (n=97)	>20 (n=87)		
CarbE	531.18±283.70	448.54±154.55	509.43±195.27	551.91±167.61	3.377	0.019
BChE	43.52±19.44	41.3±26.24	40.42±15.69	37.12±13.86	0.924	0.430
PonE	146.31±79.60	135.56±67.81	137.09±66.68	152.66±75.06	0.955	0.415
AChE	127.11±7.89	124.21±9.03	125.06±9.47	126.54±9.27	0.840	0.473

Table 4. Esterase activity (nmol·ml^{-1}·min^{-1}) of workers with different working time in directly exposed group

External Exposure level (mg/m3)	Number	CarbE (nmol·ml^{-1} min^{-1})	BchE (nmol·ml^{-1} min^{-1})	PonE (nmol·ml^{-1} min^{-1})	AChE (U)
0~3	124	485.08±188.90	42.36±20.62	136.75±67.54	136.75±67.54
3~6	63	556.43±175.35	37.33±14.67	152.59±71.18	125.76±9.52
>6	54	528.44±176.70	35.56±12.78	145.04±76.04	126.72±8.77
F value		3.417	3.450	1.093	0.812
p value		**0.034**	**0.033**	0.337	0.446

Table 5. Relationship between the external exposure level and esterase activity

Similar research was done by other Chinese colleagues, for example, they (Lin et al., 2007) investigated 56 parathion exposed workers (as exposed group) and 120 non-exposed persons (as control group) and reported that there were significant differences ($p < 0.001$) of the activity of BChE, AChE, CarbE, and PonE compared with control group, but no difference ($p > 0.05$) in plasma β-glucuronidase (β-GD) activity. And the rates of abnormity (below the lower limit of activity reference range) were 37.5% and 48.2% for CarbE and BChE respectively, which were all significantly higher than that of AChE ($p < 0.001$). But there was no significant difference between PonE activity (5.4%) and AChE activity ($p > 0.05$).

2.2 Dialkylphosphate (DAP) metabolites in Urine

On the other hand, there are clear evidences from biological monitoring studies that dialkylphosphate (DAP) metabolites of OPs can be detected in urine after OPs exposure. Six common DAP metabolites, e.g, dimethylphosphate (DMP), dimethylthiophosphate (DMTP), diethylphosphate (DEP), diethylthiophosphate (DETP), diethyldithiophosphate (DEDTP), and dimethyldiithiophosphate (DMDTP) have been determined. These metabolites are non-specific to a particular organophosphate metabolism of different OPs can give rise to similar urinary metabolites. Urinary DAP metabolites reported in a number of studies are summarized in Table 6.

These metabolites in urine are useful to estimate exposure to several OPs. In the cross-sectional study mentioned above, we found that DMP and DETP concentration of workers in the directly exposed group was significantly higher than that of indirectly exposed group (Table 7). Workers in different workshops have different urinary metabolites whereas the type of job influenced the concentration of urinary metabolites (Table 8 and 9). However, we didn't find that the total exposure time will affect the urine level of DAP metabolites (Table 10).

Name	DAP metabolites	Name	DAP metabolites
Dichlorvos	DMP	Malathion	DMP, DMTP, DMDTP
Chlopyrifos	DEP, DETP	Methidathion	DMP, DMTP
Mercaptophos	DEP, DETP	Mevinphos	DMP
Diazinon	DEP, DETP	Paraoxon	DEP
Dichlofenthion	DEP	Parathion	DEP, DETP
Azinphos-methyl	DMP, DMTP, DMDTP	Methyl parathion	DMP
Dimethoate	DMP, DMTP, DMDTP	Phorate	DEDTP
Fenitrothion	DMTP	Diethquinphione	DEP, DETP
Malaoxon	DMP	Metriphonate	DMP

Table 6. Urinary DAP metabolites of different OPs

Group	Number	Median of Urinary DAP metabolites concentration (μg/gCr)				
		DMP	DEP	DETP	DMDTP	DEDTP
Directly Eexposed	161	0.01	1.06×102	9.41	2.18×102	97.48
Indirectly Exposed	122	0.00	8.24×102	8.02	2.21×102	95.10
z value		-4.839	-0.981	-2.733	-0.682	-1.165
p value		**0.000**	0.326	**0.006**	0.495	0.244

Table 7. Urinary DAP metabolites concentration of subjects in different exposed groups

DAP metabolites	Type of Workshops			*p* value
	Methamidophos (n=51)	Dimethoate (n=65)	Other OPs (n=45)	
DMP	0.00	0.00	0.00	0.137
DEP	1292	725	1471	**0.045**
DETP	8	8	8	0.394
DMDTP	342	50	480	**0.004**
DEDTP	90	88	98	**0.037**

Table 8. Urinary DAP metabolites concentration (median) of directly exposed workers in different workshops

DAP metabolites	Type of Processes			*p* value
	Packers (n=26)	Operators (n=109)	Inspectors (n=26)	
DMP	0.00	0.00	0.00	0.623
DEP	1307	1180	737	**0.016**
DETP	8	8	15	0.534
DMDTP	222	275	523	0.140
DEDTP	143	88	99	**0.008**

Table 9. Urinary DAP metabolites concentration (median) of workers with different job title in directly exposed group

DAP metabolites	Working Age Groups (years)		z value	*p* value
	≤20 (n=84)	>20 (n=77)		
DMP	0.00	0.00	-0.104	0.917
DEP	109	871	-0.338	0.698
DETP	9.41	10.9	-1.080	0.280
DMDTP	232	159	-0.688	0.491
DEDTP	110	95	-0.264	0.792

Table 10. Urinary DAP metabolites level (median) of workers with different exposure time in directly exposed group

Another study, done by our research group, investigated in detail 30 workers packaging dimethoate from a pesticide plant. Urine samples of each participant pre- and post-workshift were collected. The results showed that 100% of the workers had at least one DAP metabolite present in both pre-shift and post-shift urine samples. DMP and DMTP were the most frequent metabolites (100%) found, followed by DMDTP, DEP, DETP and finally DEDTP (Table 11). DAP metabolites with dimethyl moieties (DMP, DMTP, and DMDTP) were detected at higher concentrations than those with ethyl moieties (DEP, DETP, and DEDTP) in both time points (pre- and post- workshift). Moreover, DMP, DMTP and DMDTP concentration in the post-shift urine samples were significantly higher than that in the pre-shift urine samples (Table 12).

Groups	Detection percentage (%) of urinary DAP metabolites					
	DMP	DEP	DMTP	DMDTP	DETP	DEDTP
Pre-shift	100.0	40.0	100.0	90.0	20.0	0.0
Post-shift	100.0	53.3	100.0	96.7	26.7	6.7

Table 11. The detection percentage of urinary DAP metabolites of subjects in exposed groups

Groups	Urinary DAP metabolites concentration (μg/gCr)					
	DMP	DEP	DMTP	DMDTP	DETP	DEDTP
Pre-shift	371±1.9*	102±2.1	891±2.4*	302±2.3**	78±2.7	nd
Post-shift	741±2.1	104±1.5	1479±2.1	832±2.3	74±2.2	47±1.4

nd: not detected.

*: the urinary DAP metabolites concentration of pre-shift samples are significantly lower than those of pro-shift samples ($p<0.05$).

**: the urinary DAP metabolites concentration of pre-shift samples are significantly lower than those of pro-shift samples ($p<0.01$).

Table 12. Urinary DAP metabolites concentration (geometric mean) of subjects in exposed groups

Indeed, certain levels of DAP metabolites are also detected in non-occupationally exposed populations. We tested the urine samples of 60 college students and found that more than 86% of them had at least one type of DAP metabolites in the urine. DMDTP was the most frequent metabolite (86.7%) found, followed by DMP, DMTP, DEP, and finally DETP. And

the results showed no detectable DEDTP (Table 13). DMTP were detected at much higher concentrations than other metabolites: the geometric mean of DMTP was high as 661 μg/gCr (Table 14).

Detection	Detection percentage (%) of urinary DAP metabolites					
	DMP	DEP	DMTP	DMDTP	DETP	DEDTP
Number	51	30	48	52	18	0
Percentage (%)	85.0	50.0	80.0	86.7	30.0	0.0

Table 13. The detection percentage of urinary DAP metabolites of general population

DAP metabolites	Range of concentration	25% percentile	median	75% percentile	geometric mean	geometric standard deviation
DMP	22～1026	100	170	254	166	2.3
DEP	27～383	67	114	197	110	1.9
DMTP	109～3187	404	693	1104	661	2.1
DMDTP	24～784	68	135	219	126	2.3
DETP	24～186	37	51	91	60	2.4
DEDTP	nd	nd	Nd	nd	nd	nd

Table 14. Urinary DAP metabolites concentration (μg/gCr) of general population

3. Adverse effects caused by long-term OPs exposure

3.1 Common illness caused by long-term OPs exposure

Available evidence suggests that there is a possibility of adverse effects occurring after long-term OPs exposure although these effects may be not clearly related to the inhibition of cholinesterase. Studies on health hazards to farmers who handle, store and use OPs have documented a range of non-specific self-reported symptoms that have been attributed to chronic OPs exposure. These include burning or prickling of the skin; tingling or numbness of hands and face; muscular twitching or cramps in the face, neck, arms and legs; respiratory symptoms such as chest pain, chest stuffiness, cough, runny nose, wheezing, shortness of breath, sore throat; excessive sweating; nausea, vomiting, diarrhoea; excessive salivation; abdominal pain; lacrimation and inflammation of the eyes; difficulty in seeing; restlessness; difficulty in falling asleep; trembling of hands; and irritability.

Zhao and his colleagues use Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleeping Scale (ESS) to investigate and analyze the sleeping status of 482 agricultural workers over 50 years old from 5 counties in Jiangxi province (Zhao et al., 2010). The PSQI scores of these farmers were 5.80±2.81, lower than those of general population. And the ESS scores of these farmers were 7.15±4.99, higher than those of general population. Moreover, the ESS scores of farmers who have been exposed to OPs more than 1000 days were significantly higher than other farmers (p<0.01). Zhang observed 284 occupational OPs exposed persons by dynamic ultrasonographic imaging and found a higher prevalence of fatty liver than non-exposed persons (W.P. Zhang et al., 2010).

ECG changes in workers who have been exposed to OPs were also reported. An investigation of 706 exposed workers and 707 non-exposed persons and reported that about 19.69% of the workers had abnormal ECG changes against 12.31% of the non-exposed persons (Tang et al., 2004). The abnormal ECG changes of exposed workers include sinus bradycardia, arrhythmia, incomplete right bundle branch block, and ST-T segment elevation.

Our group once analyzed a series of data of medical examination (particular ECG examination) of 87 workers exposed to three kinds of OPs and found significant differences in the prevalence of ECG abnormalities between exposed and non-exposed groups. Although the prevalence of ECG changes for exposed workers was much higher than that of prior to exposure, it did not increase with the prolongation of the exposure period. And the inhibition of AChE was not correlated to ECG disorders, which indicated that cardiac effects of OPs are not clearly related to the inhibition of AChE (Tables 15 and 16).

Groups	Number	Abnormal ECG rate	Odds ratio of prevalence	*p* value
Control	25	4.0		
Dimethoate	35	20.0	6.0	**0.07**
Methamidophos	30	13.3	3.7	0.23
Kitazin P	19	21.1	6.4	**0.09**
Totle	84	17.9	5.2	**0.07**

Table 15. ECG abnormalities of subjects in different groups

Types of ECG abnormalities		Dimethoate	Methamidophos	Kitazin P	Control
Sinus arrhythmia	Sinus tachycardia	3	4	1	0
	Sinus bradycardia	17	3	8	0
	Sinus irregularity	5	0	0	0
Ectopic arrhythmias	Premature beat	0	3	0	0
Conduction abnormalities	Right bundle branch block	4	0	0	0
Others	Low QRS wave	1	9	10	2
	Left ventricular sypervoltage	5	5	2	0
Left/right axis deviation		10	2	9	0
Total number of abnormalities		42*	26*	21*	2
Total number of subjects		410	360	145	302

*: the number of ECG abnormalities in the exposed groups are signicantly different from those of control group ($p<0.01$).

Table 16. Types of ECG abnormalities of subjects in different groups

Once we collected the information on OPs exposure history and signs and symptoms of the subjects through questionnaires and medical examinations among another exposed population. Then the weighting and total score of the signs and symptoms of neuromuscular system, respiratory system, circulatory system and digestive system was calculated. The results showed that the weighting and total symptom score in directly and indirectly exposed group was higher than that in control group, and there was a dose-response relationship between the internal exposure dose and digestive system score (Table 17~19). A higher percentage of abnormal hemoglobin was found in the workers in directly exposed group, in correlation with exposure time. The workers (working time 5~10 years) in directly exposed group showed a higher percentage of abnormal hemoglobin level, and there was dose-response relationship between the percentage of abnormal hemoglobin and accumulating external exposure dose (liner-liner association analysis (p<0.05) (Table 20 and 21). Besides this, some system scores and the percentage of abnormal hemoglobin were related to AChE activity regarded as an exposure dose (Table 22). There was negative correlation between the activity of AChE and signs scores according to correlation analysis. It showed a increasing trend of signs scores and percentage of abnormal hemoglobin with the decrease of AChE activity (Table 23).

Groups	Number	Symptom scores				
		neuromuscular system	respiratory system	circulatory system	digestive system	Total system scores
Directly Exposed	241	0.66±1.49	0.27±0.84	0.44±0.74	0.21±0.57	1.57±2.44
Indirectly Exposed	161	0.29±0.88	0.11±0.32	0.30±0.64	0.07±0.30	0.63±1.08
Control	150	0.03±0.16	0.05±0.22	0.06±0.27	0.03±0.22	0.16±0.54
H value		49.37	10.87	37.13	23.55	89.01
p value		0.000	0.004	0.000	0.000	0.000

Table 17. Total symptom scores of subjects in different groups

Groups	Total number	Number of person with abnormal symptoms	Number of person without abnormal symptoms	Ratio of abnormal symptoms (%)	X^2 value	p value
Directly Exposed	241	132	109	54.8	91.05	**0.000**
Indirectly Exposed	161	43	108	28.5		
Control	150	15	145	9.4		

Table 18. Ratio of abnormal symptoms of subjects in different groups

DETP (μg/gCr)	Number	Symptom scores				
		neuromuscular system	respiratory system	circulatory system	digestive system	Total system scores
0~7.5	53	0.83	0.15	0.25	0.11	1.34
7.5~15	49	0.80	0.22	0.41	0.18	1.61
>15	59	0.80	0.32	0.22	0.39	1.73
H value		1.063	2.642	2.603	6.900	3.674
p value		0.588	0.267	0.272	**0.032**	0.159

Table 19. The symptom scores are affected by internal exposure dose (urinary DETP levels)

Groups	Number	Abnormalities (%) of medical examinations					
		WBC	Hb	ECG	B ultrasonic	SBP	DBP
Directly Exposed	241	2.9	33.6	13.7	17.8	12.4	24.1
Indirectly Exposed	161	3.3	5.3	17.9	24.5	20.5	33.1
Control	150	3.1	15.6	17.5	15.1	6.3	19.4
X2		0.053	48.88	1.623	2.536	14.19	8.06
p		0.974	**0.0000**	0.444	0.111	**0.001**	**0.018**

WBC: white blood cell; Hb: hemoglobin; SBP: systolic pressure; DBP: diastolic pressure

Table 20. Medical examinations data of subjects in different groups

Rate of abnormalities (%)	Exposure time (years)				X^2 value	*p* value
	1~5 (n=9)	5~10 (n=48)	10~20 (n=97)	>20 (n=87)		
WBC	0	6.3	3.1	1.1	3.212	0.360
Hb	11.1	**47.9**	39.2	21.8	13.193	**0.004**
ECG	0	12.5	15.5	13.8	1.744	0.627
B ultrasonic	0	16.7	23.7	13.8	5.252	0.154
SBP	11.1	14.6	11.3	12.6	0.328	0.955
DBP	44.4	27.1	19.6	25.3	3.420	0.331

Table 21. Medical examinations data of workers with varied exposure time in directly exposed groups

AChE activity (U)	Number	Symptom scores				
		neuromuscular system	respiratory system	circulatory system	digestive system	Total system scores
0~120	67	1.07	0.46	0.54	0.34	2.42
120~127	54	0.59	0.15	0.39	0.20	1.33
127~134	74	0.49	0.26	0.49	0.14	1.36
>134	46	0.41	0.13	0.28	0.13	0.96
H value		10.018	16.278	3.723	11.564	8.490
p value		0.018	**0.001**	0.293	**0.009**	**0.037**

Table 22. The symptom scores were realted to the AChE activity

AChE activity (U)	Number	Abnormalities (%) of medical examinations					
		WBC	Hb	ECG	B ultrasonic	SBP	DBP
0~120	67	1.5	56.7	7.5	16.4	4.5	11.9
120~127	54	5.6	35.2	20.4	14.8	14.8	25.9
127~134	74	1.4	25.7	13.5	17.6	13.5	29.7
>134	46	4.3	10.9	15.2	23.9	19.6	30.4
X^2 value		2.724	28.840	4.330	1.591	6.398	7.813
p value		0.436	**0.000**	0.228	0.662	0.094	**0.049**
Trend X^2 value		0.157	28.051	0.878	0.959	5.164	6.330
p value		0.692	**0.000**	0.349	0.327	0.023	**0.012**

Table 23. The raiao of medical examination abnormalities were related to the AChE activity

We also compared the 686 health surveillance records in 1979 and 1995 in Shanghai Pesticide Factory to understand changes of health status among employees and evaluate the effectiveness of occupational health measures herein. We noted that less symptoms and signs score in 1995 than 1979. Higher percentage of abnormal blood pressure was found among the first year new workers. With the pass of time, the percentage of such change also increased. There were no differences of hemoglobin levels among workers who engaged in different sectors and with different working ages. ANOVA test revealed that the activity of cholinesterase in 1995 was significant higher than 1979. The job code (which dominants the magnitude of OPs exposure) was a main affecting factor to the enzyme activity. Better health status in 1995 than in 1979 was also found based upon the data of 139 workers who had received two-times examinations in 1979 and in 1995. These results confirmed that the general health status of workers exposed to pesticides was better in 1995 than in 1979 in this pesticide factory. It indicated that the occupational health measures taken during this period of time were effective.

In Shanghai Pesticide Factory, we also observed the typical tolerance phenomenon to OPs. The trend of change of ChE and clinical score among the contractor workers exposed to different levels of OPs were carefully studied. The trend of changes in blood ChE and score since starting exposure to 3 or 4 months were expressly present. We found that the ChE and score of packing workers sharply declined since the starting of exposure; there were

significant exposure-effect correlations. After withdrawing of those who were poisoned (ca. 2%) in 40-60 days, the ChE and score dropped less steep and then turn to flat. It indicated that body developed tolerance to low-level exposure to OPs in 40-60 days. High level (or higher toxicity) exposure caused poisoning in portion of the workers, but the remainders tolerated the exposure, and kept ChE and score in a steady horizon, though fluctuated and less than normal.

3.2 Neurobehavioural effects caused by long-term OPs exposure

Some, but not all, epidemiological studies demonstrated that long-term exposure to OPs may be associated with impaired neurobehavioural performance. Clinical features that have been reported include anxiety disorder, depression, psychotic symptoms, dysthymic disorder (DSM-III-R); short-term memory problems, learning disorders, attention-deficit disorders, information processing problems, eye-hand coordination problems and delayed reaction time, and autonomic dysfunction.

Zhang and his colleagues conducted a survey on a representative sample of 9811 rural residents in Zhejiang province (J.M. Zhang et al., 2009). These residents were asked about the storage of pesticides at home and about whether or not they had considered suicide within the 2 years before the interview. The Chinese version of the 12-item General Health Questionnaire (GHQ) was administered to screen for mental disorder. They found that the unadjusted odds ratio (OR) for the association between pesticide storage at home and suicidal ideation over the prior 2 years was 2.12 (95% confidence interval, CI: 1.54–2.93). After adjusting for gender, age, education, socioeconomic status, marital status, physical health, family history of suicidal behaviour, GHQ caseness and study design effects, the OR was 1.63 (95% CI: 1.13–2.35). These results indicated an association between OPs exposure and suicide ideation in rural areas of China.

3.3 Effects of long-term OPs exposure on the human reproduction

Another important feature of OPs is their endocrine disrupting effects and potential adverse impact on both male and female reproductive function. Studies carried out employing chronic exposure of animals to low doses of the OPs showed a reduction in reproductive function, both female and male. And a number of epidemiology data also demonstrated the deleterious reproductive effects of chronic exposure to OPs in occupational and/or environmental settings.

Lv and her colleagues investigated the cross-sectional association between OPs use and menstrual function among 298 women working at a OPs factory (Lv, 2004). Women were aged 21-45 years, premenopausal, not pregnant or breastfeeding, and not taking oral contraceptives. Menstrual cycle characteristics of interest included symptoms before the menstruation begins; cycle length (short cycles, long cycles, irregular cycles); missed periods (not experiencing a period for more than 6 weeks in the last 12 months); menstruation amount (large, small); and dysmenorrhea. After controlling for age, working time, and education level, the author found that women who used pesticides experienced more pre-menstruation symptoms and increased odds of irregular menstrual cycles compared with women who never used pesticides.

Zhang and her colleagues observed 601 female workers in the first production line of the pesticide factory and 873 unexposed female workers according to the reproduction occupational epidemiological method (S.H. Zhang et al., 2004). Then they reported a

significantly higher incidence of premature delivery (8.20%), post-mature delivery (7.64%), spontaneous abortion (2.83%), and pregnancy induced hypertension syndrome (6.41%) in the exposed group than the unexposed group (p=0.000, 0.003, 0.004, 0.035).

Li's investigation also showed an increased incidence of irregular menstruation, spontaneous abortion, and infertility in the OPs exposed group when compared with the control group (G.R. Li et al., 2000).

Li and Zou surveyed 161 male farmers exposed to OPs and 161 unexposed men via epidemiological questionnaires. Then these subjects received genital examinations, and their semen samples were collected for analysis. The authors found a decrease in sperm viability and percentage of sperm with forward progression, and normal sperm morphology. The semen density of farmers in the exposed group was 76.0±84.8×10^6/mL, significantly lower than those in the unexposed group (100.0±56.4×10^6/mL). Logistic regression analysis showed that chronic exposure to OPs would influence the sperm quality (W.Y. Li et al., 2004; Zou et al., 2005).

3.4 Effects of long-term OPs exposure on fetal and childhood health

Large amount of evidence have shown that fetuses can be exposed to pesticides. OPs pass through the blood–brain barrier and placenta and have also been found in amniotic fluid. In addition, the young may receive greater exposure than adults, because they eat, drink, and breathe more per unit of body weight. They are closer to the floor and surfaces where pesticides may settle, and have extensive hand-to-mouth contact. Recent studies have shown that fetuses and young children have lower than adult levels of detoxifying enzymes and their brains are developing rapidly. This suggests that the nervous system of the fetus and young children is several-fold more susceptible to potential neurotoxic effects of such low-dose OPs exposure.

Wang and his colleagues investigated the association between neurodevelopment and behavior of 301 children. Child neurodevelopment was assessed by the Gesell Development Schedule at 2 years of age. Developmental quotients (DQs) were obtained in motor, adaptive, language and social areas. They reported that geometric mean (GM) for children DAP metabolites (μg/g) were DMP: 10.38; DMTP: 6.56; DEP: 7.27; DETP: 14.26; DEDTP: 4.46 (Table 24). They found a significant correlation between DAP levels and children neurodevelopment (Table 25 and 26. They also found the DQs were higher in high dose exposure group than in the low dose exposure group. There was highly significant difference between these two groups (p=0.03) (Table 27). In addition, DAP levels were positively associated with 8-OHdG in urine (r=0.594, p=0.000) (Wang, 2009).

DAP metabolites	Detection percentage (%)	GM	Range	P25	P50	P75	P95
DMP	41.9	10.38	1.17~724.43	3.95	8.93	23.70	125.60
DMTP	36.5	6.56	0.07~478.63	2.87	5.90	13.12	58.64
DEP	71.8	7.27	0.06~169.82	3.51	7.16	14.79	54.61
DETP	69.1	14.26	1.1~977.24	5.30	12.91	37.15	128.82
DEDTP	2.7	4.46	1.07~72.44	2.46	4.45	7.69	18.36

Table 24. Creatinine-adjusted OPs urinary DAP metabolites levels among children (μg/g) (n=301)

DQ score	Mean±SD	Normal development percentage (%)	Delayed development percentage (%)
Behavioral ability	103.07±7.59	99.67	0.3
Adaptability to environment	107.03±11.87	98.67	1.3
Verbal ability	104.27±16.22	93.7	6.3
Adaptability to people	96.11±7.34	97.3	2.7

Table 25. Distribution of GSD DQ score (n=301)

DAP metabolites	Behavioral ability		Adaptability to environment		Verbal ability		Adaptability to people	
	â (95%CI)	*p*	Â (95%CI)	*p*	â (95%CI)	*p*	â (95%CI)	*p*
DMP	-0.20 (-6.88~6.35)	0.94	0.05 (-9.03~11.03)	0.85	0.02 (-13.32~13.45)	0.99	-0.25 (-9.61~3.24)	0.76
DMTP	0.12 (-2.399~6.06)	0.39	0.49 (-5.28~7.53)	0.73	-0.07 (-10.90~6.20)	0.59	-0.15 (-6.20~2.00)	0.31
DEP	-0.19 (-5.13~4.53)	0.90	-0.10 (-9.68~4.98)	0.53	-0.04 (-11.16~8.39)	0.78	-0.18 (-7.40~1.98)	0.26
DETP	-0.47 (-13.16~0.90)	0.09	-0.44 (-19.6~1.71)	0.10	-0.11 (-17.35~11.09)	0.67	-0.16 (-8.90~4.75)	0.55
DEDTP	0.13 (-1.58~7.54)	0.20	0.07 (-4.41 9.42)	0.48	0.06 (-6.12~12.34)	0.51	0.05 (-3.41~5.44)	0.65

Table 26. Adjusted coefficient (â) (95%CI) in points on the Gesell scores of children neurodevelopment for log10 unit increase in pesticide urinary metabolites (n=301)

	DQ scores	High dose group (n=212)	Low dose group (n=89)
Behavioral ability	Mean ± SD (range)	103.36±7.33 (83~125)	102.36±8.17 (90~124)
	Normal (%)	99.53%	100.00%
Adaptability to environment	Mean ± SD (range)	107.34±11.85 (83~136)	106.28±11.94 (79~135)
	Normal (%)	99.06%	97.75%
Verbal ability	Mean ± SD (range)	105.02±15.93 (66~146)	102.5±16.96 (66~138)
	Normal (%)	94.34%	92.13%
Adaptability to people	Mean ± SD (range)	96.99±7.3 (82~133)	94.02±7.02 (71~121)
	Normal (%)	98.11%	95.51%

Table 27. Gesell scores in two dose groups (n=301)

Wang also collected and analyzed urine samples of 187 pregnant women to evaluate the relationship of maternal prenatal DAP levels with birth outcomes. The results showed that GM of DAP metabolite levels (μg/g) of pregnant women were DMP: 25.75; DMTP: 11.99; DEP: 9.03; DETP: 9.45; DEDTP: 0.75. They did not found the evidence that OP pesticides at current levels adversely affect fetal development.

Luo analyzed the birth outcome data of 5571 prenatal infants in a rural area of Guangdong Province and reported that 1.13% of them were born with deformity including hydrops fetalis syndrome, neural tube defects, hydrocephalus, and congenital equinovarus. Further logistic analysis found a relationship between maternal exposure to OPs and birth defects (Luo, 2004).

3.5 Other health problems caused by long-term OPs exposure

By analyzing the death cause data of a cohort including 2270 workers employed for at least 1 year before Jan 1, 1983 and a sub-cohort of 1018 of them worked at OPs exposed workshop in a pesticide factory, we investigated the cause of death and mortality of cancer among OPs exposed workers and evaluated the relationship between long-term occupational OPs exposure and cancer occurrence. This study was followed up from Jan 1, 1983 to Dec 31, 2004. The death cause spectrum of OPs exposed workers was similar to that in reference population locally, but higher mortality of malignant tumor was found in OPs exposed workers. The SMR for all cancer, and malignant cancer were 120.2 and 119.6 respectively. SMR for malignant tumor of bladder, lung and stomach cancer were 303.7, 141.2, and 137.5 respectively ($P<0.01$). Chi-square test showed tumor mortality of exposed workers was higher than that of non-exposed workers ($P<0.01$), indicating the risk of malignant tumor death increased with exposure to OPs (Table 28 and 29).

Hong tested DNA damage in peripheral lymphocytes of workers exposed to OPs via single cell microgel electrophoresis (SCGE) and found that the cometic rate of peripheral lymphocyte among OPs exposed workers was (2.8±1.9)%, significantly higher than that in control group ($p<0.01$). The amount of T lymphocyte α-ANAE in peripheral blood among OPs exposed workers was also significantly higher than that in control group ($p<0.01$). These results suggested that chronic exposure to OPs may lead to genetic damage (Hong et al., 2002).

We studied the M_3 gene expression in peripheral blood lymphocyte of workers exposed to diamethoate and explore its role in the toxic effects of OPs. The lymphocytes in peripheral blood from 33 workers exposed to diamethoate and 15 control people were isolated and treated with saline and diamethoate in vitro, respectively. RT-PCR technique was used in determine M_3 gene expression. Basal and inducible gene expression levels were measured. The result was presented in ratio of optical density of sample mRNA and that of the reference (β-actin) as: (M_3 O.D.×353)/(248×β-actinO.D.). There (OD) no significant difference of basal gene expression level between the exposed group and control group, (1.49±0.20) versus (1.49±0.45); while the inducible gene expression level was significantly higher in exposure group to the control group, (1.92±1.07) versus (1.22±0.19). No difference was found between male and female people in both exposed and control group. The inducible gene expression level was higher in the operators than in the packers, which maybe attribute to the difference of exposure time. The inducible M3 gene expression level showed a gradient increment with the elongation of the working age: <5yr(1.69±0.95), 5～25yr (1.91±1.03), >25yr (2.09±1.25). These indicated that after long-term exposure to OPs, the basal M3 receptor gene expression level in the exposed workers did not show any difference with the control group, but the inducible gene expression level (treated with OPs in vitro) would increase and the level was related to the degree of OPs exposure.

population	Reference population		Cohort of exposed group		Expected deaths	SMR
	Death toll	Mortality	Death toll	Mortality		
All death cause	149511	819.60	263	719.19	300	87.7
All cancer	41484	227.41	100	273.46	83	120.2
Malignant tumors	41306	226.43	99	270.72	83	119.6
Nasopharyngeal cancer	519	2.85	0	0.00	1	0.0
Esophageal Cancer	2285	12.53	5	13.67	5	109.2
Gastric cancer	7258	39.79	20	54.69	15	137.5*
Intestinal cancer	3499	19.18	5	13.67	7	71.3
Liver cancer	5333	29.23	14	38.28	11	131.0
Lung cancer	10248	56.18	29	79.30	21	141.2*
Brest cancer	1229	6.74	2	5.47	2	81.2
Cervical cancer	216	1.18	0	0.00	0	0.0
Bladder cancer	657	3.60	4	10.94	1	303.7**
Leukemia	825	4.52	1	2.73	2	60.5
Benign tumors	81	0.44	1	2.73	0	615.8**
Other tumors	9334	51.17	19	51.96	19	101.5
Other diseases	108027	592.19	164	448.47	217	0.76

*: P<0.05. **: P<0.01.

Table 28. The cause of death and mortality of both OPs exposed workers and reference population

Groups	Male			Female		
	Death from tumors	Death from others	Total	Death from tumors	Death from others	Total
OPs exposed population	46	54	100	12	8	20
Reference population	36	91	127	3	13	16
Total	82	146	227	15	21	36
	X^2=7.556, p=0.006			X^2=6.223, p=0.013		

Table 29. Constituent ratio of death in OPs exposed population and reference population

4. Interaction of genetic polymorphisms and long-term OPs exposure

While this review has focused on health problems caused by long-term OPs exposure via a number of different ways including occupational, dietary, lifestyle or medicinal, it should be recognized that it is likely that polymorphisms within a variety of genes may affect susceptibility to OPs induced toxicity. Much of the work in this field has focused on OPs metabolism and detoxification pathways.

One of our studies examined whether BChE and PonE polymorphisms influenced susceptibility in OPs exposed population. We determined BChE-K, PonE-192 and PonE-55 genotypes of 75 OPs exposed workers using PCR-PFLP. And then their accumulative symptom scores and the whole blood AChE activity (mmol·h^{-1}·ml^{-1}) were measured as health index. We analyzed their health condition related to single gene site of the three gene loci to determine which kinds of genotype were susceptible. Then, we used the multiple variance analysis to see if there existed interactions among these three gene loci. Finally, we established the multi-factor linear regression equation, considering some other factors that might affect the health status such as age, gender and exposure time. The results showed that the mean AChE activities of the exposed workers with BChE-K genotype UU (61 cases), genotype UK(12 cases)and genotype KK (2 cases) were respectively 105.0±23.0, 84.4±16.4, 79.0±9.9. The accumulative symptom scores were respectively 3.7±3.8, 9.2±3.0, 12.5±0.7. The AChE activities of the exposed workers with PonE-192 genotype BB (37 cases), genotype AB (27 cases) and genotype AA (11 cases)were respectively 116.8±15.1, 91.2±15.6, 72.3±21.4. The accumulative symptom scores were respectively 2.0±3.2, 6.7±3.3, 9.7±1.8. Similarly, the AChE activities of the exposed workers with PonE-55 genotype LL (70 cases) and genotype LM (5 cases) were 102.4±23.0, 82.8±22.0. The accumulative symptom scores were 4.5±4.2, 9.2±3.6. Single variance analysis showed that the accumulative symptom scores of the individuals with abnormal homozygote of these three gene loci were the highest, which indicated that they were most susceptible to OPs exposure. Multiple variance analysis showed there were no interactions among the three gene loci. Age, gender and exposure time had no statistical significance while genotypes of the three gene loci had significant relationship to health status. In conclusion, we found that the genotypes of BChE-K, PonE-192 and PonE-55 are associated with susceptibility to OPs exposure.

Another work of our research group detected the genotypes of enzymes (PonE-192, PonE-55, BChE, P450 and NAT2) and the polymorphic distribution via 7900 genotype detecting system and CMOS Chip technique. We found that the abnormal allele frequency of PonE-192, PonE-55 and BChE was respectively 37.8%, 1.9% and 13.7% whereas the abnormal homozygote frequency of PonE-192 and BChE was 15.0% and 1.6% with no abnormal homozygote of PonE-55 (Table 30). The genotypes of all enzymes reached Hardy-Weinberg balance.

We further analyzed the effects of the genetic polymorphism of enzymes on urinary DAP metabolites, esterase activity, signs and symptoms. The results showed that the polymorphism of P450 metabolic enzymes (CYP1A2, CYP2E1) influenced the concentration of urinary DAP metabolites (DEP, DEDTP) (Table 31). The genotypes of PonE-192 and PonE-55 influenced the activity of PonE. The genotype of PonE-192*AA as well as PonE-55*ML appeared with low activity (Table 32). Lower activity of the same genotype of PonE-192 and PonE-55 (working duration less than 20 years) was found, while the BChE activity of workers more than 20 working years had the higher inhibition. We also found a relationship between PonE, BChE and exposure dose by controling the influence of genetic polymorphism (Table 33). But there was no significant relationship between genetic polymorphism and examination abnormalities of exposed workers (Table 34). The activity of PonE was lowest in the workers with genotype of PonE192*AA + PonE55*ML + BChE*KK, and the AChE activtity was lower while signs scores was higher. The genotype of PONE192*AA + PonE55*ML + BChE*KK was the most sensitive. The liner regression analysis showed the polymorphism of PonE and BChE affected the activity of AChE, indicating that the gene polymorphism influence the health effects caused by OPs exposure (Table 36).

Gene loci	Genotypes	Cases	Allele	Allele cases	Allele frequency
	Gln/Gln(AA)	32	Gln	161	0.378
PonE-192	Arg/Gln(BA)	97			
	Arg/Arg(BB)	84	Arg	265	0.622
	Met/Met(LL)	205	Met	418	0.981
PonE-55	Leu/Met(ML)	8			
	Leu/Leu(MM)	0	Leu	8	0.019
	Ala/Ala (UU)	179	Ala	416	0.863
BChE*K	Thr/ Thr (KK)	58			
	Ala/Thr (UK)	4	Thr	66	0.137
	AA	114	A	145	0.797
CYP1A1	A/G	62			
	GG	6	G	37	0.203
	GG	55	G	103	0.575
CYP1A2	G/A	95			
	AA	29	A	76	0.425
	AA	8	A	44	0.243
CYP2E1	A/T	72			
	TT	101	T	137	0.757
	GG	104	G	125	0.839
NAT2	G/A	42			
	AA	3	A	24	0.161

Table 30. The genotypes of enzymes and the polymorphic distribution

Gene loci	Genotypes	Number of people	Urinary DAP metabolites (μg/gCr)				
			DMP	DEP	DETP	DMDTP	DEDTP
	AA	114	0.00	928	9.95	252	101
CYP1A1	A/G	62	0.00	187	8.36	151	109
	GG	6	0.00	512	103.7	355	60
p value			0.142	**0.015**	0.446	0.606	0.262
	GG	55	0.00	177	9.24	355	104
CYP1A2	G/A	95	0.00	145	9.96	164	101
	AA	29	0.00	402	7.39	149	111
p value			0.988	**0.027**	0.486	0.432	0.931
	AA	8	0.00	844	9.96	245	88.7
CYP2E1	A/T	72	0.00	104	12.9	222	125
	TT	101	0.00	150	7.53	222	94.2
p value			0.189	0.527	0.195	0.795	**0.032**
	GG	104	0.00	111	9.41	169	109
NAT2	G/A	42	0.00	996	9.39	181	86
	AA	3	21.8	191	6.84	655	79.8
p value			0.079	0.920	0.414	0.419	0.164

Table 31. The influence of polymorphism of P450 metabolic enzymes on urinary DAP metabolites level

Gene loci	Genotypes	Number of people	Esterase activity			
			BChE	CarbE	PonE	AChE
BChE	UU	179	33.26±9.13	512.91±186.09	150.81±98.64	122.00±6.68
	UK	58	40.52±17.00	552.31±116.9	148.67±70.05	126.19±9.40
	KK	4	39.34±18.28	500.87±189.18	140.65±70.33	123.60±8.71
p value			0.709	0.183	0.735	0.134
PonE-192	AA	32	43.99±31.17	518.04±183.97	94.32±44.18	123.66±10.68
	AB	97	39.43±14.91	503.79±195.26	154.32±71.54	125.69±8.09
	BB	84	39.89±16.25	518.47±193.92	146.04±68.57	125.53±9.56
p value			0.475	0.924	**0.000**	0.541
PonE-55	LL	205	40.37±18.98	511.87±190.3	144.25±69.53	125.36±9.25
	LM	8	38.49±7.79	623.61±97.37	85.45±50.75	123.88±7.45
p value			0.781	0.101	**0.019**	0.653

Table 32. The influence of esterase genetic polymorphism on esterase activity

Gene loci	Genotypes	Number of people	working age		t value	*p* value
			≤20 years	≥20 years		
PonE-192	AA	32	90.53±33.21	98.11±53.86	-0.479	0.635
	AB	97	137.36±63.34	175.62±76.17	-2.701	**0.008**
	BB	84	141.09±71.92	152.32±64.49	-0.743	0.459
PonE-55	LL	205	133.27±66.14	157.73±71.55	-2.538	**0.012**
	LM	8	109.27±50.97	61.62±43.56	1.421	0.205
BChE	UU	179	42.32±21.92	35.74±11.71	2.562	**0.011**
	UK	58	39.31±15.89	41.74±18.24	-0.542	0.590
	KK	4	33.26±9.13			

Table 33. The influence of esterase genetic polymorphism on esterase activity (nmol/ml·min) of workers in different working age groups

Gene loci	Genotypes	Number of people	Abnormalities (%) of medical examinations					
			WBC	Hb	ECG	B ultrasonic	SBP	DBP
BChE*K	UU	179	2.2	32.4	14.0	19.0	12.3	24.6
	UK	58	5.2	37.9	12.1	15.5	12.1	22.4
	KK	4	0	25.0	25.0	0	25.0	25.0
p value			0.389	0.693	0.988	0.333	0.751	0.783
PonE-192	AA	32	0	28.1	15.6	18.8	12.5	28.1
	AB	97	4.1	32.0	10.3	17.5	14.4	18.6
	BB	84	3.6	35.7	17.9	15.5	9.5	26.2
p value			0.308	0.715	0.334	0.893	0.602	0.361

Table 34. The examination abnormalities of exposed workers in different genetic polymorphism

BChE*K	PonE-192	PonE-55	Number	PonE (nmol/ml·min)	AChE (U)	Symptom scores
UU	AA	LL	1	83.39	123.00	2.00
UU	BB	LL	1	144.04	131.00	0.00
KK	AA	LL	22	97.91	124.5	1.64
KK	BB	LL	59	143.67	125.85	1.27
KK	BA	LL	70	157.47	126.29	1.70
UU	BA	LL	2	187.90	117.00	1.00
KU	AA	LL	5	114.10	118.20	1.80
KU	BB	LL	23	151.87	125.00	1.39
KU	BA	LL	22	147.88	124.64	1.18
KK	**AA**	**ML**	4	**52.59**	126.00	**5.00**
KK	BA	ML	2	134.83	121.50	0.50
KU	BA	ML	2	101.80	122.00	2.00

Table 35. The relationship between multi-genetic polymorphism and esterase activity and symptom scores

5. Conclusion

We present the research results conducted in China by Chinese scientists, mostly our research group. From these, we believe that the health problem caused by OPs exposure can't be ignored, though the exposure-response was not clearly elucidated. It is good that with the economic development towards better, the working condition has been improved and workers have less exposure to OPs. The traditional types of organophosphorus pesticides with high acute toxicity, such as methamidophos, parathion; methyl parathion and phosphamidon were prohibited in China, However, long-term and low level exposure to OPs is still a serious health problem and we should pay more attention to these public problems.

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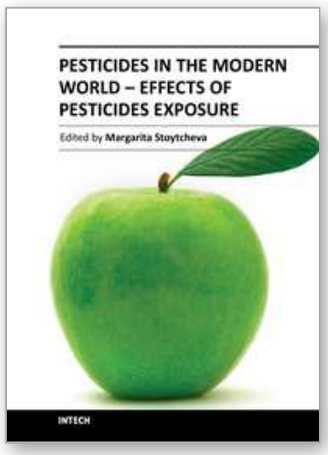

Pesticides in the Modern World - Effects of Pesticides Exposure

Edited by Dr. Margarita Stoytcheva

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950â€™s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestockâ€™s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising worldâ€™s population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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