Role of individual susceptibility in risk assessment of pesticides

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Abstract

Objectives—This study presents criteria for assessing the individual pesticide burden of workers in the chemical industry.

Methods—A group of 1003 workers exposed to methylparathion or ethylparathion (alkyl phosphates), propoxur (carbamate), or cyfluthrin (pyrethroid) was investigated. After exposure to methylparathion or ethylparathion the methylparathion or ethylparathion and methylparaaxon or ethylparaaxon concentrations in plasma, the p-nitrophenol concentration in urine, and the activities of cholinesterase and acetylcholinesterase were measured. For exposure to propoxur the propoxur concentration in plasma, the 2-isopropoxyphenol concentration in urine, and the cholinesterase and acetylcholinesterase activities were measured. For exposure to cyfluthrin the cyfluthrin concentration in plasma was measured.

Results—At the same propoxur concentration only workers with a low individual acetylcholinesterase activity reported symptoms. Workers who metabolised cyfluthrin rapidly reported less symptoms than workers with a lower rate of metabolism. This tendency was also evident in cases of mixed exposure (cyfluthrin and methylparathion).

Conclusions—In the assessment of exposure to pesticides susceptibility of the individual person has to be considered.

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Keywords: risk assessment; pesticides; individual susceptibility

Alkyl phosphates, carbamates, and pyrethroids are among the pesticides most often used. People handling pesticides do not only include workers in the chemical industry (production, filling, formulation), farmers, and pest control operators but also the consumers. The applicator should bear in mind that an improper use of pesticides may lead to adverse health effects.^{1,2} For objective assessment of exposure to pesticides it is recommended that the pesticides and specific enzymes in blood and the corresponding metabolites in urine are measured by standard biological monitoring.^{3–7} The measurement of the pesticide in blood is important, because in many cases the unchanged pesticide is responsible for adverse health effects. The renally eliminated metabolites often represent the detoxified part of the pesticide. The amount of metabolites in urine gives information about the magnitude of

Table 1 Overview of applied methods

Substance	Matrix	Method	Detection limit ^{ref} (µg/l)
Ethylparathion	Plasma	GC/MS	5.0 ²¹
Ethylparaaxon	Plasma	GC/MS	10 ²¹
Methylparathion	Plasma	GC/MS	5.0 ²¹
Methylparaaxon	Plasma	GC/MS	10 ²¹
p-Nitrophenol	Urine	GC/MS	1.0 ²²
Propoxur	Plasma	GC/MS	10 ²³
2-Isopropoxyphenol	Urine	HPLC	10 ²⁴
Cyfluthrin	Plasma	GC/MS	0.5 ^{25, 26}

GC/MS=gas chromatography/mass spectroscopy; HPLC=high performance liquid chromatography.

exposure and in some cases about the metabolic capacity of the subjects.^{6–11} Several studies have shown that comparable pesticide concentrations may lead to totally different biological effects.^{9,12–14} For assessing individual susceptibilities, the key enzymes essential for pesticide metabolism should be measured. Alkyl phosphates, carbamates, and pyrethroids are metabolised by esterases. An inhibition of the acetylcholinesterase activity indicates an exposure to alkyl phosphates or carbamates.¹⁵ On the other hand, this enzyme is not a marker of exposure to pyrethroid. Here, no suitable marker of effect is known yet.¹⁶

It is known that up to 30% of the population has low cholinesterase and paraoxonase activities.^{17–19} These polymorphisms are of considerable practical importance because they may lead on the one hand to an overdose of local anaesthetics, but on the other hand to a successful treatment of otherwise fatal alkyl phosphate poisoning.²⁰ The symptoms reported after carbamate and alkyl phosphate intoxication are similar, but in intoxication by carbamate, symptoms disappear much earlier and fatal developments are rare. By contrast with alkyl phosphates, after carbamate poisonings plasma and erythrocyte cholinesterase activities return to the initial level within a few hours.¹⁵

Material and methods

Data on 169 workers handling ethylparathion, 135 handling methylparathion, 233 handling propoxur, 440 handling cyfluthrin, 19 handling methylparathion and cyfluthrin, and seven handling propoxur and cyfluthrin are presented. The concentration of each pesticide in plasma and the corresponding metabolites in urine was measured. An overview of the applied methods is given in table 1. The activities of the cholinesterases in plasma and the acetylcholinesterase in erythrocytes were assessed directly by kinetic enzyme/substrate measurements as already described.²⁷ The creatinine content of the urine was measured as described previously.²⁸ The analytical methods used were subject to statistical quality control

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Table 2 Mean findings of 127 workers after an ethylparathion accident

Workers (n)	Ethylparathion (µg/l plasma)	Ethylparaoxon (µg/l plasma)	ChE inhibition (%)	AChE inhibition (%)	Symptom frequency n (%)
24	650	<10	12	9	0
39	580	10–50	84	47	4 (10)
55	530	50–100	100	71	31 (56)
9	610	>100	100	78	9 (100)

Blood was drawn 30 minutes after exposure. ChE=cholinesterase activity; AChE=erythrocyte acetylcholinesterase activity.

Findings of 42 workers routinely handling ethylparathion (25 µg/m³). Median (range) values are given. AChE=erythrocyte acetylcholinesterase activity.

in accordance with the German TRGS 410 (technical guidance for harmful substances).^{29–31} Parathion concentration in air was measured as already described.³²

Results

PARATHION

Table 2 presents findings of 127 workers after accidents with ethylparathion (data given as averages). Blood was drawn 30 minutes after the accident. There was a relation between the concentration of ethylparaoxon in plasma and cholinesterase inhibition. This was not the case for ethylparathion. The workers mentioned had increased salivation, running nose, productive cough, visual disturbances, headache, and gastrointestinal irritations. There was a correlation between the frequency of symptoms reported and the plasma concentration of ethylparaoxon. Moreover, the extent of inhibition of cholinesterase and acetylcholinesterase correlated with the frequency of symptoms.

After acute ethylparathion intoxications, ethylparathion was detectable in plasma up to 16 hours later and the metabolite p-nitrophenol

was excreted in the urine for up to 4 weeks. Cholinesterase activity regenerated at a rate of 3%–9% a day and acetylcholinesterase activity at a rate of 1%–2% a day (data not shown).¹⁵

The figure shows data (median (range)) for 42 workers routinely handling ethylparathion. This group of workers was divided into two groups (n=33 and n=9) depending on the correlation between high p-nitrophenol excretion and low inhibition of acetylcholinesterase and vice versa. Although, the level of exposure was the same for all workers (25 µg/m³ air), the concentration of p-nitrophenol in the urine varied between 190 and 410 µg/g creatinine and the acetylcholinesterase was inhibited between 2% and 49%. Sampling was performed at the end of the workshift. The lower the p-nitrophenol concentration in the urine, the more the inhibition of acetylcholinesterase. Thus, from the relation between the inhibition of erythrocyte acetylcholinesterase and the extent of p-nitrophenol excretion, indirect information on the variation of paraoxonase activity could be obtained.

PROPOXUR

Twenty four workers exposed for 4 hours to propoxur (2.0 mg/m³) were investigated (no accident occurred). No measurable inhibition of acetylcholinesterase and cholinesterase was found. The metabolite of propoxur 2-isopropoxyphenol was mainly excreted during the first 8 hours. Twenty four hours after exposure 2-isopropoxyphenol was no longer detected in the urine (data not shown).

Table 3 shows data of 135 workers exposed to propoxur after an accident. Blood was drawn 30 minutes after the intoxication. After the intoxication, the inhibition of acetylcholinesterase varied between 17% and 64%. The individual acetylcholinesterase activity was measured in the pre-employment medical examination. In 100 workers the pre-employment acetylcholinesterase activity was below the range of the published reference values (2900–4100 U/l).²⁷ The values of inhibition of acetylcholinesterase were related to the individual pre-exposure values. The absolute inhibition of acetylcholinesterase was similar in all the subjects and the different percentage was due to the different individual baseline. The symptoms lacrymation, sweating, tiredness, dizziness, and visual disturbances were only mentioned from workers whose baseline acetylcholinesterase activity was <3000 U/l. Symptoms were assessed by a medical doctor during the examination.

CYFLUTHRIN

In table 4 data of 10 workers exposed to cyfluthrin are presented. As a marker of exposure, cyfluthrin was measured in plasma. Cyfluthrin is rapidly metabolised as shown by the course. Assuming a simple first order decay of cyfluthrin in plasma, the individual half life differed widely between people (0.5–2 hours). Skin paraesthesia of the exposed area, burning, tingling, and itching sensations of the skin were reported twice. The other workers did not have any symptoms. Symptoms were assessed by a

Table 3 Mean findings of 135 workers with different individual baseline AChE activities after a propoxur accident

Workers (n)	AChE baseline values (U/l)	Propoxur (µg/l plasma)	AChE inhibition (%)	Symptom frequency n (%)
4	>4000	960	17	0
31	3000–4000	850	21	0
45	2000–3000	630	29	4 (9)
38	1000–2000	710	47	10 (26)
17	<1000	490	64	13 (76)

Blood was drawn 30 minutes after the accident; for the determination of the individual baseline AChE values blood was drawn in the pre-employment medical examination. AChE=erythrocyte acetylcholinesterase activity; reference values for AChE=2900–4100 U/l.²⁷

Table 4 Findings of 10 workers exposed to cyfluthrin

Cases	Age (y)	Type of exposure	Exposure path	Sampling time after exposure	Cyfluthrin ($\mu\text{g/l}$ plasma)	Cyfluthrin half life in plasma (min)	Symptom type (duration)
1	24	Intoxication	Oral/inhalative/dermal	35 min	189	59	Skin paraesthesia (5 h)
				3 h	34		
2	45	"	"	38 min	93	86	Skin paraesthesia (1 h)
				2 h	48		
3	38	"	"	28 min	74	47	None
				2 h	19		
4	29	"	Oral/inhalative	30 min	38	50	None
				2 h	11		
5	43	"	Oral/inhalative	25 min	21	19	None
				1 h	6		
6	31	"	Dermal	50 min	13	33	None
				2 h	3		
7	45	"	Dermal	30 min	34	20	None
				1 h	12		
8*	27	Production	Oral/inhalative/dermal	16 h	<0.5	—	None
9*	33	Filling	"	16 h	2.7	—	None
10*	56	Formulation	"	16 h	<0.5	—	None

* Investigated at the annual occupational health preventive examination. Half life of cyfluthrin in plasma is assumed to follow a simple first order decay.

Table 5 Mean findings of workers handling methylparathion, propoxur and cyfluthrin

Exposures	Workers (n)	Methylparathion ($\mu\text{g/l}$ plasma)	Propoxur ($\mu\text{g/l}$ plasma)	Cyfluthrin		AChE inhibition (%)	Clinical symptom frequency n(%)
				($\mu\text{g/l}$ plasma) *	Half life in plasma (min)		
Single substances	135	233	—	—	—	49	0 (0)
	74	—	784	—	—	53	8 (11)
	427	—	—	96	39	9	0
	3†	—	—	89	137	9	3 (0.7)
	12	269	—	139	54	47	0
Mixtures	7†	241	—	135	312	44	7 (37)
	7	—	837	145	76	51	0 (0)

Blood was drawn at the end of the workshift except for cyfluthrin exposure (30 min and 3 h after exposure).

*Concentration of cyfluthrin 30 min after exposure.

†Individual data is shown in table 6. Half life of cyfluthrin in plasma is assumed to follow a simple first order decay.

AChE=erythrocyte acetylcholinesterase activity.

medical doctor during the examination. In the first case the high initial cyfluthrin concentration may explain the symptom whereas in the second case the slow metabolic rate seems to be the predominant factor for the presence of the symptom.

Table 6 Individual data from table 5 for seven workers with mixed exposure to methylparathion and cyfluthrin compared with three workers with single exposure to cyfluthrin (all of these workers reported symptoms)

Cases	Sampling times after exposure	Methylparathion ($\mu\text{g/l}$ plasma)	Cyfluthrin ($\mu\text{g/l}$ plasma)	Cyfluthrin half life in plasma (h)	AChE inhibition (%)
1	30 min	217	155		
	4 h		101	6	46
2	30 min	257	138		
	4 h		99	7	51
3	30 min	189	171		
	4 h		144	14	37
4	30 min	314	98		
	3 h		40	2	53
5	30 min	205	120		
	3 h		55	2	31
6	30 min	234	116		
	3 h		58	3	58
7	30 min	272	147		
	3 h		76	3	34
1	30 min	—	97		
	3 h		30	1.5	9
2	30 min	—	95		
	3 h		48	2.5	9
3	30 min	—	74		
	3 h		40	2.8	12

AChE=erythrocyte acetylcholinesterase activity.

Half life of cyfluthrin in plasma is assumed to follow a simple first order decay.

MIXED EXPOSURE

Table 5 shows the frequencies of reported symptoms after different exposure scenarios. Blood was drawn at the end of the workshift. Only for cyfluthrin, was blood drawn twice (30 minutes and 3 hours after exposure). After an exposure to methylparathion, no symptoms were reported. At an average propoxur concentration of 784 $\mu\text{g/l}$ plasma, eight workers reported symptoms—such as tiredness, sweating, etc—and at an average cyfluthrin concentration of 96 $\mu\text{g/l}$ plasma, three workers reported irritations of the eyes, mouth, throat, or skin. These three workers had a slow degradation rate in common (half life: 2.3 h). Individual data for these three workers is shown in table 6. Mixed exposure to methylparathion and cyfluthrin caused skin paraesthesia in seven workers (individual data are shown in table 6), whereas there were no clinical abnormalities after simultaneous exposures to pyrethroid and carbamate. In these cases, cyfluthrin was degraded with a half life of about 1 hour.

Discussion

The aim of this study was to present some criteria for evaluating an individual exposure to pesticide. To meet this task, workers exposed (single or mixed exposure) to the pesticides methyl or ethylparathion (alkyl phosphates),

propoxur (carbamate), or cyfluthrin (pyrethroid) were investigated.

To assess exposure to alkyl phosphate—for example, parathion—paraoxon and the main metabolite p-nitrophenol should be measured in plasma and urine after exposure. Simultaneous determination of p-nitrophenol and acetylcholinesterase activity provides indirect information on the activity of the individual paraoxonase. The pathophysiological effects of alkyl phosphates are independent of their chemical structures. It is thus sufficient to measure the inhibition of activity of acetylcholinesterase in each worker to be able to estimate the associated adverse health effects. This procedure is only appropriate if the specific effect of a pesticide on short term overexposure is identical to the effect of long term low dose exposure. It was shown in the scientific literature that after alkyl phosphate poisoning the measurement of acetylcholinesterase can be used as a representative biomarker for the effects of alkyl phosphates in the neurons and as a criterion for deciding whether to use an antidote.¹⁰

For assessing exposure to carbamate—for example, propoxur—propoxur in plasma and 2-isopropoxyphenol in urine can be measured. The individual acetylcholinesterase baseline activity plays an important part in the occurrence of symptoms after intoxication. Therefore, as a marker of susceptibility the erythrocyte acetylcholinesterase should be determined in workers before they handle carbamates or alkyl phosphates.

The pyrethroid cyfluthrin is metabolised very quickly with the elimination half life for the metabolites being about 6 hours.³³ For assessing a pyrethroid exposure the corresponding metabolites are routinely measured in urine.^{14 33–35} However, several studies have shown that there is no correlation between the metabolite concentration in urine and the symptoms mentioned.³⁶ On the other hand, cyfluthrin can only be measured in plasma up to several hours after exposure. By contrast with alkyl phosphates and carbamates, pyrethroids do not inhibit the activity of cholinesterase.²⁵ It is not yet known which enzyme would be a suitable marker of pyrethroid susceptibility.^{16 25} Workers with a high rate of metabolism reported symptoms less often than subjects with a low metabolic rate. This tendency was also evident for mixed exposure (cyfluthrin and parathion). Therefore, the individual rate of cyfluthrin degradation in plasma can be considered to be an indirect indicator of enzyme activity.

Sometimes an exposure to several pesticides has to be evaluated. With a common metabolic pathway synergistic effects might be possible. However, in this study only seven out of 19 workers exposed to pyrethroid and organophosphate reported symptoms. They all had a slow metabolism. Exposure to pyrethroid and carbamate did not lead to any complaints.

Conclusions

In the assessment of exposure to pesticides, the importance of individual susceptibility has to be

taken into account. At the same dose level, individual susceptibility determines whether or not a clinical intoxication or symptoms appear. For an occupational or environmental medical assessment in workers routinely handling pesticides it is desirable not only to measure the unchanged pesticides in the blood and their metabolites in the urine, but efforts should be made to investigate the individual metabolism—for example, by directly measuring the relevant enzymes or by determining the half life of the pesticide.

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