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## Effect of Chlordimeform on Cardiovascular Function in Occupational Exposures

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**Abstract: Effect of Chlordimeform on Cardiovascular Function in Occupational Exposures: Zhijun Zhou, et al. Department of Occupational Health, Shanghai Medical University**—To understand the possible effects of an insecticide, chlordimeform, on the human cardiovascular system, this work was carried out. Pre- and post-exposure, the medical examinations, especially cardiovascular functions, were meticulously done in farmers spraying 0.125% solution of chlordimeform for 3 consecutive days and packers packing chlordimeform for one month. The exposure level was measured by means of the urinary excretion of chlordimeform and its main metabolite, 4-chlor-o-toluidine, as well as the air concentration in the work place and skin contamination by using a regional proportional sampling strategy. The alterations, though mild and diverse, were significant compared to their own pre-exposure background. The changes in heart rate, blood pressure and some EKG parameters, such as T wave, P wave, PR interval and QT interval were noticed. The cardiovascular functional changes were usual and sensitive findings in the exposed persons, and their importance in health surveillance needs to be emphasized.  
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**Key words:** Chlordimeform, Cardiovascular effect

Chlordimeform, N'-(4-chloro-o-tolyl)-N,N-dimethyl formamide, is an insecticide and acaricide used in this country since seventies (Fig. 1). The production of this chemical is now prohibited, because of its suspected carcinogenicity<sup>9</sup>, but in some places it continues to be used. Toxicological studies have shown the changes in cardiovascular function besides other adverse effects. Abrupt reduction in heart rate and systemic blood pressure, arrhythmia, and changes in ECG were observed in laboratory animals<sup>1–3</sup>. Cardiac and respiratory collapse have been reported due to its acute lethality<sup>4</sup>. The

explanation of such changes is proposed to be associated with its structure similarity to Lidocaine<sup>5, 6</sup>.

Although such adverse effects have been well anticipated from animal studies with large doses, adverse effects in human subjects after exposures have been neither studied nor reported systematically. An investigation on the such changes in farmers spraying chlordimeform and in the workers packing chlordimeform was therefore conducted.

### Materials and Methods

#### Subjects

Sixteen farmers (8 male and 8 female, aged  $33.8 \pm 6.2$  years), engaged in spraying chlordimeform (0.125% water solution) manually with knapsack sprayers in the cotton field joined this study. They worked 3–4 h per day for 3 consecutive days. The amount of chlordimeform used by each person was about 150 g/day.

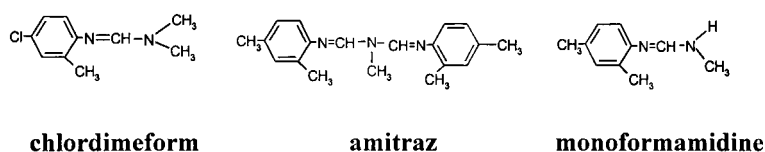
In addition, fourteen (2 male and 12 female, aged  $34.8 \pm 11.9$  years) workers packing chlordimeform were involved. The procedures included filling the glass bottles with 25% formulation through a pipe, inserting stops to the bottles, screwing the covers on tightly, putting on the labels, inserting into sheaths made of straw, transferring the bottles into boxes and sealing them. None of them had been exposed to chlordimeform until starting on this job this year.

#### Measurement of exposure

Exposure was mainly assessed by biological monitoring, routine air analysis and measurement of dermal contamination by regional proportional sampling<sup>7</sup>. The urine samples were collected systematically prior to, during and after the shift and the next morning. Air in the breathing zone of working places was collected with a personal sampler. Chlordimeform was measured by gas-chromatography with an NP detector<sup>8</sup>. Chlordimeform and its main metabolite 4-chlor-o-toluidine were measured separately. The result was expressed as total chlordimeform and calculated with following formula

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**Fig. 1.** Chemical structure of formamidines.

**Table 1.** Exposure levels of chlordimeform

Subject	Sample (unit)	Number	Mean $\pm$ SD	GM
Sprayer	Air (mg/m <sup>3</sup> )	16	0.031 $\pm$ 0.027	0.025
	Skin ( $\mu$ g/cm <sup>2</sup> )	64	4.251 $\pm$ 3.732	3.240
	Urine (mg/l)*	64	1.950 $\pm$ 1.671	1.214
Packer	Air (mg/m <sup>3</sup> )	11	0.107 $\pm$ 0.088	0.073
	Skin ( $\mu$ g/cm <sup>2</sup> )	12	2.713 $\pm$ 0.533	2.142
	Urine (mg/l)*	20	1.267 $\pm$ 1.283	0.662

\*collected at the end of the shift

**Table 2.** Changes in cardiovascular functional parameters in sprayers with short time exposure to chlordimeform

Parameter	Prior to exposure	After exposure (3 days)	Difference	Paired t values	P value
Dias. press (mmHg)	82.3 $\pm$ 13.2	81.9 $\pm$ 13.6	- 0.4 $\pm$ 1.72	0.33	0.750
Sys. press (mmHg)	112.9 $\pm$ 12.5	113.2 $\pm$ 16.4	0.3 $\pm$ 1.34	0.34	0.750
Heart rate	72.4 $\pm$ 12.1	63.9 $\pm$ 6.9*	- 8.5 $\pm$ 8.8	3.86	0.0015
P wave (mV)	971 $\pm$ 167	1065 $\pm$ 135*	94 $\pm$ 22	2.60	0.0202
P-R interval (sec.)	0.142 $\pm$ 0.024	0.152 $\pm$ 0.031	0.010 $\pm$ 0.020	1.99	0.0654
QT interval (sec.)	0.392 $\pm$ 0.040	0.441 $\pm$ 0.073*	0.049 $\pm$ 0.007	2.74	0.0153
T wave (mV)	228 $\pm$ 75	306 $\pm$ 85*	78 $\pm$ 73	4.27	0.0007

according to the pharmacokinetics of chlordimeform<sup>8)</sup>:

$$\text{Total Chlordimeform} = \text{amount of Chlordimeform} + 1.4 * \text{amount of 4-chlor-o-tolumidine}$$

#### Physical examination

Besides the general medical check-up, the functional parameters of the cardiovascular system on ECG were examined in detail for farmers prior to and after exposure, and for packers at 0, 3, 7, 15 and 30 days after exposure.

#### Statistical analysis

Values were expressed as the mean  $\pm$  standard deviation (SD). The paired t-test was used to compare the difference in some observed indices among sprayers and packers pre- and post-exposure to chlordimeform. P values less than 0.05 were considered significant.

#### Results

The air concentration, skin contamination and urinary

excretion of chlordimeform and its metabolite (expressed as total chlordimeform) are listed in Table 1.

Paired comparison of several parameters of cardiovascular function in farmers previous to and after 3 days exposure to chlordimeform showed that the difference in heart rate, height of the p wave, Q-T interval, amplitude of the T wave and PR interval were statistically significant (Table 2).

The results of longitudinal observation of the changes in cardiovascular function parameters in 22 packers are shown in Table 3. The urinary excretion of chlordimeform was increased with the increase in exposure time. Compared with that prior to exposure, the change in heart rate, Q-T interval, PR interval, systolic pressure and diastolic pressure were statistically significant. These changes were noticed after 3 days' exposure.

#### Discussion

The effects of chlordimeform on the cardiovascular

**Table 3.** Changes in cardiovascular functional parameters in packers exposed to chlordimeform

Parameter	Exposure time (day)				
	0	3	7	15	30
Urinary CDM (mg/l)	0	0.311	0.627	0.642	0.773
Sys. press (mmHg)	111 ± 8.6	105 ± 7.7*	105 ± 12.0*	102 ± 10.0*	102 ± 9.6*
Dias. Press (mmHg)	71 ± 7.1	69 ± 9.3	63 ± 10.0*	65 ± 8.2*	64 ± 9.8*
Heart rate	64.3 ± 9.9	69.6 ± 8.6*	67.2 ± 6.5	70.0 ± 9.4	71.4 ± 12.0*
P-R interval (sec.)	0.131 ± 0.0215	0.140 ± 0.018*	0.140 ± 0.021*	0.141 ± 0.020*	0.143 ± 0.032*
QT interval (sec.)	0.398 ± 0.0182	0.404 ± 0.023	0.412 ± 0.017*	0.418 ± 0.022*	0.412 ± 0.023*

\*paired t test, compared with that prior to exposure,  $p < 0.05$

system in animals have been demonstrated. The main findings were arrhythmia, bradycardia, premature contraction, atrioventricular block, P-R interval variation, increased amplitude of S and T waves and decreased amplitude of P and R waves. Chlordimeform 10 mg/kg appeared to cause these changes in rats<sup>1-3</sup>). In the acutely intoxicated persons, little attention was paid to the changes in cardiovascular effects in the early stage. At that time methemoglobinemia, hematuria and acute hemorrhagic cystitis were emphasized. But since the 1980s more and more cases have been reported to have cardiovascular changes and in some cases this was an important reason for death<sup>4</sup>).

In our study, the paired comparison test was employed to detect the possible adverse effect of chlordimeform on the cardiovascular system in two groups of occupational exposures: one of sprayers with short term exposure, and the other of packers with long term exposure. Because the paired test can control the possible confounding effects among different individuals, the present study design seems to be sensitive enough to find the adverse effects of chlordimeform on the cardiovascular system. The positive findings in two groups could be useful to confirm these effects of chlordimeform on a human population.

Based on the metabolic kinetics, it was estimated that the intake of chlordimeform by the sprayers was 0.09 mg/kg.bw/d, and by packers 0.05 mg/kg.bw/d in our study. This level was lower than the threshold dose 10 mg/kg in the rat inducing adverse effects. Under a such low level exposure, changes in cardiovascular functional parameters of sprayers and packers were still detectable and significant, indicating that probably humans are more sensitive than other species to the effect of chlordimeform on cardiovascular system.

It was noted that the changes in packers and sprayers were not exactly the same. This inconsistency could be explained by the dilation of the peripheral blood vessels exerted directly by chlordimeform. This action was prominent in the case of longer and accumulative exposure. Recovery from this effect would take a long

time, because it was detectable long after a shift<sup>5,6</sup>).

The chance of exposure to chlordimeform will be rare, since its production and use are prohibited. But we should pay attention to its homologues, amitraz and monofomamidine, which are used instead of chlordimeform, since they have similar structures and toxicological effects (Fig. 1)<sup>1,2,5</sup>).

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