ASSESSMENT OF POTENTIAL ACUTE HEALTH EFFECTS IN AGRICULTURAL WORKERS EXPOSED DURING THE APPLICATION OF CHLORDIMEFORM

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Assessment of Potential Acute Health Effects in Agricultural Workers Exposed During the Application of Chlordimeform

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Agricultural workers exposed to chlordimeform (Cdf) used as a pesticide on cotton in Imperial County, California, were monitored during the 1982 application season. Cdf metabolites were found in the urine of 132 workers and were positively correlated with the length of exposure and nature of job activity. Persons mixing and loading and engaged in miscellaneous tasks such as cleaning and maintenance of equipment had the greatest exposure. There was no evidence of urinary tract irritation by microscopic analysis of the urine, nor were significant differences found between preseason and postseason serum chemistry results. Despite the use of protective clothing and closed system transfer devices, Cdf was absorbed by workers as evidenced by urinary metabolite excretion.

Chlordimeform (Cdf), a formamidine chemical, was introduced as an insecticide in the late 1960s. Initial use was on deciduous fruits and cole crops. Later, in 1972, it was registered to control *Heliothis* species on cotton.

In 1975, employees in a Cdf packaging plant developed symptoms of urinary tract irritation, including blood in their urine.[1] This was the first indication of potential major adverse health effects.

In 1976, mice given Cdf in a long-term feeding study had an extraordinarily high incidence of malignant hemangioendotheliomas.[2] Distribution of Cdf products ceased while further evaluations were done. Cdf was reintroduced in 1980; however, California did not reregister its use.

In 1981, California cotton growers in the Imperial Valley petitioned the California Department of Food and Agriculture (CDFA) for use of Cdf due to increasing pest pressure and growing insect resistance to available chemicals. A cotton-pest abatement district was established allowing limited use of Cdf as part of a strict integrated pest management program. A medical monitoring program for exposed workers was required. During the 1982 cotton growing season, workers were monitored for exposure and potential health impacts.

Materials and Methods

Workers received specific safety training before being allowed to work with Cdf. Training included informing workers of identified hazards and proper work procedures.

An initial blood test was required to screen for liver, kidney, and pancreatic function (eg, sequential multichannel autoanalyzer) (SMA)-12 or SMAC panel). A follow-up blood test was required at the end of the application season. In addition to the blood tests, baseline urinalysis and urine cytologic examinations were required. Workers were then required to submit two urine samples for analysis each week. After three consecutive days of Cdf exposure, a sample was submitted for Cdf metabolite analysis. A second sample was submitted the next morning for urinalysis, cytology, and a second metabolite determination. Workers were instructed in "clean catch" techniques to avoid extraneous sample contamination.

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Workers were given a brief questionnaire to ascertain prior history of urinary difficulties and to identify possible confounding factors. The number of pounds of Cdf used by each employer and the number of acres treated during the application season were recorded.

Analyses were performed using the Statistical Analysis Systems.[3]

Results

A maximum of six applications at a rate of 0.25 pounds/acre were made to 375 different field locations. Workers were divided into four exposure categories: pilots; mixers/loaders; flaggers; and "other." This last category includes plane washers, mechanics, and miscellaneous helpers. Baseline urine samples were available for 118 (89.4%) workers. Table 1 shows the study population by job, sex, age, and previous Cdf exposure experience.

Questionnaire and Exposure Records

Adequate responses to the medical questionnaire were obtained from 111 workers (84.1%). There were no significant differences in alcohol, cigarette, or diet soda use among worker groups. No workers reported previous urinary tract problems.

Workers reported exposure to Cdf an average of 2.5 days per week with a mean of 7.0 hours.

Blood Chemistries

The obtaining of blood chemistries at the beginning of the season was fairly complete. At the end of the season, however, compliance was poor. Preseason blood samples were obtained from 81 workers (61.4%) and postseason samples were obtained from 25 workers (18.9%). Only 11 workers (8.3%) provided both samples to allow for pre-Cdf and post-Cdf application comparisons. Analysis of these blood samples did not reveal any significant differences.

Urinary Metabolites

On the average, individual workers were exposed less than three days per week. Therefore, urine sampling was adjusted to obtain a specimen after three consecutive exposure days or the maximum predictable exposure period each week.

More than 1,000 urine specimens were submitted for Cdf metabolite analysis. No metabolites were detected in approximately two thirds of all samples (limit of detection = 0.05 ppm). Mean metabolite concentrations are shown in Table 2. There was close agreement between concentrations in specimens collected immediately after completing work and specimens collected the following morning. Immediately after work the mean metabolite concentration was 0.12 ppm. The mean concentration for samples collected the next morning was 0.10 ppm. To determine the "worst case," the highest value of either the immediate postwork sample or the following-morning sample was used for a maximum mean concentration of 0.13 ppm.

Mean urinary metabolite concentrations were significantly higher for mixers/loaders *v* flaggers ($P < .01$). Mean concentrations were also significantly higher for "other" workers *v* pilots ($P < .001$) and flaggers ($P < .001$). Exclusion of the four highest Cdf metabolite concentrations, possibly related to isolated incidents of poor work practice, did not alter these findings. Significant differences, were not found between work groups for the mean number of exposure hours.

The highest urinary concentration recorded, 8.6 ppm, was found in a urine sample from a mixer/loader who reportedly removed his gloves while making some equipment adjustments. This concentration occurred in the immediate postwork sample with the following morning's sample having 0.82 ppm.

Simple regression analyses demonstrated urinary metabolite concentration to be significantly related ($P < .04$) with hours of exposure. For these analyses, baseline

TABLE 2
Mean Cdf Metabolite Concentrations (ppm) for the 11-Week Application Period

Work Group	Immediate Postwork			Following Morning		
	N	Mean	SD	N	Mean	SD
All groups	535	0.12	.41	572	0.10	.23
Pilots	145	0.08	.10	163	0.08	.10
Mixers/loaders	156	0.19*	.71	162	0.15†	.36
Flaggers	202	0.07	.08	213	0.07	.09
Others	32	0.25	.45	34	0.21‡	.36

* Significantly greater *v* flagger group ($P < .01$).
† Significantly greater *v* pilots ($P < .01$) and flaggers ($P < .001$).
‡ Significantly greater *v* pilots ($P < .001$) and flaggers ($P < .001$).

TABLE 1
Distribution of Study Sample by Worker, Job, and Sex* With Mean and Median Workers' Age and Years of Previous Pesticide Exposure

Work Groups	Both Sexes		Male	Female	Age		Previous Pesticide Use (yr)		Previous Cdf Use (yr)	
	N	%	N	N	Mean	Median	Mean	Median	Mean	Median
All groups	132	100.0	108	18	35.5	31	10.5	7	2.8	3
Pilots	34	25.8	34	0	45.9	50	20.3	20	3.1	3
Mixers/loaders	33	25.0	30	2	33.2	29	8.1	7	3.0	2
Flaggers	55	41.7	35	16	27.6	26	3.7	2	1.7	2
Others	10	7.5	9	0	29.5	30	9.5	11	2.5	3

* Sex was not specified for: one mixer/loader, four flaggers, and one "other."

values were included. Samples below the detectable limit were considered to be zero. The positive relationship between Cdf metabolite concentration and exposure hours is not demonstrated when analysis includes only samples with greater than the detectable limit (0.05 ppm). There was no trend for increasing urinary metabolite concentrations with progression of the application season, controlled for hours of exposure.

Urinalysis

Two pilots and one mixer/loader had minimal increases in the number of RBCs in their urine. There was no apparent relationship of this to Cdf exposure. There were no clinically significant, abnormal RBC findings in flaggers or workers categorized as "other." Outside of individual variations, cytologic examinations also were not clinically significant.

A statistically significant relationship was not found between the frequency of urinary blood or epithelial cells and number of Cdf exposure hours (χ^2, $P > .05$). A lack of association between exposure and urinary cell measures was further demonstrated with the finding that no statistically significant difference existed between urinary output of blood or epithelial cells during the week of highest exposure (based on number of hours worked) and baseline measures.

Discussion

All workers exposed to Cdf were found to have metabolites in their urine at some time during the application season. The finding of higher urinary metabolite concentrations in mixers/loaders and "others" is consistent with the nature of their work. Mixers/loaders and equipment maintenance workers are more consistently exposed to chemical concentrates compared with the other groups.

The concentration of metabolites in randomly voided urine specimens fluctuates with volume and is influenced by climatic conditions, individual health status, and physical activity. Dermal absorption and urinary excretion of Cdf was studied in a human volunteer subject (unpublished data). Metabolites appeared in urine within four hours. Metabolite concentrations in separately voided specimens varied up to sevenfold. The rate of excretion expressed as micrograms per hour had a maximum variation of 29%. Approximately 37% of the absorbed dose was accounted for by urinary excretion. Approximately 75% of the urinary excretion occurred during the first 24 hours. These findings are similar to metabolism studies in laboratory animals.[4–7]

Increasingly higher metabolite concentrations were voided by mixers/loaders, with increasing duration of exposure to Cdf. This occurred despite protective clothing and use of "closed" mixing and transfer systems. Without total urine volume, Cdf metabolite concentrations in random samples are, at best, a qualitative indication of exposure.

Although the mean concentrations of Cdf metabolites in parts per million (ppm) showed little variation between urine samples obtained immediately after a work shift *v* samples obtained the following morning, variability potential is demonstrated by the highest concentration of 8.6 ppm in an immediate postwork sample, falling to 0.82 ppm the following morning. Using the concentration of metabolites in a single urine specimen to estimate weekly absorption is inappropriate. This requires 24-hour urine collections.

Neoplasia often has an extended latency between a chemical exposure and overt cell transformation. Because weekly fluctuations are not likely, frequent urine cytologic monitoring seems unjustified. Urinary cytologic studies on an annual basis, both preapplication and postapplication seasons seem more reasonable.

Weekly urinalysis was not sensitive to the low exposures experienced in this study. Routine urinalysis would seem appropriate on a seasonal basis. Interim urinalysis during the application season, based on clinical indications or excessive exposure, should also be considered.

The intensive monitoring of pest control workers during the 1982 cotton growing season was to determine whether protective measures mandated by CDFA would be adequate in preventing excessive worker exposure. The main question facing agricultural workers is how to keep exposures to a minimum, thereby reducing risk of adverse effects. Pest control workers handle a variety of chemicals on a single work shift. There are many pest control operators and the "workplace" is spread over a wide geographic region without a fixed entry and exit point compared with factory settings. Exposure activity varies depending on pest pressures. This complicates exposure monitoring of pest control workers for specific chemicals.

In agriculture, worker monitoring is accomplished by private practice physicians. Uniformity in monitoring is not attainable. Fixed industry has access to physicians specializing in occupational medicine, and accustomed to work force monitoring. Rural physicians, on the other hand, find it necessary to incorporate worker monitoring into their private practice. This deemphasizes the occupational and workplace factors essential to effective epidemiology. The present study does not address long-term risk potential for workers regularly exposed to Cdf.

Conclusions

1. Careful handling of Cdf and wearing protective clothing and equipment minimizes absorption of Cdf, but does not eliminate it.

2. Mixers/loaders and miscellaneous workers are the most likely to encounter measurable exposure.

3. Monitoring urine from workers for Cdf metabolites on a weekly basis is qualitative at best.

4. Frequent urinalysis and cytologic studies are not

sensitive measures for preventive health monitoring of low-level exposure.

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