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The effect of the 14-day agricultural restricted entry interval on azinphosmethyl exposures in a group of apple thinners in Washington state

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Abstract

We examined the effect of the 14-day agricultural restricted entry period on absorbed pesticide doses in a group of twenty experienced apple thinners. Thinners entered orchards 1–49 days following azinphosmethyl applications. Urine samples ($n = 296$) collected throughout the thinning season were analyzed for the three dialkylphosphate metabolites of azinphosmethyl to estimate absorbed daily doses. Separate dose distributions were created for samples collected when the interval was <14 days, or 14 days or more; geometric mean doses for these two categories differed by a factor of two (42 and 19 μg/kg/day, respectively; $p < 0.0001$). Dose estimates were compared to US Environmental Protection Agency and California EPA regulatory guidance values for occupational azinphosmethyl risk. None of the doses exceeded the U.S. EPA NOAEL (560 μg/kg/day), but nearly all had a margin of exposure of less than 100. Addition of a 10-fold uncertainty factor to California EPAs NOAEL produced a guidance value of 75 μg/kg/day. Only 2.4% of the doses exceeded this value for re-entry intervals 14 days or more, while 27% exceeded the value for re-entry intervals <14 days. We conclude that the 14-day restricted entry interval provides an appropriate level of worker health protection under the field conditions studied.

Keywords: Re-entry interval; Exposure; Fieldworker; Apple thinner; Azinphosmethyl; Organophosphorus pesticides

1. Introduction

Pesticide residues on foliage and other surfaces after applications represent a hazard for agricultural re-entry workers (Spear, 1991). Workers whose jobs involve extensive hand contact with treated plants, such as thinners and harvesters, can receive substantial dermal exposures, and are the subject of occupational health concern. Safe entry intervals, known formally in the United States as restricted entry intervals (REIs), have served as a primary risk management strategy for such workers for the past 30 years (Knaak et al., 2002; Maddy, 1974; Serat, 1973). The U.S. EPA Worker Protection Standard, first promulgated in 1992, established 48 h restricted entry intervals for Toxicity I and II category compounds (high and moderate toxicity for skin, eye, or systemic exposures), including the organophosphorus insecticide azinphosmethyl (*O*,*O*-dimethyl *S*-[4[oxo-1,2,3-benzotriazin-3(4*H*)-yl]-methyl phosphorodithioate) (USEPA, 1992). In 1998 U.S. EPA extended the azinphosmethyl REI from 2 to 14 days based on a risk analysis conducted during product re-registration (USEPA, 1999).

Risk assessments for agricultural re-entry workers are developed from models that combine measurements of pesticide residues on crop surfaces (dislodgeable foliar residues, or DFRs) with estimates of chemical transfer from the crop surfaces to the worker's skin (USEPA, 1999). The exposure and risk estimates from such models have not generally been tested in observational studies, nor has biological monitoring been employed routinely to estimate exposures and risks in agricultural re-entry workers (Fenske, 1997).

The University of Washington Field Research and Consultation Group conducted a study of apple thinner

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exposure to azinphosmethyl in Washington State apple orchards during the 1994 growing season (Simcox et al., 1999). Urine samples were collected from workers on a regular basis. Data from this study afford an opportunity to evaluate the impact of changing from a 2-day to a 14-day REI through estimation of worker daily doses from biological monitoring. The purpose of this paper is to compare worker dose levels on days less than 14 days post-application with dose levels 14 or more days post-application, and to examine the regulatory mplications of this analysis for apple thinners exposed to azinphosmethyl.

2. Methods

Data for this analysis were derived from a study of 20 experienced apple thinners in central Washington State in 1994 (Simcox et al., 1999). Exposure data were collected in three apple orchards during the six-week thinning season. All orchards were treated with azinphosmethyl periodically to control the codling moth. Apple thinning is a task in which workers remove a number of immature fruit from trees to encourage proper growth of the remaining fruit. Thinning requires substantial contact with fruit, leaves, and branches.

2.1. Pesticide applications and foliar residues

Azinphosmethyl application rates were determined from the pesticide application spray records maintained by the orchard manager. Most orchards in Washington State, including those in the current study, are divided into geographic blocks, each of which receives individually scheduled pesticide applications. For the orchards in the current study, pesticide spray dates were recorded for each block.

Azinphosmethyl residue levels on plant surfaces were measured through leaf punch samples (40 leaf punches per sample) collected periodically during the study (Simcox et al., 1999). Two or three samples were collected at a time, and mean dislodgeable foliar residue (DFR) levels were calculated from these samples. Doran et al. (in press) present a complete description of pesticide spray dates and leaf punch collection dates for each of the orchards.

For each orchard, mean DFR values were plotted against the number of days since the most recent pesticide application to the trees from which the samples were collected (Doran et al., in press). Regression analyses were then used to generate site-specific decay curves and equations describing the relationships between DFR and days post-application. These equations were used to calculate site-specific DFR values for re-entry intervals of 2, 7, 14, and 21 days at each orchard. These values were then compared to U.S. EPA estimates of DFR levels resulting from azinphosmethyl applications under current regulatory guidelines (USEPA, 1999).

2.2. Post-application worker location

Block-specific application information was coupled with daily worker location to calculate the length of the re-entry interval for each worker on each study day. Daily worker location was determined by on-site monitoring of work crews by research staff. The day of pesticide application in an individual block was recorded as day 0. Thus, the length of the re-entry interval for any worker thinning in that block on the next day was considered to be 1 day, and so on. Workers visited between one and four blocks per day. On days when thinning occurred in more than one block, re-entry intervals were calculated assuming that the worker had spent the entire day in the block with the most recent pesticide application. This assumption affected less than 10% of the data, and results were unchanged when these data were excluded.

2.3. Biological monitoring procedures

Spot urine samples were collected from each worker on each study day. Detailed sample collection, storage, and transport procedures were described in the original paper (Simcox et al., 1999). Samples from the original study were included in this analysis if the following criteria were met: (1) the sample was collected at the end of a day of active thinning in an azinphosmethyl-treated orchard block, (2) field records indicated the specific orchard block for the worker on that day, and (3) spray records were available to document the application day for the orchard block. Samples were analyzed for the three dialkylphosphate (DAP) metabolites of azinphosmethyl—dimethylphosphate (DMP), dimethylthiophosphate (DMTP), and dimethyldithiophosphate (DMDTP)—by the method described by Moate et al. (1999). Samples with concentrations below the limit of detection (LOD) were assumed to contain concentrations equal to one-half the LOD (LOD = 0.04 μg/ml). Metabolite concentrations were corrected for average recovery efficiencies (DMP = 39%; DMTP = 80%; DMDTP = 62%).

2.4. Dose estimates

Absorbed daily doses were estimated according to the following equation:

$$\mathrm{ADD} = [\mathrm{DAP}_{\mathrm{dimethyl}}] \cdot \mathrm{Vol_u} \cdot \mathrm{MW_{azm}} \cdot \mathrm{CF_u} \cdot 1/\mathrm{BW}. \quad (1)$$

In this equation, ADD is the absorbed daily dose in units of μg/kg/day. $[\mathrm{DAP}_{\mathrm{dimethyl}}]$ is the total dimethyl dialkylphosphate molar concentration in the urine sample (μmol/L), calculated as the sum of the molar concentrations of the three dimethyl DAP metabolites. Vol_u is the daily urinary excretion volume (0.919 L/day), derived from a fieldworker study in California that reported an average of 919 ml of urine excreted in 24 h (SD = 406 ml) for 300 samples (Spencer et al., 1993). MW_{azm} is the molecular weight of azinphosmethyl, 317 g/mol (or μg/μmol). CF_u is the correction factor (1/.7) for incomplete excretion of azinphosmethyl in urine, derived from a human volunteer study (Feldman and Maibach, 1974), and 1/BW is the adjustment for body weight (kg) of the individual worker. Body weight data collected during field study.

In this analysis the spot urine samples were assumed to represent steady state conditions, and azinphosmethyl exposure during apple thinning was assumed to be the only source of the dimethyl DAP metabolites.

2.5. Statistical analysis procedures

Absorbed daily dose estimates were normally distributed following log-transformation. Analysis of variance (ANOVA) techniques were used to compare dose distributions calculated from urine samples collected on days when re-entry intervals were either less than 14 days or 14 days or more. Dose estimates were also analyzed for the individual workers based on re-entry day: an average dose was calculated from all samples for each worker, and this value was compared to the average of the doses from samples collected when the re-entry interval exceeded 13 days using a paired *t* test. The percent difference between these two values was also calculated as follows:

$$\%\text{difference} = ((\text{Mean}_{\text{total}} - \text{Mean}_{\geqslant 14\text{ days}})/\text{Mean}_{\text{total}}) \times 100\%, \quad (2)$$

where $\text{Mean}_{\text{total}}$ is the arithmetic mean of all doses for an individual worker (μg/kg/day), and $\text{Mean}_{\geqslant 14\text{ days}}$ is the arithmetic mean of that worker's doses on days when his or her re-entry interval exceeded 13 days (μg/kg/day). All data were stored in Microsoft Excel and analyses were conducted in STATA (STATA 6, College Station, TX).

2.6. Regulatory guidance values

The U.S. EPA has reported a no observed adverse effect level (NOAEL) of 0.56 mg/kg/day based on a one-week study of dermal exposure in rats (U.S. EPA, 2001). This value is the basis of its short-term occupational azinphosmethyl risk assessments. Typically, the U.S. EPA adds uncertainty factors to NOAELs to establish acceptable levels of risk. For occupational exposures, a margin of exposure (MOE) approach is employed, where the MOE is defined as the NOAEL divided by the daily dose. For a majority of worker exposure scenarios, the target MOE is 100, incorporating a 10-fold uncertainty factor each for intra- and inter-species differences (U.S. EPA, 2001).

The California Environmental Protection Agency (Cal EPA) has conducted an independent assessment of worker risk based on a registrant-sponsored human volunteer NOAEL study, and has reported a NOAEL of 0.75 mg/kg/day (USEPA, 2001). In this case the target MOE is 10, incorporating an uncertainty factor for intra-species differences only. Apple thinner dose estimates derived from the Washington State study were compared to three regulatory guidance values: (1) the U.S. EPA NOAEL (560 μg/kg/day); (2) the U.S. EPA NOAEL with an MOE of 100 (5.6 μg/kg/day); and (3) the Cal EPA NOAEL with an MOE of 10 (75 μg/kg/day).

3. Results

3.1. Pesticide applications and foliar residues

Azinphosmethyl application rates and measured dislodgeable foliar residue levels were compared to current regulations and estimates of corresponding residue levels (Table 1). Under present regulations, the maximum allowable azinphosmethyl application rate for apples is 1.5 lbs of active ingredient per treated acre (lbs a.i./acre) (U.S. EPA, 2001). In 1994 the maximum application rate allowed was 2 lbs a.i./acre. Application rates at orchard sites 1 and 3 ranged from 0.875 to 1 lbs a.i./acre, falling within current regulatory limits. However, at orchard site 2 azinphosmethyl was applied at 2 lbs a.i./acre. U.S. EPA models predict DFR values ranging from 3.1 (2 days post-application) to 1.4 μg/cm^2 (21 days post-application) for an application rate of 2 lbs a.i./acre (USEPA, 1999). The DFR levels measured at Site 2 in this study were substantially lower than these estimates (Table 1). DFR values at Sites 1 and 3 in our study were higher than values predicted by the U.S. EPA model at 2 days post-application, but not on subsequent days. The U.S. EPA report did not include confidence intervals for

Table 1
Extrapolated DFR levels (μg/cm^2) from the current study and U.S. EPA estimated DFR levels for a range of application rates (lbs a.i./acre)

	Application rate (lbs a.i./acre)	Days post-application			
		2	7	14	21
EPA scenarios					
1	1	1.56	1.26	0.93	0.7
2[a]	1.5	2.34	1.9	1.4	1.1
3	2	3.12	2.5	2.2	1.4
Current study					
Site 1	0.875–1	2.41	1.56	0.84	0.46
Site 2	2	1.31	1.11	0.89	0.71
Site 3	1	3.64	1.72	0.60	0.21

[a] The current regulatory limit for azinphosmethyl application is 1.5 lbs a.i./acre.

its model estimates, but it is likely that such confidence intervals would be relatively broad, and that the DFR levels in our study would fall within a range of expected values. These findings indicate that the exposure potential at these worksites is comparable to that experienced by re-entry workers today.

3.2. Dose estimates

A total of 296 urine samples met the inclusion criteria for this analysis; i.e., they were collected during active thinning when worker location and application history were fully documented. The geometric mean dose estimate based on the total dimethyl DAP concentration for all samples was 27 μg/kg/day (geometric SD = 2.4), and ranged from 3.5 to 310 μg/kg/day (Table 2).

The interval between the most recent azinphosmethyl application in an orchard block and active thinning in that block ranged from 1 to 49 days. Pesticide dose distributions calculated by number of days post-application (<14 days, or ⩾14 days) are presented in Table 2. Daily dose estimates were significantly higher for workers on days when the re-entry interval was less than 14 days (42 vs. 19 μg/kg/day; ANOVA, $p < 0.0001$).

Absorbed daily dose estimates are plotted against re-entry intervals in Fig. 1. Regression analysis produced the log-normal equation: $y = 108 - 60.8(\log(x))$, with $r^2 = 0.26$. Thus, this model indicates that 26% of the variability in ADD is explained by the length of the re-entry interval. Fig. 2 shows the average absorbed daily dose estimates by weeks post-application, where one week post-application includes the day of application (0–6 days), two weeks post-application includes days 7–13, and so on. Figs. 1 and 2 demonstrate that doses drop sharply over time, and that doses appear to plateau after two weeks.

Average doses (arithmetic mean) for individual workers over the entire sampling period ranged from 20 to 88 μg/kg/day (Table 3). These doses were significantly higher than average worker dose estimates calculated only from urine samples collected on days when the re-entry length was greater than 13 days (paired t test; $p < 0.0001$). Average dose estimates decreased by an average of 38%, with decreases ranging from 3 to 77%.

Table 2
Dose estimates (μg/kg/day) by interval between pesticide application and active thinning

	<14 days	⩾14 days	Total
N	131	165	296
Geometric mean	42*	19*	27
Geometric SD	2.5	2.0	2.4
Range	3.6–310	3.5–130	3.5–310
Percentiles			
10th	13	8	9
25th	22	12	15
50th	45	19	25
75th	79	29	46
90th	140	42	92

* $p < 0.0001$, ANOVA.

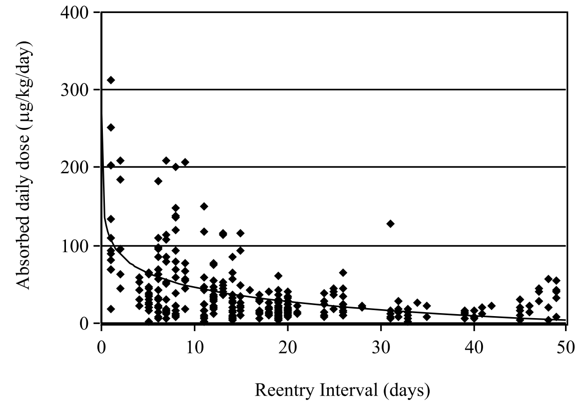

Fig. 1. Absorbed daily doses (μg/kg/day) vs. number of days since the most recent pesticide application in the block where thinning occurred ($y = 108 - 61(\log(x))$: $r^2 = 0.26$).

3.3. Comparison with regulatory guidance values

Doses estimates were compared to three regulatory guidance values in order to assess risk (Table 4). None of the doses exceeded the U.S. EPAs NOAEL of 560 μg/kg/day. Conversely, very few doses were low enough to yield an MOE of 100: when re-entry was <14 days, 98% of the doses exceeded 5.6 μg/kg/day; when re-entry was ⩾14 days, 96% exceeded this value.

The MOEs for doses at the 50th percentile were 12 and 29 for re-entry periods <14 days and ⩾14 days, respectively. The MOEs for doses at the 90th percentile were 4 and 13 for re-entry periods <14 days and ⩾14 days, respectively.

When an MOE of 10 was added to the California EPA NOAEL of 7.5 μg/kg/day to yield a guidance value

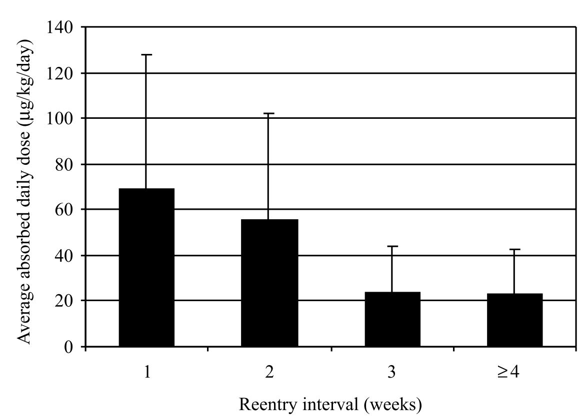

Fig. 2. Average absorbed daily dose estimates (μg/kg/day) by weeks post-application. N sizes are as follows: 1 week = 56, 2 weeks = 75, 3 weeks = 93, ⩾4 weeks = 72. Error bars indicate 1 SD.

Table 3
Arithmetic mean absorbed daily doses (μg/kg/day) by individual worker estimated from samples collected on all days, and on days when the worker's re-entry interval was ⩾14 days

Worker	*N* (all samples)	Mean dose[a] (all samples) (μg/kg/day)	SD (all samples) (μg/kg/day)	*N* (⩾14 days)	Mean dose[a] (⩾14 days) (μg/kg/day)	SD (⩾14 days) (μg/kg/day)	Percent decrease (%)[b]
1	21	29	15	18	26	14	10
2	21	22	14	18	21	13	7
3	17	40	34	9	33	39	19
4	15	49	48	8	26	11	46
5	16	70	67	9	35	34	50
6	16	37	30	9	23	18	37
7	15	81	81	7	30	19	63
8	16	43	48	6	22	4.8	48
9	8	39	35	2	17	9.2	58
10	14	24	21	7	12	4.5	51
11	12	58	58	3	14	3.1	77
12	18	54	61	7	26	10	52
13	17	28	29	6	13	7.6	54
14	18	32	34	8	19	10	42
15	16	20	14	14	19	13	6
16	12	19	16	11	18	16	3
17	13	26	11	12	25	11	3
18	15	33	31	4	11	6.1	66
19	8	88	57	4	61	32	30
20	8	50	28	3	25	11	49
Total	296			165		Mean	38

[a] Arithmetic mean dose. Mean doses of all samples are significantly higher than mean doses of samples collected when REIs exceed 13 days (paired t test, $p < 0.0001$).

[b] Percent decrease = {(Mean total dose − mean dose ⩾14 days)/mean total dose} × 100%. Percent decrease represents the percentage by which the dose would decrease if the re-entry interval had been restricted to ⩾14 days.

Table 4
Percent of dose estimates exceeding three benchmark doses (μg/kg/day)

	Dose	Re-entry interval (%)	
	(μg/kg/day)	<14 days	⩾14 days
U.S. EPA NOAEL	560	0.0	0.0
CalEPA, MOE = 10	75	27	2.4
U.S. EPA NOAEL, MOE = 100	5.6	98	96

of 75 μg/kg/day, just 4 of the 165 doses (2.4%) for re-entry intervals greater than or equal to 14 days exceeded this value. In contrast, 36 of the 131 doses (27%) for less than 14-day re-entry were above 75 μg/kg/day.

4. Discussion

The principal purpose of this study was to employ biological monitoring data to evaluate the impact of a 14-day restricted entry interval on azinphosmethyl exposures among apple thinners. We chose to convert dialkylphosphate metabolite measurements to azinphosmethyl dose estimates so that the values reported here could be compared directly with several regulatory guidance values. Had we used the dialkylphosphate metabolite concentrations rather than dose estimates for the REI evaluation, results would have been similar, since nearly all of the inputs in Eq. (1) are constants (worker body weight is the exception).

We found that the 14-day REI reduced worker doses by approximately 2-fold, whether looking at daily doses as independent measurements, or examining the average doses of individual workers. We also found that a change in the REI from 2 to 14 days resulted in most worker doses falling below a regulatory guideline that employs a NOAEL value coupled with a 10-fold uncertainty factor, as is the case for the California EPA. None of the worker doses exceeded the U.S. EPA NOAEL established in rats, nor the NOAEL derived from human volunteer studies that was the basis for the California EPA guidance value. Nearly all worker doses produced a margin of exposure value less than 100. From a practical standpoint, a 14-day re-entry interval appears to be a reasonable regulatory requirement, since doses were significantly higher when re-entry intervals were less than two weeks. Fig. 2 shows that while dose estimates dropped sharply in the first two weeks, they appeared to plateau at longer intervals.

Several limitations to this analysis can be noted. First, we calculated dose estimates from spot urine samples. It would have been preferable to collect 24-h urine samples, but such procedures were not possible under these field conditions. Spot urine sampling likely increased the random error in the dose estimates, though this error may have been reduced by collecting samples at generally the same time each day (the end of the workshift). Second, we used a simple deterministic model to calculate dose from urinary metabolite levels. Probabilistic methods would be preferable, but were not practical for this analysis. Third, the model used does not incorporate the pharmacokinetics of azinphosmethyl. A human volunteer study of dermal exposures indicated that peak excretion of azinphosmethyl metabolites in urine occurs approximately 24–48 h after exposure (Feldman and Maibach, 1974), whereas in this study we assumed that the urine sample collected after work was representative of the current day's exposure. To address this issue, we also analyzed these data on the assumption that the metabolite concentrations in the urine samples were the results of exposure the day prior to collection. Results of the analysis were unchanged. We therefore conclude that our categorization of exposures according to re-entry day is a reasonable approach, and that the results reported here would likely be obtained even if a more sophisticated pharmacokinetic analysis were used.

A fourth limitation is related to the use of dimethyl dialkylphosphate metabolites as biomarkers of azinphosmethyl exposure during apple thinning. It is possible that some of the metabolites measured in workers' urine were the result of dietary exposures, or of OP pesticide exposure outside of thinning. To address the issue of dietary exposure we examined metabolites levels in these same workers either pre- or post-thinning, as well as metabolite levels in a concurrent control population (Simcox et al., 1999). For the most part these levels were at or below the limit of detection, so it is unlikely that dietary exposure contributed substantially to the metabolite levels observed. We do know that some of the workers continued to work after the cessation of apple thinning, either as landscapers or cherry pickers. It is possible that some of the metabolites measured in their urine could have been the result of exposure to pesticides in these work settings. On the other hand, it is known that workers carry azinphosmethyl residues home from work, and that residues can be found in their vehicles (Curl et al., 2002; Lu et al., 2000). Such para-occupational exposures may have contributed to metabolite levels, but they can be considered the direct result of apple thinning activities.

A fifth limitation is related to the analytical procedures employed in this study. The quantification of the dimethylphosphate metabolite of azinphosmethyl proved problematic for these samples. The recovery of this analyte from spiked samples was only 39%, and quality assurance samples run during the analysis indicated that the accuracy of DMP measurements was lower than for the other dimethyl dialkylphosphate metabolites. We included the DMP values in order to obtain the best estimate of absorbed dose, but their inclusion adds to the uncertainty of these dose estimates.

In regard to pesticide application procedures, we noted that the maximum permissible rate of azinphosmethyl application has changed since 1994 (2 lbs a.i./acre reduced to 1.5 lbs a.i./acre). However, pesticide application rates exceeded present regulatory guidelines at only one orchard in the current study, and DFR levels fell within the range expected from current applications at that orchard (Table 1). While application rates at the two other orchards did not exceed existing regulations, DFR levels at these orchards were higher immediately following application than is predicted by the U.S. EPA's current model. This may be due to the fact that several pesticide applications occurred at sites 1 and 3 throughout the study period, while only one application occurred at site 2 (Doran et al., in press). Other research has monitored DFR levels in peach orchards four to nine weeks following azinphosmethyl application (McCurdy et al., 1994; Schneider et al., 1994). Schneider et al. (1994) report DFR levels as high as 1.72 $\mu g/cm^2$ seven to nine weeks post-application with an application rate of 1.5 lbs a.i /acre. This value exceeds the U.S. EPA estimate for two weeks post-spray at this application rate. These findings suggest that foliar residues from pesticide applications can be highly variable, and that in some situations U.S. EPA models may underestimate DFR levels in orchards immediately following azinphosmethyl application.

The limitations cited above indicate that the data used in this analysis have components of variability and uncertainty that cannot be fully quantified. Nonetheless, the statistical results of the analysis indicate large differences that are unlikely to be due to chance.

Biological monitoring data have not generally been employed to evaluate worker exposures for regulatory purposes. Instead, regulatory agencies have relied on predictive models generated from quasi-experimental studies that may constrain exposure variability and produce biased exposure estimates (Fenske and Teschke, 1995). The apple thinner study described was observational in design, and therefore captured the routine behaviors of workers under their normal working conditions. Such studies provide an important means of testing the risk assessment models developed from more scripted exposure scenarios, and provide a means to evaluate the impact of risk management strategies such as the restricted entry interval.

5. Conclusion

This study examined the effect of the 14-day restricted entry interval on absorbed daily pesticide dose in a group of 20 apple thinners. Workers entered orchards 1 to 49 days following azinphosmethyl applications, and dose estimates calculated from urine samples collected from these workers demonstrated that absorbed pesticide dose decreased quickly with increasing re-entry intervals. We found that the 14-day REI reduced worker doses by approximately 2-fold, whether looking at daily doses as independent measurements, or examining the average doses of individual workers. This longer REI also resulted in the reduction of almost all worker doses to below a regulatory guideline that employs a NOAEL value coupled with a 10-fold uncertainty factor. From a practical standpoint, a 14-day re-entry interval appears to be a reasonable regulatory requirement, since doses were significantly higher when re-entry intervals were less than two weeks.

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