Report to the California Legislature

California's Cholinesterase Test Results Reporting and the Medical Supervision Program

Department of Pesticide Regulation
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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This report and appendices are available online at
http://www.cdpr.ca.gov/docs/legbills/reports/reg/regulatory.htm

EXECUTIVE SUMMARY

California's Medical Supervision Program ("Program") is designed to protect agricultural workers who regularly handle organophosphate and carbamate pesticides (OP/CB) (Title 3, California Code of Regulations, section 6728). The Program requires employers to contract with a medical supervisor to monitor the blood cholinesterase levels of these workers. The pesticides covered by the Program inhibit cholinesterase, an enzyme essential for proper neurological function. The California Department of Pesticide Regulation (DPR) is responsible for overall administration of the Program, with assistance from the Office of Environmental Health Hazard Assessment (OEHHA) in outreach and education of medical supervisors, and from the California Department of Public Health (CDPH) in approving laboratories performing cholinesterase testing.

The Program was established in 1974 when the use of cholinesterase-inhibiting pesticides was very prevalent in California agriculture. Pesticide Use Report data from 1995 to the present shows the use of all cholinesterase-inhibiting pesticides has declined nearly three-fourths. However, according to the most recent pesticide use data available, OP/CB use from 2008-2013 has remained between 4.1 to 5.1 million pounds per year. The Program has been reviewed on a number of occasions and updated to improve worker protection. It was most recently augmented in January 2011 when Health and Safety Code (HSC) section 105206 was implemented, requiring the reporting of laboratory cholinesterase test results to DPR. Under HSC §105206, DPR and OEHHA, in consultation with CDPH, are to collect and analyze cholinesterase test results and prepare a report for the Legislature by December 31, 2015. Unless extended by the legislature, the laboratory reporting and analysis will sunset on January 1, 2017. This report summarizes the review of the Program and test results, and presents findings and recommendations about the utility of laboratory reporting and the overall effectiveness of the Program.

From 2011-2013, DPR received over 90,000 cholinesterase test results from the reporting laboratories. A majority of the reported tests appeared to have been ordered for clinical reasons unrelated to the Program. Criteria were established to identify individuals undergoing cholinesterase tests who were likely in the Program. Spatial analysis of test results for this population further confirmed that these were likely workers in the Program as location of tests corresponded to regions of high OP/CB use. In addition to evaluating the pattern of cholinesterase test results, a medical supervisor survey (based on physicians ordering cholinesterase tests), inspection of growers in high-use OP/CB areas, and in-person visits with medical supervisors, augmented our knowledge of the overall effectiveness of the Program. The following provides findings and recommendations based on the analysis of the cholinesterase tests received and survey results.

Findings

DPR and OEHHA used multiple approaches to evaluate the effectiveness of the medical supervision program for illness surveillance and prevention and found that:

- Overall, the Program appears effective in protecting agricultural workers handling cholinesterase-inhibiting pesticides.
- Most individuals identified as part of the Program did not have depressed cholinesterase activity levels and when depressions occurred, most workers' activity levels recovered rapidly.
- Most medical supervisors who regularly ordered cholinesterase testing were aware of their responsibilities.
- Over half of the growers surveyed were familiar with the Program but had varying levels of understanding of specific requirements.
- Improvements in the electronic reporting system, further outreach to participants, and coordination across agencies responsible for the Program have significant potential to improve efficiency and performance.

On evaluation of the utility of laboratory-based reporting of cholinesterase testing for illness surveillance and prevention, DPR and OEHHA found that based on the data reported from 2011-2013, the utility of the data analysis is hampered by the inclusion of thousands of records from individuals who are not in the Program, and by missing data on the purpose of the test.

- Current laboratory-based reporting has some challenges such as laboratories reporting all cholinesterase tests regardless of their relevance to the Program; deficiencies in the electronic reporting system; and failure of some medical supervisors to communicate the purpose of the test to the laboratories.
- Certain assumptions were therefore made in order to evaluate the data. These assumptions introduced uncertainties in our findings and conclusions.
- DPR and OEHHA are working with the laboratories to improve their reporting, and conducting outreach to medical supervisors to emphasize the importance of including the purpose of the test on requisition forms. DPR and OEHHA plan to analyze the 2014-2016 data and provide an update to the Secretary of CalEPA by December 31, 2017, and thereafter, if reporting of cholinesterase test results is continued.

Recommendations and Future Directions

While the reporting requirements need to be improved to provide more targeted and accurate information, our review indicates the Program appears to be successful and current ongoing activities will help enhance its effectiveness including:

DPR/OEHHA - Recommendations	Lead Agencies/ *Participants*	Legislation Required
• Cholinesterase reporting should continue at least through December 31, 2018 in order to obtain additional data with clearer information on the purpose of the test and to allow further evaluation of the Program.	Leads: DPR, OEHHA *Participant: CDPH*	Yes
• Transferring cholinesterase reporting responsibilities from the laboratories to the medical supervisors may ultimately be a more efficient way to implement the Program.	Leads: DPR, OEHHA	Yes

DPR/OEHHA – Future Directions	Lead Agencies/ *Participants*	Legislation Required
• Enhance outreach and training to increase understanding of the Program by the medical supervisors, employers, laboratories, and the County Agricultural Commissioner (CAC) staff.		No
❖ Develop materials and conduct outreach efforts for the employers on their roles and responsibilities under the Program, such as, record retention of employees' cholinesterase test results and medical supervisor recommendations.	Lead: DPR *Participant: CAC*	
❖ Promote and expand the medical supervision training, emphasizing the provisions of HSC §105206 and continuing in-person visits to the medical supervisors.	Lead: OEHHA	
❖ Conduct focused headquarters inspections of Pest Control Operators similar to those that DPR conducted with growers.	Lead: DPR *Participant: CAC*	
❖ Increase the County Agricultural Commissioners' awareness of the Program; include a module on the Program during Enforcement Training.	Lead: DPR *Participant: CAC*	
❖ Coordinate with CDPH on outreach efforts to the laboratories. Develop clear requisition slips that require indication of the purpose of the cholinesterase test.	Lead: CDPH *Participant: DPR*	
• Continue coordination between DPR, OEHHA and CDPH to enhance the effectiveness of the Program.		No
❖ Improve reporting of information specified under HSC §105206(b).	Lead: DPR *Participants: CDPH, OEHHA*	
❖ Develop a list of currently active medical supervisors and update it regularly.	Lead: OEHHA	

I. INTRODUCTION AND BACKGROUND

A. Introduction

California's medical supervision program ("Program") monitors the activity of a key enzyme, cholinesterase (ChE) in the blood of agricultural workers who regularly handle Toxicity Categories I and II organophosphate (OP) and N-methyl carbamate (CB) pesticides (CCR Title 3, section 6728; see Appendix A1). ChE is critical for the normal function of the nervous system, and even transient reductions in ChE activity level can lead to toxic symptoms that are characteristic of these two pesticide classes.

This report was prepared in accordance with the provisions of California Health and Safety Code section 105206 (Appendix A2) to evaluate the effectiveness of the Program and the utility of laboratory-based reporting of ChE test results for pesticide-related illness surveillance and prevention. The report summarizes a larger body of work that was conducted to evaluate the Program. Details of these efforts can be found in the Appendices.

This report is a collaborative effort between the Department of Pesticide Regulation (DPR) and the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the California Department of Public Health (CDPH).

In addition to an evaluation of the reporting process and analysis of the ChE test results, we conducted supplementary activities to better evaluate the Program, such as: 1) surveying medical supervisors by mail, 2) conducting in-person visits with medical supervisors, and 3) inspecting employment records of a select group of employers in areas of high OP/CB use.

B. Background

California Medical Supervision Program

The Program was enacted in 1974 when OPs and CBs were some of the most commonly used pesticides in California agriculture. Their use has tapered off, however, according to the most recent pesticide use data available, OPs/CBs use from 2008-2013 has remained between 4.1 to 5.1 million pounds per year.

Both OPs and CBs work as a pesticide by inhibiting ChE, which breaks down the neurotransmitter acetylcholine, leading to the death of an insect. OPs and CBs can also affect humans by inhibiting ChE, and at high exposure levels cause a variety of acute symptoms of neurological poisoning. The acute symptoms, which include vomiting, diarrhea, and increased respiratory secretions, can sometimes mimic other illnesses, and sometimes people can be sub-clinically affected without showing major acute symptoms. Due to the potential for sub-clinical effects or misdiagnosis of the acute effects, it can be useful to test for the depression of ChE in order to identify potential overexposure.

Because it is difficult to directly measure the levels of ChE in the nervous system, red blood cell (RBC) ChE and plasma ChE are tested instead. RBC ChE is the same ChE found in the nervous system and is thought to better reflect the ChE enzyme in the nervous system.

Furthermore, different ChE-inhibiting pesticides have different binding affinities for either RBC or plasma ChE. For these reasons, it is useful to test for the depression of ChE in both RBC and plasma in order to identify potential overexposure. Additionally, individuals have varying ChE levels. Therefore, it is important for each individual to have a baseline value before they handle OP/CBs. An individual's ChE depression is more accurately detected when compared to their own baseline value. A more detailed discussion of OPs and CBs, their mode of action and human health effects can be found in Appendix A3.

The goal of the California Medical Supervision Program is to protect pesticide handlers from excessive exposure to OPs and CBs. It requires employers to contract with a licensed physician as a "medical supervisor" to periodically test the ChE level of workers who regularly handle these pesticides (Figure 1). For a more detailed description of the structure and requirements of the Program, refer to Appendix B1.

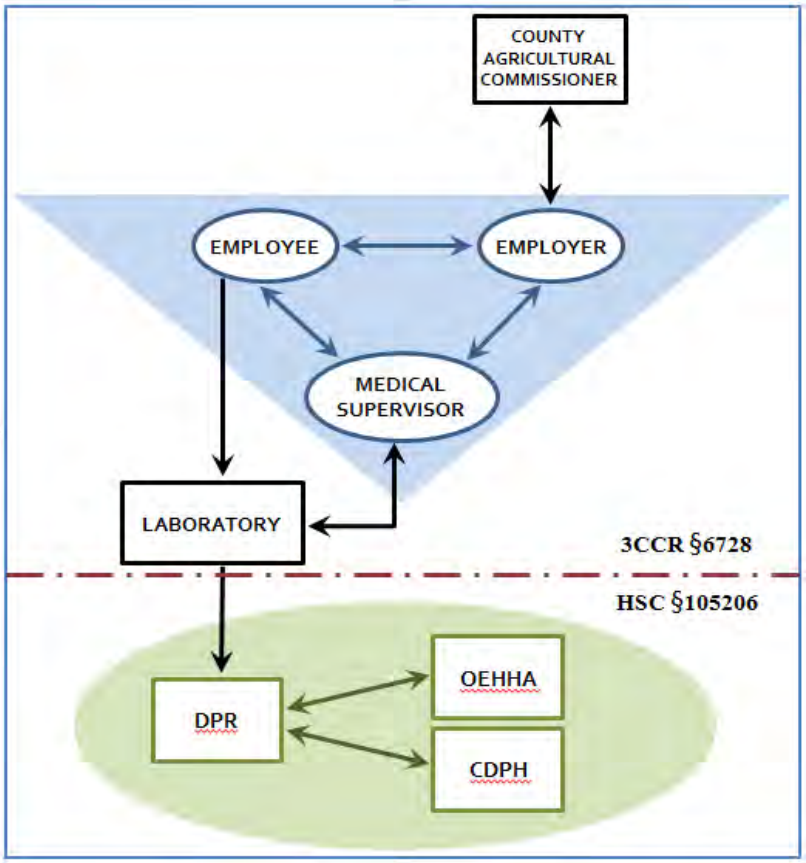

Figure 1: *Framework of the Medical Supervision Program.*

Since its inception, the Program has been reviewed on a number of occasions. These reviews have resulted in a number of recommendations that were adopted including: raising the "action threshold," changing the definition of workers that need to be under the Program, establishing the employee's individual ChE baseline value, using a specific analytical method to measure ChE levels, and specifying the frequency of testing. Additional changes, such as requiring employers to inform the medical supervisor of an employee's pesticide exposure status to determine the "purpose of test," and clearer guidelines for enforcement of the Program's requirements could improve the program. A more detailed description of the reviews, recommendations and implementation status can be found in Appendix A4.

Under the Program, employers who have an employee that meets the minimum regulatory requirement of regularly handling[1] OPs and CBs shall have a contract with a medical supervisor. The medical supervisor shall establish baseline values of RBC and plasma ChE during non-exposure periods for each employee, and periodically measure ChE activity levels while the worker handles OPs/CBs. If either RBC or plasma ChE is depressed below 80% of the baseline (that is, more than 20% depression from the baseline), it triggers an action response (Table 1). If a worker's ChE activity level drops more than 30% from the RBC baseline or more than 40% from the plasma baseline, he/she shall be removed from the exposure source. Following a worker's removal, his/her RBC and plasma ChE activity level must be monitored, and he/she is not allowed to work with or handle OPs and CBs until RBC and plasma ChE activity levels return to at least 80% of the baseline. The various RBC and plasma ChE depression levels discussed are called *action levels*, and they serve as a guide to protect workers from excessive exposure to OPs/CBs.

Table 1: *Action levels of RBC and plasma ChE and the associated actions required under the medical supervision program.*

% Depression from baseline	RBC ChE	Plasma ChE
≥20%	Prompt retesting of employee and evaluation of work practices by employer	
≥30%	Immediate removal of employee from further exposure	--
≥40%	--	Immediate removal of employee from further exposure

Health and Safety Code section 105206

In 2011, Health and Safety Code §105206 added a laboratory-based reporting requirement to evaluate the Program. Medical supervisors are now required to indicate the purpose of the test on the laboratory requisition slip. In addition, they shall ensure that the person tested receives a copy of the ChE test results, and any recommendations, within 14 days of receiving the results. Furthermore, the laboratories that perform ChE testing on human blood drawn in California as part of the Program are now required to report the test results, purpose of the test, specific information pertaining to the employee, his/her employer, the medical supervisor and the laboratory performing the analysis to DPR. ChE tests performed in response to a suspected or known exposure to ChE inhibitors that may or may not have resulted in illness are also included in the reporting requirement. Specific information on the required data elements that are to be included in a submitted report by the laboratories can be found in Appendix B2.

[1] "Regularly handle" is defined as mixing, loading, or applying pesticides for more than six days in a 30-day period (3CCR §6000).

Under HSC §105206 DPR shall share information from the ChE reports with OEHHA and CDPH on an ongoing basis. All information reported pursuant to this section shall be confidential, as provided in HSC §100330, except that OEHHA, DPR and CDPH may share the information with the appropriate county agricultural commissioner and local health officer for the purpose of surveillance, case management, investigation, environmental remediation, or abatement.

Upon completion of a report to the Legislature on December 31, 2015, laboratory reporting of ChE test results will continue until this reporting requirement sunsets on January 1, 2017. If the Legislature continues the reporting requirement beyond the sunset date, then laboratory analysis and data analysis will continue into 2017 and beyond.

II. FINDINGS

From 2011 to 2013, we received 91,093 ChE test results, representing 18,039 unique individuals, from the six laboratories approved by CDPH to perform ChE testing for occupational health surveillance. The data had to be manually reviewed to: identify and remove duplicates, correct formatting errors, identify missing information, and correct typographical errors. In addition to ChE tests ordered by medical supervisors under the Program, there are other reasons for ordering ChE tests such as pre-operative testing, Alzheimer's drug monitoring, liver disease screening, and aging research studies. Laboratories are not able to distinguish tests conducted under the Program from those that are performed for other reasons and therefore report all results to DPR. Extensive work had to be done to identify the results of tests that were conducted under the Program. We applied criteria to exclude individuals who were not likely part of the Program. For example, test results were excluded if the age of the

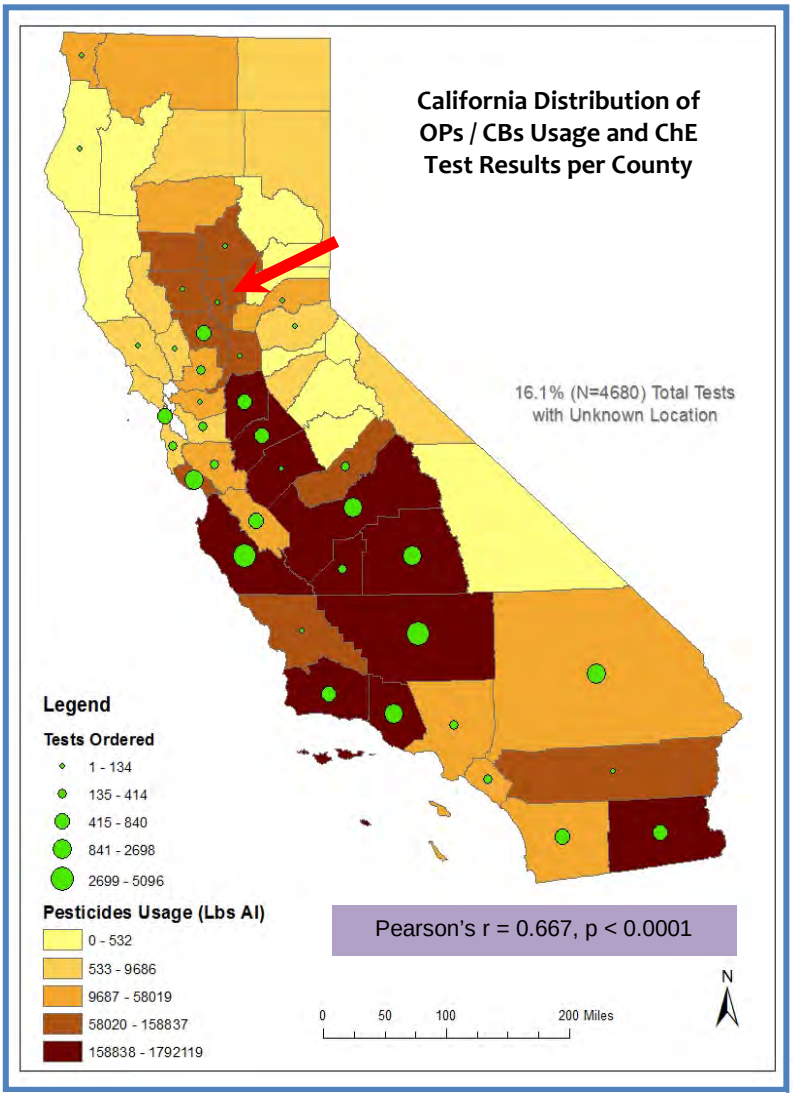

Figure 2: *Geographic distribution of OPs/CBs types I and II use (2011 – 2013) and number of ChE test results by county.*

patient was greater than 75 or less than 16; or if the test results were for RBC or plasma ChE but not both, as required under the Program. We analyzed the test results, relying on assumptions and inferences. In particular, the reports often contained incomplete or missing information related to the purpose of the test, making it necessary for us to make assumptions about which test results represented 'baseline' values, and which test results may have been post-application. Depending on how we assigned 'baseline' values, the frequency of potential ChE depression varied somewhat. To supplement the ChE test results analysis, we also conducted: 1) a medical supervisor survey by mail, 2) in-person visits with medical supervisors, and 3) on-site growers' headquarters inspections. See Appendices C, D, E and F for details on these activities.

Participation of Workers in the Program

After data review and exclusion of test results that were unlikely part of the Program, geographic analysis showed that there is a good correlation, as indicated by the Pearson's r value[2] (r = 0.667), between the number of test results by county and OP/CB use (Figure 2). The majority of the ChE test results were from the central region[3] of California which had the highest OP/CB usage. In addition, over half of the medical supervisors identified in the survey and from the in-person visits were from this area (Figures 3 and 4). Furthermore, the majority of the medical supervisors identified in the survey specialize in Occupational Medicine (Figure 4). Compared to other specialties, occupational medicine specialists are more likely to see patients for work-related agricultural cases, including workers who handle OPs/CBs.

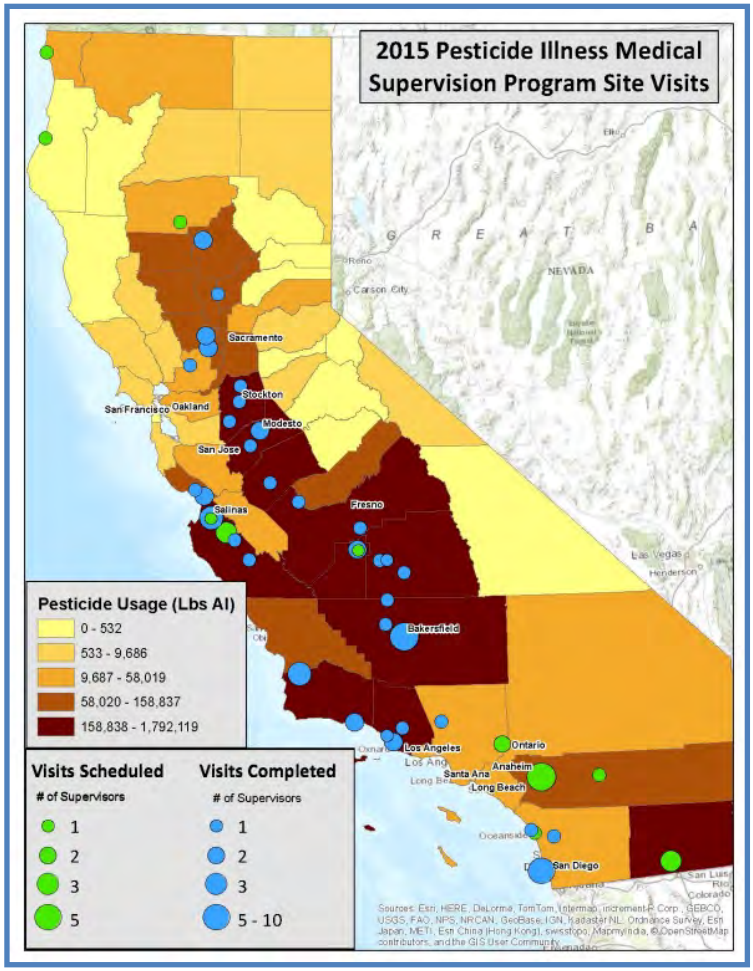

Figure 3: *Geographic distribution of OPs/CBs types I and II used (2011 – 2013), and location and number of in-person visits. (Total number of physicians visited, n=60)*

[2] Pearson's correlation coefficient (r) is a statistical measure of the strength of an association between two variables. The closer the r is to 1 or -1, the stronger the linear correlation. A value of 0 denotes no linear correlation.

[3] Based on DPR's Enforcement Branch's county distribution. Refer to Figure F1 in Appendix F.

However, geographic analysis also showed that there were very few ChE test results from some regions with relatively high OP/CB use (e.g., northern California counties represented by the red arrow in Figure 2). One possible explanation is that individuals in these high OP/CB use areas might not regularly handle these pesticides. This is supported by the focused headquarters inspection results which revealed that growers in this region did not have employees who regularly handled OPs/CBs (Figure 5). These growers stated that they limit their employees handling of OPs/CBs to six days or less in a 30-day period, although this could not be confirmed by pesticide use records. Additionally, three contracted medical supervisors interviewed in this region stated they had not seen patients who were under the Program so they had not submitted ChE test orders in the last few years.

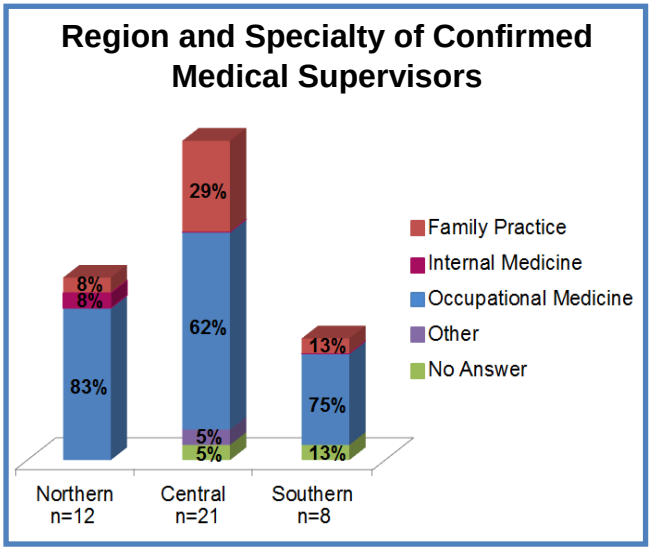

Figure 4: *Region and specialty of confirmed medical supervisors. (Total number of medical supervisors who responded to the survey, n=41.)*

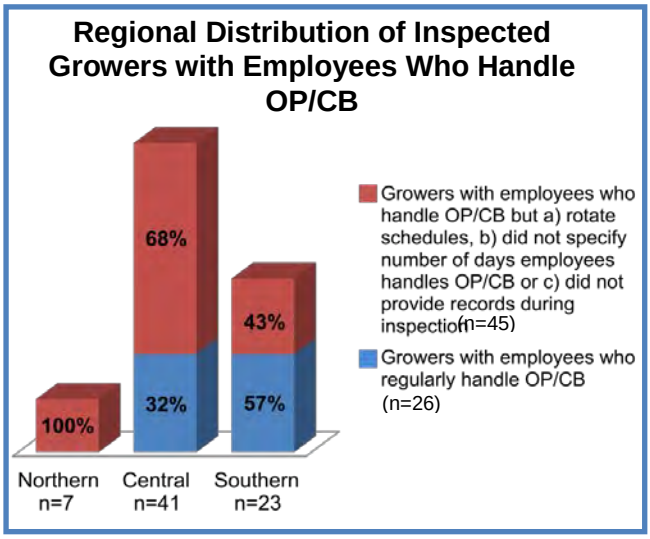

Figure 5: *Number of growers with employees who handle OP/CB by region. "Regularly handle" is defined as handling pesticides more than six days in any 30-day period.*

Patterns of ChE Activity Level and Frequency of ChE Depressions

There were 1,338 individuals who were tested numerous times over the three-year period, allowing a time course evaluation of ChE activity levels. Figure 6 represents five different patterns of individual ChE activity levels. These results illustrate variations in the frequency,

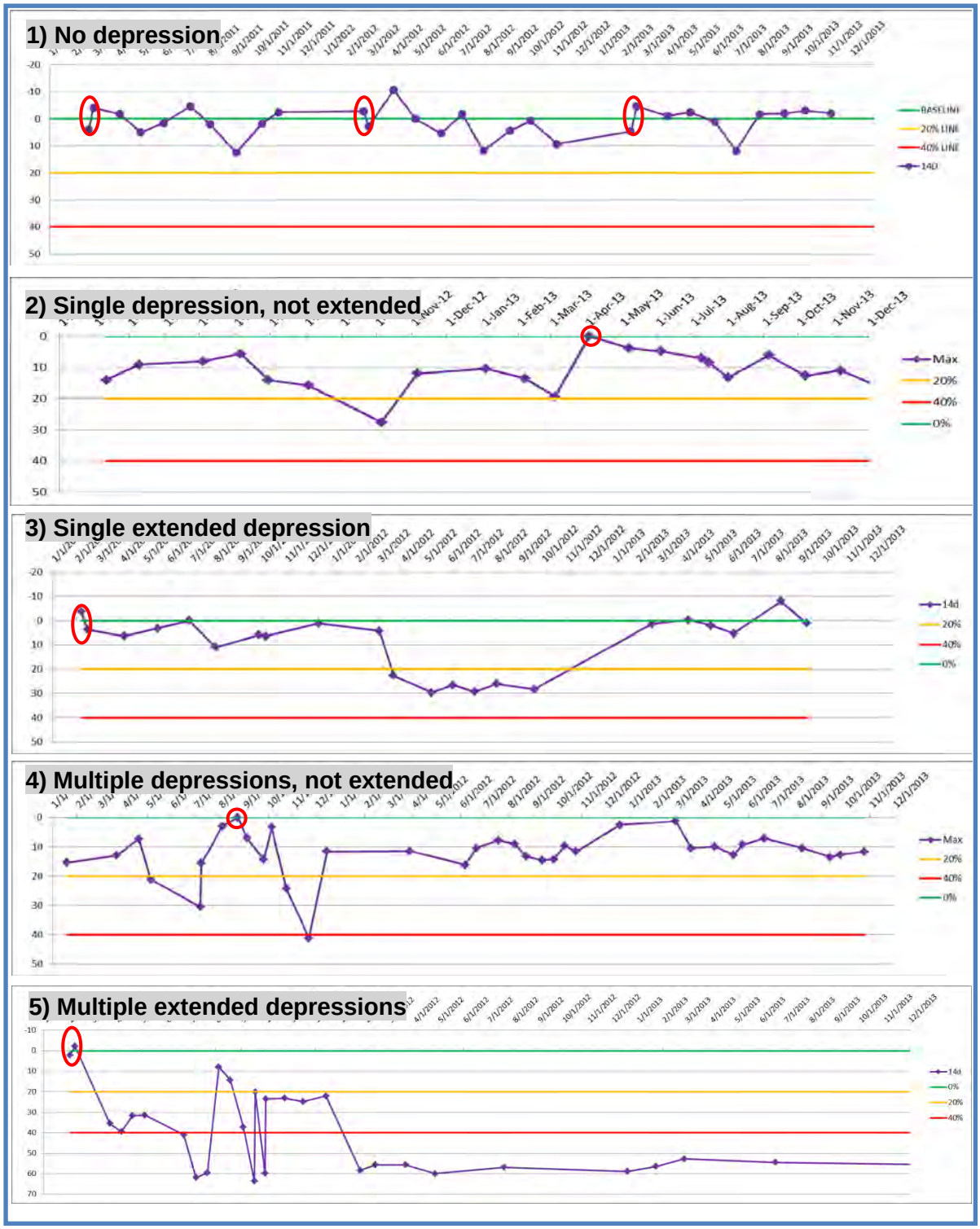

Figure 6: *Individual test results that represent different plasma ChE activity level patterns.* ***1)*** *no depression that exceeded action levels,* ***2)*** *single depression with prompt return to >80% of baseline level,* ***3)*** *single depression with slow return,* ***4)*** *multiple depressions with prompt return,* ***5)*** *multiple depressions with slow or no return. Y axis is percent depression from baseline. Green line represents the baseline of the individual. Red circled values are baselines.*

magnitude and duration of ChE depression that meet or exceed the various action levels (<80% of baseline estimate).

Of the 1,338 individuals who had multiple test results, about half (n=663) had a fairly clear 14-day baseline ChE value (that is, two blood samples collected 3-14 days apart during the non-spraying season) established according to the *Guidelines for Physicians*. These were identified as the most reliable baseline data ("Approach 1"). However, 14-day baseline estimates were not available for the rest of the population (n=675). In order to include these individuals in our analysis of depression frequencies, a more conservative approach ("Approach 2") was used. Approach 2 used each individual's highest ChE test result from 2011-2013 as an estimated baseline. Since a maximum ChE value could always be identified, Approach 2 was utilized in the analysis of all 1,338 individuals who had multiple test results. However, Approach 2 likely overestimates the percent of individuals with ChE depression.

We estimated the degree of over-estimation of baseline value introduced using Approach 2. The 14-day baseline estimate derived using Approach 1 was compared with the maximum value estimate derived using Approach 2 for those individuals who had both baseline values available. On average, the Approach 2 estimate of baseline was 12% higher than the estimate derived using Approach 1. Therefore, Approach 2 may overestimate the number of depressions that exceed one of the action levels.

It is worth noting that the need to use these two approaches to baseline determination arose because the test purpose was seldom provided with the ChE test reports. Consequently, baseline ChE values were inferred solely from the data.

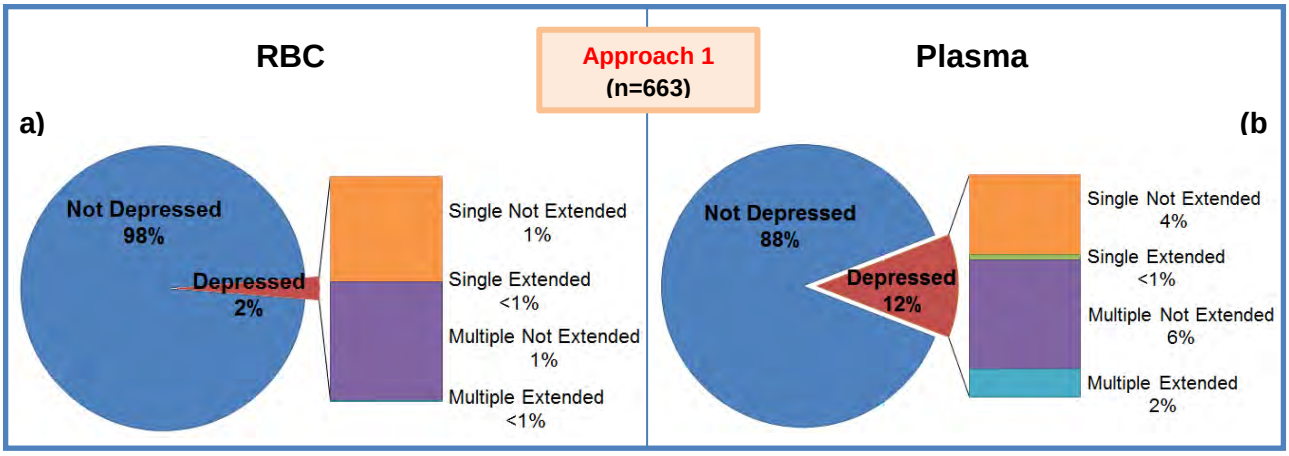

Figure 7: *Overall distribution of individuals (n=663) by type of ChE depression (single, multiple, extended or not extended) using* ***Approach 1*** *(14-day estimate of ChE baseline): RBC ChE (**a**) and plasma ChE (**b**).*

Of the 663 individuals that were analyzed using Approach 1, most had no ChE depression that exceeded an action level (98% based on analysis of RBC ChE results, 88% based on plasma ChE results) (Figure 7). This is consistent with findings from in-person visits with medical supervisors, who stated that they rarely saw cases with ChE depressions that required re-assessment of pesticide handling activities or removal of an employee from the workplace. Of the individuals with ChE depressions, we identified those who experienced depressions multiple times, and those whose depressions persisted for an extended period

of time[4]. Nearly all these depressions did not persist for an extended period of time ("not extended"), indicating prompt return to acceptable ChE activity levels (>80% of baseline value) and suggesting that action had been taken to reduce further exposure. However, some individuals experienced multiple ChE depressions (<2% based on RBC ChE results, 8% based on plasma ChE results). This suggests that, for these individuals, effective intervention to alter the work practices that led to exposure did not occur.

ChE activity levels in all 1,338 individuals were also evaluated using Approach 2 which, as discussed earlier, increases the likelihood that one or more of the action levels will be exceeded. As expected, the percentages of total ChE depressions, single and multiple depressions, and short-term and extended depressions were all higher when Approach 2 was used to identify baseline ChE value. For example, when Approach 2 was used, the percentage of individuals that had potentially experienced significant ChE depression increased to 13% based on analysis of RBC ChE results and 37% based on plasma ChE results.

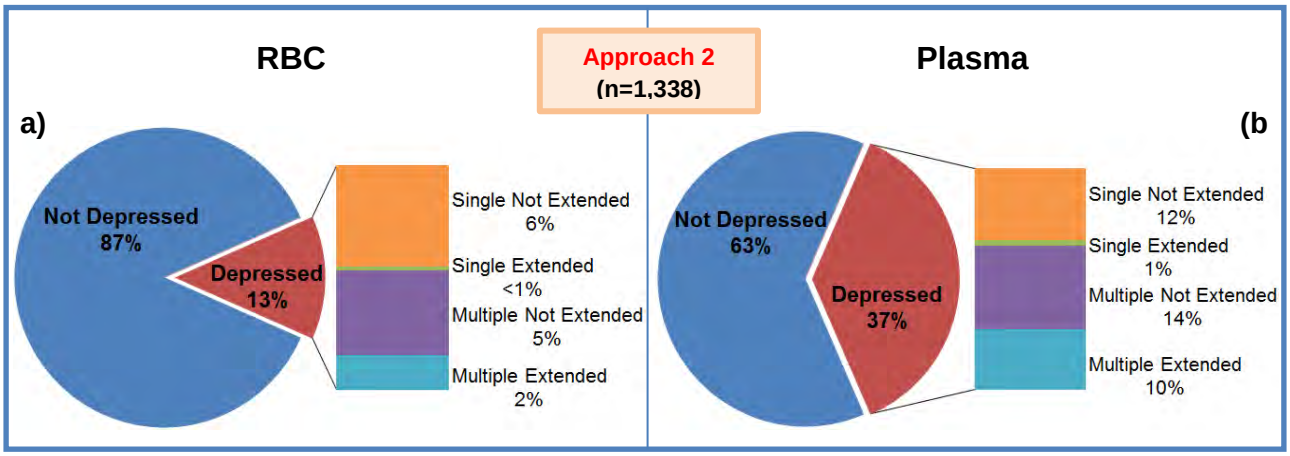

Figure 8: *Overall distribution of individuals (n=1,338) by type of ChE depression (single, multiple, extended or not extended) using* ***Approach 2*** *(maximum value estimate of ChE baseline): RBC ChE (**a**) and plasma ChE (**b**).*

We believe that the 14-day baseline is a better indicator of the "true" baseline because (1) it is consistent with the preferred method for baseline determination, as described in the *Guidelines for Physicians*, (2) two samples collected within a 14-day period provides additional support for the presumption that an individual participates in the Program, and (3) the second test result provides confirmation of the first baseline result. The maximum value baselines were on average 12% higher than the 14-day baselines. The use of the maximum value baseline, in effect, makes it more likely that an individual's test result will meet or exceed one or more action level. Therefore, even though Approach 2 includes data from all the individuals participating in the Program, the results obtained using Approach 1 (Figure 7) probably provides a more accurate reflection of the Program's effectiveness.

[4] At least three consecutive ChE test results that exceeded an action level within three months.

Level of Awareness of the Program by Medical Supervisors and Growers

The medical supervisor survey and in-person visits showed that most medical supervisors were aware of their responsibilities in the Program, and that there was communication between them and the growers. Feedback from the in-person visits indicated that medical supervisors who frequently ordered ChE tests were very knowledgeable about their responsibilities, and were more aware of Program changes and updates. Conversely, medical supervisors who ordered ChE tests less frequently tended to be less knowledgeable of the Program (Figure 9).

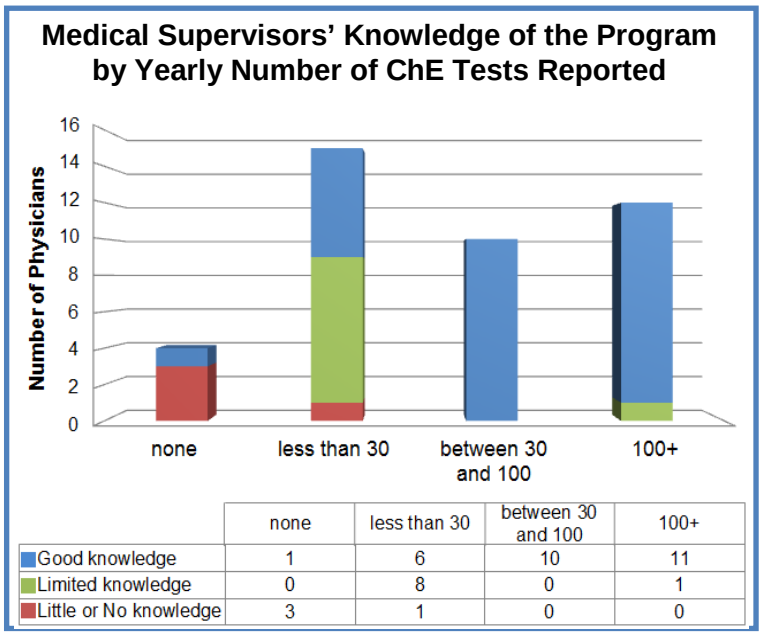

Figure 9: *Level of medical supervisors' understanding of the Program based on the number of ChE tests they reported ordering within the last 3 years. (n=41)*

A medical supervisor was judged to have "good knowledge" or "limited knowledge" of the Program based on the interviewer's overall impression. In making this judgment, the interviewer considered the medical supervisor's (1) knowledge of Program's overall structure , (2) familiarity with the Guidelines for Physicians, (3) understanding of the medical supervisor's responsibilities, and (4) familiarity with Program updates (HSC §105206).

Although medical supervisors are not required to track the handling activities of individual workers, the medical supervisor survey indicated 44% were informed of the number of days an employee handled OPs/CBs while an equal proportion were not informed (Appendix D, Figure D4). This information was mostly provided by the employer and to some extent the employees themselves.

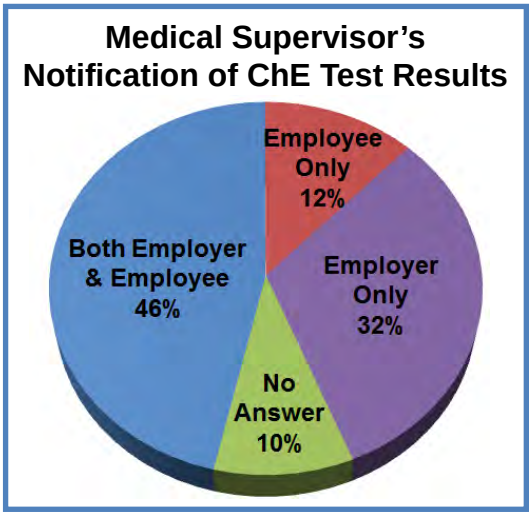

Figure 10: *Person notified by medical supervisor of the ChE test results. (Total number of medical supervisors who responded to the survey, n=41.)*

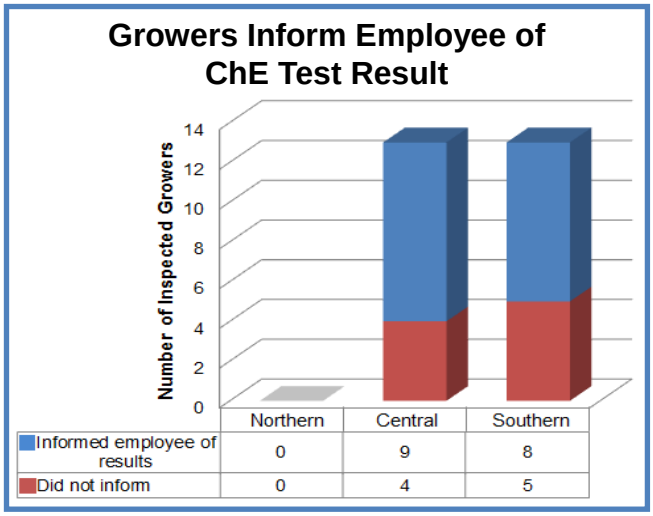

Figure 11: *Number of growers in the Program who informed employee of his/her ChE test results. (n=26)*

The medical supervisor survey indicated a majority of the medical supervisors notified the employee, the employer or both, of the employee's ChE test results (Figure 10). However, we do not know the extent to which the information provided was a copy of the actual laboratory report or a summary from the medical supervisor. We also do not know if the employee received this information within 14 days[5]. Some medical supervisors informed only the employer, and it is possible that these results were then relayed to the employee. This is supported by the information from the focused headquarters inspections that revealed two-thirds of the growers informed their employees of ChE test results (Figure 11). In instances where the ChE test results reached or exceeded action levels, over three-quarters of medical supervisors stated that they recommended an appropriate action for the employer to take (Figure 12). Although not a requirement of medical supervisors, it is good medical practice for physicians to follow up and confirm that employers modified their employees' work activities as recommended.

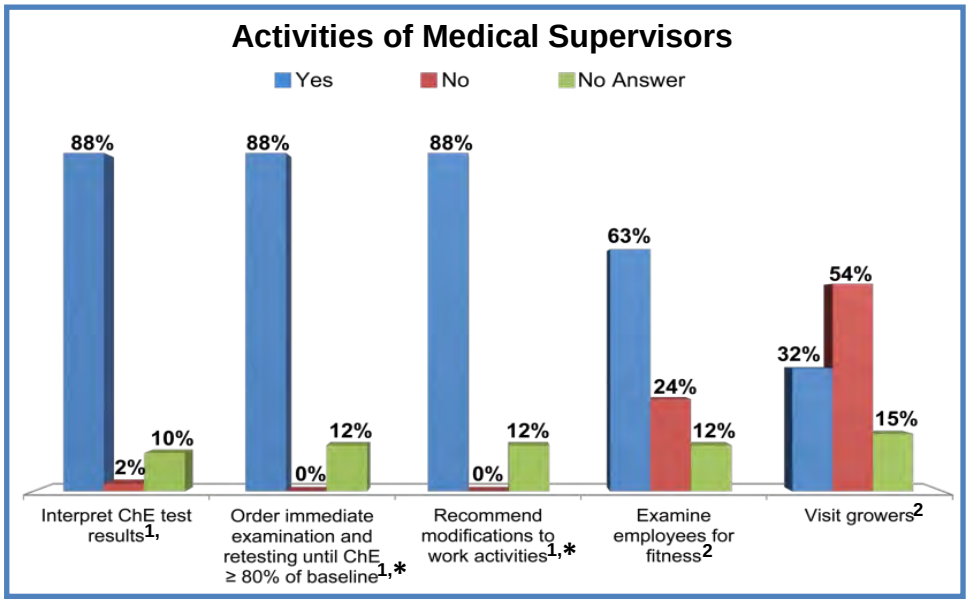

Figure 12: *Program required activities (1) of medical supervisors and those that are recommended in the Guidelines for Physicians (2). (Total number of medical supervisors who responded to the survey, n=41.)*
** - When employee's ChE test results reach or exceed action level.*

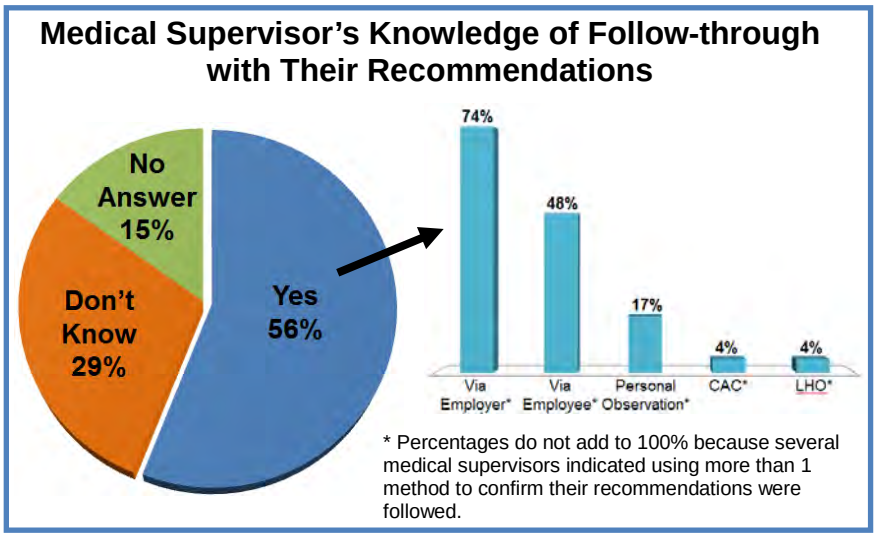

Figure 13: *Knowledge of follow-through with recommendations and method by which medical supervisors learned their recommendations were followed. (Total number of medical supervisors who responded to the survey, n=41.) CAC: County Agricultural Commissioner. LHO: Local Health Officer.*

[5] HSC §105206(c): medical supervisor ordering the test shall ensure that the person tested receives a copy of the ChE test results and any recommendations from the medical supervisor within 14 days of the medical supervisor receiving the result.

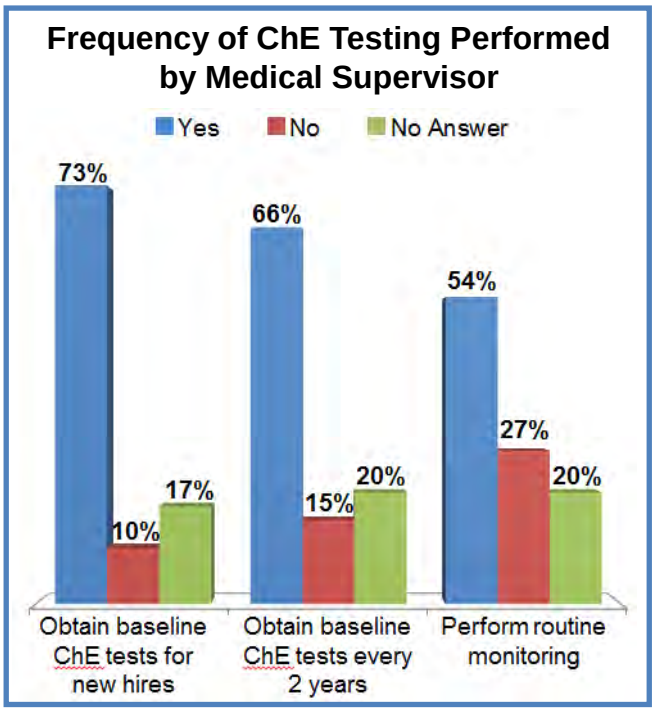

Figure 14: *Frequency in which medical supervisors obtain baseline for new hires, verify baselines and perform routine monitoring. (Total number of medical supervisors who responded to the survey, n=41.)*

According to the medical supervisor survey, 56% knew that their recommendations were followed, mostly communicated through the employer (Figure 13). In addition, a third of the medical supervisors stated they have visited an employee's worksite as recommended in the *Guidelines for Physicians* (Figure 12).

Half of the medical supervisors surveyed stated they perform ChE testing for routine monitoring[6] (Figure 14). Less than a third did not and we do not know their reasons. Several medical supervisors interviewed in 2015 stated they no longer see patients who require ChE monitoring under the Program. This information is consistent with one of the primary findings of the focused headquarters inspections in which growers stated they managed their employees' schedules so that each employee would not have to handle OPs/CBs for more than six days in a 30-day period (Figure 5).

From the focused headquarters inspections, we found that over half of the growers were familiar with the Program but had varying levels of understanding of its specific requirements (Figure 15). A majority of the growers who are in the Program were aware of their responsibilities. Over half of these growers kept a copy of the medical supervisor agreement at their headquarters, with two-thirds of them providing a copy to the CAC. The same proportion of growers retained records[7] as required (Figure 16).

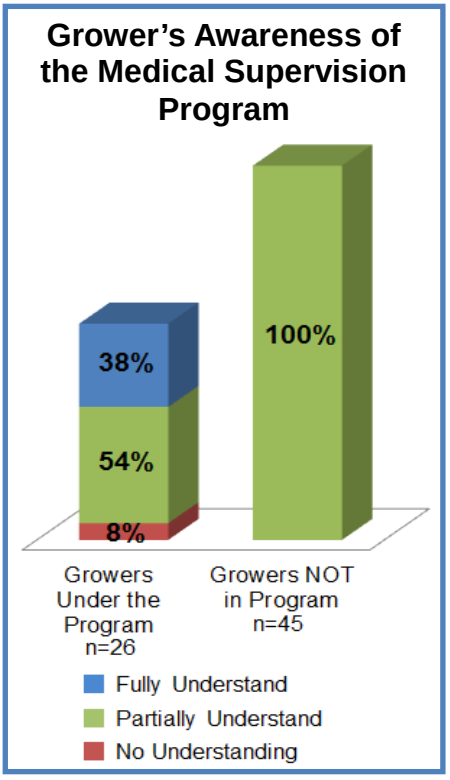

Figure 15: *Grower's level of understanding of the Program. (n=71)*

[6] 3CCR §6728(c)(2)(B) and (C): After three tests at 30-day intervals, further periodic monitoring shall be at intervals specified in writing by the medical supervisor. Where the medical supervisor has made no written recommendation for continued periodic monitoring, the testing shall be 60 days.

[7] 3CCR §6728(c)(3) states employer shall keep a record of the agreement with medical supervisor, OP/CB use records, all recommendations received from the medical supervisor, and all employee's ChE test results for 3 years.

Nearly all of the growers in the Program (n=25, 96%) received test results that did not reach action levels and, hence, did not require an investigation or modification of their employees' work practices. This is consistent with our analysis of the ChE test results which showed a low frequency of depression (Figures 7 and 8).

One grower indicated that he had an employee whose ChE activity level was below the laboratory's normal reference range. Having been informed of this by the medical supervisor, the employer voluntarily removed him from handling OPs/CBs (Appendix F, Figure F8). We do not know this employee's handling history or previous ChE test results. The grower took action based solely on this employee's single ChE test result.

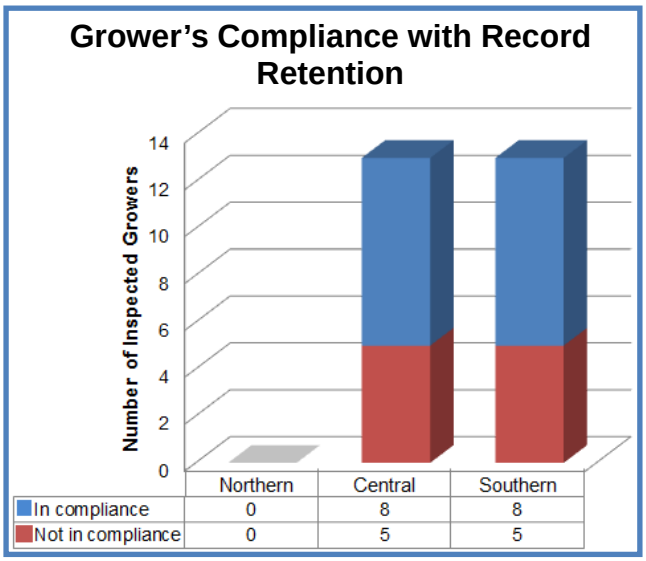

Figure 16: *Number of growers in the Program who retained their employee's ChE test results and medical supervisor recommendations. (n=26)*

Utility of Laboratory-Based Electronic Reporting

Reporting is an important tool for assessing exposure to OPs/CBs and prioritizing follow-up activities to improve worker safety. ChE test reports can be used to evaluate the Program and assess its effectiveness on a statewide basis. Combined with Pesticide Use Report data, these results allowed us to determine the correlation between the number of test results reported from a county and the amount of OP/CB used in that county (Figure 2). Areas where this correlation was not observed may warrant additional investigation. Furthermore, these reports allowed us to identify instances where a group of individuals showed a similar pattern of ChE depression (See Appendix C).

Our analysis of laboratory-based reporting (Appendix B) and ChE test results (Appendix C) helped us identify program elements that can be improved. For example, the distribution of individuals with ChE test results that exceeded action levels could be interpreted as an indicator of the effectiveness of the Program (Figures 7 and 8). Ideally, we would hope to see a minimal number of individuals with ChE depressions, or if they did have a ChE depression, it would not be repeated or prolonged, possibly indicating that the employer took action to prevent additional exposure. If an individual has repeated or prolonged depressions that exceed action levels, this suggests that long-term remedies are needed (e.g., implementing engineering controls, improving work practice, or providing better training to protect these workers).

For additional details on ChE data analysis, focused headquarters inspection, and medical supervisor survey and in-person visits, refer to the Appendices.

III. CHALLENGES

The current reporting structure presents some challenges in analyzing the data and evaluating the utility of this tool.

A. Submission of Cholinesterase Test Reports

Laboratories are aware of the required data elements to report and generate their own reports using our recommended Excel spreadsheet format. For the purpose of implementing a secure mechanism for electronic reporting, we utilized an existing web-based tool for laboratories to securely submit ChE reports to DPR. However, this tool merely transmits files so reports may still contain deficiencies (e.g., missing columns, duplicate records, typographical errors) that contributed to the difficulties we experienced in receiving complete data to analyze. Moreover, laboratories simply transmit the information but do not know whether individuals are workers in the Program, or the purpose of the test. See Appendix B2 for details.

B. Purpose of Cholinesterase Test

We currently receive all ChE test results from the six approved laboratories in California. Approximately three-quarters of the data appeared to be unrelated to the Program. Furthermore, the reports often contained incomplete or missing information related to the purpose of the test, the ordering physician and the employer.

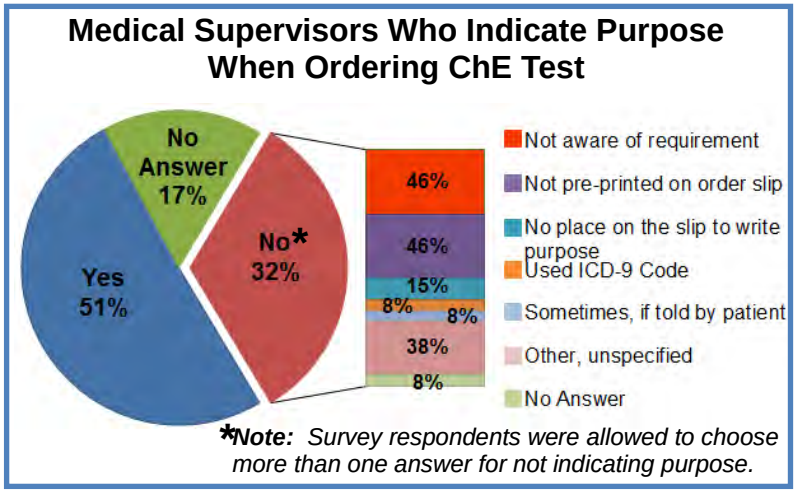

Figure 17: *Number of medical supervisors who indicated purpose of test when ordering ChE test and reasons for not indicating for those who do not indicate purpose of test. (Total number of medical supervisors who responded to the survey, n=41.)*

Although we sent letters to health care providers in 2011 reminding them of the requirement to indicate the purpose of ChE tests using specified terminology (see Appendix B2), only half of the medical supervisors in our survey reported that they indicate the purpose when submitting a ChE test requisition. Moreover, the ChE reports received continue to have a variety of 'purpose of test' entries, making it difficult to interpret in relation to the workers' pesticide handling activities. The medical supervisors who did not indicate the purpose of the ChE test stated that the main reasons were: 1) not being aware of the requirement, and/or 2) not having standard terms for purpose pre-printed on the laboratory requisition slip (Figure 17).

While most of the data elements required by HSC §105206 are straightforward, clearly conveying the purpose of the ChE test is complicated. It works on the premise that the employer, medical supervisor, their staff, and the drawing and/or reference laboratories all

have a common understanding of what is meant by the purpose of a ChE test as it relates to the patient's OP/CB handling activities. Unfortunately, this premise is not always reflected in the ChE test reports. This suggests that outreach to all involved parties, and a laboratory requisition slip containing all of the necessary information related to the Program, are essential to effectively utilize the electronic-based laboratory reporting tool. If the medical supervisors reported data directly to DPR, then all outreach and education efforts could be focused on this group of physicians.

Of the 91,093 test results received, 83.4% did not have a purpose entered. Of the 16.6% that had a purpose entered: 2.4% as 'baseline', 8% as 'periodic testing' (monitoring, follow-up, routine, etc.), 0.1% as 'exposure' and 6.1% as other entries (unavailable, CA test, etc.). See Appendix B2 for variations of entries for the purpose of test. The true purpose of these tests under the Program remains unclear because of: 1) the variety of entries for purpose reported (approximately 240 variations), and 2) the inaccuracy in the laboratories' interpretation of the purpose based on orders they receive. Without accurate information on the purpose of the ChE tests and ability to identify test results related to the Program, evaluating the data was challenging because we could not definitively identify the population of interest and we could not differentiate between baseline and routine periodic testing.

We used assumptions and inferences to develop exclusion criteria and used them to screen out ChE test results that may not be related to the Program. This not only increased the workload, but also could have led to misclassification of data.

To differentiate baseline test results from routine monitoring (follow-up) test results, we explored alternative methods to analyze the data (Figure 18). Analyzing three years of data (2011-2013) from the 1,338 individuals who appeared to be in the Program, about half (n=663) had two tests taken within 14 days during the low-spraying season[8]. Collection of two samples within a two-week time frame is consistent with the recommended procedure for baseline determination, as described in the *Guidelines for Physicians*. The baseline value for these individuals was calculated by averaging the results from these two tests, and this process was designated Approach 1. However, 14-day baseline estimates were not available for the rest of the population (n=675). In order to analyze the frequency of ChE depression of the entire population, the highest test result obtained over the 2011-2013 time period was used as an alternative estimate of the baseline value. This process was designated Approach 2, and we consider it to be more conservative because it likely leads to overestimation of the percent of individuals with ChE

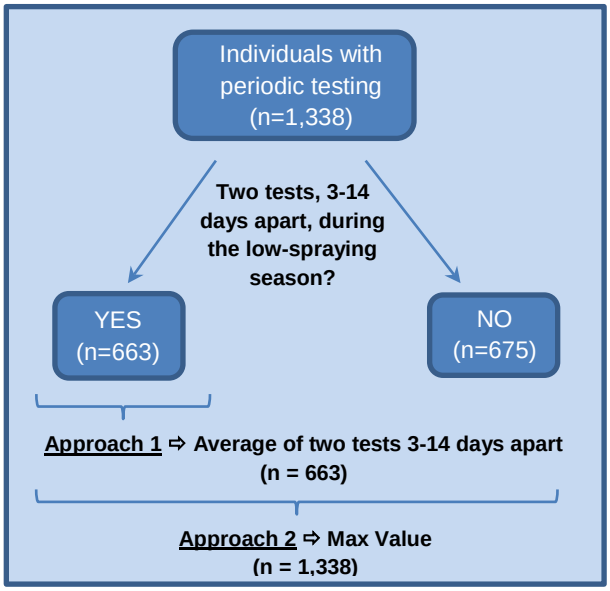

Figure 18: *Diagram of the two different approaches to determine baseline values for analysis.*

[8] Five months with the lowest OP/CB pesticide use in California: November through March.

depression. Nevertheless, Approach 2 allowed us to analyze data from all the individuals that had multiple test results because a maximum ChE value could always be identified.

Both of the approaches we used to determine the baseline ChE value are based on inferences and only provide estimated baselines. Results generated using these approaches are presented in the Findings section (Figures 7 and 8). These figures show large differences in the frequency of individuals with depressions using the two approaches (2 vs.13% for RBC ChE and 12 vs. 37% for plasma ChE). Regardless of the approach used, similar ratios were calculated for the four types of depressions (single *vs.* multiple and extended *vs.* not extended). Overall, both approaches showed that most individuals did not experience any type of depression.

C. Employee's Worksite

The employee's worksite could be used to assess the level of participation of workers under the Program. However, this information was not provided in the ChE test reports, nor is it required. To overcome this data gap, we used the physician's location as a surrogate for the employee's location to determine the correlation between test results and county-specific Pesticide Use Record data. This method may incorrectly assign an employee to a wrong county if that employee was seen by a medical supervisor located in a different county.

D. Employer Profile

Of the 71 focused headquarters inspections of growers who used OPs/CBs, only 26 indicated that they were in the Program (Figure 5). Although these inspections provided a snapshot of employers under the Program, it was a small sample and not representative of all of them. To obtain a more comprehensive understanding of the Program, we need to gather more information including inspections of Pest Control Operators who generally employ more workers that regularly handle OPs/CBs.

E. Accuracy of Medical Supervisor Information

We conducted ancillary activities to supplement our understanding of the Program such as: 1) a medical supervisor survey by mail, 2) in-person visits with medical supervisors, and 3) a focused growers' headquarters inspections to supplement our understanding of the Program. One of the major hurdles in conducting these activities was the absence of an accurate and complete list of medical supervisors and their contact information. We were unable to obtain this information from the ChE test reports due to the following:

- Information on the ordering physician is not always provided.
- The name provided in a laboratory report may not be a physician and/or medical supervisor. The person can be a non-physician who may or may not be working under the direction of a medical supervisor.
- The population of active medical supervisors appears to be dynamic. From 2011 to 2013, some physicians who had been identified as medical supervisors had retired or were no longer active, and others became medical supervisors after we had completed the data gathering process.

The lack of a complete and accurate list of medical supervisors prompted us to cast an extremely wide net when we conducted the medical supervisor survey. Indeed, of the physicians who were mailed a survey (n=699), we were only able to identify 6% (n=41) as being medical supervisors. An up-to-date list of medical supervisors would have facilitated and targeted our activities and is critical in conducting future outreach efforts. Our current outreach efforts led to identification of physicians who were previously not recognized as medical supervisors. We confirmed that they were medical supervisors through in-person visits.

IV. SUMMARY AND CONCLUSIONS

The Medical Supervision Program (3CCR §6728) was designed to protect the health and safety of pesticide workers who regularly handle cholinesterase-inhibiting pesticides, when OPs/CBs were the most commonly used pesticides to control insects. During the last 40 years, new insecticides have entered the marketplace and the use of OPs/CBs has declined.

HSC §105206 requires laboratories to submit to DPR ChE test results of workers handling OP/CB Toxicity Category I and II pesticides. The statute also requires laboratories to submit ChE test results for persons who were allegedly exposed or exposed to OPs/CBs and became ill from this exposure. DPR and OEHHA, in consultation with CDPH, are mandated to prepare a report on the effectiveness of the Program and the utility of the laboratory-based reporting of ChE for pesticide-related illness surveillance and prevention.

In this report, we evaluated the effectiveness and utility of the Program using data obtained from three different sources:

- information derived from the ChE test results
- feedback and suggestions provided by medical supervisors through a mail-in survey and in-person visits
- information obtained from growers' headquarters inspections

Utility of Laboratory-Based Reporting of ChE for Pesticide-Related Illness Surveillance and Prevention

We found the ChE data useful for evaluating specific requirements of the Program particularly when supplemented by physician surveys and visits, and grower inspections. However, its usefulness was limited because many of the reported test results were unrelated to workers in the Program, and by the lack of accurate information regarding the purpose of the ChE tests. When the ChE data is not accompanied by information on the purpose of the test and the worker's occupational history, the complexity and difficulty of analysis and interpretation are increased, therefore reducing the reliability of the findings.

We analyzed the geographic distribution of ChE tests and OP/CB use, and found a significant correlation, which indicates workers are participating in the Program where anticipated. We noticed there is a lack of correlation in some regions (e.g., Northern San Joaquin Valley). Information derived from inspections of growers' headquarters in those regions indicates most of their workers do not regularly handle OPs/CBs and, thus, are not

required to participate in the Program. Future in-person visits of medical supervisors and professional applicators in these regions may confirm this finding.

Effectiveness of the Program

While evaluating the Program, we identified possible improvements in communication that would help to more fully evaluate the Program and contribute to its continued success. For example, the manner in which information is conveyed among Program participants is not clear. Improvements in communicating ChE test results to employees and documenting whether a worker has been handling OPs/CBs for more than six days in a 30-day period would be useful. In addition, the Program requires the collaboration of various agencies (DPR, OEHHA, CDPH and the County Agricultural Commissioners), each with their own regulatory authority and responsibility. The Program also requires collaboration and communication between employers, workers, medical supervisors, and laboratories. Enhancing educational materials and outreach efforts to improve communication among all Program participants would strengthen our efforts to monitor the Program's effectiveness to enhance protection of California's agricultural workers.

Using information from the ChE data, feedback from medical supervisors, and reports from grower inspections, we conclude that overall, the Program appears to be effective in protecting agricultural workers handling OPs/CBs in California. Medical supervisors and growers are mostly knowledgeable about their respective responsibilities and roles in the Program. However, since the medical supervisors are responsible for several facets of the Program (e.g., evaluating the employee, submitting ChE test laboratory requisition forms, receiving ChE tests results from the laboratory, and informing the employee and the employer of the test results), it may make sense to also transfer the ChE reporting responsibility to the medical supervisors. This requirement could allow the agencies to target their education efforts to one group, and could facilitate more complete and timely reporting which will consequently enable prompt data analysis, evaluation and the determination of action levels when necessary.

While, due to the current reporting requirement and practices, it has been difficult to obtain accurate information, our analysis of the ChE data indicates a majority of individuals did not experience ChE depression. For those who did, most of them had their ChE level rebound within a short period of time, suggesting that the employer took corrective measures and prevented the worker from further exposure to OPs/CBs. However, we also found that some individuals had multiple short-term depressions in 2011-2013, suggesting that effective communication between medical supervisor and employer did not occur or exposure to OPs/CBs was not minimized and/or eliminated.

The survey and in-person visits revealed that most medical supervisors were aware of, and complied with, the requirements of the Program. However, not all medical supervisors were aware of the new provisions of HSC §105206. This suggests that further outreach to the medical supervisors is necessary to improve their understanding of the program and it's reporting requirements.

A major obstacle in conducting the survey and in-person visits was the absence of an existing registry of medical supervisors. As a result, we compiled our own list from submitted test reports that may not accurately capture the medical supervisors in the Program. The absence of an up-to-date registry of medical supervisors limits our ability to identify and survey medical supervisors, and also limits the effectiveness of our ongoing outreach efforts.

Information obtained from focused headquarters inspections indicated that while growers have a general understanding of the Program, they also have varying levels of awareness of some of the specific requirements. One finding is that some growers manage workers' schedules to limit their exposure to OPs/CBs to less than six days in a 30-day period. Of the growers participating in the Program, most did not have employees whose ChE test results required any action. However, the number of headquarters inspections conducted was small and focused on growers. Additional inspections of Pest Control Operators, who also employ pesticide handlers, would provide additional data on the Program. Despite the limitations of the reported ChE results, our analysis suggests that we identified workers in the Program and many of them did not have cholinesterase depressions in 2011-2013.

V. RECOMMENDATIONS AND FUTURE DIRECTIONS

Electronic-based reporting gives us the ability to analyze test results on a statewide scale. The survey and in-person visits with medical supervisors as well as the focused growers' headquarters inspections provided additional insight into the Program. The information from these various components helped identify program strengths as well as elements in need of further improvement. While most of our results supported the strengths of the Program, a proportion of workers still exhibited ChE depressions suggesting that workplace practices can be improved. The findings also indicate that growers and medical supervisors may not have a complete understanding of their responsibilities. All these results point to the following recommendations (Table 2) and future directions (Table 3):

***Table 2**: DPR and OEHHA Recommendations*

DPR/OEHHA - Recommendations	Lead Agencies/ *Participants*	Requires Legislation?
• The cholinesterase reporting should continue at least through December 31, 2018 in order to obtain additional data with clearer information on the purpose of the test and to allow further evaluation of the Program.	Leads: DPR, OEHHA *Participant: CDPH*	Yes
• Transferring cholinesterase reporting responsibilities from the laboratories to the medical supervisors may ultimately be a more efficient way to implement the Program.	Leads: DPR, OEHHA	Yes

***Table 3**: DPR and OEHHA Future Directions*

DPR/OEHHA – Future Directions	Lead Agencies/ *Participants*	Requires Legislation?
• Enhance outreach and training to increase understanding of the Program by the medical supervisors, employers, laboratories, and the County Agricultural Commissioner staff.		No
❖ Develop materials and conduct outreach efforts for the employers on their roles and responsibilities under the Program, such as, record retention of employees' cholinesterase test results and medical supervisor recommendations.	Lead: DPR *Participant: County Agricultural Commissioner*	
❖ Promote and expand the medical supervision training, emphasizing the provisions of HSC §105206 and continuing in-person visits to the medical supervisors.	Lead: OEHHA	
❖ Conduct focused headquarters inspections of Pest Control Operators similar to those that DPR conducted with growers.	Lead: DPR *Participant: County Agricultural Commissioner*	
❖ Increase the County Agricultural Commissioners' awareness of the Program; include a module on the Program during Enforcement Training.	Lead: DPR *Participant: County Agricultural Commissioner*	
❖ Coordinate with CDPH on outreach efforts to the laboratories. Develop clear requisition slips that require indication of the purpose of the cholinesterase test.	Lead: CDPH *Participant: DPR*	
• Continue coordination between DPR, OEHHA and CDPH to enhance the effectiveness of the Program.		No
❖ Improve reporting of information specified under HSC §105206(b).	Lead: DPR *Participant: CDPH, OEHHA*	
❖ Develop a list of currently active medical supervisors and update it regularly.	Lead: OEHHA	

VI. ON-GOING ACTIVITIES

To address some of the issues identified, we initiated the following activities:

A. The Online Monitoring Tool

DPR is working with the University of California, Davis on an online tool to capture data required by HSC §105206. This tool can improve communication between medical supervisors and reference laboratories. It can also enhance the data quality and the timeliness of ChE test results submission by the laboratories, and provide the data needed to adequately assess the utility of the program to reduce or eliminate agricultural worker health effects from handling OP/CB pesticides. Meanwhile, DPR will continue to work with the laboratories to improve reporting of the information required by HSC §105206. Details on this tool can be found at:
http://pesticide-education.phs.ucdavis.edu/CholinesteraseMonitoringTools.php.

B. OEHHA's in-person visits to medical supervisors

OEHHA has conducted in-person visits and trainings with 70% of the 87 medical supervisors it has identified, and is conducting telephone interviews and trainings with the remainder. OEHHA intends to continue periodic in-person meetings with medical supervisors. The purpose of these visits is to: 1) inform them of the reporting requirements under HSC §105206, 2) provide a copy of the 2015 *Guidelines for Physicians* and a list of available training resources, 3) remind them of their responsibilities as medical supervisors; 4) obtain feedback on how medical supervisors implement the Program. Assessing the impact of this outreach on the quality of electronic laboratory reporting and the implementation of the Program will be useful in targeting future efforts and identifying resource needs. See Appendix E for additional information.

C. DPR working with CDPH on laboratory approval process

Following a meeting in June 2015, DPR initiated discussions with CDPH on the process for certifying laboratories that perform ChE tests. The purpose of these discussions is to find ways that may allow CDPH to ensure adequate quality control of the analytical methods for the cholinesterase test and for DPR to collect better information from the laboratories.

VII. GLOSSARY OF TERMS

3CCR §6728: Title 3, section 6728 of the California Code of Regulations, on Medical Supervision

AB 1963: Assembly Bill that added the Health and Safety Code section 105206 requiring California Department of Public Health-approved laboratories to submit cholinesterase test results of workers under the medical supervision program to the Department of Pesticide Regulation. AB 1963 was signed by the governor in September 2010 and became law on January 1, 2011.

Accession Number: A unique number assigned to each blood specimen by the laboratory submitted for analysis. The accession number protects a patient's privacy by functioning as a unique identifier rather than using the patient's name or other personal identifier.

Action Levels: A depression in the level of cholinesterase activity that meets one of the following thresholds:

- If either red blood cell or plasma cholinesterase is depressed below 80% of the baseline (that is, more than 20% depression from the baseline), it triggers a reassessment of work activities.
- If a worker's cholinesterase level drops more than 30% from the red blood cell baseline or more than 40% from the plasma baseline, he/she is removed from the exposure source.
- Following a worker's removal, his/her red blood cell and plasma cholinesterase must be monitored, and he/she is not allowed to work with or handle Toxicity Categories I and II organophosphate and carbamate pesticides until red blood cell and plasma cholinesterase levels return to at least 80% of the baseline.

Baseline: Red blood cell and plasma cholinesterase determinations measured prior to an employee's exposure to Toxicity Categories I and II organophosphate and carbamate pesticides. By regulation, a baseline cholinesterase test is required of all employees who will "regularly handle" these pesticides regardless of the frequency of subsequent monitoring. Once the baseline is determined, subsequent test results are evaluated as a percentage of the baseline activity.

Carbamate (CB): An organic compound with structural features that result in inhibition of cholinesterase enzymes, which are critical to normal function of the nervous system. Aldicarb, carbofuran, carbaryl (Sevin®) and methomyl are examples of carbamate pesticides.

CDPH: California Department of Public Health

Cholinesterase (ChE): An enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine, and helps the nervous system to work properly. Under the Medical Supervision Program, two types of cholinesterase (plasma and red blood cell (RBC)) are required to be measured for all covered employees to account for the differences in the mode of action of cholinesterase-inhibiting pesticides.

- **Plasma Cholinesterase**: Considered to be more labile than red blood cell cholinesterase and is thus less reliable in reflecting actual enzyme depression at neuro-effector sites. It is generally more rapidly inactivated by exposure to organophosphates/carbamates.
- **RBC Cholinesterase:** Biochemically the same enzyme as the acetylcholinesterase located at the neuro-effector cell synapses. It is often depressed more slowly than plasma cholinesterase by exposure to organophosphates/carbamates.

County Agricultural Commissioner (CAC): Primary enforcement agents, at county level, for the State pesticide laws and regulations, and local ordinances.

DPR: Department of Pesticide Regulation, a department of the California Environmental Protection Agency.

Drawing Laboratory: Any laboratory that collects specimens (i.e., draws blood) from tested persons. Although these laboratories perform basic analyses, they send complex or infrequently ordered laboratory tests to a reference laboratory for analyses.

Guidelines for Physicians: The document, *Guidelines for Physicians Who Supervise Workers Exposed to Cholinesterase-Inhibiting Pesticides*, prepared by the Office of Environmental Health Hazard Assessment. This handbook describes the medical supervision program and the responsibilities of the medical supervisors. The 5th edition of this document was released in 2015.

Handler: Any person who:

i. Mixes, loads, transfers, or applies pesticides.
ii. Cleans, adjusts, handles, or repairs the parts of mixing, loading, or application equipment that may contain pesticide residue.
iii. Acts as a flagger.

HSC §**105206**: Health and Safety Code section 105206, codified into law by the enactment of AB 1963, that took effect on January 1, 2011. This section shall remain in effect only until January 1, 2017, and as of that date is repealed, unless a later statute enacted before January 1, 2017, deletes or extends that date.

Laboratory Requisition Slip: Form provided by the laboratories for ordering physicians to use when submitting specimen samples for analysis.

Medical Supervisor: Under HSC §105206, a licensed physician (M.D. or D.O.) who has a written agreement with employers of agricultural workers who regularly apply cholinesterase-inhibiting pesticides in Toxicity Categories I and II, to examine the employees for fitness, order cholinesterase tests, and to make the necessary recommendations based on the results of an employee's cholinesterase test results.

OEHHA: Office of Environmental Health Hazard Assessment, a department of the California Environmental Protection Agency.

Organophosphate (OP): A general term for esters of phosphoric acid that constitute the common structural element of many insecticides. These pesticides are toxic because they inhibit cholinesterase enzymes and impair normal function of the nervous system. Organophosphates are a large class of commercial pesticide products; examples include parathion, malathion, chlorpyrifos, and naled.

Pesticide Use Report (PUR): A comprehensive report of all agricultural pesticide use in California. Use data are submitted monthly to County Agricultural Commissioners, who in turn, report this data to the Department of Pesticide Regulation.

"Program:" Medical Supervision Program (3CCR §6728) as used in this document.

Purpose of Test: Under HSC §105206, a medical supervisor must indicate on the test order the reason for ordering cholinesterase tests for an employee.

- **Baseline**: Pre-exposure test ordered to establish the individual's normal level of a worker under medical supervision.
- **Routine (Monitoring)**: Test ordered for *periodic testing/follow-up assays* of a worker under medical supervision.
- **Event (Evaluation of suspected pesticide illness)**: Test ordered to identify effects of a suspected or reported pesticide exposure.

Reference Laboratory: An independent referral or diagnostic facility equipped with state-of-the-art equipment, and trained personnel to conduct various types of tests not otherwise available in most laboratories. Hospitals, laboratories and physicians will often use a reference laboratory for more complex or less frequently utilized tests.

Signal Word: One word used to indicate the acute toxicity of the formulated pesticide product.

i. **Danger**: Highly toxic by at least one route of exposure.
ii. **Warning**: Moderately toxic if ingested, absorbed through the skin, or inhaled.
iii. **Caution**: Slightly toxic if eaten, absorbed through the skin, or inhaled.

Toxicity Categories I and II: Refers to U.S. Environmental Protection Agency's classification system for pesticides that addresses the acute toxicity of these products.

i. **Toxicity Category I**: Highly toxic; Signal word "Danger."
ii. **Toxicity Category II**: Moderately toxic; Signal word "Warning."