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SUBJECT: Additional Information Related to the Department of Pesticide Regulation's (DPR's) 2018 California Neonicotinoid Risk Determination and Addendum

This document provides additional information regarding DPR's scientific methodology for (1) bridging plant residue data, (2) bridging No Observed Effect Concentration (NOEC) toxicity data, and (3) determining samples to include in calculation of plant residues.

1. Clarification on the plant residue bridging strategy

As part of DPR's neonicotinoid reevaluation, DPR required registrants of each nitroguanidine-substituted neonicotinoid active ingredient (AI) to conduct plant residue trials on a selection of representative California crops. In many cases, residue data was only available for one or two crops within a specific crop group as defined in Title 40 Code of Federal Regulations [(40 CFR) §180.41]. Because DPR did not have plant residue data for every crop with all four nitroguanidine-substituted neonicotinoid AIs, the data needed to be bridged. DPR relied upon two types of bridging: (1) bridging data from one crop to another within a crop group for the same AI and, (2) bridging data from one AI to another within a crop group. No bridging of data occurred from one crop group to another crop group.

Crop-to-crop bridging within a crop group for the same AI:
In cases where residue data was deficient for a specific crop, DPR bridged residue data from another crop within the same crop group to the missing crop. Bridging residue data between crops within the same crop group is supported by the fact that members of the same crop group are typically taxonomically and physiologically related. In general, for trials conducted on a crop that resulted in residues below the respective toxicity endpoints (NOECs), indicating low risk, DPR determined that the same application rate and timing would also be classified as low risk for other crops within the same crop group. If all trials conducted on crops within a crop group had

residues that exceeded the respective toxicity endpoints, indicating high risk, DPR assigned a high risk determination to the other crops within the same crop group.

If trials using the same application rate and timing on multiple crops resulted in residues exceeding the NOECs in some, but not all crops in the same crop group, DPR used a weight of evidence approach to determine risk for crops that were not tested. Weight of evidence refers to a systematic approach scientists use to evaluate the totality of scientific evidence to assess if the science supports a particular conclusion. In this case, the number of trials with residues exceeding versus not exceeding the NOEC and the sample size (n value) in each trial was considered when determining if a tested rate and timing would be considered high or low risk for crops that were not tested.

DPR also considered whether a specific crop produces both nectar and pollen when bridging residue data crop-to-crop within a crop group. For instance, within the fruiting vegetables crop group, residue data was available for pepper, which produces both nectar and pollen, and tomato, which only produces pollen. Thus, when determining risk for fruiting vegetables that were not tested, crops that produce nectar were bridged to pepper, since the tomato data did not report nectar residues.

AI-to-AI bridging within a crop group:
Where possible, DPR's preference is to base risk determinations for a particular AI on residue data conducted with that same AI. However, there were cases in which, within a crop group, all of the submitted data for an AI exceeded the respective toxicity endpoints and a low risk application rate and timing could not be determined based on active ingredient-specific data. There were also cases where there was no plant residue data available within a crop group for a specific AI. In such instances, DPR used residue data from the same crop group from a trial testing a different nitroguanidine-substituted neonicotinoid AI as surrogate data. For example, if a residue trial testing a different AI on the same crop group resulted in residues below the toxicity endpoints of the AI that was missing data, DPR considered the application rate and timing tested in that trial to be low risk for the AI that required bridging.

Crop group-to-crop group bridging:
In some cases, no residue data were available for any nitroguanidine-substituted neonicotinoid AI for an entire crop group. Initially, DPR's 2018 California Neonicotinoid Risk Determination and Addendum (Table 6) stated that residue data conducted on stone fruits were bridged to tree nuts due to these crop groups being taxonomically related. However, after further investigation, DPR found that almonds are the only crop within the tree nuts crop group that are taxonomically related to the stone fruits crop group (same genus, *Prunus*). The majority of tree nuts are in a different family than the majority of stone fruits. Further, it was clear from the residue data that different crop groups can result in very different magnitudes of residues,

even between trials conducted at similar application rates and timings. Thus, residue data from one crop group may not be an accurate representation of resulting residues in another crop group. Accordingly, DPR updated its bridging strategy to exclude crop group to crop group bridging.

2. Additional rationale for using the pollen NOEC value for clothianidin as surrogate data for the thiamethoxam and dinotefuran pollen NOEC values

Pollen colony feeding studies were not available for thiamethoxam or dinotefuran, necessitating the use of another nitroguanidine-substituted neonicotinoid AI as a surrogate. Therefore, DPR bridged the pollen NOEC value for clothianidin to thiamethoxam and dinotefuran. While imidacloprid also had an available pollen NOEC from a colony feeding study, it was the highest concentration tested, and thus there is more uncertainty in the concentration in pollen that begins to elicit colony-level effects (lowest observed effect concentration; LOEC). In contrast, the pollen NOEC for clothianidin is considered to be more reliable, as the pollen colony feeding study testing clothianidin was able to determine the concentration in which colony-level effects occur (LOEC).

In addition, the toxicity and chemical properties of thiamethoxam and dinotefuran are more similar to clothianidin, further supporting this bridging strategy. The chemical structures of thiamethoxam and clothianidin are related as clothianidin is a natural degradate of thiamethoxam. The toxicity of clothianidin and thiamethoxam to bees is also similar[1]. For dinotefuran, lab data on file indicate it may be the least toxic of the four nitroguanidine-substituted neonicotinoid AIs. Thus, the pollen NOEC for dinotefuran was bridged from clothianidin, as clothianidin resulted in a higher NOEC (less toxic) than that of imidacloprid. Based on the relative toxicity in the lab setting, DPR determined that bridging the pollen NOEC for dinotefuran from imidacloprid's pollen NOEC would have been an unrealistic and overestimation of risk.

3. Clarification on the types of pollen and nectar samples included when calculating percentiles from crop residue studies

It is known that pollen and nectar are digested by enzymes in the bee-stomach, mixed, and diluted between the times of collection and storing in the hive.[2,3,4] The plant residue trials considered in the neonicotinoid reevaluation did not always collect nectar and

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[1] DPR. (2018). California Neonicotinoid Risk Determination. Sacramento, CA: DPR.
[2] Anderson, et al. (2011). An Emerging Paradigm of Colony Health: Microbial Balance of the Honey Bee and Hive (Apis mellifera). Insectes Sociaux 58(4), 431-444.
[3] Oddo, L.P., Piazza, M.G., and Pulcini, P. (1999). Invertase Activity in Honey. Apidologie 30(1), 57-65. DOI: 10.1051/apido:19990107.
[4] Von der Ohe, W. (1994). Unifloral Honeys: Chemical Conversion and Pollen Reduction. Grana 33(4-5), 292-294, DOI: 10.1080/00173139409429013.

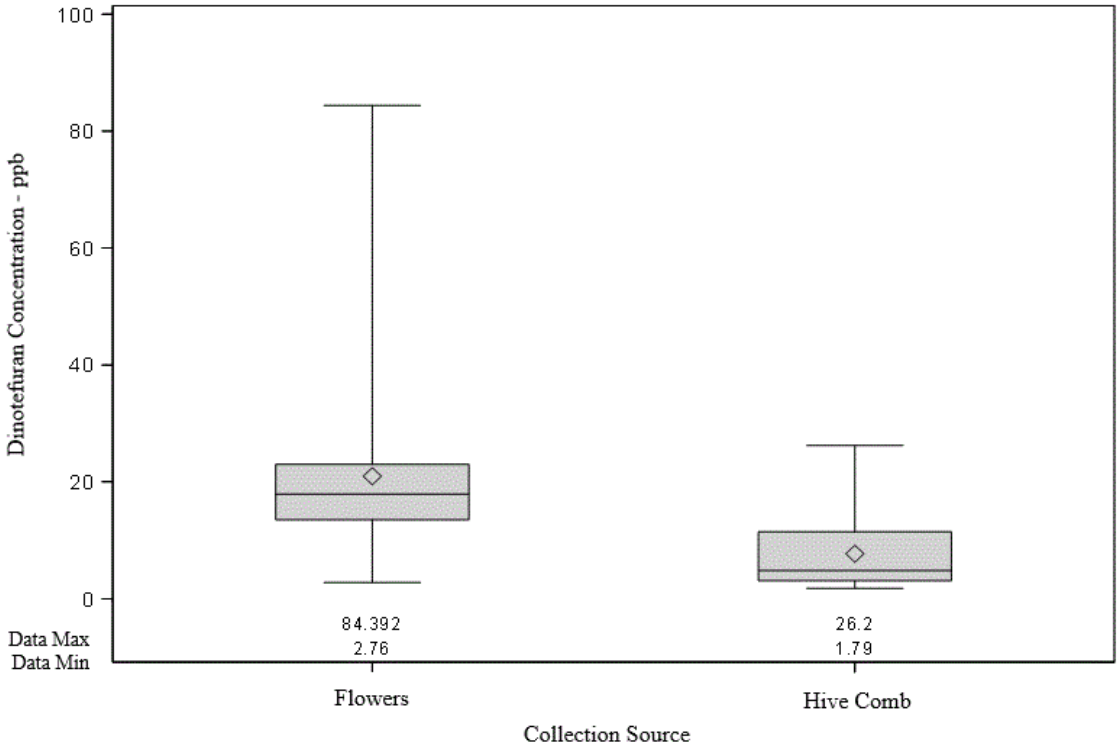
pollen directly from flowers for residue analysis. In a few trials, samples of nectar and/or pollen were also collected from bee stomachs, pollen traps, and/or hive comb (stored food). As the measured residues from plant residue studies are compared to a NOEC value derived from measured concentrations in sucrose solution or pollen patties that have not been processed and handled by bees, it is important to investigate whether the samples collected from bees or within the hive are representative of residues in pollen and nectar collected directly from flowers.

DPR conducted an additional investigation into the difference in residues recovered from the various collection sources for nectar and pollen. DPR statistically compared the magnitude of residues recovered between the various sources of collected nectar and pollen samples for multiple dinotefuran trials. This analysis consisted of pooling residue data from trials conducted on the same crop group and at the same application rate and timing, as there were insufficient samples within a single trial to do a proper statistical comparison. Using non-parametric Wilcoxon, Median, and Empirical Distribution Function tests, DPR looked for potential significant differences between the distributions of recovered concentration data between collection sources for the following scenarios:

1. Nectar source comparison for soil applications to cucurbit vegetables (Figure 1; study IDs: S16-02009, 10934.4104, and S16-01165): bee stomach data excluded due to low number of samples.
2. Pollen source comparison for foliar applications to fruiting vegetables (Figure 2; study ID: 10934.4103).

Results from this analysis indicate that measurements of dinotefuran residues in samples collected from bees or within the hive were significantly lower in concentration than residues in samples collected directly from the plant flowers (Figures 1 and 2). The ratio of parent to total residue was also different whereby parent dinotefuran residue consisted of a greater portion of the total residue in samples obtained from flowers. Back calculation of concentrations measured in the hive to project original concentrations in flowers is complicated by the apparent enhanced degradation of parent residue for samples taken from within the hive. Based on this analysis, DPR determined that the magnitude of residues recovered from nectar and/or pollen that have been processed and handled by bees (samples collected from bees or within the hive) may not be representative of the magnitude of residues expected in samples collected directly from flowers. Thus, only samples that were collected directly from flowers are considered in the current residue percentile calculation. Using only samples collected directly from flowers will ensure a proper comparison between residues and NOECs derived from colony feeding studies.

Figure 1. Comparison of the range in dinotefuran concentration between nectar collected from flower or hive comb sources for soil applications applied to cucurbits at 0.54 lbs. ai/A from budding to early flowering.



Both the amount of dinotefuran recovered, total residue, and the ratio of parent to total residue were significantly greater in flowers than in hive comb collected samples.

Figure 2. Comparison of the range in dinotefuran concentration between pollen collected from flower or bee (pollen baskets) sources for foliar applications applied to fruiting vegetables at 0.27 lbs. ai/A at flowering.

Note that dinotefuran residues are transformed to base 10 logarithm. Both the amount of dinotefuran recovered and the ratio of parent to total residue were significantly greater in sampled flowers than in pollen samples collected from bees. Total residue was also greater for flower samples but only the Wilcoxon test indicated a significant difference between the two sources.