**PESTICIDE REGISTRATION**
**AND EVALUATION COMMITTEE (PREC)**
**Meeting Minutes – July 17, 2020**

## Committee Members/Alternates in Attendance:

Amalia Neidhardt – Department of Industrial Relations (DIR)
Brian Larimore – Department of Resources Recycling and Recovery (CalRecycle)
Dave Tamayo – Structural Pest Control Board (SPCB)
James Seiber – University of California (UC), Davis, Department of Environmental Toxicology
Jeff Fowles – Department of Public Health (DPH)
Katherine Sutherland-Ashley – Office of Environmental Health Hazard Assessment (OEHHA)
Kevi Mace – California Department of Food and Agriculture (CDFA)
Lynn Baker – Air Resources Board (ARB)
Matt Hengel – University of California, IR-4 Program
Rich Breuer – State Water Resources Control Board (SWRCB)
Ruben Arroyo – CA Agricultural Commissioners and Sealers Association (CACASA)
Stella McMillin – Department of Fish and Wildlife (DFW)
Tulio Macedo – Department of Pesticide Regulation (DPR)
Valerie Hanley – Department of Toxic Substances Control (DTSC)

## Visitors in Attendance:

*Note: Only attendees who identified themselves using their full name are listed below*

Anne Katten – California Rural Legal Assistance Foundation
Carolyn Yee
Caley Crawford
Dave Lawson – Western Plant Health Association
Emily Saad – Exponent
Eric Lauritzen
James Nakashima – Office of Environmental Health Hazard Assessment (OEHHA)
Jean Mari Peltier
Jing Tao
Ouahiba Laribi – Office of Environmental Health Hazard Assessment (OEHHA)

## DPR Staff in Attendance:

Aron Lindgren – Pesticide Registration Branch
Brenna McNabb – Pesticide Registration Branch
Brittanie Clendenin – Pesticide Registration Branch
Christopher Collins – Environmental Monitoring Branch
Daisy Dong – Human Health Assessment Branch
Denise Alder – Pesticide Registration Branch
Edgar Vidrio – Environmental Monitoring Branch
Jason Carter – Environmental Monitoring Branch

**DPR Staff in Attendance continued:**

Jazmin Gonzalez – Environmental Monitoring Branch
Jennifer Teerlink – Environmental Monitoring Branch
Jesse Cuevas – Director's Office
Kara James – Pesticide Registration Branch
Laura Benn – Pesticide Registration Branch
Lisa Calhoun – Enforcement Branch
Maziar Kandelous – Environmental Monitoring Branch
Minh Pham – Environmental Monitoring Branch
Nan Singhasemanon – Pesticide Programs Division
Rochelle Cameron – Pesticide Evaluation Branch
Russell Darling – Pesticide Registration Branch
Shelley DuTeaux – Human Health Assessment Branch
Shelley Lopez – Pesticide Registration Branch
Svetlana Koshlukova – Human Health Assessment Branch
Val Dolcini – Director's Office

1. **Introductions and Committee Business – Tulio Macedo, Acting Chair, DPR**

a. Approximately forty-seven (47) people attended the meeting.
b. DPR published the chlorpyrifos alternative report on July 16, 2020.
c. DPR continues to update the COVID-19 webpage as additional information and resources become available.

2. **Overview of DPR's Neonicotinoid Reevaluation and Upcoming Mitigation Webinars – Russell Darling and Brittanie Clendenin, DPR**

Over the last several years, honeybee colony decline has triggered worldwide concern. The most common factors involved in colony decline include predatory insects, malnutrition, genetic diversity in queen bees, and direct or indirect pesticide exposure. These factors can have complex interactions and cause compounding effects, however, because DPR has regulatory authority over pesticides, the department's efforts are focused strictly on the interaction between pesticides and pollinators.

Several categories of pesticides may be affecting bees, including fungicides, insecticides, tank mixtures, or a combination thereof. DPR received early adverse effects reports identifying possible risk to bees from exposure to imidacloprid. This active ingredient is part of a class of chemicals called nitroguanidine-substituted neonicotinoids (neonics), which also include clothianidin, dinotefuran, and thiamethoxam. Neonics are a systemic pesticide, meaning they have the ability to translocate throughout the plant once absorbed through the roots or foliage. These pesticides can be applied as a foliar or soil application, and are especially effective on sucking insects, such as aphids. Neonics are registered for use on a wide variety of crops, including citrus, pome fruit, stone fruit, cotton, and cereal grains. They were developed as an

alternative to organophosphates and carbamates. Imidacloprid was first registered in California in 1994, while the other three active ingredients were registered in 2004.

A reevaluation can be triggered in a variety of different ways, such as issues with phytotoxicity or efficacy, or concerns over impacts on worker health or the environment. As mentioned previously, the neonic reevaluation was triggered by adverse effects data submitted by the registrant, which showed high levels of imidacloprid in both leaves and blossoms of treated plants. These levels were high enough to be expected to be hazardous to bees. Based on DPR's evaluation of the adverse effects data, DPR issued California Notice 2009-02, which formally placed the four neonic active ingredients into reevaluation in February 2009. The reevaluation focuses on outdoor agricultural uses of neonics and does not include products that are not relevant to the concerns that prompted the reevaluation. This means that products such as ant and cockroach baits or indoor use products were not pulled into the reevaluation. For more information on the specifics of the initiation of this reevaluation, visit DPR's Neonicotinoid Reevaluation Web page.
<https://www.cdpr.ca.gov/docs/registration/reevaluation/chemicals/neonicotinoids.htm>

After DPR initiated the reevaluation, staff began working collaboratively with U.S. EPA and the Health Canada Pest Management Regulatory Agency to determine data requirements and develop study designs. DPR's neonic reevaluation relies on data submitted by the registrants as well as peer-reviewed open literature studies. The studies that the registrants performed were conducted using protocols that had been approved by all three agencies. DPR was interested in being able to characterize the exposure and the effects of neonics on bees and colonies. The specific data required included honeybee toxicity studies, colony feeding studies, and pollen nectar residue studies. DPR worked with U.S. EPA on the preliminary pollinator risk assessments, looking at acute toxicity endpoints as well as preliminary residue studies and colony feeding studies. U.S. EPA issued the preliminary risk assessment for imidacloprid in January 2016 and for clothianidin, thiamethoxam, and dinotefuran in January 2017.

DPR intended to continue collaborating with U.S. EPA towards completing final pollinator risk assessments, however the completion due dates established by the California legislature were incompatible with U.S. EPA's timeline. In 2014, the governor signed into law Assembly Bill 1789, which became Section 12838 of the California Food & Agricultural Code. The law essentially established timeframes for milestones in DPR's neonic reevaluation. The first milestone was a risk determination document, to be completed and submitted to the state legislature by July 2018. The law also states that mitigation efforts are to be implemented after the completion of the risk determination.

In July 2018, DPR published the California Neonicotinoid Risk Determination. For this risk determination, DPR scientists assessed data from residue trials of the four neonicotinoids at various rates and timings, and compared them to colony feeding studies. The data from the colony feeding studies was used to determine residue levels that pose no significant toxicity to bees. The residue studies assessed in the document were conducted under worst-case scenarios, based on the maximum application rates and minimum reapplication intervals listed on

California labels over a two-year period. Throughout the review of the data, DPR scientists identified risks to bees when using neonics on a number of crops. After publishing the risk determination document, DPR received additional information that was then incorporated into an addendum to the risk determination and published in January 2019. These documents were used to inform DPR's risk mitigation efforts. For more information regarding the scientific methods that were used in producing this risk determination, view the risk determination document. <https://www.cdpr.ca.gov/docs/registration/reevaluation/chemicals/neonicotinoid_risk_determination.pdf>

Since publishing the January 2019 addendum to the risk determination, DPR has been working on how to appropriately mitigate the identified risks. Staff have pursued finding a complex balance between the need to keep a critical crop protection tool available, while simultaneously trying to understand current cultivation practices, pest pressures, and use patterns. DPR used that understanding to develop proposed mitigation measures to protect bees. In addition to the worst-case scenario residue studies, DPR has additional studies on file that were not based on worst-case scenarios. In the time since publishing the addendum, DPR has reviewed these studies to identify whether lower application rates could serve as a mitigation option. As DPR worked to develop mitigation measures, many different factors were considered during the decision making process, including current pest management practices, critical pest issues, resistance management, and the level of pollinator exposure for each crop.

DPR is proposing to implement the needed mitigation measures by adopting regulations, rather than through label changes. Although requiring label changes would be more direct, it is important to note that DPR is preempted by federal law from requiring changes to the pesticide product labels. The draft regulations include both general mitigation measures and specific mitigation by crop group. The uses of neonics pose different risks depending on the crop to which they are applied, and in some cases, depending on which neonic is used.

DPR is planning to present the proposed mitigation through public Zoom webinars on August 11, 2020 from 3:00 p.m. to 5:30 p.m. and August 12, 2020 from 5:30 p.m. to 8:00 p.m. The webinars will be presented in both English and Spanish, and will also be available to stream through the CalEPA webcast page. <https://video.calepa.ca.gov> Additional information, including the text of the draft regulation and presentation slides for the webinar, will be sent out through DPR's California Notice to Stakeholders electronic mailing list. Following the webinars, DPR will have an open 30-day comment period to solicit comments from stakeholders. DPR will consider all feedback and make adjustments to the mitigation where appropriate. The goal is to develop the final rule making package and begin the official public notice process later this year.

While DPR progresses through the rulemaking process for neonics, the department has already instituted several bee protections. The California Managed Pollinator Protection Plan is a central location document to find all of California's initiatives to protect pollinators, including current laws and regulations, citrus bee protection areas, bee protection practice agreements, bee registration and notice of applications, and current label language.

In January 2020, U.S. EPA released the Preliminary Interim Decision for each of the neonic active ingredients. U.S. EPA conducted a broader risk assessment, which assessed impacts to pollinators, human health, aquatic risks and ecological risks. Although DPR is preempted from requiring changes to pesticide product labels, U.S. EPA proposed several label changes in their Preliminary Interim Decision to protect bees and address other risks. The comment period for this document closed on June 18, 2020, and the next steps are to review the comments and publish a final decision.

***Committee Comment***

Kevi Mace expressed appreciation for the specificity of the mitigation measures as opposed to a broader approach.

***Public Comment***

Eric Lauritzen asked when U.S. EPA is expected to issue a final decision and if that decision will affect DPR's decision on mitigation. Russell Darling responded that U.S. EPA will need to review and respond to comments before making a final decision, so there is no current information on an expected date for a final decision.

**3. <u>2019 Air Monitoring Results – Minh Pham, Christopher Collins, and Jazmin Gonzalez, DPR</u>**

In 2019, DPR collected air samples at eight locations as part of the Air Monitoring Network (AMN). The goal of the AMN is to monitor for 31 pesticides and 5 breakdown products in ambient air. Study 309, which focuses on air monitoring of 1,3-Dichloropropene (1,3-D) in Merced and Fresno counties, also continued throughout 2019. This marks the fourth year of continuous monitoring for this project. Both studies utilize 24-hour samples collected weekly. The samples were analyzed by a joint effort including CDFA and CARB. Results are expressed in parts per billion (ppb) of pesticides measured in the gaseous form.

No state or federal agency has established health standards for pesticides in air. Therefore, DPR in consultation with OEHHA developed health screening levels to place the air monitoring results in a health-based context. As a result, DPR staff are able to estimate the potential for adverse health effects by comparing the measured air concentrations to these health screening levels or regulatory targets. Screening levels are based on a preliminary assessment of possible health effects. A measured concentration that is above the screening level does not necessarily indicate a health concern, but it does indicate the need for a refined evaluation. Regulatory targets are established after a formal risk assessment of a chemical's toxicity and potential exposures. Regulatory targets will always supersede screening levels if both exist for a particular chemical. DPR puts measures in place based on regulatory targets to limit exposures and thereby avoid adverse effects. A measured concentration above the regulatory target does not necessarily indicate an adverse health effect has occurred, but it does indicate that restrictions on the pesticide use may need to be modified. Four pesticides monitored in the AMN (chloropicrin,

methyl bromide, methyl isothiocyanate and 1,3-D) have regulatory targets for one or more exposure periods.

DPR began the AMN in 2011 at three sampling locations. In 2016, an approved budget change allowed for the expansion of the AMN to eight total sampling locations for a period of two years, in collaboration with CARB. In 2019, DPR operated the sampling sites in Chualar, Santa Maria, and Watsonville, while CARB operated the sites in Cuyama, Lindsay, Oxnard, San Joaquin, and Shafter. That same year, the sampling site in Shafter was relocated from Shafter High School to Sequoia elementary, and the site in Santa Maria was moved from a CARB monitoring location to Bonita Elementary School. Sampling at the new sites began on February 26 and November 12, respectively.

Of the 31 pesticides and 5 breakdown products monitored, 11 were not detected at any of the eight monitoring sites, 15 were only detected at trace levels, and 10 were detected at quantifiable concentrations. In this context, non-detections refer to all samples with measured concentrations below the Method Detection Limit (MDL), and trace detections are measured concentrations between the Limit of Quantitation (LOQ) and the MDL. The sites in Lindsay and San Joaquin had the highest number of possible detections due to the highest number of valid samples collected. Santa Maria had the highest percent of possible detections when both trace and quantifiable detections are considered. Shafter had the highest percentage of quantifiable detections at 1.6%.

Ten percent of 1,3-D samples from Shafter registered as quantifiable detections, the highest percentage for this chemical. Ten percent of chloropicrin samples from Watsonville registered as quantifiable detections. Methyl isothiocyanate (MITC) was observed at quantifiable concentrations at all eight sites, but did not exceed any thresholds. The highest percentage of quantifiable detections for this chemical (41%) occurred at the site in Shafter.

Screening levels for pesticides are categorized as acute (24 hour concentrations), subchronic (4 or 13 week concentrations), or acute (annual concentrations). The chemical with the highest percent of the acute screening level was 2,2-dichlorovinyl dimethyl phosphate (DDVP) at 5.2%. The chemical with the highest percent of the subchronic screening level was chloropicrin at 59%. The chemical with the highest percent of the chronic screening level was MITC at 58%. None of the monitored pesticides exceeded their acute, subchronic, or chronic screening levels in 2019.

The highest acute concentration of chloropicrin was 1.032ppb, detected at Oxnard. The highest acute concentration of MITC was 1.532ppb, detected at San Joaquin. The highest subchronic concentration of chloropicrin was 0.2ppb, detected at Oxnard. The highest subchronic concentration of MITC was 0.43ppb, detected at San Joaquin. The highest annual average for chloropicrin was 0.2ppb, occurring at Shafter. The highest annual average for MITC was 0.058ppb, occurring at San Joaquin. No screening levels or regulatory targets were exceeded for acute, subchronic, or chronic concentrations.

As part of the AMN analysis, DPR determines cumulative exposures for the 14 organophosphate pesticides: acephate, bensulide, chlorpyrifos and its oxygen analog (OA), DDVP, DEF, diazinon + OA, dimethoate + OA, malathion + OA, oxydemeton methyl, and phosmet. These pesticides all have a common mode of action in regards to human health - the inhibition of the cholinesterase enzyme. Cholinesterase breaks apart the neurotransmitter acetylcholine, which is vital for the transmission of nerve impulses. Cumulative exposure was estimated using a hazard quotient and hazard index approach. The hazard quotient is equal to the detected air concentration divided by the screening level. The hazard index is the summation of the hazard quotients for each of the 14 organophosphate pesticides. None of the hazard indices exceeded a value of 1.0 at any of the sampling locations during 2019. This indicates that even for the 14 combined organophosphate pesticides, a sum screening level was not exceeded.

DPR also estimates cancer risks for pesticides that have been designated as potential carcinogens by both California and the U.S. EPA. This measurement can only be performed for pesticides measured at quantifiable amounts at AMN monitoring locations. Cancer risk is equal to the estimated cancer potency factor in humans, times the mean lifetime (70-year) air concentration, times the normalized breathing rate of a human adult. In the absence of 70-year monitoring data, the lifetime air concentration is taken as the mean annual concentration for all available monitoring years. The value of lifetime air concentration assumes continuous exposure at this concentration over a 70-year period.

Of the 31 pesticides and 5 breakdown products monitored in the AMN, seven are classified as carcinogens: 1,3-D, chlorothalonil, DDVP, diuron, iprodione, oxydemeton methyl, and propargite. During the 2019 monitoring year, 1,3-D and DDVP were measured at quantifiable concentrations in at least one of the sampling locations. DPR has determined the cancer potency factor to equal $0.35(mg/kg\text{-}day)^{-1}$ for DDVP and $0.014(mg/kg\text{-}day)^{-1}$ for 1,3-D. Cancer risk regulatory targets for DDVP have not been established. However, risk in the range of 1.0E-05 to 1.0E-06 or less is generally considered to be at the limit of what is considered to be negligible. For DDVP, the average risk for 2019 was determined to be 1.5E-06 in San Joaquin (15% of target) and 5.4E-07 in Santa Maria (5.4% of target).

Eleven of the 31 pesticides and 5 breakdown products monitored were not detected at any monitoring location, and 15 were only detected at trace levels. Ten pesticides were detected at quantifiable levels: 1,3-D, chloropicrin, Dacthal, DDVP, EPTC, malathion and its oxon, MITC, pp-dicofol, and trifluralin. The chemicals with the highest number of detections from all monitoring locations were MITC (17.5%), chloropicrin (3.4%), and malathion (3.4%). None of the hazard indices for a hypothetical combined 14 organophosphate compound exceeded 1.0 at any of the sampling locations during 2019.

In 2019, DPR sampled for 1,3-D in ten communities spanning seven counties in California, as part of both the AMN and Study 309. The objective of Study 309 was to monitor 1,3-D in high-use areas of the Central Valley and to evaluate the effectiveness of 1,3-D mitigation measures implemented in 2017. Monitoring locations for this study were selected based on 1,3-D use within five miles of the community boundary. The chosen sites were Delhi, which ranks 16$^{th}$

statewide and 1st in in Merced County, and Parlier, which ranks 36th statewide and 6th in Fresno County. Monitoring began on December 1, 2016 at both sampling locations, and one 24-hour air sample is collected per site per week on a randomly-selected day.

The Study 309 results are analyzed by the CDFA lab, which can achieve a 0.01ppb reporting limit, as opposed to CARB's 0.1ppb reporting limit. 1,3-D was measured at quantifiable concentrations in 82% of samples collected at Parlier and 78% of samples at Delhi using the CDFA reporting limit and 10% of samples at Shafter using the CARB reporting limit. Shafter had the highest maximum acute concentration at 3.2ppb, which represents 2.9% of the 110ppb screening level. Parlier had the highest maximum subchronic (90-day average) concentration at 0.78ppb, representing 26% of the 3ppb screening level. Parlier also had the highest maximum chronic concentration at 0.27ppb, or 14% of the 2ppb screening level. Delhi, Parlier, and Shafter had more frequent detections, compared to all other sites.

DPR has established a cancer risk regulatory goal of 1.00E-05. By inserting that value into the cancer risk equation mentioned earlier, the maximum mean lifetime air concentration equals 0.56ppb. A comparison of the annual concentration by sampling location shows Parlier as having the highest overall average concentration at 1.24ppb. However, the data also shows that concentrations have decreased at this site from 2.94ppb in 2018 to 0.27ppb in 2019. All other sites were well below the 0.56ppb target.

Due to diminished resources and limited operational capacity, the Air Monitoring Network is only operating at three monitoring sites: Santa Maria, Watsonville, and Shafter. CDFA is currently the only lab for all analysis. Several samples were submitted to the CARB lab around the time of the closure due to COVID-19. DPR recently received these results, however the data may or may not be viable, due to the inability to analyze the samples during the 30-day holding window. As a result, there may be two or three weeks of missing data due to chemical stability and storage criteria. Additionally, there will be no data for the five inactive sites from March 8, 2020, onward.

In Spring 2020, DPR received VOC results that indicated two sequential 1,3-D detections in Shafter, which measured at 4ppb and 20ppb. No acute or subchronic exceedances were observed. DPR has been in contact with the Kern County Agricultural Commissioner's office about these exceedances and will continue to discuss these and other detections throughout the year. In particular, DPR is interested in determining if there are underlying causes for these spikes, such as changes to agricultural practices, climate, or pest pressures.

DPR released and posted online the final Study 309 Annual Report for 2019. The draft Air Monitoring Network Results for 2019 have also been posted online and are open for public comment. Comments on the 2019 AMN draft report will remain open until August 31, 2020 and may be directed in writing to Maziar Kandelous via email at Maziar.Kandelous@cdpr.ca.gov or via post at the address listed below:

Maziar Kandelous
Department of Pesticide Regulation
PO Box 4015
Sacramento, CA 95812-4015

***Committee Comment***

Ruben Arroyo asked for an explanation of the relationship between the number of spikes or exceedances and probability of developing cancer as a result. Minh Pham explained that the 70-year average is meant to represent lifetime exposure levels. Minh added that the average shown in the presentation is somewhat skewed as it reflects only three years of data. Minh further explained that if subsequent years show repeated low concentrations, the average will trend downward, while if frequent higher concentrations are reported, the average will trend upward.

***Public Comment***

Eric Lauritzen commented that overall, the data seems to reflect good results with respect to screening levels. Eric then asked about the threshold trigger for additional review, specifically whether one exceedance would trigger a review, if it would depend on the amount of exceedance, whether or not the AI is a factor, and whether the current results would prompt any additional review. Minh Pham replied that if any of the collected results trigger an exceedance, then DPR will look into the matter further. Minh added that staff may prioritize based on department policies, what chemicals are involved, and other projects staff are working on.

Robert (no last name provided) asked if AMN locations are chosen to standardize the distance to surrounding fields that may be applying the monitored pesticides, and if not, whether results are adjusted to account for the distance. Minh Pham clarified that the AMN focuses on ambient air concentrations, rather than application site concentrations. Minh added that the ambient air levels are a representation of the exposures of normal citizens within that community.

Anne Katten commented that the DPR risk assessment also has the cancer endpoint of 0.1ppb using the systemic mode of action, which is considered plausible. Anne added that Shafter and Delhi both exceed that level, and Santa Maria is very close. Anne further added that while monitoring once a week allows for more monitoring locations, it may lead to missed peaks, which could account for the higher numbers recorded in 2018, if monitoring coincided with peak application days and specific weather patterns. Minh Pham replied that the department is currently looking into the exceedances Anne mentioned. Minh added that the decision to monitor weekly, as opposed to more frequently, was made due to limited resources, which have become

even more limited as a result of the expiration of the partnership with CARB as well as current COVID-19 regulations.

**4. <u>Addendum to the Sulfuryl Fluoride Risk Assessment – Daisy Dong, DPR</u>**

Sulfuryl fluoride is a colorless and odorless gas that is used as a fumigant. It is more soluble in lipids than in water, and is mainly used in structural fumigation in California, although it is also approved for commodity fumigation. It was first registered in the U.S. in 1959, and was subsequently registered in California for structural and non-food fumigation (1990; 1997) and food commodity fumigation (2005). In 2017, the total yearly use equaled 3.7 million pounds.

In 2006, DPR completed a risk characterization document on sulfuryl fluoride for structural fumigation, and additional studies have been submitted by the registrant in the time since. In 2016, DPR initiated the addendum process by reevaluating the toxicological database, because the registrant specifically requested a consideration of reducing the database uncertainty factor. To temporarily address this request, DPR published the interim reference concentrations for residential bystanders and workers for acute and short-term exposures in 2017. DPR finished the draft addendum in December 2018, invited external scientific review in 2019, and published the revised addendum with response to comments in July 2020.

Sulfuryl fluoride breaks down in the body mainly through hydrolysis. The main breakdown products include fluoride, fluoride sulfate, fluoride sulfate adducts, and sulfate. Sulfuryl fluoride mainly targets the respiratory system (nasal and lung inflammation), teeth (dental fluorosis), kidneys (hyperplasia, decreased protein droplets and organ weights, and glomerulonephropathy), and the nervous system (increased motor activity, electrophysiological effects, tremors, and brain vacuolation in the basal ganglia).

Between the years of 1992 and 2017, there were 204 reported cases of exposure to sulfuryl fluoride in California. The main symptoms reported affected the nervous system, pulmonary system, and the gastrointestinal tract. Nervous system symptoms included headache, dizziness, lightheadedness, fatigue, and tingling or numbness in the face, hand, foot, lip, mouth, and tongue. Pulmonary system symptoms included shortness of breath, cough, chest pain, and lung congestion and edema. Gastrointestinal system symptoms included nausea, vomiting, abdominal pain, diarrhea, and stomach pain.

Reference Concentrations (RfCs) are target air concentrations to humans that are likely to be without appreciable risk of deleterious effects. This value is calculated by dividing the critical endpoint concentration by the uncertainty factors that are appropriate to the exposure scenario. In this addendum, the exposure scenario refers to residential bystanders for structural fumigation. Residential bystanders include the home residents, as well as all neighbors and residents (including children) surrounding the treated house.

The first step to derive the RfC is to determine the point of departure (POD). POD is the point on a toxicological dose-response curve, corresponding to an estimated low or no effect level,

usually derived from animal studies. The second step is to calculate the duration adjusted POD ($POD_{ADJ}$). This is to adjust the animal exposure duration to human exposure scenarios. In the case of residential bystanders, the exposure duration is 24 hours per day, seven days per week. The third step in the process is to calculate the human equivalent concentration (HEC). HEC is the external air concentration that produces the same internal target tissue dose in humans as that achieved in laboratory animals. The process of converting animal POD to HEC is also referred to as dosimetric adjustment. The final step is to determine the total uncertainty factors (UF). The commonly used default UFs include 10x interspecies variability ($UF_A$), 10x intraspecies (human) sensitivity ($UF_H$), and 10x gaps in the database ($UF_{DB}$). Each of these uncertainty factors can be subdivided into two components – 3x pharmacokinetics and 3x pharmacodynamics. Pharmacokinetics explains the relationship between the external dose and the internal dose. Pharmacodynamics explains the relationship between the internal dose and the effect, or the sensitivity of the target tissue. Both pharmacokinetics and pharmacodynamics can be different between humans and animals, as well as between different human individuals. The interspecies uncertainty factor is usually reduced from 10x to 3 when HEC is used as the numerator for the RfC derivation. This is because the HEC calculation already accounts for the pharmacokinetic difference between animals and humans.

HEC is very critical and the calculation involves different methodologies. HEC is the product of the adjusted POD and the dosimetric adjustment factor (DAF). In general, methodologies depend on whether the toxic effect is classified as a systemic mode of action or a portal of entry mode of action, and different DAFs are used for different modes of action. For systemic mode of action, in the case of sulfuryl fluoride induced brain lesions, that means toxic metabolites access the brain via the respiratory tract, through the blood, and finally to the brain. For this calculation, the DAF would be one, based on the 1994 and 2012 U.S. EPA RfC guidelines. Alternatively, the HEC can be calculated using the sulfuryl fluoride physiological based pharmacokinetic (PBPK) model. For the portal of entry mode of action, different default DAF are recommended by U.S. EPA RfC guidelines, depending on where the toxic effect occurred in the respiratory tract. If the toxic effect occurs in the nasal cavity, the DAF would equal one. However, if the toxic effect occurs in the tracheobronchial or pulmonary region, the DAF is usually greater than two.

However, in the case of sulfuryl fluoride induced brain lesions, it is difficult to classify this neurotoxic effect as either systemic or portal of entry mode of action. Regulatory agencies from the U.S., Europe, Australia, and Canada all assumed a systemic mode of action for sulfuryl fluoride in their toxicological evaluations. The assumption is that neurotoxicity is caused by fluoride, which reaches the brain through systemic circulation. However, a systemic mode of action cannot explain the high fluoride concentration in the brain or the brain lesions in the basal ganglia region that resulted from inhaled sulfuryl fluoride.

DPR staff reviewed and analyzed non-inhalation studies of sodium fluoride in the open literature. This analysis provided additional information on how fluoride behaves in the brain through systemic circulation. Non-inhalation studies show that fluoride is relatively impermeable to the blood-brain barrier, resulting in relatively low concentrations of fluoride in the brain and a ratio of brain to plasma of less than one. Based on the previous assumptions, one would expect similar

fluoride brain-to-plasma ratios from the sulfuryl fluoride inhalation studies and the sodium fluoride non-inhalation studies. However, DPR's analysis of the data showed a 20-fold difference between the ratios in sodium fluoride non-inhalation studies and sulfuryl fluoride inhalation studies.

Similarly, DPR staff found that the sulfuryl fluoride inhalation induced brain lesions were different from the sodium fluoride studies. In the sulfuryl fluoride inhalation studies, the brain region was characterized by vacuoles in the basal ganglia. These vacuoles were observed across all species: mouse, rat, rabbit, dog, and one human case. In animals, the vacuoles were only found after repeated exposure for at least two weeks, and were reversible in one rat study (with a limited sample size of N=2). In the human case, however, the brain lesion occurred only after 14 hours of acute exposure and there is no data to indicate the lesion is reversible. No studies of sodium fluoride reported any basal ganglia lesions.

DPR's analysis clearly shows that fluoride accesses the brain differently between sulfuryl fluoride inhalation exposure and sodium fluoride non-inhalation exposure. The neurotoxic effect of sulfuryl fluoride cannot be readily classified as a systemic or portal of entry mode of action. This inhibits the calculation of HEC as it is dependent on the classification of the mode of action. Further, the HEC is critical in the derivation of RfC as well.

For background, in 2006, DPR proposed an acute reference concentration of 0.122ppm for residential bystanders. The acute POD was derived from a two-day neurotoxicity study in adult rats. The RfC was calculated based on the assumption that fluoride is the toxic species and that fluoride gets to the brain via systemic circulation. In 2017, DPR updated the acute RfC to 0.41ppm. The acute POD remained the same, but the database uncertainty factor decreased from ten to three, based on analysis from the new database. In the 2018 draft addendum, the acute POD remained the same, however DPR proposed a new intranasal route of entry for sulfuryl fluoride induced neurotoxic effects. This proposal is based on the idea that sulfuryl fluoride enters the brain directly from the nasal cavity, bypassing blood circulation. Staff used this information to calculate HEC for all possible methods and assumptions, resulting in an RfC range of 0.048ppm to 3.26ppm.

In the final addendum, the POD for acute exposure remains the same as the 2006 RCD, however the HEC calculation incorporates all comments and recommendations from the external reviewers, the registrant, and U.S. EPA. The final HEC was calculated based on three assumptions: that neurotoxic effect occurs through 1) a systemic mode of action, 2) a portal of entry mode of action at the nasal cavity, and 3) an unknown mode of action. Sulfuryl fluoride PBPK model could not be used due to uncertainties and lack of validation with inhalation data in the human compartment. The acute RfC for residential bystanders was calculated based on these three assumptions, resulting in a range of 0.25ppm to 0.75ppm. The 2020 final addendum underwent peer-review from an external scientific panel. For more information, view the final addendum at <https://www.cdpr.ca.gov/docs/whs/active_ingredietn/sulfuryl-fluoride.htm>.

As a reminder, the information provided above is only one step in the process of DPR's work on sulfuryl fluoride. Additional conversations and documents will be forthcoming.

***Committee Comment***

Jim Seibert asked how this information affects the registration status of sulfuryl fluoride and its use as fumigation season nears. Shelley DuTeaux replied that the addendum to the risk assessment was initiated in response to a request from the registrant to review the database uncertainty factors. Shelley clarified that sulfuryl fluoride is not technically in reevaluation, so there is no current change to the registration status as either a structural or commodity fumigant. Shelley added that there may be future changes to mitigation or risk management decisions going forward, as DPR continues to evaluate the science.

***Public Comment***

Tom (no last name provided) asked what the next steps are in the sulfuryl fluoride risk assessment process, and how this information will affect mitigations, if any. Jesse Cuevas replied that next steps will include additional conversations about the data, which may impact the scientific documents, or eventual risk management decisions and mitigations.

James Nakashima commented that some of the respiratory symptoms may be due to the chloropicrin warning agent that is used in sulfuryl fluoride structural fumigations, and not sulfuryl fluoride itself. Daisy Dong agreed that when sulfuryl fluoride is used to fumigate a house, the warning agent chloropicrin is always used. Daisy added that this is why the presentation focused more on the nervous system, pulmonary system, and gastrointestinal tract as opposed to direct irritant effects.

Tom (no last name provided) asked if this information changed the potential exposure or the threshold testing level target of 0.5ppm. Shelley DuTeaux replied that there are no changes to the values in the current mitigation documents.

## 5. Agenda Items for Next Meeting

The next meeting is scheduled for September 18, 2020 at 10:00 a.m. This meeting will be held virtually on the Zoom platform and broadcast live on the CalEPA webcast page. <https://video.calepa.ca.gov/>

The Update on Wastewater Monitoring presentation has been rescheduled to the September 18, 2020 meeting.

James Seiber requested an update on dicamba and 1,3-D.

Dave Tamayo requested a discussion on transparency and access issues related to evaluation reports.

## 6. Adjourn