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DATE: December 11, 2017

SUBJECT: Response to Public Comments Submitted by Dow AgroSciences LLC on the DPR Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant (Risk Characterization Document dated August 18, 2017)

I. INTRODUCTION

The California Department of Pesticide Regulation (DPR) received comments dated October 2, 2017 regarding the August 18, 2017 draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant as part of the public comment process. Many of the comments submitted in October 2017 are substantially similar to comments received from Dow AgroSciences LLC (DAS) on March 28, 2016 regarding the December 31, 2015 draft Risk Characterization Document (RCD) for chlorpyrifos or to DPR's response to comments received from the Office of Environmental Health Hazard Assessment (OEHHA). Those responses are available at http://www.cdpr.ca.gov/docs/whs/active_ingredient/chlorpyrifos.htm. Comments received from DAS that are unique to the August 2017 draft evaluation are responded to below.

I. EXPOSURE ASSESSMENT COMMENTS

DAS Comment: The AGDISP modeling can be refined to more realistically reflect any potential particles sizes in the air with drift. In the current assessment, 100% of the particles in the drift are assumed to be inhaled. But, recognizing that only a small fraction of any particles in the air can be inhaled and even a smaller percentage are respirable and bioavailable, results in further risk reductions by orders of magnitude, e.g., as much as, or greater than 1000-fold.

> **HHA Response:** HHAB is exploring appropriate methods related to adjustments for inhalable fraction and will incorporate any appropriate methods in the next draft.

DAS Comment: The current screening-level assessment over-estimates potential exposures. Refinements are possible and significantly reduce the exposure estimates and resulting risk estimates. The draft evaluation includes estimates of potential non-occupation bystander (adults

and children) exposure from spray drift aerosol particles. This spray-drift exposure is estimated to contribute up to 95% of the total aggregate exposure. The worst-case scenario in the draft evaluation is for a young child standing and playing only a few feet from the edge of a field during application. This current assessment should be considered a screening-level assessment. Overall, there are more than a dozen factors contributing to the unrealistic, remote probability of the exposure scenario occurring. Taking into account the probability of just some of the pieces of this exposure scenario such as the an application being made, being downwind of the application, living next to an agricultural field, etc., the chances of the scenario accurately occurring can be shown to extremely low and unrealistic. Scientifically-supported refinements can be made to develop a more realistic assessment.

> **HHA Response:** Likelihood of exposure and the resulting risk is not part of this risk assessment. However, it should be noted that this risk assessment addresses the potential risk associated with current legal uses of chlorpyrifos. The maximum application rates used to estimate exposures for each application method are the highest legal rates. For potential residential bystander dermal exposure, it is assumed the exposure occurs on turf that receives spray drift residue associated with a legal agricultural application nearby a home. The potential inhalation exposure occurs in the same setting during the legal application. In the end, the residential bystander scenarios chosen represent the reasonable worst case legal agricultural application scenarios in California.

DAS Comment: In the draft evaluation, it is assumed that the bystander is exposure [*sic*] to drift with 100% of the spray being an inhalable aerosol particle. In reality, only a small fraction of the total aerosol mass will be in a size range that can be inhaled, potentially deposited in the respiratory tract and bioavailable. The fact that actually a large percentage of any potential drift that could reach a bystander would be in the vapor phase and not aerosol is extremely impactful on the resulting potential risk estimate…

In line with EPA's statement, DPR presented an estimate of the droplet sizes less than 10 µm in diameter and stated that these fractions could be used as an adjustment of the calculated concentrations. However, it does not appear that such adjustment was done, which resulting [*sic*] in significant overestimation of the degree of exposure from inhalation of aerosols. In addition, the unused respirable fractions presented (Appendix A of Appendix 2) do not consider that the droplet size distribution (DSD) is not a constant with height… Based on direct discussion with Dr. Harold Thistle (US Forest Service), the developer of the AGDISP model, a methodology was developed to estimate the airborne DSD at any point in space. Dr. Thistle advised that setting the ground reference height (in the "Advanced" settings in the AGDISP interface) to the height desired (1.7 or 5 feet, for child and adult breathing height, respectively) and setting the "transport" value to the desired downwind distance (also called the flux plane), the output of the Point DSD would be a good estimate of the DSD at that point in space. According to Dr. Thistle, this yields the DSD passing through a horizontal plane at the vertical flux plane, essentially a point (technically a line; shown in red in Figure IV.1 below) in space…

The calculated 1-hr average concentrations are very similar to the values produced by CDPR. The volume fraction results show that the fraction of the droplet in the respirable range (<10 µm) are extremely small, with no value greater than 0.0003 (i.e., 0.03%). Thus refined estimates of the air concentrations will be on the order of 10-6 mg/m3 (i.e., ng/m3) or less. The particles <100 µm in size may possibly be inhaled, but will largely be trapped in the upper respiratory system and potentially be ingested. These fractions are much smaller than estimated in DPR's assessment (pg 41 of Appendix 2); for example, at 2.3 pound/acre, 100 feet downwind, the DPR-calculated fraction at <10 µm (i.e., not accounting for changes with height) was 0.0851 (vs. 1.5x10-5 to 2x10-4 shown here). Adjusting for these fractions, if they are deemed to be significant, will reduce such potential exposure by an order of magnitude or more.

> **HHA Response:** HHA is exploring appropriate methods related to adjustments for inhalable fraction and will incorporate any appropriate methods in the next draft.

DAS Comment: There are more than a dozen factors contributing to the unrealistic, remote probability of this scenario occurring and indicate the need for further refinement. No label use allows for an application that occurs every day for 21 days. A field application is a discrete, defined event and potential bystander exposure through inhalation would be limited at worst to a short duration, such as 1 hour or less, but as mentioned above, the assessment done by CA DPR creates an exposure estimate as if a child is at edge of field for 21 days. Any exposures through other routes, such as dietary, that might occur on those days would be much less than assumed in the CA DPR approach. Maximum label use rates, rather than typical use rates are assumed. The child in the bystander scenario is always considered to be downwind of the application, thus receiving the maximum possible exposure. Every day the child is also assumed to be engaged not only in activities which result in high contact with surfaces that receive the hypothetical drift, but also ones that maintain an elevated breathing rate. Even if this was true for one application, it is unrealistic to assume it happens every day for 21 consecutive days. Taking into account the probability of just some of the pieces of the exposure scenario occurring, such as treatment during an agricultural season, being downwind of an application, living next to an agricultural field, etc., the chances of the bystander scenario occurring are very low. Such remote probabilities are not realistic for regulatory decision-making.

> **HHA Response**: DPR's August 2017 draft evaluation did not perform the described "inhalation and dermal exposure calculations for 1 – 1.5 hours every day for 21 days in a row." The 21 days exposure scenario was employed by US EPA for deriving route-specific PoD values in the agency's 2014 human health risk assessment of chlorpyrifos.

DAS Comment: The issue of inhalation of aerosol was addressed by US EPA (2014). EPA concluded that, "*the vapor, rather than the aerosol, is the relevant form for evaluation of bystander volatilization exposures… Because field volatilization is the production and release of vapor into the atmosphere after sprays have settled on treated soils and plant canopies, the vapor, rather than the aerosol, is the relevant form for evaluation of bystander volatilization exposures…*"

HHA Response: This comment on the significance of vapor versus aerosol for evaluating bystander exposure is noted.

DAS Comment: In Appendix 2, Table 20 (pg 23 of Appendix 2), the units of air concentration are shown at ng/m^3. The units should be in ng/L (as output by AGDISP). The correct unit conversion was done in calculating the MOE values in the main body of the document, but this error should be corrected by clarity. The caption of Figure 7 (pg 24) contains the same error.

HHA Response: Noted and this error has been corrected in the December 2017 draft evaluation.

DAS Comment: Acceptable MoE's can be obtained through refinements in key aspects of the assessment… (2) Modeling a more realistic particle-size distribution of potential drift… The AGDISP modeling can be refined to more realistically reflect any potential particles sizes in the air with drift. In the current assessment, 100% of the particles in the drift are assumed to be inhaled. But, recognizing that only a small fraction of any particles in the air can be inhaled and even a smaller percentage are respirable and bioavailable, results in further risk reductions by orders of magnitude, e.g., as much as, or greater than 1000-fold.

HHA Response: With respect to "(2) Modeling a more realistic particle-size distribution of potential drift," please see responses to similar comments, above.

III. TOXICOLOGY COMMENTS

DAS Comment: One of the biggest contributors to the over-estimation in the current assessment is the PoD used. Currently, the PoD creates an exposure estimate as if that child is at the edge of the field exposed to an application every day for 21 consecutive days. Such an exposure scenario is not realistic, is inappropriate, and is not even possible under current label restrictions; the PoD should not and must not assume scenarios inconsistent with the label. Refinement of just the PoD to be consistent with the true episodic nature of applications, even for a conservative scenario accounting for other possible daily exposures (dietary, dermal), would lower the predicted risk 10- to 50-fold.

HHA Response: It is noteworthy that the PBPK-PD model was used to derive the PoDs for characterizing the risk associated with exposure to chlorpyrifos. HHA, however, did not perform the aforementioned calculations of inhalation or dermal exposure for 1- 1.5 hours every day for 21 days in a row or for generating any other human exposure estimates. Conceptually, the use of the computer model for generating the NOEL is identical to the use of experimental animal systems. The 21 day exposure scenario was employed by US EPA for deriving route-specific PoD values in the Agency's 2014 risk assessment of chlorpyrifos. HHA commonly uses repeated dosing studies for establishing an acute or short term NOELs based on toxicological consideration (for examples see the

DPR Risk Characterization Document for 1,3-Dichloropropene, available at http://www.cdpr.ca.gov/docs/risk/rcd/dichloro_123115.pdf).

DAS Comment: The current draft evaluation significantly over-estimates potential exposure and risk. Refinements discussed in these comments demonstrate acceptable levels of risk and Margins of Exposure (MoE) with current use patterns, and therefore chlorpyrifos does not meet the criteria for listing as toxic air contaminant.

HHA Response: The revised draft includes detailed discussion of the HHA decisions, assumptions, and approaches used to calculate exposure and risk.

DAS Comment: DAS disagrees with the contention in the draft evaluation that there is collective evidence from zebrafish, humans, and animals which associates chlorpyrifos with irreversible developmental toxicity at levels below the current protective endpoint of cholinesterase inhibition. Scientifically, a proposed mechanism of action linking chlorpyrifos with developmental neurotoxicity, despite attempts to identify one, is lacking; a point confirmed at several EPA Scientific Advisory Panel meetings. Without a mode of action, there is no biological plausibility for the claim. In addition, there are fundamental methodological confounders and challenges which preclude verification of a strong association, and definitely not a causal relationship. While DPR has stated that there is amble evidence to support such effects at below the current endpoint, a thorough review of the evidence provided shows errors in reporting tables, but even more importantly, in virtually all the studies cited, cholinesterase inhibition was observed and there were no effects below that level.

The use of PBPK/PD modeling for developing scientifically-supported chemical-specific rather than generalized default values for UFs has been adopted by both U.S. EPA and CA DPR. The current PBPK/PD was recently expanded to be applicable to all stages of human pregnancy. These model enhancements have been peer-reviewed and published in the scientific literature. This new model version was submitted to CA DPR in August, 2015. This new model should be used and supports a reduction in the current Intraspecies UF from 10X to 4X.

HHA Response: For the past 10 or more years, studies in animals and humans have indicated that exposure to chlorpyrifos is associated with neurodevelopmental and behavioral effects. While chlorpyrifos is an AChE inhibitor, evidence shows that this may not be the only target. The MOA (AOP) has not been determined for chlorpyrifos related neurodevelopmental and behavioral effects in the developing young. In addition, the key events leading to these effects are unknown (discussions on these studies are presented in the 2017 RCD). In 2015, US EPA conducted a systematic literature review on neurodevelopment effects and concluded that the weight of evidence analysis supports the retention of the 10X FQPA for all OPs, including chlorpyrifos. The errors in the tables have been noted and corrected. HHA reviewed the updated pregnancy PBPK-PD model and relevant discussions were included in the August 18, 2017 draft RCD (see Sections II.B.4. and VI.D.).

DAS Comment: DPR has responded to DAS that there "is ample evidence from recent studies to support neurodevelopmental and behavioral effects at doses below those that inhibit RBC AChE." A thorough review of this evidence in the Current Draft Evaluation reveals errors in reporting tables, but more importantly in virtually all of the cited studies, cholinesterase inhibition was observed and there were no effects reported below the threshold for cholinesterase inhibition, clearly opposite of the claim that DPR makes.

> **HHA Response:** The errors in the tables have been corrected. For effects occurring at or below doses inhibiting ChE see Carr et al 2015; Carr et al., 2017, Lee et al. 2015, and Silva et al. 2017.

DAS Comment: DAS disagrees with the inconsistent characterization that chlorpyrifos causes/may cause/may be associated with neurodevelopmental effects or overt toxicity, particularly [emphasis added] at exposure levels that do not inhibit cholinesterase activity. DAS contends that there is scant and insufficient experimental evidence to suggest that chlorpyrifos may even speculatively be associated with neurodevelopmental or neurobehavioral effects below the threshold for cholinesterase inhibition, despite the widespread, but erroneous perspective, that there is a growing body of evidence to support such.

> **HHA Response:** The statement on page 3 was modified to be consistent with our stance that exposure to CPF may be associated the neurodevelopmental outcomes as reported in the epidemiological and animal toxicity studies at exposure levels that might not result in ChE inhibition.

DAS Comment: To investigate the appropriateness of the default 10x or Intraspecies Uncertainty Factor for pregnant workers, the current Multi-Route PBPK/PD model was expanded to include systemic exposure and RBC effects predictions during all stages of human pregnancy in April 2015 (Poet 2015). This Pregnancy PBPK model was then used to validate the applicability of the new 4X data-derived extrapolation factor (DDEF) for the chlorpyrifos POD in humans to pregnant women as well.

Changes were made in physiology in the PBPK model based on the relevance to CPF and CPFoxon disposition and pharmacodynamics, and using well-established reference values for human pregnancy (Poet 2015, MRID 49635101)… These important changes are included in the CPF model for pregnancy, built on the lifestage platform so either age-specific parameters or initial body weight-specific parameters can be used as the initial condition at the beginning of gestation… Enzyme activity incorporated into the PBPK model, across life-stages and in pregnant women, was based on in vitro measurements of CYP and PON1 rates in liver tissue and PON1 rates in plasma across a wide age range. Final ranges of enzyme activity used in the model were far wider than the measured values to accommodate a conservative estimate of variation in this critical model parameter across a human population. Also, age-based increases in enzyme ontogenies were included in the PBPK model.

> **HHA Response:** HHA discussed at length its basis for invoking a default UF of 10 to account for intra-human variability as based on inhibition of RBC AChE in the August 18, 2017 draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant.

DAS Comment: As stated following release of the 2015 RCD and reiterated here, DAS disagrees with this broad, generalized statement that purports to link studies of various quality and not anchored by an identified and verified mode of action (in ZF, animals, humans), particularly at dose levels below the threshold for cholinesterase inhibition. CA DPR also fails to bring into the analysis any weight of evidence. There are multiple reviews in the peer reviewed scientific literature that describe the epidemiology evidence as inadequate, inconsistent and biologically implausible. (Burns et al. 2013; Eaton et al. 2008; Li et al. 2012; Mink et al. 2012; Needham 2005; Prueitt et al. 2011; Reiss et al. 2015; Zhao et al. 2005). These publications highlight that the results for chlorpyrifos reported by the Columbia investigators must be robustly compared to findings in other studies. DAS disagrees with the premise that neurobehavioral deficits in children were due to chlorpyrifos exposure and therefore disagrees with the contention that evidence exists in humans to support neurodevelopmental deficits below the threshold where AChEI occurs (Please see further discussion in Epidemiology Section). For animals, there is no compelling or consistent evidence to support the contention that neurodevelopmental outcomes occur at exposures below where AChEI occurs.

> **HHA Response:** HHA reviewed the entire animal database for CPF, including the older reviews cited by DAS as well as the more recent studies (Carr et al 2015; 2017, Lee et al. 2015; Silva et al. 2017). HHA also significantly expanded its review of human epidemiology studies in the August 2017 draft evaluation. In addition to the major prospective cohort studies, both the Hazard Identification and the Risk Appraisal sections of the August 2017 draft evaluation mention a review of additional studies including observational analyses, pooled analyses, and recent published reviews. The August 2017 draft evaluation also includes a discussion of the studies that tried to predict exposures, those that used specific or non-specific urinary metabolites, as well as those that made direct measurement of the parent compound as a marker of exposure, and acknowledges the strengths and weaknesses of many of these studies. Many new epidemiology and/or human exposure studies are available that warrant review.[1] HHA looks forward to the Scientific Review Panel's discussion in the upcoming Toxic Air Contaminant meetings on the use of evidence from the most current epidemiological studies in the chlorpyrifos risk assessment.

DAS Comment: In many of the in vivo and in vitro studies, cholinesterase has not, in fact, been measured. Most of the studies have employed doses (> 1 mg/kg/day) that are certainly associated with RBC cholinesterase inhibition and this is the conservative (protective against brain ChEI)

[1] Schmidt RJ, et al., 2017; Ismail AA, et al., 2017; Burke RD, et al., 2017; Sieke C, et al., 2017; Fluegge KR, et al., 2016; Gunier RB, et al., 2017; Ismail AA, et al., 2017; Muñoz-Quezada MT, et al., 2017; Rousis NI, et al., 2016; Gunier RB, et al., 2016; Mamczarz J, et al., 2016; de Gavelle E, et al., 2016; and Rohlman DS, et al., 2015.

endpoint upon which regulatory bodies globally base human exposure limits. In the case of the ZF studies and evidence that has been brought forward, there are design flaws and methodological confounders (use of DMSO as a carrier) that prevent this line of evidence from supporting the contention that chlorpyrifos in ZF is causally linked to neurobehavioral toxicity, particularly at exposures below where ChEI occurs. In fact, in many of the studies cited, ChEI was not measured and in some cases where it was, inhibition was reported, thus, contradicting the overarching statement about a causal link at low chlorpyrifos exposures.

> **HHA Response:** HHA reviewed the neurodevelopmental studies on behavior and cognition effects and identified those where effects are either as sensitive as or more sensitive than AChE inhibition (see discussion in the revised evaluation).
> With respect to DAS comment on the use of DMSO as a carrier, please see HHA responses to DAS comments from August 18, 2017.

DAS Comment: In a review of the studies, cholinesterase activity was measured in most studies, but not in others. Thus in those studies in which it was not measured, it cannot be claimed that there are effects below the threshold for cholinesterase inhibition.

In those studies in which cholinesterase activity was measured, the vast majority showed decrements (i.e., inhibition) in cholinesterase activity which is completely incongruent with the DPR statement that there is ample evidence for neurodevelopmental/behavioral effects below the threshold for cholinesterase inhibition because not only was ChEI measured, but in fact a review of the 'effects' reported, failed in the vast majority of studies to find any effects below the threshold for ChEI.

DAS would contend that there is almost no evidence (not ample evidence as contended by DPR) to support the case for neurodevelopmental and behavioral effects below the threshold for cholinesterase inhibition.

> **HHA Response:** See HHA responses earlier in this memorandum and also the reviews of the recently published studies by Silva et al., 2017 and Buntyn et al., 2017 in the revised RCD.

DAS Comment: 1) DAS would reiterate strongly that this statement also fails to consider two published, GLP, guideline-compliant studies conducted as part of the required registration process and which in fact did employ dose levels below (in some cases well below) 1 mg/kg/day and evaluated not only cholinesterase inhibition but neurotoxicological outcomes/findings as well. The developmental neurotoxicity study (Maurissen et al 2000) employed dose levels of 0.0, 0.3, 1, and 5 mg/kg/day, while the comparative cholinesterase assay (Marty et al., 2012) employed dose levels ranging in general from 0.05 (fully 20X lower than 1 mg/kg/day) to 5 mg/kd/day (pups) or 10 mg/kg/day (adults). 2) On another point, while DPR noted above that in its selection of critical studies it did not include studies that used DMSO or subcutaneous administration, in fact, some of the studies cited by DPR did in fact employ these experimental

facets or designs. 3) DPR notes that Carr et al (2013) and Carr et al (2014) were the only studies reporting overt toxicity with the same NOEL as AChE inhibition. A review of these two studies reveals that in Carr et al (2013) the lowest dose/exposure used was 1 mkd, which while it may be a threshold for brain ChEI, that level is certainly above the threshold for RBC ChEI, the endpoint upon which chlorpyrifos is regulated globally. While brain ChEI is the appropriate biological target, in fact, as a conservative surrogate, risk assessments globally use RBC ChEI, which is a lower threshold than brain ChEI. In Carr et al (2014), there was no reported brain ChEI, but in fact serum ChEI was reported following exposure to 0.5 mkd and thus, the statement that overt toxicity was observed at the same NOEL for AChE inhibition is erroneous in this case. There was no NOEL for serum ChEI in this study.

> **HHA Response:** 1) DPR's comprehensive risk assessments review and summarize all relevant studies available in the database. These include studies that are used to determine PoDs, as well as studies providing weight-of-evidence or support information. HHA will cite studies that employ routes of administration that mimic expected routes of exposure in humans if they provide information pertinent to the selection of critical PoDs. HHA has previously responded to DAS comments on the use of DMSO as a vehicle in toxicology studies (see August 18, 2017 DPR responses to DAS comments). In the Carr et al studies, plasma ChE (25.7%) inhibition was within the normal range of human variability, whereas enzymes involved in brain endocannabinoid metabolism were significantly inhibited at this dose.

DAS Comment: As indicated above, chlorpyrifos has been thoroughly evaluated in four standard guideline studies covering three different species and in a guideline developmental neurotoxicity (DNT) study in rats. These study designs were developed through multi-stakeholder expert input and continual review over the course of many years to explicitly include those parameters required for a thorough and robust design aimed at identification of developmental and reproductive toxicity (DART) effects. In the absence of maternal toxicity, there was no evidence of chlorpyrifos-induced postnatal developmental effects, including no evidence of physiological deficits and neurological or neurobehavioral deficits. DAS notes that there were developmental variations in the presence of maternal toxicity, but does not concur that there were developmental malformations, as noted by DPR in its 2017 Current Draft Evaluation.

> **HHA Response:** We revised the text to indicate that the effects observed in fetuses were developmental delays and variations.

DAS Comment: Further, DAS is interested in what studies DPR refers to that have measured fetal brain cholinesterase activity. Beyond these points, DAS is not aware of *in vivo* studies that confirm developmental neurotoxicity in rats or mice through an identified and confirmed mode of action and more importantly, what adverse outcome is actually reported or manifested. It is insufficient to associate a finding such as altered endocannabinoid signaling without then determining and confirming what the actual apical adverse outcome is.

The only chlorpyrifos developmental neurotoxicity (DNT) study available today that meets the study design requirements of regulatory agencies world-wide is the guideline and GLP compliant chlorpyrifos DNT study conducted by Drs. Alan Hoberman (study director) and Robert Garman (pathologist) at Argus Laboratories (Maurissen et al., 2000). The published abstract of this study is printed below and a Table from the publication is reprinted after that to denote that cholinesterase inhibition in dams was established, but that no neurodevelopmental effects were observed in the absence of cholinesterase inhibition.

> **HHA Response:** The selected statements from the DPR RCD represent summary findings from studies in rats and mice reporting altered development of the nervous system following gestational exposure to chlorpyrifos. Although ChE activity was not always measured concurrently, the doses used in these studies were previously tested with regard to effects on the ChE activity. For example, the threshold for fetal brain AChE inhibition in rats was reported as 2 mg/kg/day (Qiao et al., 2002) and the threshold for RBC AChE was about 1 mg/kg/day. However, studies in pregnant animals using doses lower than these levels found neurodevelopmental or neurobehavioral effects in the offspring (Carr et al., 2015, 2017; Silva et al., 2017). While such changes were consistently reported in the in vivo animal toxicology studies, there are limited data which establish thresholds for the neurodevelopmental effects.

DAS Comment: The histogram, shown in Figure 7 (pg. 61-62) illustrates the active (true actives + actives: red) and inactive (blue) CPF and CPF-oxon assays along with their intended target families. The histogram should be reconstructed to only focus on those data deemed by the Agency to be "truly active" (i.e., above the cytotoxicity burst) versus the inactive assays. This is consistent with verbiage in the draft report that states "the 'burst region' represents a grey area where true chemical-receptor interactions and assay interference due to cytotoxicity/apoptosis may result in a false positive response".

The value derived by the Agency as the cut-off concentration for *Burst Activity* was the same across all of the assays; however, it is likely that individual assays had inherently different "noise" associated with their *Burst*. The finding that many of the assays deemed by the Agency as *True Actives* corresponded to generalized activities that were not specific to AChE or neurotoxicity suggests these might have been secondary to non-specific basal cytotoxicity occurring within that model system but above the Agency's specified Burst cut-off value. For estrogen, androgen and thyroid receptor pathways, both chlorpyrifos and chlorpyrifos oxon compounds were only active within the burst region. This finding contradicts the Agency's indication of potential for endocrine disruption from CPF exposure at higher doses, thus, no relationship of these data to endocrine activity should be made. Moreover, chlorpyrifos has been thoroughly evaluated through the EPA EDSP program and is considered not be endocrine-active for any endpoint evaluated. No further testing by the EPA was recommended. Visually, the Toxicological Priority Index (ToxPi) was intended to represent a weighted combination of relevant data as component slices of a unit circle, with each slice representing one piece of information. The ToxPi components in Figure 9 (pg. 65-66) of the Agency's draft report

included any actives as defined on the ToxCast Website but was not broken down for true actives. The ToxPi graphs should be reconstructed to only focus on those data deemed by the Agency to be "truly active" (i.e., above the cytotoxicity burst) versus the inactive assays. This is consistent with verbiage in the draft report that states "the 'burst region' represents a grey area where true chemical-receptor interactions and assay interference due to cytotoxicity/apoptosis may result in a false positive response".

> **HHA Response:** HHA is in a process of evaluating the latest updates on ToxCast, Zebrafish models and other relevant bioassays and will incorporate the new data into the final RCD for chlorpyrifos.

DAS Comment: In addition to previously described enhancements to the PBPK model (See Section B. Uncertainty Factor of 10X for Intraspecies Variability) and subsequent comments below, DPR HHA responded to DAS that "*At the time DAS submitted the pregnancy PBPK-PD model to DPR, HHA was in the final stages of completion of its draft RCD, for which we adopted the US EPA (2014) non-pregnancy PBPK-PD modeled PoDs. We will evaluate the pregnancy model for use in estimating the internal chlorpyrifos dosimetry in the future."* DAS would strongly recommend that DPR now use the model to its full advantage in evaluating PoDs and assessing intraspecies uncertainty factors while finalizing the risk assessment for chlorpyrifos. Importantly, it is also not clear why DPR has removed characterization of the model enhancements to address pregnancy (included in the 2015 RCD) in the 2017 Current Draft Evaluation as the following text is no longer present.

> **HHA Response:** HHA examined the "Peer Review of Physiologically Based Pharmacokinetic/Pharmacodynamic Model for Chlorpyrifos" prepared by SciPinion sponsored by DAS and submitted to DPR in 2017. In this report, concerns have been raised about the model capabilities to estimate AChE inhibition in the fetus and neonate, that is "It seems, however, that the model would not be adequate to estimate PK/PD during certain specific periods, such as the fetal period and early life (months 0 to 6 months)." The discussion about the model characterization has been added back into the revised evaluation document.

DAS Comment: Poet (2015) made comparisons between pregnant and non-pregnant women by using Monte Carlo distributions (including DDEFs) to simulate human variability in response to CPF oral and dermal exposures. Results show that during pregnancy circulating CPF is decreased and CPFoxon is increased, when compared to non-pregnant women, especially at high doses (>0.5 mg/kg). RBC AChE inhibition occurs at doses that are 3-20% less than for non-pregnant women as previously predicted in the life-stage PBPK-PD model (Poet et al. 2014). The most effective dose of CPF resulting in 10% RBC AChE inhibition (ED10) is equivalent between pregnant and non-pregnant women and DDEF are consistent for all simulated populations. The PBPK-PD pregnancy model also shows 10% inhibition of RBC AChE occurring at 0.1-1.0 mg/kg/d for oral, 10-150 mg/m3 for inhalation (2 hr acute; 2 hr/d, 21-d) and 10-150 mg/kg/d for dermal (4 hr acute; 4 hr/d, 21-d). The range indicates ~10% RBC AChE

inhibition at steady-state (low value) and acute (high value). Their final conclusion was that a DDEF (extrapolation, or uncertainty factor) of 4x (protects >99% of the population) was sufficient to protect males and females, nonpregnant women and pregnant women (basically all cohorts) from dermal and oral CPF exposures.

> **HHA Response:** The US EPA 2014 risk assessment stated, "While the current PBPK-PD model Chlorpyrifos Human Health Risk Assessment accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women who may be pregnant, the agency is applying the standard 10X intra-species extrapolation factor for women of child bearing age." In 2017, the pregnancy model was published, however, the pregnancy portion of the published model was similar to the one reviewed by US EPA in their 2014 risk assessment.

DAS Comment: In Section II.B.4 of the Current Draft Evaluation, (p. 43) DPR states: *"The simulated median for 10% RBC AChE inhibition in pregnant women was at doses of 3- 20% less than nonpregnant women; however variability was also less in pregnant women). Pregnant women were only slightly more sensitive to CPF exposure than non-pregnant women; however at the 10th percentile the values were very similar. This may be due to the decreased variability introduced by the bootstrap technique."*

The use of the bootstrap technique has been shown to provide variability well beyond that measured in representative samples of a population. As shown in Table 5 of the Risk Characterization document (p. 42), the range of variability in most sensitive metabolic parameters calculated with the bootstrap analysis was shown to be 3.5-10-fold wider than those reported by Smith et al. (2011), and 2-fold wider than variability seen in metabolic activity from large microsomal sample studies (Crespi, 2009, Parkinson 2004, Zhang 2015).

The slightly lower variability predicted in pregnant women is most probably due to one or more biochemical or physiological changes during gestation. For example, metabolic conversion of chlorpyrifos to oxon is predicted to increase slightly during pregnancy, while detoxification to the TCPy metabolite would decrease (Poet 2017), which could reduce inter-person variability. Also, partitioning of chlorpyrifos from blood into tissues would be expected to decrease as well, since lipid content in plasma increases during gestation (Poet 2017), which could result in decreased intraspecies variability in metabolic clearance…

These important changes are included in the CPF model for pregnancy, built on the lifestage platform so either age-specific parameters or initial body weight-specific parameters can be used as the initial condition at the beginning of gestation. All model additions, changes, mathematical implementations, and model code are included in the Pregnancy PBPK model report, submitted to the US EPA in April 2015 (Poet 2015) and to CA DPR in August 2015. For all simulations in

that report, either age was set to 30 years, or a body weight of 69 kg, consistent with US EPA, 2015 and the Exposure Factors Handbook mean body weight for females (US EPA 2011, Table 8-5). DAS recommends that DPR revisit its commitment to reviewing updates to the model to estimate dosimetry and application to risk assessment as we believe that this demonstrate convincingly that the 10X UF for intraspecies variability (owing to possible biological/physiological changes during pregnancy lifestage) can be reduced to 4X which is scientifically robust and supportable.

> **HHA Response**: We corrected the statement from the Poet et al (2017) summary by using DAS suggestions above regarding variability and the bootstrap technique. We have presented and discussed the PBPK-PD model additions, changes, sensitivity tests, impact of model variability and model uncertainties in the revised draft. DPR has reviewed dosimetry updates and our position remains that a default 10x intraspecies factor is necessary due to database deficiencies described in the 2015 and 2017 chlorpyrifos risk assessments.

DAS Comment: DAS disagrees strongly with the DPR contention and perspective that the "combination of these effects is a Tier 1 screening indicator that CPF has endocrine disrupting effects." DAS notes that the Current Draft Evaluation contains significantly more information on ToxCast results and assays and would remind DPR and all interested parties about the caution EPA places on ToxCast data particularly relative to its utility and appropriateness for predictive toxicity purposes.

> **HHA Response:** HHA removed the discussions on indicators of endocrine disrupting effects for CPF in the revised RCD.

DAS Comment: The Columbia study is not useful for addressing the question of whether neurodevelopmental effects occur at exposure levels lower than those associated with acetylcholinesterase inhibition or for additional uncertainty factors. The Columbia study alone is not sufficiently robust to make a causal inference of any given health effect and chlorpyrifos exposure. In following several hundred children for a more than a decade, the Columbia study has reported associations of several adverse health associations with prenatal chlorpyrifos exposure as measured in cord blood. The study has also reported adverse health associations with exposure to air pollution, bisphenol A, lead, phthalates, polybrominated diphenyl ethers, and second-hand smoke (http://ccceh.org/our-research/scientific-papers), demonstrating the large scope of the study, and multifactorial nature of childhood development. A number of limitations of the study have been highlighted in several publications, public comments and FIFRA SAPs.

1. All of the Columbia chlorpyrifos-related publications are based upon a single spot sample collected for exposure. This sample was collected at the time of the birth of the child. It was not timed with an application, nor can it be used to determine exposure *in utero*.
2. The analytical method used in the Columbia study has not been validated at the low concentrations reported in maternal/cord blood from Columbia study subjects.

3. The Columbia study analyses made no lipid adjustments to the plasma chlorpyrifos concentrations Chlorpyrifos is a lipophilic compound (log Kow 4.96), which is known to partition into lipids (Lowe et al. 2009). Recent studies have shown that the blood: tissue partition coefficients for chlorpyrifos are altered during pregnancy, consistent with documented changes in blood lipid chemistry during gestation (Lowe et al. 2009; McMullin et al. 2008). Estimates of internal exposure are best made by adjusting plasma concentrations to lipid levels (Haddad et al. 2000; Lin et al. 2002). For example, if two women were exposed to the same dose of chlorpyrifos, and one woman had higher levels of plasma lipids, her plasma chlorpyrifos concentration would be higher, even though total body burdens are equivalent, due to a higher blood:adipose partition coefficient.
4. Finally, there are credible alternative explanations for the observed effects. Because of these limitations, it is even more important to compare age and outcome specific results of the Columbia study with other epidemiology studies. There are multiple reviews in the peer reviewed scientific literature that describe the epidemiology evidence as inadequate, inconsistent and biologically implausible. (Burns et al. 2013; Eaton et al. 2008; Li et al. 2012; Mink et al. 2012; Needham 2005; Prueitt et al. 2011; Reiss et al. 2015; Zhao et al. 2005). These publications highlight that the results for chlorpyrifos reported by the Columbia investigators must be robustly compared to findings in other studies. As other researchers have noted, it is crucial to conduct quantitative sensitivity analyses when important policy decisions are to be based on the results of epidemiology research. (Burns et al. 2014; Christensen et al. 2015; Jurek et al. 2008).

   HHA Response: For clarification, HHA did not use the Columbia Center for Children's Environmental Health study to establish the point of departure (the regulatory target). The points of departure proposed in the August 2017 draft are based on cholinesterase inhibition similar to those found in the 2014 US EPA revised Human Health Risk Assessment. As explained in DPR's response to comment received from Dow AgroSciences LLC on the December 2015 draft, the Columbia Cohort study does not provide dose-response data for quantitative risk assessment. Likewise, DPR did not set a regulatory target based on the Columbia Cohort, but rather quantitative assessments derived from physiological-based pharmacokinetic-pharmacodynamic modeling. However, DPR has an obligation to review all data concerning any potential human health effects from exposure to chlorpyrifos as part of the department's completeness and transparency of the risk assessment process. Therefore, DPR did its due diligence to critically review all ongoing epidemiological studies that are investigating associations between potential gestational environmental exposures and health outcomes in offspring later in life.

DAS Comment: The CA DPR's Draft Evaluation is an early-tier screening level assessment. The comments provided show that multiple factors in the assessment unrealistically over-estimate bystander exposure and resulting risk. Refinement of even some of these factors is possible and will reduce estimated exposure and risk thousands of fold and show that current

buffers are adequate and protective of human health. The current draft evaluation is not robust enough for regulatory decision-making and is inconsistent with labeled uses, and these refinements should be incorporated before any additional restrictions are placed on the use of chlorpyrifos. With these refinements, chlorpyrifos is shown not to meet the criteria as a potential toxic air contaminant.

- The current regulatory endpoint is protective and there is no compelling, reliable, and valid scientific (animal or human) evidence that chlorpyrifos exposure is linked with neurodevelopmental effects in humans below this endpoint. There is no scientific basis for the additional 10X Uncertainty Factor (UF) proposed in the draft evaluation.
- While epidemiology studies are cited as evidence of a link between chlorpyrifos and neurodevelopment effects, a full analysis of available studies does not support such a claim. Other regulatory agencies have concluded that the epidemiology studies do not justify the claim of a causal association between chlorpyrifos exposures and neurodevelopmental effects, and have confirmed cholinesterase inhibition as the protective regulatory endpoint.
- Overly conservative dermal and non-dietary oral exposure estimates further compound the over-estimation of risk and can be refined.
- Real-world incident and monitoring data indicate DPR's draft evaluation over-estimates actual exposure and therefore risk. The current draft evaluation also significantly overestimates potential exposure and risk.
- Acceptable MoE's can be obtained through refinements in key aspects of the assessment:
- Use of PBPK modeling to develop Points of Departure (PoD) that more accurately reflect real-world exposure scenarios, (2) Modeling a more realistic particle-size distribution of potential drift; (3) Updating the interspecies Uncertainty Factor (UF); (4) Reduction of the additional 10X UF based on claims of potential neurodevelopmental effects.

In conclusion, the current regulatory endpoint is protective of all potential health effects. Further scientifically-valid refinements to the assessment show that current uses have accepted MoEs, existing buffers are protective, and chlorpyrifos does not meet the criteria to be classified as a Toxic Air Contaminant.

> **HAS Response:** The 2107 RCD followed the latest US EPA practices and guidance documents to estimate more refined exposure and risks. For example, HHA employed the human US EPA's PoDs from the PBPK-PD model and their highly refined dietary exposure assessment. In addition, HHA conducted its own CA-specific probabilistic drinking water exposure assessment and a spray-drift exposure assessment based on the latest US EPA guidance document.