Brian R. Leahy
Director

Department of Pesticide Regulation

Edmund G. Brown Jr.
Governor

M E M O R A N D U M

TO: Shelley DuTeaux, PhD MPH
Chief
Human Health Assessment Branch

VIA: Svetlana Koshlukova, PhD — *[original signed by S. Koshlukova]*
Senior Toxicologist
Risk Assessment Section

Eric Kwok, PhD DABT — *[original signed by E. Kwok]*
Senior Toxicologist
Exposure Assessment Section

FROM: Carolyn M. Lewis, MS DABT — *[original signed by C. Lewis]*
Research Scientist III
Risk Assessment Section

Mai Ngo, PhD — *[original signed by M. Ngo]*
Staff Toxicologist
Exposure Assessment Section

Terrell Barry, PhD — *[original signed by T. Barry]*
Research Scientist IV
Exposure Assessment Section

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SUBJECT: Response to U.S. EPA's Comments on DPR's Dicrotophos RCD

The Department of Pesticide Regulation's Human Health Assessment Branch (HHAB) posed charge questions to U.S. EPA when submitting our Risk Characterization Document (RCD) for dicrotophos dated December 30, 2015 for review. The charge questions posed, U.S. EPA's response, and HHAB's subsequent comments follow.

Charge Question 1: A BMD (benchmark dose) analysis was conducted by DPR on all of the studies with brain ChE data using the exponential models and the Hill model to identify critical NOELs.

U.S. EPA's Response: *As part of the EPA Registration Review risk assessment for dicrotophos, a robust analysis of updated BMDs was performed and documented in Appendix 2 of the dicrotophos risk assessment. The BMD output files are also available in the BMD memo by Liccione and Holman (D414900, TXR 0056878 dated 1/28/2014, 438 pgs). As with DPR, the EPA relies on a BMR (benchmark response) of 10%, with the*

estimation of the $BMDL_{10}$ as an alternative to the NOAEL. The EPA relies on the BenchMark Dose Software (BMDS) as it consists of a nested family of 4 increasingly complex models that are fit simultaneously by the software. The Hill Model does not afford this flexibility. The Technical Briefing in August 2001 and the Science Advisory Panel (SAP) meeting of September 2001[1] centered on the potential for a flat region in the low dose portion of the dose-response curve. This potential low-dose flat region was explored by the EPA, with the subsequent revision of an equation to improve model fits. The SAP agreed with this approach and noted that the equation improved fits for many OPs with little response at low dose levels. Therefore, as part of the extensive review of the BMD modeling approach, the EPA practice is to rely on the lowest AIC score or best fitting model among the various models, including both Exponential and Hill models, as well as to ground truth the estimated 10% inhibition dose observed in the study. As part of the ground truthing process, data quality (e.g., dose spread, variability) and visual inspection of the model fits are taken into consideration besides statistical criteria.

The DPR Risk Characterization document for dicrotophos did not present the various model AIC scores in order for the EPA to compare with the Exponential models, therefore the EPA could not determine if the Hill Model indeed fit the data better than the Exponential model. If DPR provides the AIC scores then EPA is willing to review and discuss their conclusions. A general comment from the review of the DPR risk characterization document is that both DPR and the EPA spent many resources updating BMDs for the dicrotophos assessments.

HHAB's Comment: U.S. EPA's document with the BMD analysis for dicrotophos does not appear to include any output for the Hill model. HHAB has added an appendix to the revised RCD for dicrotophos that includes the BMDS output that is exported to Excel. Including the individual output files for each model run would be too voluminous. The output exported to Excel includes not only the AIC for each model, but the p-vales for the 4 tests for fit, the scaled residuals and the BMD and BMDLs. Under each batch run is a note explaining the reasons for the model selection. In many cases HHAB selected the same exponential model as U.S. EPA, but there were a number of cases were the Hill model had a lower AIC and a lower BMDL. HHAB agrees that in general the model with the lower AIC should be selected. There was one exception in the 28-day inhalation brain ChE data for males. The exponential model 2 had the lowest AIC and scaled residuals, but HHAB selected the exponential model 4 because the Test 4 p-value was larger indicating a better fit. Also, the BMDL for the exponential model 4 was lower, so it was considered more health protective. It appears that U.S. EPA does not always adhere to using the model with the lowest AIC. One example was with the brain ChE data for males in the 28-day dermal study. U.S. EPA selected the exponential model 4 even though model 5 had a lower AIC, noting a better visual fit with model 4. HHAB recognized that

[1] *Preliminary Cumulative Hazard and Dose-Response Assessment for Organophosphorus Pesticides: "Determination of Relative Potency and Points of Departure for Cholinesterase Inhibition." September 5 and 6, 2001. Available at: https://www.epa.gov/sap/fifra-scientific-advisory-panel-historical-meetings*

professional judgment should be applied with the model selection, and that there needs to be some flexibility in not strictly adhering to using the model with the lowest AIC. However, in this case HHAB selected model 5 because it not only had the lowest AIC, but had the largest Test 4 p-value and the smallest scaled residuals. All of which indicated the model 5 had the best fit.

Charge Questions 2: A $BMDL_{10}$ of 0.03 mg/kg/day was selected by DPR as the critical NOEL for evaluating acute oral exposure to dicrotophos based on brain ChEI in PND8 rat pups (Moxon, 2003).

> **U.S. EPA's Response**: *The EPA relied upon the same ChE data (PND 8 and 15) from the CCA study (MRID 46153205) and same endpoint (brain ChE) as the DPR. However, the EPA BMD analysis relied upon the Exponential model instead of the Hill Model, thus resulting in a different BMD and BMDL than the DPR. The DPR Risk Characterization document did not provide the AIC scores in order to determine model fit. As indicated in the response to question #1 above, the Hill Model generally does not fit ChE data as sufficiently as the Exponential model. Therefore, the difference in the DPR acute $BMDL_{10}$ of 0.03 mg/kg/day compared to the EPA $BMDL_{10}$ of 0.07 mg/kg/day is an artifact of model selection, and the Hill Model fit cannot be verified.*

HHAB's Comment: HHAB disagrees that the Hill model generally did not fit the ChE data. In our experience, the Hill model often fits the ChE data better than any of the exponential models based on having the lowest AIC. While the difference in the BMDL between the Exponential model and the Hill model is an artifact due to model selection, the AIC for the Hill model was lower (-52.99864) than the Exponential model (models 4&5 lowest at -47.43038). HHAB stands by its selection of the BMDL derived from Hill model for this data set, which happens to be the lowest BMDL.

Charge Question 3: A BMDL of 0.025 mg/kg/day for brain ChEI from the subchronic neurotoxicity study in adult female rats was selected by DPR as the critical NOEL to evaluate the steady-oral exposure to dicrotophos (Horner, 1995).

> **U.S. EPA's Response**: *The EPA provides in each updated OP risk assessment, including the dicrotophos risk assessment, the ChE data available to determine the phenomenon known as steady state. As presented in Table 4.3.2.1 of the EPA dicrotophos human health risk assessment (page 14), both brain and RBC BMD_{10s} are presented from a single dose to repeat dosing thru 735 days. The BMDs presented are based on modeling provided in the Liccione and Holman memo (D414900 dated 1/28/2014). The Hill Model was not run for dicrotophos since the Hill Model does not typically fit ChE data as well as the Exponential models. To evaluate the point of departure for the steady state assessment, 40 BMD analyses were evaluated to support the risk assessment. The EPA practice is to then ground truth the BMDs and BMDLs for each model run. Once that step is completed, the dose spread and variability in the data are considered by looking at the mean and standard deviation (SD)*

from the dose groups and compared with the corresponding BMD and BMDL. The step is performed in order to consider the impact of dose spread and variability on the BMDL estimate since some BMDs and BMDLs may be an artifact of either dose spread or variability in the data. As part of this process, the dicrotophos team evaluated all of the model runs as presented in the dicrotophos BMD memo. However, the EPA did not rely on the lowest BMDL in the 40 runs. Instead the EPA used a weight of evidence approach and considered a number of studies for the steady state endpoint of brain ChEI with a BMD_{10} of 0.04 mg/kg/day and $BMDL_{10}$ of 0.03 mg/kg/day, rather than a single BMD of and BMDL of 0.0025 mg/kg/day from the SCN.

HHAB's Comment: First by way of clarification, HHAB's BMDL from the subchronic neurotoxicity study in rats is 0.025 mg/kg/day, not 0.0025 mg/kg/day. HHAB was unable to find documentation for practice of ground truthing the BMDs and BMDLs for each model run (Liccione and Holman memo; D414900; Jan 28, 2014). Therefore, the rationalization involved in deriving one BMDL that is not specific to a given data set is not entirely clear. In general, it has been HHAB's practice to select the lowest NOEL or the lowest BMDL, particularly if the BMDL has the lowest AIC and adequately fits the data. The Hill model produced the lowest AIC with BMDLs of approximately 0.025 mg/kg/day for females at 3 different time points in the subchronic neurotoxicity study. This value was the most representative yet health protective point of departure (POD) to use for evaluating steady-state exposure. Finally, our BMDL of 0.025 mg/kg/day from the subchronic neurotoxicity study in rats is essentially the same as the U.S. EPA's steady state endpoint (BMDL of 0.03 mg/kg/day) for the of brain ChEI.

Charge Question 4: A $BMDL_{10}$ of 2.1 mg/kg/day from the 28-day dermal study in rats was selected by DPR as the critical NOEL to evaluate dermal exposure for both short-term and steady-state exposures (Noakes, 2001).

U.S. EPA Response: *There are a number of differences between DPR and EPA on how the dicrotophos dermal hazard assessment was evaluated. First, the EPA relied on a route specific 28-day dermal toxicity rat study (MRID 46484501) that provided brain ChE inhibition data for use as the endpoint and point of departure for the dermal risk assessment. A BMD_{10} of 3.3 mg/kg/day and $BMDL_{10}$ of 2.1 mg/kg/day was established by EPA based on brain cholinesterase inhibition data in females. The EPA then accounted for the differences in skin permeability of the rat skin compared to human skin by applying the rat and human in vitro data. Specifically, the refined dermal equivalent dose (RDD) for human skin was derived by applying a ratio of animal and human absorption values obtained from in vitro data (MRID 45099502). The RDD was calculated according to current OPP guidance as outlined below:*

Refined Dermal Equivalent Dose (RDD) (mg/kg/day)=

$$\textit{Dermal PoD (mg/kg/day)} \times \frac{\textit{Animal In Vitro Absorption (\%)}}{\textit{Human In Vitro Absorption (\%)}}$$

The DPR risk characterization document was difficult for the EPA to review as the various steps taken to perform the dermal hazard assessment were not clearly outlined. The DPR relied on the same dermal BMD and BMDL as the EPA. However, the EPA and DPR calculated slightly different absorption values for both rats and humans based on policy differences (e.g., use of mean values vs. 95% upper confidence limit values, inclusion vs. exclusion of residues on the skin). The DPR also appeared to adjust for the number of hours of exposure of rats and humans (6 hours vs. 8 hours), which is not current practice for the EPA. It also appears that DPR then refined the rat dermal toxicity study by applying the triple pack studies, including the in vivo data, to an already route specific dermal study. It is noted that for the EPA the use of all triple pack studies is only applicable to an oral study, not a route specific dermal study. Therefore, this step is not consistent with practices used by NAFTA countries for applying dermal absorption data, and essentially double counts the in vivo dermal absorption potential in the rat study. The DPR also states in the risk characterization document that a human "internal" dose was calculated of 0.92 mg/kg/day, which is lower than the original rat dermal BMDL of 2.1 mg/kg/day, which would imply that dermal absorption would be greater for humans than in rats. The lower point of departure does not make sense based on ground truthing the triple pack dermal data. A higher point of departure would be expected when applying in vitro data given rat skin is generally 3-10 times more permeable than human skin. As a result, the EPA does not support the current dermal assessment performed by DPR.

HHAB's Comment: There was no disagreement regarding the BMD analysis for the 28-dermal toxicity study. The difference between U.S. EPA and HHAB lays in the adjustments for dermal absorption. U.S. EPA used external dosages for PODs and exposure. HHAB used internal dosages because we aggregate worker dermal and inhalation exposures. HHAB's Risk Assessment Section (RAS) used the rat *in vivo* dermal absorption study to adjust the BMDL to an internal dose. HHAB's Exposure Assessment Section (EAS) used the *in vitro* animal, *in vitro* human, and *in vivo* animal dermal absorption data (taken together as the "triple pack") to determine an appropriate human dermal absorption factor (DAF). This is consistent with the NAFTA Dermal Absorption Group Position Paper On Use of *In Vitro* Dermal Absorption Data in Risk Assessment (NAFTA TWA, 2008). The human DAF was applied to calculations of the internal dose resulting from occupational and bystander exposures to dicrotophos. Both U.S. EPA and Health Canada's PMRA have utilized the triple pack method for assessing dermal absorption values for the purpose of risk assessment (please refer to HHAB comments to U.S. EPA response for Charge Question 8). From the response above, U.S. EPA appears to have a different interpretation of the "triple pack" approach was applied to dicrotophos exposure and risk assessment than HHAB.

Charge Question 5: A $BMDL_{10}$ of 0.42 g/L from the 28-day inhalation study in rats was selected by DPR as the critical NOEL to evaluate inhalation exposure for workers and bystanders for all exposure durations (Blair, 2010).

U.S. EPA Response: *The EPA and DPR relied on the same study (MRID 48146702) and ChE data for the inhalation assessment. However, DPR noted an error in the EPA BMD analysis for the inhalation study. Therefore, the EPA corrected the input error and updated the inhalation BMD analysis to a sample size of 5 animals/sex/dose instead of the 10 animals/sex/dose previously analyzed at the high dose. The updated inhalation BMD output file is now available (Liccione, D432892, TXR 0057426). The updated analysis presents a comparison of both the Exponential and Hill models along with corresponding AIC scores and p values. It is noted that the Hill model was not the most appropriate; the Exponential model AIC score was lower and adequately fit the data. Therefore the Hill model is not the best fitting model to the inhalation data. This is in contrast to the DPR statements throughout the risk characterization document that the Hill Model typically fits better. The updated BMD and BMDL values are higher than the previous EPA values of 0.67 and 0.62 µg/L/day, respectively. Therefore, the updated Exponential model with BMD/BMDL of 0.705/0.652µg/L/day will be used in the EPA dicrotophos risk assessment. In contrast, the DPR relied on the Hill model with a resulting BMDL of 0.42 µg/L/day. This is not supported by the model fit and appears to be an arbitrary selection of the lowest BMDL number without consideration of AIC values and ground truthing the ChE data. Another difference in the inhalation assessment is that the EPA does not convert to internal dose as the DPR indicates. The EPA provided the oral equivalent dose for the inhalation assessment since the exposure assessment is not relying on air concentrations but instead on mg/kg/day. The rat inhalation toxicity study was performed over 6 hours/day, therefore the conversion equation also includes 6 hours exposure for both non-occupational and occupational assessments. Overall, differences in BMD policy between the EPA and DPR as well as in modeling practices that ultimately lead to differences in the dicrotophos inhalation point of departure between the two agencies.*

HHAB's Comment: HHAB derived the BMDL value of 0.42 µg/L/day from male brain ChE data by using the Exponential model 4 rather than the Hill model. The BMD and BMDL that U.S. EPA obtained after correcting the group size is the output from the Exponential Model 2. Model 2 does have the lowest AIC, but Model 4 had a higher p-value for Test 4 indicating it had a better fit and visually it appears to have a better fit near the BMD and BMDL. When considering both male and female brain ChE data, the results from Model 4 were more similar to output from other models, with the exception of Model 2. Therefore, HHAB considered Model 4 output more representative and more health protective.

Charge Questions 6: DPR RAS concluded there was insufficient evidence to conduct a quantitative assessment for carcinogenicity based on the increase in thyroid tumors in male mice observed in a 105-week oncogenicity study (Milburn, 1998).

U.S. EPA Response: *The EPA also concluded there was insufficient evidence for carcinogenicity for dicrotophos. However, it is noted that DPR reviewed ToxCast assays for informing the thyroid tumors observed in cancer study. The EPA cautions DPR that the*

thyroid pathway is not sufficiently developed for use by ToxCast and therefore should not be relied upon or used to inform risk assessments.

HHAB's Comment: No conclusions were draw from the ToxCast data in HHAB's discussion. The evidence for thyroid tumors was insufficient without consideration of the ToxCast data because the increase was only seen in one sex in one species. The ToxCast data was discussed to provide some possible non-genotoxic mechanisms for the thyroid tumors. However, DPR did not make any assumptions in this regard. A sentence was added to the RCD indicating that the thyroid pathway has not been fully developed in ToxCast at this time.

Charge Question 7: Dietary and drinking water exposure were evaluated by DPR using a deterministic approach with mean residues in cottonseed oil from field trial studies and a probabilistic approach with residues in finished drinking water from the PDP database, respectively.

EPA Response: *The DPR relied upon a slightly lower point estimate for the cottonseed oil (0.0367 ppm) than the EPA (0.043 ppm). This point estimate came from using 1/2 LOQ (level of quantification) for the non-detect (nd) while the EPA used the full LOQ. The DPR also relied upon PDP drinking water monitoring samples while the EPA relied upon the EPA's Environmental Fate and Effects Divisions (EFED's) modeling distributions of Estimated Drinking Water Concentrations (EDWCs) for the estimate. The EPA practice is not to rely on PDP water samples for risk assessment. These differences lead to differences in resulting risk estimates.*

HHAB Comment: It appears that there are two sources for the difference in cottonseed oil residue values used by DPR and U.S. EPA. First is the selection of ½ LOQ vs. full LOQ. Second, is that is appears that U.S. EPA may be using different residue studies which may not have been submitted to DPR. That being said, the differences in residue values used for dietary exposure from cottonseed oil are minor when compared to the differences in drinking water estimates derived from modeling versus USDA Pesticide Data Program (PDP) values. The modeling approach may represent a worse-case scenario. The PDP drinking water data may represent a lower bound estimate of exposure because of sampling may miss peak concentrations. HHAB's current practice is to use residues from DPR surface and ground water programs to derive an upper bound estimate of exposure. However, DPR is not currently monitoring for dicrotophos because it has no registered uses in California. HHAB recognizes these issues and is in a process of updating its own risk assessment guidance, including guidelines for modeling of the drinking water exposure and the incorporation of California-specific drinking water data from the State Water Resources Control Board.

Charge Question 8: A mathematical approach in qualifying in vitro dermal absorption data for use in exposure assessment is being used by DPR for the first time. Since a peer review of this approach has not been performed, a level of uncertainty is case upon the dermal exposure estimates.

U.S. EPA Response: *The EPA does not agree with a new mathematical approach since the steps used to apply triple pack data when using an oral endpoint has been agreed upon by NAFTA countries*[2]*. These steps are used on toxicity data to adjust an oral point of departure with data from the full triple pack studies to calculate a refined dermal equivalent dose. DPR has taken part in discussions for particular chemicals (e.g., linuron) where these steps have been applied and DPR has been in agreement with the EPA on the application of these steps. The EPA was not certain of the various steps taken by DPR in adjusting the dermal absorption for dicrotophos as it was not outlined in one place in the DPR risk characterization document. It appears that a ratio of the 95% upper confidence limit values from animal in vitro and animal in vivo studies was used in order to determine the reliability of the data by comparing to unity and then DPR assumed human in vivo absorption was equivalent to the 95% upper confidence limit value from the human in vitro data. It was not clear how this human in vivo value was then used for risk assessment since it seems that only the in vivo rat dermal absorption value was used to adjust the rat dermal toxicity point of departure. The EPA calculates the same ratio for animal data; however, it is calculated using mean values and it is no longer compared to unity. A ratio of ≤3 is considered adequate based on a review of well-conducted triple pack studies to date and allows for variability often observed in these in vitro studies*[3]*. Although this ratio is calculated as part of the triple pack evaluation, the critical criterion for accepting triple pack data are related to protocol similarities (e.g., same test material, similar doses, similar methodologies, etc.) according to current guidance. As described above, when a point of departure from a rat dermal toxicity study is used to evaluate risks from dermal exposures, the EPA applies the ratio of the human and animal in vitro studies to calculate a refined point of departure since in vivo dermal penetration has already been accounted for inherently in the dermal rat toxicity study. As such, the EPA recognizes the differences in policy for mathematical approaches evaluating the reliability of triple pack data, but does not agree with how DPR has utilized the dermal absorption data for risk assessment.*

HHAB Comments: The NAFTA Dermal Absorption Group Position Paper On Use of ~~*I*~~*in Vitro* Dermal Absorption Data in Risk Assessment (NAFTA TWA, 2008) discusses the use of *in vitro* animal and human and *in vivo* animal dermal absorption data in combination to derive a human dermal absorption factor (DAF) (the "triple pack" method). This method is based on the assertion that *in vitro* data alone is unreliable for the determination of a human DAF. The triple pack method has been utilized by both U.S. EPA (2008; 2010; 2013) and PMRA (2011; 2015), two of the main developers of this approach. Additionally, the OECD guidance cited in the agency's review of the dicrotophos RCD states that, "The term "Triple Pack" refers to the three

[2] NAFTA Dermal Absorption Group position paper on use of *in vitro* dermal absorption data in risk assessment (2008).
[3] OECD (2011). OECD Guidance Notes on Dermal Absorption Values. Environmental Directorat, Organisation for Economic Co-Operation and Development. Paris, 2011.

types of dermal absorption study: 1) *in vivo* animal; 2) *in vitro* animal; and 3) *in vitro* human ... The combined use of data from the three studies and two testing systems offers the potential for greater accuracy in estimating human dermal absorption because it corrects for the generally higher permeability of animal skin compared to human skin. Application of the data to refine dermal absorption values can vary between regulatory authorities…" (OECD, 2011)

With the triple pack, the ratio of the *in vitro* animal to *in vivo* animal data is taken to determine how well the *in vitro* test conditions predict *in vivo* dermal absorption. If this ratio is approximately one (1), the conclusion would be that the *in vitro* test conditions are suitably predictive and the *in vitro* human dermal absorption derived under the same experimental conditions as the animal study may be used as an approximation of the human dermal absorption factor. HHAB has gone a step beyond the triple pack method defined in the NAFTA position paper (2008), by calculating a 95% confidence interval for the estimated human DAF. This could be considered a refinement of the method since it takes into account data quality and variability. The refined human DAF of 26.3% was used to adjust the external dermal doses from the 28-day dermal rat toxicity study to internal doses.

Charge Question 9. Worker exposure estimates by DPR were based on PHED surrogate data and do not consider newer available data.

> **U.S. EPA Response:** *EPA recognizes that DPR has not fully embraced the use of the newer available exposure data generated by the AHETF (Agricultural Handlers Exposure Task Force) at this time. The unit exposure values which EPA is currently using are available to DPR online and any supporting information can be provided to facilitate potential adoption of the current EPA values if DPR so desires. Otherwise, it is recognized as a difference between the approaches used by the two different agencies.*

HHAB Comments: AHETF provided DPR with the worker exposure database, which HHA is in the process of reviewing for use as surrogate handler exposure estimates when chemical-specific data are unavailable. Once the data evaluation is completed, the dicrotophos EAD will be updated based on AHETF data. The uncertainties attributed to PHED data for developing exposure estimates will be considered during the mitigation phase.

Charge Question 10. Aerial concentrations of dicrotophos from ground boom applications cannot be estimated by DPR due to limitations in the AgDRIFT model.

> **U.S. EPA Response:** *EPA does not assume inhalation exposure from spray drift as it would be a violation of the label. This issue is clearly described in the SOP for spray drift risk assessment included at www.regulations.gov (Docket ID EPA-HQ-OPP-2013-0676). It should also be noted that the AgDRIFT model which is the basis for this SOP is only mechanistic for aerial applications and thus does not have an inherent capability to predict inhalation exposures for bystanders from spray drift due to groundboom applications if DPR maintains the desire to calculate such values.*

HHAB Comments: During pesticide spraying, the spray plume could drift off-site via advection and contaminate the nearby areas via deposition. Accordingly, inhaling the airborne pesticide prior to its deposition and (or) contact with the contaminated surfaces after its deposition are the potential exposure pathways. Unlike agricultural handers, the existing label language on Restrictive Entry Interval (REI) does not apply to bystanders. Hence, even though the aerial application of pesticide is in compliance with the product label, exposure pathways including inhalation could potentially occur.

As correctly pointed out by U.S. EPA, AgDRIFT model is not designed for predicting inhalation exposure from spray draft due to ground boom. For this reason, such a prediction was not performed in the dicrotophos exposure assessment.

Charge Question 11: DPR RAS used 10% brain ChEI in rats as the critical toxicity endpoint for short-term and steady-state exposure to dicrotophos for all scenarios. Therefore, the target MOE was 100 assuming humans are 10-fold more sensitive than rats and there is a 10-fold variation in the sensitivity of the human population.

> **U.S. EPA Response**: *The EPA is in agreement with DPR regarding the 10% change in brain ChE inhibition as the critical toxicity endpoint as well as the 10x intraspecies and 10x interspecies uncertainty factors. However, as DPR is aware from the EPA dicrotophos risk assessment, the EPA is also retaining a 10x FQPA factor for all lifestages except for adults 50-99 to account for potential sensitivity observed in the epidemiological literature.*

HHAB's Comment: There is no disagreement with U.S. EPA, so no additional comment is needed.

Charge Question 12: DPR RAS is considering the use of an additional uncertainty factor of 10 with dicrotophos to protect infants, children and women of child-bearing from potential neurodevelopmental toxicity by non-ChE mechanisms (U.S. EPA, 2015d).

> **U.S. EPA Response**: *The EPA is currently retaining the 10x FQPA factor for all OPs for protection of infants, children and women of child-bearing age.*

HHAB's Comment: HHAB will take this into consideration in reevaluating whether to apply an additional 10X uncertainty factor to all OP's for possible neurodevelopmental effects through non-ChEI mechanisms.

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