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DATE: July 30, 2021

SUBJECT: RESPONSES TO COMMENTS FROM EXTERNAL PEER REVIEW OF THE CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION TOXICOLOGICAL PRIORITY INDEX (TOXPI) PRIORITIZATION FRAMEWORK FOR PESTICIDE EXPOSURE AND RISK ASSESSMENTS

On April 5, 2019, Human Health Assessment (HHA) Branch received comments on the proposal of Department of Pesticide Regulation (DPR) "Toxicological Priority Index (ToxPi) Prioritization Framework for Pesticide Exposure & Risk Assessment" from four external peer reviewers via an Interagency Agreement between the California Environmental Protection Agency and the Regents of University of California according to 2006 California Environmental Protection Agency External Scientific Peer Review Guidelines[1]. The four reviewers as nominated by the University of California, Berkeley (in alphabetical order) were Dr. Janice Chambers of Mississippi State University, Dr. Richard Fenske of University of Washington, Dr. David Reif of North Carolina State University, and Dr. Mark Robson of Rutgers University. Each of the reviewers was requested to comment on whether the proposal is "based upon sound scientific knowledge, methods, and practices" via addressing three specific charge questions. Of the four reviewers, Dr. David Reif and Dr. Mark Robson accepted the proposal with no revision. However, after the completion of this study, a newer version of ToxPi software (i.e., software version 2.3 available at https://toxpi.org/) becomes available; hence, Dr. Reif recommended updating the ToxPi constructions with the latest version of the software. Because comments

1 Senate Bill 1320 (Sher), Chapter 295, statutes of 1997, mandates that before any CalEPA Board, Department, or Office adopts a final version of a rulemaking, the scientific findings, conclusions, and assumptions on which the proposed rule are based must be submitted for independent external scientific peer review. This requirement is incorporated into the California Health and Safety Code Section 57004. The current Guidelines are available at https://dtsc.ca.gov/wp-content/uploads/sites/31/2018/07/Cal-EPA-ESPR-Guidelines.pdf. Under the current Interagency Agreement, the University of California, Berkeley provides nominations of qualified candidates for expert reviews of other technical work products of interest to the People of California, https://ceparev.berkeley.edu/other-peer-reviews/

from the remaining two reviewers are not extensive, instead of developing a separate memorandum for each of these reviewers, we combined responses to the comments from Dr. Chambers and Dr. Fenske, below.

Charge Question 1. Five product profile indices are proposed for characterizing exposure and toxicity potentials of a pesticide product for prioritizing products for entering into the pesticide exposure and risk assessments.

Comment # 1: Dr. Chambers commented that, "*in order to consider the risk to humans, the data on which human hazard assessments are based must be used, in most cases the mammalian data on rodents and non-rodent species that have been used to justify the pesticide's registration. These toxicity data are not used in the ToxPi approach,*" and that "*the document equates the proportion of active ingredient to potential toxicity to the human receptor without considering mode of toxic action, short-term or long-term toxic effects (i.e., hazard), dose-response assessment including threshold/no observed adverse effect level (NOAEL) (i.e., part of the hazard assessment within the risk assessment paradigm) arising from the mammalian data. So the conclusions overstep the information that can be derived from the ToxPi approach. The PPI is absolutely a valuable part of the ToxPi calculation, but it refers to only exposure assessment, not risk assessment (because it does not have appropriate hazard data for potential human toxicity). The document and Conclusion 1 should not refer to toxicity potential, but only to exposure potential."*

Response: We agreed with the comments that PPI_{norm} construction should consider experimental toxicity data such as toxicity threshold point of departure (POD) values (e.g., no-observed-effect-level [NOEL] or lower bound benchmark dose [BMDL]). Also, to ensure the definition of PPI is compatible with other activity-specific exposure indices, its deviation was modified by specifically expressing the index as a function of exposure and renaming it "Product Exposure Index (PEI)." Toxic potency of a pesticide can be characterized by its toxicity threshold (the POD), derived from a no-observed-effect-level (NOEL) or lower bound benchmark dose (BMDL). Because 100 is a commonly accepted margin of exposure (MOE) for non-carcinogenic risk, a NOEL/100 or a BMDL/100 can be considered as a dose which does not represent a health concern. After unscaling the POD by absorption factor (AF), the adjusted POD can be viewed as a baseline exposure value. Accordingly, the overall pesticide product exposure potential is then as a combination of baseline exposure and other activity-specific exposures. In term of index derivation, given that all the products have the same A.I., the normalized PEI values of all products based on an identical toxicity threshold alone would be equal to one. It is noteworthy that a POD value is generally

derived from an experimental animal study based on the technical ingredient or neat chemical (i.e., ~100%). Hence, for constructing the PEI_{norm}, the percent A.I. was used as a scaling factor to reflect that the percent of A.I. in the product is not 100%, and that the toxic effect of product is associated with the amount of active ingredient present. In other words, the baseline exposure would increase with the amount of A.I. present. Therefore, the PEI_{norm} is calculated using the percent A.I. in each product as follows:

$$\text{Product Baseline Exposure} = \text{POD}/(100 \times \text{AF}) \times \text{A.I.}$$

Where:
POD = point of departure
AF = absorption factor
A.I. = percent of active ingredient in product

$$PEI_{norm} = \frac{(\text{POD}/(100 \times \text{AF}) \times \text{A.I.})_{individual}}{(\text{POD}/(100 \times \text{AF}) \times \text{A.I.})_{maximium}}$$

$$PEI_{norm} = \frac{\text{POD}/(100 \times \text{AF}) \times (\text{A.I.})_{individual}}{\text{POD}/(100 \times \text{AF}) \times (\text{A.I.})_{maximium}}$$

For a given exposure pathway, because both "individual" and "maximum" have the same POD, constant (i.e., 100), and AF values, therefore, PEI_{norm}, can be simplified as

$$PEI_{norm} = \frac{(\text{A.I.})_{individual}}{(\text{A.I.})_{maximium}}$$

This equation is identical to the "original" PPI_{norm}. We will add texts to clarify the aforementioned approach.

Comment # 2: Dr. Chambers commented that, "w*hile little information is provided in the document regarding the nature of these illness reports, the self-reports that I am familiar with do not try to determine whether the illness relates logically to the mode of action of the pesticide, do not consider possible solvent or vehicle effects, extenuating circumstance (such as existing illness) that could be the basis of the report, or "worried well" reports from fear or anxiety. The report indicates that the illness reports were "definite, probable or possible", and the third category is certainly equivocal. So there is little confidence that these illness reports can be used to "validate" the ToxPi approach*."

Response: We acknowledged the aforementioned concerns raised by Dr. Chambers. However, in the absence of data to suggest otherwise, because of the same active ingredient was involved in the ToxPi constructions, it is not unreasonable to assume that all products elicit their toxic responses via the same mode of action and that the toxicity induced by a product can be attributed to its pesticidal active ingredient instead of its co-formulating "inert" ingredient(s). Regarding the quality of Pesticide Illness Surveillance Program (PISP) database, we are aware of its limitation for use as a "definitive proof" for the ToxPi approach. However, the observed association, or lack thereof, between the product ToxPi score and illness incidence could serve as a roadmap for obtaining the needed data for refinement (please also see response to Comment #27).

Comment #3: Dr. Fenske stated, "*The DPR report would benefit from greater discussion of its ToxPi methodology in the following areas: (1) A more detailed discussion of the Gangwal et al. 2012 paper and the ways in which the DPR analysis is similar to and different from this EPA analysis; (2) A discussion of why the five product profile indices are given equal weight in the calculation of the overall ToxPi score; (3) A discussion of why the overall ToxPi score is calculated by the simple summing of the five product profile indices*."

Response: We have added the suggested topics into appropriate sections of the final proposal. Briefly, (1) both the study by Gangwal (2012) and this study employed the ToxPi model to support the development of prioritization decision frameworks. Accordingly, a series of normalized model parameters serving as exposure surrogates was used for the ToxPi construction in both studies. However, in the study by Gangwal *et al.* (2012), the focus was on multiple pesticides. For characterizing human exposure to multiple pesticides, the model parameters employed were historical uses, environmental fate parameters, and residues on raw agricultural commodities of these pesticides. By contrast, the focus of this study was on a single pesticide active ingredient. For minimizing the inherent data uncertainties and avoiding potential bias due to missing or incomplete information on the exposure surrogates as described in Gangwal *et al.* (2012), this study derived the model parameters using activity-based exposure equations (Beauvais *et al.*, 2007; USEPA, 2012) and information available on the product labels via a publicly available database (https://apps.cdpr.ca.gov/docs/label/labelque.cfm). (2) The current proposal weighted the five product indices equally for constructing the ToxPi. The rationale of the equal-weight assignment is that for indices associated with pesticide exposures, each addresses a particular exposure scenario: HEI_{norm} for the pesticide handling, REI_{norm} for reentering into the pesticide treated areas, BEI_{norm} for the indirect pesticide usages, and IEI_{norm} for interaction with the pesticide contaminated indoor environments. For index concerning the product

toxicity, PEI_{norm}, regardless of the exposure scenarios assessed, the inherent toxicity of pesticide product is associated with the amount of active ingredient present (please see also response to Comment #1). Hence, equal-weighted assignment is a reasonable approach to reflect the unique role assumed by each of the indices. (3) Human exposure to pesticides can occur via a variety of venues and activities. However, for each of the population subgroups, pesticide exposure from each of the venues and activities may not be equal. For example, under an indoor environment, children may be exposed more to a pesticide than adult because of the longer time spent inside than outside or due to their hand-to-mouth activity. Hence, for assessing an overall exposure potential of a pesticide product in a population (i.e., adults, women of childbearing age, and children), a linearly combining these exposure indices is a reasonable approach for capturing the different exposure venues and activities exhibited by the different subgroups. Regarding the pesticide toxicity, PEI_{norm} was used to add the importance of baseline exposure to the overall exposure potential of pesticide products based on the amount of active ingredient present.

Comment #4: Dr. Fenske commented, "*One limitation in using these product profile indices for prioritizing exposure and risk assessments is their inability to incorporate information on vulnerable populations. For example, pregnant women may be a sub-population of agricultural reentry workers or bystanders; infants may be a sub-population of those who contact pesticides indoors. That said, it is clear that DPR is well aware of the importance of vulnerable sub-populations, as evidenced in the Conceptual Model presented in the report. Here "sensitive populations" and "infants and women of child bearing age" are recognized explicitly as exposure receptors. As DPR progresses in its development of this framework, it will be important to consider how vulnerability of certain population groups can be addressed more completely*" and that *" As DPR considers future use of the ToxPi method, it might be worthwhile to consider that the relative importance of product potency in the calculation of an overall ToxPi score is affected by the number of indices included in the ToxPi analysis. In the current case, product potency represents 20% of the total score. What if DPR decided to create an additional index (for example, separating bystander exposure into general population bystanders and vulnerable population bystanders)? Then product potency importance would be diminished, now representing only one-sixth of the total score. Would a change such as this make a difference in terms of product prioritization?"*

Response: The prioritizing of pesticide products that enter exposure and risk assessment requires relevant toxicity endpoints and exposure scenarios. The toxicity endpoint selected needs to protect the most sensitive human receptor of interest (e.g., women of childbearing

age) and the exposure scenarios selected need to address the highest exposure conditions associated with different life-stages (e.g., children) and (or) activity patterns (e.g., mouthing). In this study, the selection of toxicity endpoint is addressed through PEI_{norm} and the selection of exposure scenarios is addressed through HEI_{norm}, REI_{norm}, BEI_{norm}, and IEI_{norm}. As detailed in response #1, given that the same active ingredient is involved, regardless of the POD selected, the relative ranking of PEI_{norm} values is applicable to all population subgroups including women of childbearing age. With respect to the exposure scenarios, this study employed different indices for capturing exposures associated with the product handling (i.e., HEI_{norm}), reentry into the treated areas (i.e., REI_{norm}), the indirect product usages (i.e., BEI_{norm}), and interaction with the contaminated indoor environments (i.e., IEI_{norm}). Except for REI_{norm}, the normalized expression of these indices does not contain age- or gender-specific physiological parameters (e.g., body weight or breathing rate), indicating that the relative ranking of these indices is applicable to all life-stages. For deriving the REI_{norm}, the only age-specific parameter is the transfer coefficient, and as stated on page 28, this study employed the maximum transfer coefficient. As mentioned previously, the PEI_{norm} should protect other toxicological effects observed at higher doses; similarly, each of the exposure indices (i.e., HEI_{norm}, REI_{norm}, BEI_{norm}, and IEI_{norm}) should capture the highest scenario-specific exposure anticipated among different population subgroups. Hence, adding more exposure and toxicity indices would not improve the representativeness of the current proposal. However, the relative contribution of different indices (currently at 20% each) to the overall ToxPi score can be adjusted (i.e., by explicitly adjusting slice weights) to address concern for increased exposure in a specific population subgroup(s). Please also see response to Comment #11.

Charge Question 2. Normalization algorithm employed in Toxicity Priority Index (ToxPi) was used to derive the five product profile indices for recruiting pesticide products into the pesticide exposure assessment.

Comment #5: Dr. Fenske stated, "*Use of fixed exposure times is also common. In this section, however, there is only mention of a fixed exposure time for pesticide handlers rather than reentry workers (8 hours/day) and for residential bystanders rather individuals reentering treated turf (1.5 hours/day). The assignment of fixed exposure times here should be clarified.*"

Response: The fixed exposure time assignment of different human receptors (i.e., handler, reentry worker, and bystander) is consistent with the reasonable "maximum" values as

described in the worker exposure assessment polices of DPR and USEPA. We have clarified the text as suggested.

Comment #6: Dr. Fenske stated, "*For agricultural reentry, does DPR translate the lbs A.I. per acre application rate into micrograms per square centimeter foliar residue? We know that a large fraction of applied material does not reach its target (e.g., leaves) in most agricultural applications. Please clarify how mass of active ingredient per foliar surface area is determined based on the label application rate for agricultural products*."

Response: The U.S. EPA has developed an estimation method for deriving dislodgeable foliar residue value of a pesticide based on its application rate. This method is to account for the fact that, for a given application, not all the pesticide applied reaches the foliar surface, as Dr. Fenske pointed out. On page 27 of the proposal, we applied the USEPA recommended adjustment factor of 0.25, 0.02 or 0.01 (depending on the product formulation) to derive the amount of transferable residues from the cyfluthrin-containing products (USEPA, 2017). We have clarified the text as suggested.

Comment #7: Dr. Fenske stated, "*It is assumed that inhalation exposure is negligible. This assumption is probably reasonable, but it should be noted that vapor pressure for cyfluthrin is comparable to that of other semi-volatile pesticides (e.g. azinphosmethyl). We have measured azinphosmethyl on passive samplers located quite distant from treated areas following applications. At high temperatures it is likely that cyfluthrin vapors are inhaled by agricultural reentry workers; given the very low dermal absorption of cyfluthrin reported by EPA, it is possible that the inhalation route could represent a measureable fraction of STADD for these workers.*"

Response: Using the aerosol-air partition model of Mackay (2001) and assuming the total suspended particulates (TSP) in ambient air of 40 $\mu g/m^3$, the expected fraction of cyfluthrin (vapor pressure of 3×10^{-8} mmHg at 20°C) on the particulate is 84%. By contrast, using the same TSP, the expected fraction of azinphos-methyl (vapor pressure of 2.3×10^{-7} mmHg at 25°C) on the particulate is 60%, indicating that azinphos-methyl has a higher tendency to enter into vapor phase than cyfluthrin. In addition, using the AOPWIN software within Estimation Programs Interface (EPI) Suite™ (USEPA, 2015), the atmospheric half-life of cyfluthrin is ~10 hours. Because of the restricted entry interval is 12 hours, less than 10% of the vapor phase cyfluthrin is expected to be available for the inhalation exposure. Hence, dermal exposure to the dislodgeable foliar residue is expected to be the major route of exposure to cyfluthrin for reentry workers.

Comment #8: Dr. Fenske stated, "*DPR did not attempt to calculate the STADD for bystanders. Instead, DPR chose to employ the frequency of use-sites as a metric of exposure potential. Presumably, this approach was taken because of 1) the lack of bystander exposure data, 2) the unpredictability of bystander exposure, and 3) the very high variability in exposure that occur for bystanders in proximity to pesticide applications. The report would benefit from a discussion of the choice of use-site frequency as a metric of bystander exposure."*

Response: We have elaborated the discussion on the choice of use-site frequency as a metric of bystander exposure by including Dr. Fenske's aforementioned points.

Comment #9: Dr. Fenske commented, *"The DPR report argues that "products with 251 use-sites may have more avenues for unanticipated bystander contact than products with only one usesite." Probably so, but what if that one use-site is "citrus"? An enormous number of actual applications could take place within this category."*

Response: As Dr. Fenske pointed out in Comment #8, the lack of reliable data for assessing bystander exposure renders use-site frequencies as an appropriate metric for assessing the bystander exposure potential. Also, the purpose of different exposure indices is to "rank" instead of "determine" the exposure potential of products. It is plausible that a single use-site of "citrus" could result in a high exposure potential; however, if the exposure is indeed "extensive," the "high" exposure potential would likely be captured by other indices such as HEI_{norm} and REI_{norm}.

Comment #10: Dr. Fenske stated, "*Would it be possible to determine the actual number of sites treated and the frequency of treatment on an annual basis? Presumably, data for agricultural uses are available through the California Pesticide Use Reporting System."*

Response: The California Pesticide Use Reporting (PUR) System has the needed information for performing the calculations. However, the use of PUR data for prioritizing the products entered into exposure and risk assessments was avoided due to the potential missing information such as the absence of historical use and sale data on "new" products (as stated on page 29 of the original proposal). In other words, a ranking system will generate a bias outcome if the needed information exists for some but not all of the pesticide products.

Comment #11: Dr. Fenske commented that, "*this index does not incorporate "application type", a characteristic mentioned on page 9 in the Method and Data section as being relevant to product ranking. It is known that aerial applications and ground applications using airblast/power sprayers are prone to pesticide drift much more than other application methods. This has been codified by EPA in its Application Exclusion Zone rule. Would it be appropriate or practical to incorporate application type into the Bystander Exposure Index?"*

Response: Products approved for aerial application have multiple use sites (e.g., multiple crops). In the case of cyfluthrin, the BEI_{norm} captures the exposure potential of pesticide products with multiple use sites. In addition, estimating bystander exposure to pesticide from the spray drift via aerial and ground applications is part of the routine exposure assessment processes at DPR. It is noteworthy that the proposed ToxPi framework is designed to select pesticide products to be included in human exposure and risk assessments based on a set of pre-defined criteria. These criteria, however, are not "rigid," and can be modified based on expert knowledge for including appropriate source data and (or) adding additional data as measurement, technology, or databases expand.

Comment #12: Dr. Fenske stated, "*DPR may wish to reconsider the assumption of negligible inhalation exposure in light of recent findings by Zhou et al. 2018 ("Pyrethroid levels in toddlers' breathing zone following a simulated indoor pesticide spray." JESEE, September 2018). This article suggests that inhalation of resuspended dust can occur during toddler movement on treated surfaces."*

Response: The reference that Dr. Fenske refers to has been published (Zhou, J., Mainelis, G., and Weisel, C. P. 2019. Pyrethroid levels in toddlers' breathing zone following a simulated indoor pesticide spray. Journal of Exposure Science & Environmental Epidemiology 29:389-396). For characterizing post-application exposure to pesticide via the inhalation of aerosol and vapor, the USEPA (USEPA 2012) derived the following equations:

$$STADD_{aerosol} = \frac{AA \times IR}{ACH \times BW \times V_{room}} \times [1 - e^{(-ACH \times ET)}]$$

Where:
AA = amount applied (mg A.I.)
IR = inhalation rate (m^3/hr)
ACH = air changes per hour ($hour^{-1}$)

ET = exposure time (hr/day)
BW = body weight (kg)
V_{room} = volume of room (m^3)

Using the fact that $AA/V_{room} = AR \times h_{room}$, the above equation can be rewritten as

$$STADD_{aerosol} = \frac{AR \times IR}{ACH \times BW \times h_{room}} \times \left[1 - e^{(-ACH \times ET)}\right]$$

Where:
AR = application rate (mg A.I./m^2)
h_{room} = room height (m)

$$STADD_{vapor} = \frac{M_{label} \times IR}{ACH \times BW \times V_{room}} \times \left[1 - \left(\frac{\left(ACH \times e^{-k \times ET}\right) - \left(k \times e^{-ACH \times ET}\right)}{ACH - k}\right)\right]$$

Where:
M_{label} = mass of active ingredient applied, determined from product label (mg)
IR = inhalation rate (m^3/hr)
ACH = air exchanges per hour (1/hr)
k = first order decay rate (1/hr) and
ET = exposure time (hr)
BW = body weight (kg)
V_{room} = volume of room (m^3)

Using the fact that $M_{label}/V_{room} = AR \times h_{room}$, the above equation can be rewritten as

$$STADD_{vapor} = \frac{IR \times AR}{ACH \times BW \times h_{room}} \times \left[1 - \left(\frac{\left(ACH \times e^{-k \times ET}\right) - \left(k \times e^{-ACH \times ET}\right)}{ACH - k}\right)\right]$$

Where:
AR = application rate (mg A.I./m^2)
h_{room} = room height (m)

For a given population subgroup (e.g., children) and indoor environment, except for the pesticide application rate, all terms entered in these equations are identical among all

products and can be treated as "constants." Hence, the two equations above can be rewritten as

$$STADD_{aerosol} = AR \times \left(\frac{IR}{ACH \times BW \times h_{room}} \times \left[1 - e^{(-ACH \times ET)}\right] \right)$$

$$STADD_{aerosol} = AR \times k_{aerosol}$$

Where:

$$k_{aerosol} = \left(\frac{IR}{ACH \text{ x } BW \times h_{room}} \times \left[1 - e^{(-ACH \times ET)}\right] \right)$$

and

$$STADD_{vapor} = AR \times \left\{ \frac{IR}{ACH \times BW \times h_{room}} \times \left[1 - \left(\frac{\left(ACH \times e^{-k \times ET}\right) - \left(k \times e^{-ACH \times ET}\right)}{ACH - k} \right)\right]\right\}$$

$$STADD_{vapor} = AR \times k_{vapor}$$

Where:

$$k_{vapor} = \left\{ \frac{IR}{ACH \times BW \times h_{room}} \times \left[1 - \left(\frac{\left(ACH \times e^{-k \times ET}\right) - \left(k \times e^{-ACH \times ET}\right)}{ACH - k} \right)\right]\right\}$$

The STADD (mg/kg/day) due to post-application dermal exposure from hard surfaces and carpets can be expressed as the following (USEPA, 2012a):

$$STADD_{dermal} = \frac{TR \times TC \times ET \times AF_{dermal}}{BW}$$

Where:

TR = indoor surface transferable residue ($\mu g/cm^2$)
TC = transfer coefficient (cm^2/hr)
ET = exposure time (hr)
AF_{dermal} = dermal absorption factor
BW = body weight (kg)

In the absence of chemical-specific data, the transferable residue (TR) can be estimated as following:

$TR\ (\mu g/cm^2) = AR\ (\mu g/cm^2) \times F_{ai}$

Where:

1. AR is the product application rate expressed in the unit of $\mu g/cm^2$ (USEPA 2012)
2. F_{ai} is the fraction of active ingredient available for transfer (dimensionless)

Substitute the expression of TR above into the STADD equation; therefore,

$$STADD_{dermal} = \frac{AR \times F_{ai} \times TC \times ET \times AF_{dermal}}{BW}$$

For a given population subgroup (e.g., adults) and treated indoor surface (e.g., hard surface), the terms "F_{ai} (0.08, dimensionless constant)," "TC (6800 cm^2/hr)," "Exposure Time (2 hours)," "AF_{dermal}" (0.5), and "Body Weight (70 kg)" entered into the equation are identical among all products and can be treated as "constants" (k_{dermal}). Hence, the equation above can be rewritten as

$$STADD_{dermal} = AR \times \frac{F_{ai} \times TC \times ET \times AF_{dermal}}{BW}$$

$$STADD = AR \times k_{dermal}$$

$$\text{Where: } k_{dermal} = \frac{F_{ai} \times TC \times ET \times AF_{dermal}}{BW}$$

Combined the above equations with that assessing the dermal exposure under indoor environment, for a given pesticide product, the total exposure via contact with the contaminated surfaces and inhale the pesticide aerosol and vapor is the following.

$$STADD_{total} = STADD_{dermal} + STADD_{aerosol} + STADD_{vapor}$$

$$STADD_{total} = AR \times k_{dermal} + AR \times k_{aerosol} + AR \times k_{vapor}$$

$$STADD_{total} = AR \times \left(k_{dermal} + k_{aerosol} + k_{vapor}\right)$$

Eliminate the common terms k_{dermal}, $k_{aerosol}$, and k_{vapor}, the final IEI_{norm} equation for use in the ToxPi method is the following

$$IEI_{norm} = \frac{\left(AR \times \left(k_{dermal} + k_{aerosol} + k_{vapor}\right)\right)_{individual}}{\left(AR \times \left(k_{dermal} + k_{aerosol} + k_{vapor}\right)\right)_{maximium}}$$

Therefore, the normalized value of IEI (i.e., IEI_{norm}) is calculated as

$$IEI_{norm} = \frac{(AR)_{individual}}{(AR)_{maximium}}$$

This equation is identical to the "original" $IEI_{norm.}$, meaning that the original product ranking remains unchanged regardless of the exposure pathways involved. We have added text to clarify the aforementioned approach.

Comment #13: Dr. Fenske stated, *"This index is based on the amount of active ingredient in the product. It is stated on page 13 that the "amount of active ingredient in beta-cyfluthrin containing products was converted into cyfluthrin (i.e., cyfluthrin-equivalent) using the following equation: cyfluthrin-equivalent = 2 X percent of beta-cyfluthrin." However, this conversion is not part of the product potency index as described on page 28. The development of the product potency index would be more clearly described with this differential toxicity of the two active ingredients included in Appendix A, Section C. Additionally, it would be helpful if the report included an explicit statement that inert ingredients are assumed to have no effect on the toxicity of these pesticide products, and therefore no effect on product potency."*

Response: The relative potency differences between cyfluthrin and β-cyfluthrin were incorporated during the construction of PEI_{norm}. We have revised the text to state explicitly how the differential toxicity of cyfluthrin and β-cyfluthrin was incorporated into the product potency calculation and the assumed role of inert ingredients in the product potency.

Comment #14: Dr Fenske commented, "*The normalization process used for this report is consistent with the ToxPi methodology outlined by Reif et al. 2010 and used subsequently by Gangwal et al. 2012. DPR is correct in saying that algorithms for calculating pesticide exposure in humans are multivariate. The approach used here treated a number of the variables in these calculations as constants, so it was possible to simplify the algorithms in*

some cases. I am not convinced that this means that the approach used here requires less resources and information. Here are several examples: (1) The dermal absorption factor was set arbitrarily at 0.5 for all of the exposure scenarios; however, this was possible because of an implicit assumption that cyfluthrin and beta-cyfluthrin products would have identical or very similar absorption factors. For an analysis that included more active ingredients, one would necessarily substitute chemical-specific or product-specific information on dermal absorption if it were available. So if the active ingredients or pesticide products included in a similar analysis had different dermal absorption factors, then this variable would need to remain in the exposure calculations. (2) Body weight was assigned a single value in this exercise (70 kg), but a more detailed analysis would use body weights for specific population groups; e.g., male and female; children of different ages. So body weight would not be considered a constant for such calculations. (3) DPR uses a default exposure time of 8 hours per day for agricultural work, but many workshifts exceed this nominal value. A more data-driven analysis would consider variable workshifts. (4) Perhaps it is DPR's intent to address differences for the variables cited above in its full exposure and risk assessments that will follow from a ToxPi analysis."

Response: The purpose of ToxPi is to "rank" instead of "determine" the exposure potential of products. Hence, we used generic dermal absorption factor, body weight, and exposure duration for constructing the ToxPi. However, when performing a comprehensive exposure and risk assessment on cyfluthrin and β-cyfluthrin, we will use a more refined approach as Dr. Fenske correctly interpreted, "*Perhaps it is DPR's intent to address differences for the variables cited above in its full exposure and risk assessments that will follow from a ToxPi analysis*."

Charge Question 3. Using cyfluthrin and β-cyfluthrin as an example, the proposed approach is a proof of concept for selecting representative pesticide products and their associated uses for planning and scoping of the human health risk assessment (i.e., problem formulation). The proposed approach can be used for identifying the high exposure and hazard potentials of other pesticides.

Comment # 15: Dr. Chambers commented, "…., *it (ToxPi approach) cannot be used to identify the hazard potential of other pesticides since the hazard to humans is not used in the equations within ToxPi calculations. When the risk assessors start doing the risk assessments, they must incorporate the toxicity data from the mammalian studies into their approaches*."

Response: The purpose of the ToxPi proposal is to prioritize products with a specific pesticide active ingredient for entering into a comprehensive risk assessment. This proposal is not a replacement of the comprehensive risk assessment. Also, this study adopted an approach (i.e., linear additivity), which is different from the conventional means (e.g., MOE) of integrating the information of pesticide toxicity and exposure. Hence, we will modify the study title to reflect this concept, "Toxicological Priority Index (ToxPi) Framework for Prioritization Pesticide Products into Exposure and Risk Assessment." It is noteworthy that the information gathered during the prioritization (i.e., product-specific uses) and the suite of POD values (e.g., acute, subchronic and chronic POD) obtained from the comprehensive human health risk assessment could guide the development of risk mitigation measures to alleviate the health risks associated with specific uses of a pesticide product (i.e., product-specific mitigation).

Comment #16: Dr. Fenske commented, "*The concept of a "super-product" and the use of this term may need further discussion. It is possible that such a product could exist; i.e., attain the highest normalized score in each of the five indices. As the authors point out, however, there was not such a product among those evaluated. Such a product could reasonably be called a super-product; i.e., super-hazardous to human health. But applying the term "super-product collective" to nearly half of the products evaluated drains the term of its meaning. It would seem sufficient to say that the products were initially ranked by their* $ToxPi_{overall}$ *scores, and were reviewed subsequently through each of the product profiles*."

Response: We have updated the term "super-product" to "product grouping" in the revised proposal. However, for responding to Dr. Fenske comments, we will retain the term "super-product" in here and other responses below. As Dr. Fenske correctly interpreted, the term "super-product" describes a particular product that is "*super-hazardous to human health*." At least for cyfluthrin, there is not a single product identified as "*super-hazardous*," even though such a product may exist for other pesticide active ingredients. Because consumers can use one or more cyfluthrin-containing products, the concept of "super-product collective" captures all combined uses that could potentially be "*super-hazardous to human health*." With respect to the comment on "*applying the term "super-product collective" to nearly half of the products evaluated,*" depending on the individual product exposure and toxicity attributes, the total number of products included in the "super-product collective" may change. In the case of cyfluthrin, the total number in the "super-product collective" happens to be "*nearly half of the product evaluated.*" It is noteworthy that the number of products included in the "super-product collective" is an outcome of a set of predetermined

criteria. Hence, unless other data-driven justifications exist, this number of products needs to be preserved.

Comment #17: Dr. Fenske commented, "*there would appear to be more than one option in the setting of a certain product as the benchmark product. The option selected in this analysis was to select the product with the highest overall ToxPi score. But one could have alternatively decided to define the benchmark product as the product with the highest overall ToxPi score that did not have a zero value for any of the five indices.,… It would be helpful to have a more complete discussion of the rationale for selection of the benchmark product in the report.*"

Response: The choice of highest overall ToxPi score for selecting a benchmark product is to avoid bias. While other methods exist for selection the benchmark product, the use of predetermined criteria will allow the selection process to be data-driven (i.e., objective).

Comment #18: Dr. Fenske commented, "*in the second paragraph of Section V it states, "products are ranked based on their* $ToxPi_{overall}$ *scores (Table 1); i.e., their relative contribution to the anticipated human exposure." This is not strictly true, as the* PPI_{norm} *is a part of the overall ToxPi score.* PPI_{norm} *is a relative measure of toxicity, not exposure. This may seem like a small point, but it is important to recognize that the ToxPi overall, as constructed by DPR, integrates exposure and toxicity. It is a score that reflects human health risk.*"

Response: We have modified the text from "*their relative contribution to the anticipated human exposure*" to "*their relative contribution to the anticipated human risk*" to reflect that ToxPi contains information on both the exposure and toxicity.

Comment #19: Dr. Fenske commented, "*The use of the term "high enough" to describe selection of a second benchmark product is awkward. Perhaps the language here could be revised to support the selection of BCYF32-IT.*"

Response: The selection of BCYF32-IT for IEI_{norm} is based on a product that exhibits the highest overall ToxPi score ranking with indoor uses. We have revised the text to clarify the selection of BCYF32-IT.

Comment #20: Dr. Fenske commented, "*The text on page 14 says the strategy identified an initial set of 30 products as having "a high overall exposure potential" (Table 2). Again, this*

is not strictly correct, as the ranking of the products by ToxPi$_{overall}$ scores includes the PPI$_{norm}$, a measure of toxicity rather than exposure potential."

Response: We have revised the text from "exposure potential" to "health risk potential" to reflect that ToxPi contains information on both the exposure and toxicity.

Comment #21: Dr. Fenske commented, *"The 30 products listed in Table 2 have not been selected because of their overall ToxPi score, but rather due their having at least one high score in one of the five product profile indices. This raises a question as to whether the ranking of products by overall ToxPi score is necessary to identify those products and exposure scenarios that are worthy of more detailed exposure and risk assessments."*

Response: The use of overall ToxPi scores for product ranking and individual product indices for product recruitment into a "super-product collective" is based on the premise of an existence of the most hazardous product, i.e., "the super-product." For cyfluthrin, such super-product does not exist. However, had such a "super-product" existed, the exposure and risk assessments would have been conducted based on the use pattern on this cyfluthrin-containing product. Hence, for complementing the attributes of the "super-product," individual product indices were used.

Comment #22: Dr. Fenske commented*, "Small point: re-volatilization is not an application method."*

Response: We have revised the text by removing the word "re-volatilization" to be more consistent with the definition of application method.

Comment #23: Dr. Fenske commented, *"Section VI.E wraps up the discussion of product selection for the exposure assessment process. It is only here that the high PPI$_{norm}$ scores for some products are noted. I would suggest a separate section for this index, as has been done for each of the exposure indices (VI.A, VI.B, VI.C, VI.D)."*

Response: We have revised the text as suggested.

Comment #24: Dr. Fenske commented, *"The decision to restrict this analysis to only those pesticide products that contain either cyfluthrin or beta-cyfluthrin allowed DPR scientists to explore the ToxPi methodology in an effective manner. I concur that this report provides proof of concept for evaluating pesticide products with active ingredients that share a*

common mechanism of toxicity, although there remain some rough spots. It may be possible to apply this method to organophosphorus insecticides, carbamate insecticides, pyrethroids, neo-nicotinic insecticides, triazine herbicides, or other compounds that share a common mechanism of toxicity. As discussed above, there remains a question as to whether the normalized product profile indices might be sufficient to identify products and exposure scenarios for more detailed exposure and risk assessments (i.e., the overall ToxPi score would not be needed)."

Response: Please see response to Comments # 16, 17, and 21.

Comment #25: Dr. Fenske commented, *"The methodology identifies groups of human receptors by exposure scenarios. However, it does not consider differences among humans who may be involved in one of the four exposure scenarios. As mentioned previously, the exposure scenarios do not differentiate exposures or risks for women during pregnancy, infants or small children. Consideration of these vulnerable sub-populations is an important element of current risk assessment efforts."*

Response: Please see response to Comments #4 and 15.

Comment #26: Dr. Fenske commented, "*This is likely to be the case if the analysis stays within a group of pesticides with a common mechanism of toxicity. It is not clear what would happen with a more diverse set of active ingredients. Gangwal et al. 2012 attempted to characterize exposure and toxicity for a broad set of chemicals using the ToxPi method. In their validation analysis, they were unable to show any correlation between their findings and either the NHANES biomonitoring data or conclusions of EPA's Registration Eligibility Documents.*"

Response: The goal of ToxPi proposal is to provide a non-specific platform for prioritizing the pesticide products entering into the human health exposure and risk assessment processes. In order to prioritize multiple pesticide active ingredients, the ToxPi methodology needs to include a mechanism for evaluating their relative toxicity potencies for the development of PEI_{norm}. Accordingly, the ideal candidates for such aggregate assessment would be pesticides that exhibit a common mode of action, such as cholinesterase inhibition (e.g., organophosphate and carbamate insecticides) or decreased motor activity (e.g., Type I and Type II pyrethroid insecticides). The overall ToxPi scores and (or) individual indices could be used to evaluate findings such as the NHANES or other monitoring databases (please also see response to Comment #3).

Comment #27: Dr. Fenske commented, "*The comparison of ToxPi results with the California Pesticide Illness Surveillance Program database is appropriate, and allows for a qualitative evaluation of the validity of the priority and ranking results. The ToxPi method was not able to capture five products, each which had one case report. It did, however, capture all products with multi-case reports. As the authors state, the method captured 95% of cases. It would be fruitful to explore further in a subsequent analysis why five products with cases were left out of the prioritization*."

Response: DPR's Pesticide Illness Surveillance Program (PISP) database employs three different classifications for establishing a relationship between the reported illness and exposure of pesticide: "possible," "probable," and "definite." Of the five products "missed" by the ToxPi method, four were designated as "possible" and one as "probable." Based on PISP, "possible" relationship means that, *"health effects correspond generally to the reported exposure, but evidence is not available to support a relationship,*" and "probable" relationship means that, *"limited or circumstantial evidence supports a relationship to pesticide exposure."* Because of the equivocal (i.e., "possible") and uncertain (i.e., "probable") associations of these illness incidences, the inconsistency between ToxPi prediction and the reported illness may not necessarily diminish the utility of ToxPi approach for supporting decision framework in prioritizing pesticide products for entering into exposure and risk assessment. It is noteworthy that none of the incidences "missed" by the ToxPi method is under the "definite" relationship: "*both physical and medical evidence document exposure and consequent health effects.*" This observation provides additional confidence in the ToxPi method approach for capturing those products with the highest risk of exposure or adverse health outcome.

Comment #28: Dr. Fenske commented, "*It would be an interesting exercise to provide the information you have gathered on these pesticide products to a group of exposure/toxicology/ risk experts with special knowledge of pesticides, but without the ToxPi method. Ask them to provide a ranking in terms of exposure and risk potential and see how this compares with the findings of this report. It would give us a sense of the degree to which expert judgment fails to identify pesticide products ranked highly by the approach presented here*."

Response: While the exercise suggested by Dr. Fenske can further evaluate the utility of ToxPi method, the resources needed to do so are well beyond the original scope of this study.

Comment #29: Dr Fenske commented, "*I do not consider Section III of Appendix A to be a sensitivity analysis. The major point seems to be that products with scores higher than the benchmark score within a particular exposure category are recruited into the exposure assessment process, regardless of the magnitude of the difference between a given score and the benchmark score. However, there is actual analysis; only broad observations. I would recommend reviewing and revising this section of the report.*"

Response: We have moved the sensitivity analysis section and incorporated the discussion into the main text.

Acknowledgments

I would like to thank Dr. Janice Chambers of Mississippi State University, Dr. Richard Fenske of University of Washington, Dr. David Reif of North Carolina State University, and Dr. Mark Robson of Rutgers University for their valuable inputs to strengthen the arguments presented in this work and their inputs were incorporated into the revised proposal. The reviewers' inputs were obtained under the Interagency Agreement administered by the University of California, Berkeley to conduct independent expert reviews on technical work products of interest to the People of California as required by the California state law: California Health and Safety Code Section 57004 (https://dtsc.ca.gov/wp-content/uploads/sites/31/2018/07/Cal-EPA-ESPR-Guidelines.pdf). I also thank members in the DPR Problem Formulation Workgroup especially Dr. Terrell Barry, Dr. John Sanders, Dr. Lisa Ross, Dr. Michael Zeiss, Dr. Ian Reeve, Ms. Ann Prichard, Dr. Shelley DuTeaux, and Dr. Karen Morrison for their helpful comments.

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