DEPARTMENT OF PESTICIDE REGULATION

Julie Henderson
Acting Director

Gavin Newsom
Governor

Jared Blumenfeld
Secretary for Environmental Protection

MEMORANDUM

TO: Shelley DuTeaux, Ph.D. MPH
Chief, Human Health Assessment Branch
Department of Pesticide Regulation
California Environmental Protection Agency

FROM: Eric Kwok, Ph.D., DABT
Senior Toxicologist, Human Health Assessment Branch
Department of Pesticide Regulation
California Environmental Protection Agency

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SUBJECT: TOXICOLOGICAL PRIORITY INDEX (TOXPI) PRIORITIZATION FRAMEWORK FOR PESTICIDE EXPOSURE AND RISK ASSESSMENTS

ABSTRACT[1]

Pesticide exposure assessment in humans involves selecting a set of representative products, performing a detailed examination of all the label permitted uses, and developing relevant exposure scenarios. Due to the potentially large number of pesticide application methods and use sites involved, this process is time-consuming and often requires professional, but *subjective*, judgment to triage the information. In this proof-of-concept study, an *objective* method was developed to systematically rank pesticide products for human exposure assessment based on a set of pre-determined criteria. Information employed in this study was obtained from an open access database for 66 cyfluthrin or β-cyfluthrin containing products. Exposure characterization of these pesticide products is based on five normalized product profile indices designed to capture the exposure potential of products, within known exposure settings, through activities exhibited by different population subgroups. Based on the five normalized indices, Toxicity Priority Index (ToxPi) software was used to visually rank the exposure potential of the cyfluthrin/ β-cyfluthrin containing products. The ToxPi-based toxicity predictions were assessed using Pesticide Illness Surveillance Program database. The utility of the methodology was discussed in terms of ranking exposure potential of new pesticide products, assisting with future exposure mitigations and applications to pesticides with a common mode-of-action.

Keywords: pesticide product label; exposure prioritization; ToxPi; β-cyfluthrin/cyfluthrin; problem formulation; pesticide risk assessment

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Introduction

A pesticide product is a mixture of chemicals, including the active ingredient (A.I.), that prevents, destroys, and/or repels pests. Pesticide risk assessment conducted by regulatory agencies is a process of evaluating the potential adverse health effects associated with pesticide use as specified on the product label. While health hazards based on the most sensitive population subgroups must be identified as a crucial first step, the exposure potential of a particular pesticide product is fundamental to the risk characterization. Human exposures to a pesticide product can be categorized by the product profile, for example, application methods (e.g., aerial and/or ground methods), use patterns (e.g., agricultural, or non-agricultural uses), use sites (e.g., turf and/or perimeter treatments), and amount of A.I. contained. The product profiles describe the means of pesticide release into the environment (e.g., air and soil) and indicate the pathway where human exposure will most likely occur (e.g., inhalation and direct contact). These parameters offer the necessary data for exposure characterization, which, in concert with the identification of potential human health effects, provide the foundation for risk associated with all the product exposure scenarios (USEPA 2014a).

Conventional human exposure assessment methodology requires a review of all pesticide products containing a given A.I. and the corresponding label-permitted usages in order to identify a set of representative exposure scenarios (i.e., exposure prioritization) (Beauvais 2014). For an A.I. with numerous products and uses, selecting products and identifying representative exposure scenarios can be time consuming and require subjective professional judgement to triage the scenarios prior to entering the formal exposure assessment process. However, human exposures can be broadly classified into three main categories: handlers (mixer/loader/ applicator), reentry workers/residents to the treated sites, and bystanders (occupational and residential settings). Hence, an exposure prioritization framework for product selection can be simplified by using human exposure categories instead of product/use categories. This study demonstrates a methodology that changes subjective prioritization of exposure into a standardized (objective) process for exposure assessment and subsequent mitigation. The pesticides cyfluthrin and β-cyfluthrin are used as a case study to demonstrate the utility of the method.

MATERIALS AND METHODS

Query of the California Product/Label Database identified 66 cyfluthrin or β-cyfluthrin (pyrethroid pesticides) containing products with active registrations in California (CDPR 2016a). β-Cyfluthrin is an isomeric enriched form of cyfluthrin. Because the purpose of this work is to

demonstrate a new method, the actual pesticide product names are not identified. Instead, each product is assigned an alias (Table 1). Each alias was generated by using random number-generating and concatenation functions in Microsoft Excel™ based on the original product name. Only products with active registration were considered for evaluation. A ranking strategy was needed for exposure prioritization because different products had similar use-sites, patterns, and application methods.

Table 1. Summary of the A.I., Alias Product Names, Product Profile Index Values, and $ToxPi_{overall}$ Scores of Cyfluthrin or β-Cyfluthrin Containing Products

A.I.	Alias Product Name[a]	HEI_{norm}	REI_{norm}	PEI_{norm}	BEI_{norm}	IEI_{norm}	$ToxPi_{Overall}$[c]
CYF	CYF0T	0.183	0.816	0.589	0.996	0.000	2.584*
CYF	CYF4-978T	0.183**	0.816**	0.595**	0.912	0.000	2.506
β-CYF	BCYF264-1L	0.091	0.408	1.000**	0.629	0.000	2.129
β-CYF	BCYF264B	0.091	0.408	0.605**	1.000**	0.000	2.104
β-CYF	BCYF32-1T	0.000	0.494	1.000**	0.120	0.019	1.633*
CYF	CYF99-PA	0.245**	1.000**	0.143	0.036	0.039**	1.463
CYF	CYF432-T	0.592**	0.261	0.476	0.056	0.046**	1.431
CYF	CYF9O	0.153	1.000**	0.143	0.084	0.039**	1.419
CYF	CYF-304-C	1.000**	0.111	0.143	0.108	0.019**	1.381
CYF	CYF4P	1.000**	0.111	0.143	0.100	0.019**	1.373
β-CYF	BCYF5B	0.766**	0.331	0.119	0.056	0.000	1.271
β-CYF	BCYF1363T	0.007	0.271	0.562	0.255	0.022**	1.116
CYF	CYF92-H	0.033	0.000	0.002	0.040	0.989**	1.065
CYF	CYF2-221D	0.033	0.000	0.002	0.020	1.000**	1.056
β-CYF	BCYF4T[b]	0.296**	0.065	0.476	0.147	0.023**	1.008
β-CYF	BCYF13T[b]	0.296**	0.065	0.476	0.147	0.023**	1.008
CYF	CYF55-B	0.015	0.391	0.018	0.502	0.000	0.926
β-CYF	BCYF3T	0.004	0.277	0.562	0.064	0.000	0.908
CYF	CYF1556-T	0.774**	0.000	0.024	0.044	0.052**	0.894
β-CYF	BCYF115C	0.005	0.000	0.857**	0.020	0.000	0.882
CYF	CYF5B	0.057	0.391	0.018	0.367	0.000	0.833
β-CYF	BCYF-1377T	0.035	0.065	0.476	0.191	0.023**	0.791
β-CYF	BCYF7B	0.192**	0.331	0.119	0.072	0.000	0.713
CYF	CYF32-T	0.003	0.092	0.476	0.088	0.000	0.659
CYF	CYF55-4B	0.000	0.006	0.000	0.641	0.000	0.648
β-CYF	BCYF556T	0.007	0.000	0.562	0.056	0.022**	0.646
β-CYF	BCYF56-14T	0.001	0.000	0.562	0.016	0.022**	0.600
CYF	CYF155-B	0.000	0.006	0.000	0.590	0.000	0.596
CYF	CYF4D	0.006	0.327	0.087	0.171	0.000	0.590
CYF	CYF1402-D	0.027	0.000	0.476	0.068	0.000	0.571
CYF	CYF5-3B	0.072	0.391	0.018	0.060	0.000	0.541
CYF	CYF55-B	0.056	0.375	0.018	0.080	0.000	0.528
CYF	CYF5-B	0.072	0.391	0.018	0.032	0.000	0.513
CYF	CYF55-24B	0.015	0.375	0.018	0.076	0.000	0.484
CYF	CYF155-3B	0.015	0.391	0.018	0.052	0.000	0.476
CYF	CYF721B	0.015	0.391	0.018	0.016	0.000	0.440

A.I.	Alias Product Name[a]	HEI_{norm}	REI_{norm}	PEI_{norm}	BEI_{norm}	IEI_{norm}	$ToxPi_{Overall}$[c]
CYF	CYF155-B	0.015	0.391	0.018	0.012	0.000	0.436
CYF	CYF-4D	0.004	0.000	0.229	0.175	0.000	0.408
CYF	CYF-4P	0.004	0.000	0.229	0.080	0.000	0.312
β-CYF	BCYF55-29B	0.035	0.180	0.034	0.052	0.000	0.301
β-CYF	BCYF55-2B	0.007	0.180	0.034	0.072	0.000	0.293
CYF	CYF-47P	0.018	0.000	0.002	0.100	0.099**	0.219
CYF	CYF499P	0.018	0.000	0.002	0.064	0.099**	0.183
β-CYF	BCYF-1527T	0.004	0.000	0.002	0.139	0.024**	0.170
CYF	CYF9-303P	0.021	0.000	0.002	0.116	0.026**	0.165
β-CYF	BCYF-1T	0.004	0.000	0.002	0.092	0.024**	0.122
CYF	CYF99-P	0.021	0.000	0.002	0.060	0.026**	0.109
β-CYF	BCYF72155B	0.005	0.000	0.002	0.040	0.050**	0.097
β-CYF	BCYF55-3B	0.002	0.029	0.006	0.060	0.000	0.097
CYF	CYF9-P	0.006	0.000	0.038	0.048	0.003	0.095
CYF	CYF56-C	0.059	0.000	0.024	0.012	0.000	0.095
CYF	CYF99-4P	0.006	0.000	0.038	0.044	0.003	0.091
CYF	CYF82R	0.008	0.000	0.018	0.008	0.050**	0.083
β-CYF	BCYF72155B	0.000	0.044	0.006	0.016	0.000	0.067
β-CYF	BCYF215B	0.002	0.044	0.002	0.016	0.000	0.064
β-CYF	BCYF15B	0.002	0.000	0.001	0.044	0.012	0.059
β-CYF	BCYF2B	0.002	0.044	0.002	0.008	0.000	0.056
β-CYF	BCYF72155B	0.002	0.000	0.001	0.040	0.012	0.055
β-CYF	BCYF15B	0.010	0.000	0.024	0.020	0.000	0.053
CYF	CYF7754-S	0.018	0.000	0.008	0.008	0.000	0.033
β-CYF	BCYF55-34B	0.003	0.000	0.002	0.024	0.000	0.030
β-CYF	BCYF21B	0.000	0.000	0.000	0.028	0.000	0.028
CYF	CYF8R	0.005	0.000	0.002	0.012	0.000	0.018
β-CYF	BCYF721B	0.002	0.000	0.001	0.012	0.000	0.015
CYF	CYF82O	0.005	0.000	0.002	0.004	0.000	0.010
CYF	CYF22-57O	0.003	0.000	0.002	0.004	0.000	0.008

Abbreviations: Reg., Registration; A.I., active ingredient; CYF, cyfluthrin; β-CYF, beta-cyfluthrin; HEI_{norm}, normalized handler exposure index; REI_{norm}, normalized reentry exposure index; PEI_{norm}, normalized product exposure index; BEI_{norm}, normalized bystander exposure Index, IEI_{norm}, normalized indoor exposure index.

[a] Alias product name was generated from the original name by using a random number generating and concatenation functions in Microsoft Excel.

[b] There are two products with the same name. Because of their unique product registration numbers, this assessment considers them as separate products.

[c] Individual ToxPi score value can be normalized (i.e., ToxPi score/5) to fall within the range of 0-1 for comparing the distribution of ToxPi scores to the maximum (i.e., 1) and, if needed, across models.

* Benchmark product

** index value equal or greater than the corresponding index value of the benchmark product.

For characterizing and ranking the exposure potential and toxicity of cyfluthrin/β-cyfluthrin containing products in humans, five product characteristics were employed. These characteristics were expressed quantitatively as normalized (subscript "norm") indices: (1) handler exposure index (HEI_{norm}), (2) reentry exposure index (REI_{norm}), (3) product exposure index (PEI_{norm}), (4) bystander exposure index (BEI_{norm}), and (5) indoor exposure index (IEI_{norm}). Derivations of these five indices are provided in appendix. Briefly, these five indices

were computed using standard activity-based algorithms relevant to different human exposure scenarios (i.e., handlers, reentry workers/residents, and bystanders) (Beauvais et al. 2007, USEPA 2012, USEPA 2017), selected characteristics of pesticide products (i.e., application rate, percent A.I., and number of use sites), and open access generic database (e.g., transfer coefficients) (USEPA 2017). However, several variations of the algorithms were used as described below. For the HEI_{norm}, personal protection equipment (PPE) adjustment factors (Thongsinthusak et al. 1993) were applied to the handler exposure calculations when PPE are required by a product label. PPE use was incorporated into the HEI_{norm} index calculation because it is required for the legal use of the pesticide products. For the REI_{norm}, the transfer coefficient (TC) associated with the post-application activities of citrus was used (i.e., 3600 cm^2/hr for fruit thinning; the highest TC within Tree, "Fruit", Evergreen Crop Group) (USEPA 2017) because citrus has the highest rate of product application. For the PEI_{norm}, the amount of A.I. in β-cyfluthrin containing products was converted into cyfluthrin (i.e., cyfluthrin-equivalent) using the following equation: cyfluthrin equivalent = 2 x percent of β-cyfluthrin. This equation is consistent with the fact that β-cyfluthrin is the isomeric enriched form of cyfluthrin and is twice as toxic (Dotson et al. 2010).

RESULTS

Exposure Ranking of Cyfluthrin and β-Cyfluthrin Containing Products

Figure 1 shows a sample diagram for use in the cyfluthrin and β-cyfluthrin exposure-assessment process. The software program employed to construct the diagram (i.e., ToxPi diagram) is Toxicological Priority (ToxPi) Index Graphical User interface (version 2.3; http://toxpi.org/) (Reif et al. 2010, Marvel et al. 2018). Each ToxPi diagram represents an alias product, and each slice represents a unique characteristic of the product. The slice size is determined by a normalized index value that was calculated by dividing the index value of a product by the highest index value observed among all products. For example, $HEI_{norm} = \frac{(HEI)_{individual}}{(HEI)_{maximum}}$. The sum maximum of all normalized index values combined is 5 because there are 5 indices (slices), each at the maximum normalized index value of 1, i.e.,

$$\left(\frac{HEI_{individual}}{HEI_{maximum}} + \frac{REI_{individual}}{REI_{maximum}} + \frac{PEI_{individual}}{PEI_{maximum}} + \frac{BEI_{individual}}{BEI_{maximum}} + \frac{IEI_{individual}}{IEI_{maximum}}\right)_{maximum} = 5$$

This sum of normalized index values is known as a ToxPi score (i.e., $ToxPi_{overall}$).

$$ToxPi_{overall}=HEI_{norm}+REI_{norm}+PEI_{norm}+BEI_{norm}+IEI_{norm}$$

$$ToxPi_{overall}=\sum_{n=1}^{5}\frac{(\text{Product Profile Index})_{individual}}{(\text{Product Profile Index})_{maximum}}$$

A numerical "alias product score" (ToxPi Score) for each of the 66 products was ultimately used to rank them. Based on the five normalized indices, a ToxPi diagram was constructed for each cyfluthrin or β-cyfluthrin containing product.

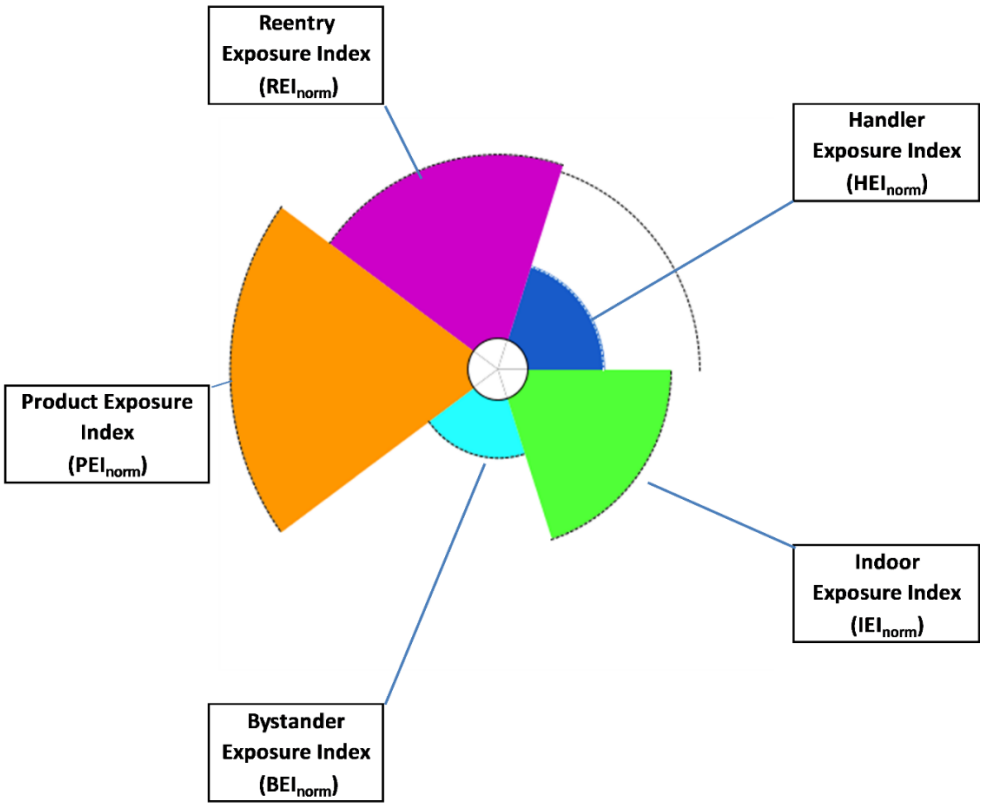

Figure 1. Sample ToxPi diagram and its five product profile indices.

Figure 2 shows the ToxPi diagrams for the cyfluthrin/β-cyfluthrin containing products that are ranked based on the individual $ToxPi_{overall}$ score from the highest (top left) to the lowest (bottom right). The size of each ToxPi diagram is proportional to the $ToxPi_{overall}$ numerical score, and the size of the slices that comprise each ToxPi diagram is proportional to the numeric score of that slice (i.e., a particular value of the index). Therefore, Figure 2 provides a visual

means to assess or rank the relative contribution of each product to potential cyfluthrin/β-cyfluthrin exposure in humans.

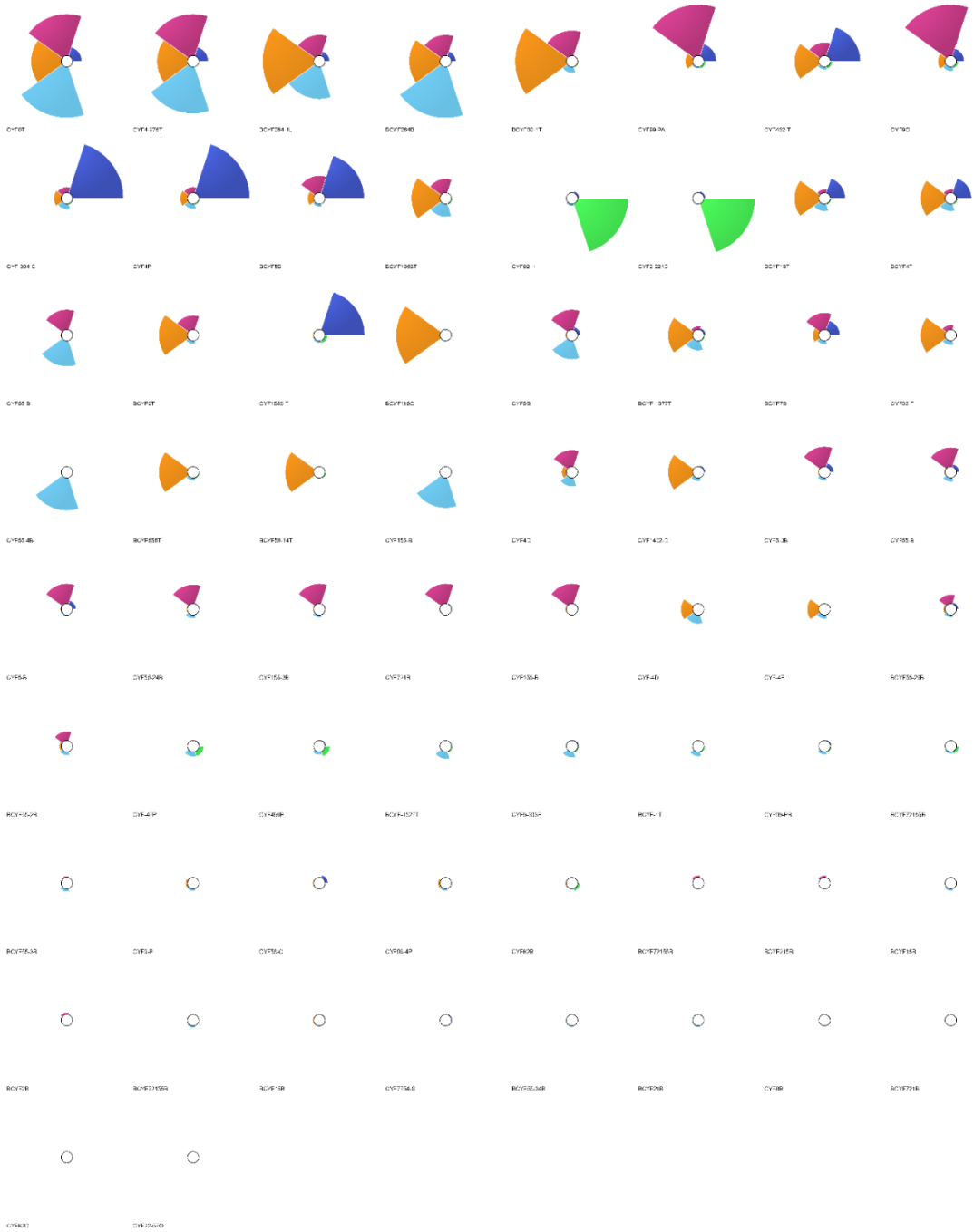

Figure 2. Ranking of cyfluthrin or β-cyfluthrin containing products from high (top left) to low (bottom right) based on the $ToxPi_{overall}$ score (as indicated by the ToxPi diagram size);

the distribution of the five normalized index values in each ToxPi diagram (as indicated by the size of each slide) is also shown (please see Figure 1 for the slide key). The alias product name is presented underneath each ToxPi diagram.

Product Recruitment for the Problem Formulation

Conceptually, exposure risk of cyfluthrin/β-cyfluthrin in humans could be based on the product with the highest human exposure potential. This product would have the highest normalized value in all the indices (e.g., handler exposure, reentry exposure, product exposure, bystander exposure, and indoor exposure [i.e., $HEI_{norm} = REI_{norm} = PEI_{norm} = BEI_{nrom} = IEI_{norm} = 1$; $\Sigma[ToxPi_{overall}] = 5$) and would be visualized in a ToxPi diagram with equally spaced and sized slices [i.e., a complete circle]). However, such a product does not exist because, as will be shown, product profiles vary among the cyfluthrin/β-cyfluthrin containing products, (Figure 2). Therefore, a *grouping* of products was used to characterize the highest human exposure potential.

That is, all cyfluthrin/β-cyfluthrin containing products were ranked (from the highest to the lowest) based on their $ToxPi_{overall}$ scores (Table 1) (i.e., their relative contribution to the anticipated human exposure). The ranking of all 66 $ToxPi_{overall}$ scores in Table 1 shows that the product exhibiting the highest $ToxPi_{overall}$ is CYF0T, with a $ToxPi_{overall}$ score of 2.584. Thus, CYF0T is designated as the benchmark product. Using this as a reference, all other products with one (or more) of their normalized index values (normalized value of the individual slices) equal to or higher than the benchmark product were recruited for developing the product group with the highest human exposure potential. It should be noted however that IEI_{norm} of CYF0T is zero, indicating that the product has no indoor use. To evaluate the exposure potential of products with indoor use, another benchmark product with the highest ToxPi score and a non-zero normalized index value of IEI_{norm} was needed, i.e., product BCYF32-1T ($ToxPi_{overall}$ = 1.633 with $IEI_{norm} = 0.019$). Subsequently, all products with a normalized IEI index value greater than or equal to 0.019 were recruited into the product group with the highest human exposure potential. Using this strategy, an initial group of 30 cyfluthrin/β-cyfluthrin containing products were identified as having the highest human exposure potential (Table 2).

Table 2. A List of 30 Products in the Cyfluthrin or β-Cyfluthrin Collective with the Highest Human Exposure Potential

A.I.	Alias Product Name[a]	Formulation	Indoor	Application Method	A.I. (%)[b]
CYF	CYF0T	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	24.74
CYF	CYF4-978T	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	25
β-CYF	BCYF264-1L	Suspension Concentrate	NO	Aerial/Ground/Chemigation (Crop)	10.5
β-CYF	BCYF264B	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	12.7
β-CYF	BCYF32-1T*	Suspension Concentrate	YES	Ground (Spray only)	10.5
CYF	CYF99-PA	Suspension Concentrate (MC)	YES	Ground (Spray only)	6
CYF	CYF432-T*	Wettable powder	YES	Ground (Turf-Use)	20
CYF	CYF9O	Suspension Concentrate (LCS)	YES	Ground (Spray only)	6
CYF	CYF-304-C	Flowable (MC)	YES	Ground (Spray only)	6
CYF	CYF4P*	Flowable (MC)	YES	Ground (Spray only)	6
β-CYF	BCYF5B*	Suspension Concentrate	NO	Ground (Spray only)	2.5
β-CYF	BCYF1363T*	Suspension Concentrate	YES	Ground	11.8
CYF	CYF92-H	Ready to Spray (RTS)	YES	Ground	0.1
CYF	CYF2-221D	Ready to Spray (RTS)	YES	Ground	0.1
β-CYF	BCYF4T[c,]*	Wettable powder	YES	Ground (Turf-Use)	10
β-CYF	BCYF13T[c]	Wettable powder	YES	Ground (Turf-Use)	10
CYF	CYF1556-T	Dusts	YES	Ground	1
β-CYF	BCYF115C	Emulsifiable Concentrate	NO	Ground	8
β-CYF	BCYF-1377T	Water Soluble Packets	YES	Ground	10
β-CYF	BCYF7B	Suspension Concentrate	NO	Ground (Spray only)	2.5
β-CYF	BCYF556T	Suspension Concentrate	YES	Ground	11.8
β-CYF	BCYF56-14T	Suspension Concentrate	YES	Ground	11.8
CYF	CYF-47P*	Pressurized Liquids/Sprays/Foggers	YES	Ground (Spray only)	0.1
CYF	CYF499P	Pressurized Liquids/Sprays/Foggers	YES	Ground (Spray only)	0.1
β-CYF	BCYF-1527T	Ready to Spray (RTS)	YES	Ground (Spray only)	0.025
CYF	CYF9-303P	Pressurized Liquids/Sprays/Foggers	YES	Ground (Spray only)	0.1
β-CYF	BCYF-1T	Ready to Spray (RTS)	YES	Ground (Spray only)	0.025
CYF	CYF99-PB	Pressurized Liquids/Sprays/Foggers	YES	Ground (Spray only)	0.1
β-CYF	BCYF72155B*	Ready to Spray (RTS)	YES	Ground (Spray only)	0.05
CYF	CYF82R	Pressurized Liquids/Sprays/Foggers	YES	Ground (Spray only)	0.05

Abbreviations: Reg., registration; A.I., active ingredient; CYF, cyfluthrin; β-CYF, beta-cyfluthrin; MC, microencapsulated concentrate; LCS, liquid capsule suspension; RTS, ready to use solution.

[a] Products ranked by Toxicological Priority Index (ToxPi) Overall score from the highest to the lowest.

[b] The percent active ingredient could be higher due to the presence active ingredient, e.g., imidacloprid, other than cyfluthrin or β-cyfluthrin.

[c] There are two products with the same name. Because of their unique product registration numbers, this assessment considers them as separate products.

* Pesticide product associated with human illness incidence as reported in the California Pesticide Illness Surveillance (PISP) Database (CDPR 2016b).

Pesticide Products to be Considered in the Exposure Assessment

An exposure scenario is defined as a situation where people may come in contact with pesticides or pesticide residues (Sanders 1999). Using the 30 pesticide products identified (Table 3) and their corresponding product profile index values (i.e., HEI_{norm}, REI_{norm}, PEI_{norm}, BEI_{norm}, and IEI_{norm}) (Table 1), exposure scenarios were derived as shown below.

A. Occupational and non-occupational handler exposure scenarios

For assessing handler exposure, ten products have HEI_{norm} index values larger than the benchmark product CYF0T (Table 1). Table 3 lists their associated Pesticide Handler Exposure Database (PHED) scenarios. The use of PHED instead of the latest Agricultural Handler Exposure Task Force (AHETF) Database is based on a more comprehensive coverage by PHED of the exposure scenarios involved in this study (28 scenarios) compared to AHETF (14 scenarios; USEPA: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data). As shown in Table 3, identical exposure scenarios exist for some products (e.g., PHED scenarios #5 and 9 are both involved in CYF0T and CYF4-978T). In other words, among these 10 products, there are only 6 unique PHED scenarios, i.e., #5, 9, 20, 23, 26, and 27. Following the HEI_{norm} score ranking (Table 1), one representative product was selected from each unique scenario for performing an in-depth exposure assessment (e.g., short-term absorbed daily dose [STADD]) determination). These 5 representative products (scenario number in parentheses) are CYF0T (5 and 9), CYF99-PA (20), CYF-304-C (23), BCYF5B (26), and CYF1556-T (27). Using application instructions on the label of these 4 representative products, an exposure assessment can be performed based on the methodologies described in Beauvais et al. (2007).

Table 3. Pesticide Handler Exposure Scenarios of Cyfluthrin and β-Cyfluthrin Products ($HEI_{norm} \geq$ "CYF0T")

A.I.	Alias Product Name[a]	PHED[b]	Handler Exposure Scenarios
CYF	CYF-304-C**	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
CYF	CYF4P	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
CYF	CYF1556-T**	27	Belly Grinder Mixer/Loader/Applicator, Granular (Assumed No Gloves)
β-CYF	BCYF5B**	26	Garden Hose End Sprayer Mixer/Loader/Applicator, Open Pour (Assumed No Gloves)
CYF	CYF432-T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF4T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF13T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
CYF	CYF99-PA**	20	Backpack Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
β-CYF	BCYF7B	26	Garden Hose End Sprayer Mixer/Loader/Applicator, Open Pour (Assumed No Gloves)
CYF	CYF0T**	5 and 9	Mixer/Loader, Open Pour, Liquids (With Gloves) and Airblast Applicator, Open Cab (With Gloves) + PPE
CYF	CYF4-978T	5 and 9	Mixer/Loader, Open Pour, Liquids (With Gloves) and Airblast Applicator, Open Cab (With Gloves) + PPE

Abbreviations: Reg., registration; A.I., active ingredient; CYF, cyfluthrin; β-CYF, beta-cyfluthrin; PHED, pesticide handler exposure database.

[a] Products are listed in the descending order of their HEI_{norm} score values.

[b] Exposure scenario as defined in Beauvais et al. (2007).

** Product selected for in-depth exposure assessment.

B. Outdoor reentry exposure scenarios

For evaluating exposure due to reentry into the treated areas, three products have REI_{norm} index values greater than the benchmark product CYF0T (Table 1), CYF4-978T, CYF99-PA, and CYF9O. Among these products, CYF0T and CYF4-978T are for agricultural use only whereas CYF99-PA and CYF9O have both indoor and outdoor applications. Using application instructions on the label of these 4 products, an exposure assessment can be performed based on the USEPA Science Advisory Council for Exposure (ExpoSAC) Policy 3 for agricultural reentry (USEPA 2017) (e.g., scouting, harvesting, and pruning etc.) and/or Standard Operating Procedures for Residential Pesticide Exposure Assessment for non-agricultural reentry (USEPA 2012) (e.g., turf).

C. Bystander exposure scenarios

For assessing bystander exposure, only one product has a BEI_{norm} index value greater than the benchmark product CYF0T (Table 1): BCYF264B. Hence, both products were selected to characterize the bystander exposures. Because both CYF0T and BCYF264B are for agriculture only use, bystander exposure scenarios (and the subsequent exposure assessments) can focus on the allowable application methods that are prone to off-site movement of the pesticide (e.g., aerial spraying and/or ground applications) (USEPA 2014a, USEPA 2013).

D. Indoor reentry exposure scenarios

Re-entry exposure for indoor settings has 22 products with IEI_{norm} index values greater than the benchmark product BCYF32-1T (Table 1). Among these 23 products, 6 unique PHED exposure scenarios are involved: scenario #13A, 16, 20, 22, 23, and 27 (Table 4). Following the IEI_{norm} score ranking (Table 1) (i.e., relative application rate [appendix A]), one product was selected from each of the 6 unique scenarios for in-depth exposure assessment (e.g., short-term absorbed daily dose [STADD]) determination) as follows: (scenario number in parentheses) CYF2-221D (13A), CYF1556-T (27), BCYF72155B (16), CYF432-T (23), CYF99-PA (20), and BCYF1363T (22). The exposure assessments for the 6 products can be performed based on the methodologies described in the Standard Operational Procedures for Residential Pesticide Exposure Assessment (USEPA 2012).

Table 4. Indoor Pesticide Exposure Scenarios of Cyfluthrin and β-Cyfluthrin Products (IEI_{norm} > "BCYF32-1T")

A.I.	Alias Product Name[a]	PHED[b]	Handler Exposure Scenarios
CYF	CYF2-221D**	13A	Aerosol Can Applicator, (No Gloves)
CYF	CYF92-H	13A	Aerosol Can Applicator, (No Gloves)
CYF	CYF-47P	13A	Aerosol Can Applicator, (No Gloves)
CYF	CYF499P	13A	Aerosol Can Applicator, (No Gloves)
CYF	CYF1556-T**	27	Belly Grinder Mixer/Loader/Applicator, Granular (Assumed No Gloves)
CYF	CYF82R	13A	Aerosol Can Applicator, (No Gloves)
β-CYF	BCYF72155B**	16	Right-of-Way Sprayer, Applicator (Assumed No Gloves)
CYF	CYF432-T**	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
CYF	CYF99-PA**	20	Backpack Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
CYF	CYF9O	20	Backpack Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
CYF	CYF9-303P	13A	Aerosol Can Applicator, (No Gloves)
CYF	CYF99-PB	13A	Aerosol Can Applicator, (No Gloves)
β-CYF	BCYF-1527T	13A	Aerosol Can Applicator, (No Gloves)
β-CYF	BCYF-1T	13A	Aerosol Can Applicator, (No Gloves)
β-CYF	BCYF4T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF13T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF-1377T	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF1363T**	22	Low Pressure Handwand Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
β-CYF	BCYF556T	22	Low Pressure Handwand Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
β-CYF	BCYF56-14T	22	Low Pressure Handwand Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)
CYF	CYF-304-C	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
CYF	CYF4P	23	Low Pressure Handwand Mixer/Loader/Applicator, Wettable Powder Formulations (Assumed No Gloves)
β-CYF	BCYF32-1T[c,]**	22	Low Pressure Handwand Mixer/Loader/Applicator, Liquid (Open Pour) (Assumed No Gloves)

Abbreviations: Reg., registration; A.I., active ingredient; CYF, cyfluthrin; β-CYF, beta-cyfluthrin.

[a] Products are listed in their descending order of their IEI_{norm} score values.

[b] Exposure scenario as defined in Beauvais et al. (2007).

[c] Although "BCYF32-1T" has identical PHED scenarios (i.e., #22) to "BCYF1363T," its inclusion for exposure scenario development is justified by its role as the "benchmark" product for IEI_{norm} and its PEI_{norm} index value (see text).

** Product selected for in-depth exposure assessment.

E. List of products for use in the cyfluthrin and β-cyfluthrin exposure assessment

Based on the results described in sections A-D above, 13 representative cyfluthrin/β-cyfluthrin containing products were selected for the exposure assessment process (Table 5). The health risk associated with pesticide use is a function of exposure and toxicity, therefore, the use of activity-based exposure criteria alone for grouping representative products may not capture those pesticide label exposure scenarios with "low" exposure but "high" toxicity. In the ToxPi diagram, product toxicity potential is characterized by an exposure index: Product Exposure Index (PEI_{norm}), and the method of developing this index is briefly described in the Discussion and Conclusions Section and further detailed in Appendix A. As can be seen in Table 1, 5 products have a higher PEI_{norm} index value than the benchmark product CYF0T. These products are CYF4-978T, BCYF264-1L, BCYF264B, BCYF32-1T, and BCYF115C. Among these products, BCYF264-1L and BCYF115C are included in the group of products with the highest human exposure potential, solely based on their Product Exposure Index (i.e., PEI_{norm}). Others have at least one "extra" index in addition to PEI_{norm}: CYF4-978T (based on HEI_{norm} and REI_{norm}), BCYF264B (based on BEI_{norm}) and BCYF32-1T (based on IEI_{norm}). Hence, BCYF264-1L and BCYF115C were added to the representative product list (based on PEI_{norm}; a total of 15 products in Table 5). The exposure scenarios consistent with the use of these two products can be developed for the exposure assessment as described in Beauvais et al. (2007).

Table 5. List of Representative Products for Entering into the Exposure and Risk Assessments of Cyfluthrin and β-Cyfluthrin

A.I.	Alias Product Name	Formulation	Indoor	Application Method	A.I. (%)[a,b]
CYF	CYF0T	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	24.74
CYF	CYF4-978T	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	25
β-CYF	BCYF264-1L	Suspension Concentrate	NO	Aerial/Ground/Chemigation (Crop)	10.5
β-CYF	BCYF264B	Emulsifiable Concentrate	NO	Aerial/Ground/Chemigation (Crop)	12.7
β-CYF	BCYF32-1T	Suspension Concentrate	YES	Ground (Spray only)	10.5
CYF	CYF99-PA	Suspension Concentrate (MC)	YES	Ground (Spray only)	6
CYF	CYF432-T	Wettable powder	YES	Ground (Turf-Use)	20
CYF	CYF9O	Suspension Concentrate (LCS)	YES	Ground (Spray only)	6
CYF	CYF-304-C	Flowable (MC)	YES	Ground (Spray only)	6
β-CYF	BCYF5B	Suspension Concentrate	NO	Ground (Spray only)	2.5
β-CYF	BCYF1363T	Suspension Concentrate	YES	Ground	11.8
CYF	CYF2-221D	Ready to Spray (RTS)	YES	Ground	0.1
CYF	CYF1556-T	Dusts	YES	Ground	1
β-CYF	BCYF115C	Emulsifiable Concentrate	NO	Ground	8
β-CYF	BCYF72155B	Ready to Spray (RTS)	YES	Ground (Spray only)	0.05

Abbreviations: Reg., registration; A.I., active ingredient; CYF, cyfluthrin; β-CYF, beta-cyfluthrin; MC, microencapsulated concentrate; LCS, liquid capsule suspension; RTS, ready to use solution.
[a] Products are listed in their descending order of the Toxicological Priority Index (ToxPi) Overall score values (Table1).
[b] Percent of cyfluthrin or β-cyfluthrin in the product.

F. Concordance between predicted high exposures versus reported human illnesses

Pesticide ranking by ToxPi can identify products with high human exposure potential that would likely contribute to illness based on their profiles (e.g., use patterns and toxicity). This expectation can be checked by comparing them with products linked to human illness reports.

Table 6 Illness Incidences from Pesticide Illness Surveillance Program (PISP) (2005-2014) Associated with Cyfluthrin and β-Cyfluthrin Products in California[a]

Active Ingredient	Alias Product Name[b]	PISP-Cases[c]
Within the product collective with the highest human exposure potential[d]		
β-Cyfluthrin	BCYF32-1T	7
Cyfluthrin	CYF432-T	6
Cyfluthrin	CYF4P	25
β-Cyfluthrin	BCYF5B	1
β-Cyfluthrin	BCYF1363T	35
β-Cyfluthrin	BCYF4T	11
Cyfluthrin	CYF-47P	8
β-Cyfluthrin	BCYF72155B	12
Outside the product collective with the highest human exposure potential[e]		
Cyfluthrin	CYF55-4B	1
β-Cyfluthrin	BCYF55-2B	1
Cyfluthrin	CYF9-P	1
Cyfluthrin	CYF56-C	1
β-Cyfluthrin	BCYF21B	1

[a] Illness incidence data retrieved by the Worker Health & Safety Branch of DPR on September 28, 2016.
[b] Only products with active registration in California are included. Product with a particular registration number but not DPR internal "alpha code" in the PISP database is assumed to be the same product with an identical registration number plus an "alpha code."
[c] Illness cases included are "definite," "probable," and "possible." The definition of these illness designations is available on the California Pesticide Illness Query (CalPIQ) website: http://apps.cdpr.ca.gov/calpiq/.
[d] Pesticide product within the product group with the highest human exposure potential (Table 2).
[e] Pesticide product outside the product group with the highest human exposure potential (Table 2).

Table 6 shows the pesticide illness incidences associated with products containing cyfluthrin/β-cyfluthrin as the A.I. from the Department of Pesticide Regulation (DPR) California Pesticide Illness Surveillance Program (PISP) database (CDPR 2016b). The PISP database contains 13 illness incidences with a total of 110 human cases involved. Eight products in Table 6, associated with illness (PISP-Case column), represent a group of products with high human exposure potential (Table 2), whereas 5 illness-associated products are not. Using "illness incidence" as a comparison metric, predictions have a 62% association. However, when the metric is "PISP cases," where usage of illness data can be maximized, the ToxPi predicted associations increased to 95%, suggesting that the method may be useful in identifying products that increase adverse health risk through exposure. For example, the PISP database contains high illness incidences associated with 13 cyfluthrin/β-cyfluthrin-containing products (Table 6). These results can then be included as part of the cyfluthrin/β-cyfluthrin exposure assessment.

G. Effect of new products on the product recruitment

As detailed in "Product Recruitment for Problem Formulation," pesticide product recruitment into the exposure assessment process is conducted by comparing the product profile indices (e.g., HEI_{norm}) between a product and its benchmark. This comparison is based on rank order (i.e., higher than or lower than) instead of the actual difference in numerical values. For example, HEI_{norm} of CYF0T is 0.183 (Table 2), and all products with a $HEI_{norm} \geq 0.183$ will be recruited into the exposure assessment process regardless of their actual numerical HEI_{norm} values. As can be seen in Table 1, the recruited products with a HEI_{norm} range from a minimum of 0.192 in "BCYF7B" to a maximum of 1 in "CYF0T" (i.e., 5% to 448% higher than the benchmark HEI_{norm} of 0.183). *Relative ranking*, instead of *numerical value*, was used for recruiting products into exposure assessment because for a given index, products with minor differences in numerical values will exhibit similar exposure profiles. Hence, when new products are added to the list for ToxPi analysis, the subsequent modifications in overall exposure scenarios, based on product profiles, would be minimal.

Integration of ToxPi Analysis Results into Human Health Risk Assessment and Mitigation

As defined by the USEPA (2014b), a conceptual model is "*a written description and a visual representation of actual or predicted relationships between humans (populations or population segments) and the chemicals or other stressors to which they may be exposed (page 25)*." Figure 3 shows a conceptual model of human risk assessment for the selected cyfluthrin/β-cyfluthrin containing products. The model consists of the stressor (i.e., cyfluthrin/β-cyfluthrin containing products), the sources of pesticide release, the exposure media and routes, the receptors of concern, and the toxicity endpoints of interest. The anticipated

sources of pesticide release were derived from the exposure scenarios based on the list of products identified. As can be seen in Figure 3, the pesticide release from these sources constitutes both direct (e.g., contact with pesticide during application) and indirect pathways (e.g., consumption of contaminated food and drinking water) for human exposure.

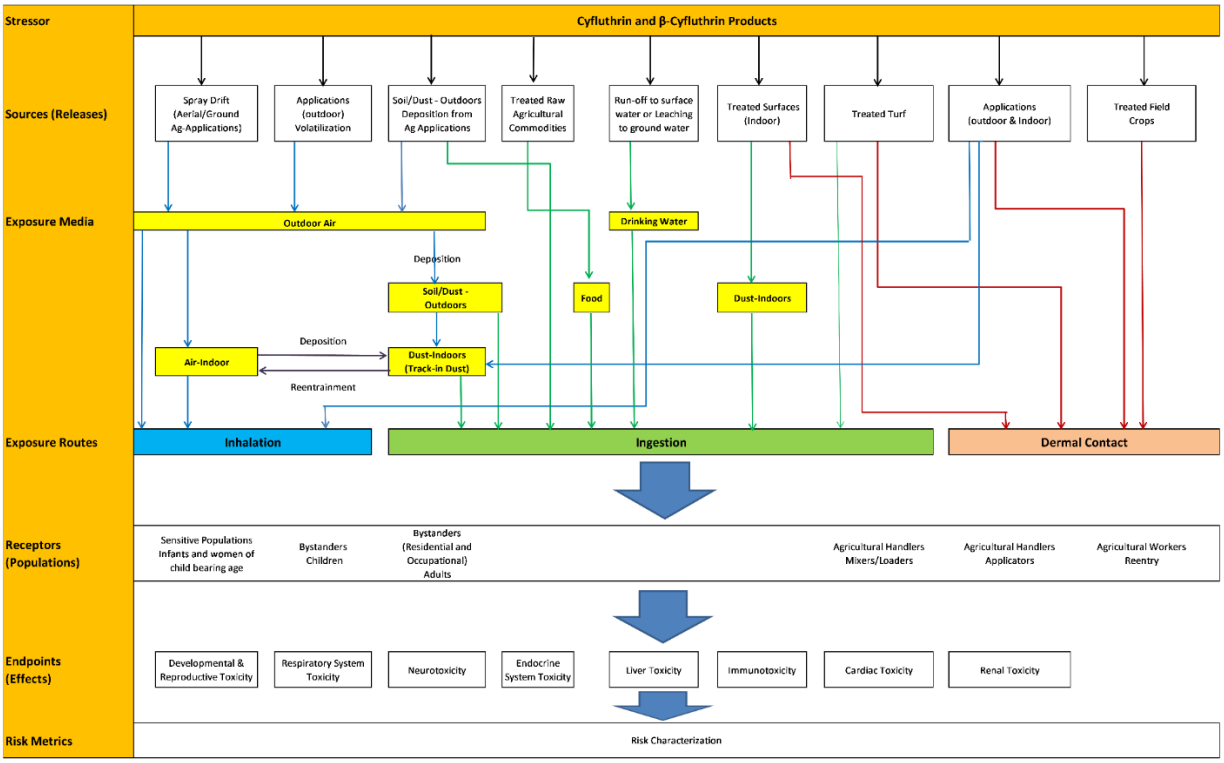

Figure 3. Conceptual model of the human risk assessment of cyfluthrin and β-cyfluthrin containing products.

Once the cyfluthrin/β-cyfluthrin exposure scenarios are identified following the ToxPi analysis, exposure database assessment methodologies can be used to evaluate pesticide exposures to agricultural handlers (Beauvais et al. 2007), reentry workers (USEPA 2017), and the general public (USEPA 2012, Driver et al. 2014, USEPA 2011). Near field computer models, e.g., Agricultural spray DRIFT (AgDRIFT) (Teske et al. 2002) and SOil Fumigant Exposure Assessment Modeling System (SOFEA) (van Wesenbeeck et al. 2016) coupled with human exposure assessment methods (USEPA 2012, USEPA 2013) can be used to assess off-site transport of the pesticides via primary spray drift and volatilization.

In the risk assessment process, once the human health points of departure (POD) (e.g., acute, subchronic, and chronic POD) are identified, they can be used with the ToxPi analysis to

associate health risk to specific pesticide use. Further, these data can be applied to targeted mitigation measures (i.e., product-specific mitigation) based on the non-fumigant risk mitigation policy of DPR (Kwok and Schaffner 2019).

DISCUSSION AND CONCLUSIONS

The purpose of this work was to develop a set of predetermined criteria to characterize and prioritize products containing a specific A.I. for use in comprehensive human health risk assessment. The first step was to define the exposure scenarios and product toxicity. In general, pesticide products were broadly categorized as "outdoor" or "indoor" based on their use patterns. Outdoor use patterns were sub-categorized into occupational (e.g., agricultural and institutional uses) and non-occupational applications (e.g., residential treatments), where each of these settings is associated with activities such as pesticide handling (i.e., mixing, loading, and/or applying) (i.e., HEI_{norm}) and reentry into the treated areas (e.g., crops or turf) (i.e., REI_{norm}) (USEPA 2017). Indoor product use activities are similar to outdoor (i.e., mixing, loading, and/or applying). However, consideration was given to reentry exposure involved a wide variety of indoor surfaces (e.g., hard surfaces and carpet, crack and crevice, and perimeter treatment) (i.e., IEI_{norm}) (USEPA 2012). The unanticipated exposure of pesticides to non-handlers required bystander exposure assessment associated with product use (i.e., BEI_{norm}) (Lewis and Tzilivakis 2017). Health risks from pesticide use is characterized by comparing anticipated exposure to a reference toxicity value (Klaassen 2019). The reference toxicity value, point-of-departure (POD), is either a no-observed-effect-level (NOEL) or lower bound benchmark dose (BMDL). In general, if the reference toxicity value derived from an experimental animal study is 100 fold higher than the anticipated exposure value, the health risk is considered acceptable, i.e., POD/exposure ≥ 100 (Kwok and Schaffner 2019). Therefore, a baseline exposure value was developed (PoD/100) to represent the intrinsic product toxicity potential (i.e., PEI_{norm}).

Subsequently, the ToxPi tool was adapted to rank products containing cyfluthrin/β-cyfluthrin for comprehensive exposure assessment. ToxPi was initially developed by the USEPA (Reif et al. 2013) to rank chemicals based on endocrine disruption (Reif et al. 2010), and/or adversely perturb toxicological pathways (Kleinstreuer et al. 2011), or to assess relative exposure (Gangwal et al. 2012). Note that while Gangwal et al. (2012) used the ToxPi tool to prioritize exposure for more than 100 different pesticide A.I.s, the current study prioritized 66 products from a single A.I. (cyfluthrin/β-cyfluthrin). Further, to minimize inherent data uncertainties and avoid potential bias due to missing or incomplete information about exposure surrogates (e.g., historical uses, environmental fate parameters, and residues on raw agricultural commodities as described in Gangwal et al. (2012)), the current study derived the model

parameters using exposure algorithms and information available on the product labels via an open access database (https://apps.cdpr.ca.gov/docs/label/labelque.cfm). Lastly, unlike the study by Gangwal (2012), the normalization procedure used in this study was applied to activity-based algorithms (appendix A) instead of numerical data values. The normalized indices removed the need for age- or sex-specific physiological parameters (e.g., body weight or breathing rate), common to exposure calculations, so that relative ranking of indices was applicable to the population subgroup of interest. Although the index criteria were predefined, the algorithm used in developing these indices can be modified as knowledge of appropriate source data and/or additions of data as measurements become available or as technology or databases expand (examples in appendix A).

This study weighted five product indices equally for constructing the ToxPi exposure model, since human exposures occur through a variety of scenarios. For example, agricultural handlers perform different activities compared to reentry workers, and children indoors may be more exposed to a pesticide than adults because of breathing rates or contact with pesticide treated surfaces (e.g., carpet). Hence, for assessing overall exposure potential of a pesticide product in a population (i.e., adults, women of childbearing age, and children), a linear combination of exposure indices is a reasonable approach for capturing the different exposure venues and activities exhibited by the different subgroups. For the index associated with product toxicity, PEI_{norm}, regardless of the exposure scenarios assessed, the baseline exposure level of pesticide product is associated with the amount of A.I. present (detailed in appendix A). Therefore, PEI_{norm} was used to emphasize the importance of baseline exposure in the overall exposure potential of pesticide products based on the amount of A.I. present. If additional data become available, the relative contribution of the different indices (currently at 20% each) to the overall ToxPi score can be modified (i.e., by explicitly adjusting slice weights) to address concern for increased exposure in a specific population subgroup(s) without adding extra indices.

In addition to the data-driven selection process, another novel approach was developed to identify a product group with the highest human exposure potential. For cyfluthrin, there is not a "single" product identified even though such a product may exist for other pesticide A.I.s. Because consumers can use one or more cyfluthrin containing products, a product *grouping* approach captured all the combined uses with the highest human exposure potential for risk assessment. The *product group* potential was achieved by evaluating individual product indices generated by ToxPi.

To appraise the ToxPi decision framework for recruiting products into the comprehensive risk assessment, the DPR PISP database was used. Because DPR Pesticide Use Reporting (PUR)

exempts reporting requirements on home-and-garden use as well as most industrial and industrial and institutional use (Yanga and Steinmann 2018), not all cyfluthrin and β-cyfluthrin containing products have use information available. In other words, products may be reported and evaluated in the PISP database but not in the PUR database due to the exemptions. Accordingly, to avoid bias due to unavailable use information, the current study employed only PISP data and conducted the evaluation in a qualitative fashion.

The PISP database employs three different classifications for establishing a relationship between the reported illness and exposure of pesticide: "possible," "probable," and "definite." As shown in Table 6, of the five products "missed" by the ToxPi method, four were designated as "possible" and one as "probable." Based on PISP, a "possible" relationship means that "health effects correspond generally to the reported exposure, but evidence is not available to support a relationship," and a "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 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 exposure 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 approach for capturing those products with the highest risk of exposure or adverse health outcome.

FUTURE DIRECTIONS

One of the goals of the ToxPi approach is to provide a non-pesticide-specific platform for prioritizing pesticide products under consideration for human health exposure and the risk assessment processes. Since data gathered from each of the product labels are focused (i.e., application rate, application method associated with largest application rate, number of use sites, and percent of A.I.), the information gathering process can be performed in an objective and timely manner. Once the data are complied, a relational database can be used to integrate other information needed for calculating the exposure indices (e.g., unit exposure values), and computer automation (e.g., Structured Query Language) can be applied to select products for entering in-depth exposure and risk assessment based on the decision logic previously described. Furthermore, because most algorithms employed are specific only to the product use patterns, the computation methods used in constructing these exposure indices are identical to all pesticide products regardless of the A.I.s involved. However, to accommodate products with different

A.I.s, the development of PEI_{norm} needs to include a mechanism for evaluating their relative potencies. An ideal application of the ToxPi approach is for pesticides with a common mode-of-action (MOA) such as cholinesterase inhibition (e.g., organophosphate and carbamate insecticides) (USEPA 2006) or decreased motor activity (e.g., Type I and Type II pyrethroid insecticides) (Wolansky et al. 2006). The overall ToxPi scores and/or individual indices could be used to evaluate findings such as the NHANES or other monitoring databases.

APPENDIX: COMPUTATIONAL METHODS OF NORMALIZED PRODUCT PROFILE INDICES

A. Normalized Handler Exposure Index (HEI_{norm}) – Potential for Dermal and Inhalation Exposures of Occupational or Non-Occupational Handlers (Mixer/Loader/Applicator)

For developing the HEI_{norm}, handler exposures from dermal and inhalation routes are evaluated under occupational and/or non-occupational settings. Short-term exposure is used for deriving the product profile index (and other indices described below) instead of the exposure from a longer term (e.g., seasonal or lifetime) because the highest exposure is anticipated from a short-term period. For the dermal exposure, short-term absorbed daily dose (STADD; mg/kg/day) of handlers can be expressed as the following (Beauvais et al. 2007):

$$STADD = \frac{UnitExp_{dermal} \times AF_{dermal} \times ATD \times AppRate}{BW}$$

Where:
$UnitExp_{dermal}$ = dermal unit exposure rate (μg/ lb A.I.) (Beauvais et al. 2007)
AF_{dermal} = dermal absorption factor
ATD = acre treated per day (acre/day)
AppRate = product application rate (lb A.I./acre)
BW = body weight (kg)

Combine the terms "ATD" and "AppRate;" therefore,

$$STADD_{dermal} = \frac{UnitExp_{dermal} \times AF_{dermal} \times Max.APD}{BW}$$

Where:
Max.APD = maximum amount applied per day (lb A.I./day)

For characterizing the inhalation exposure, the STADD can be expressed as

$$STADD_{inhalation} = \frac{UnitExp_{inhalation} \times AF_{inhalation} \times Max.APD}{BW}$$

Where:

$UnitExp_{inhalation}$ = Inhalation unit exposure rate (µg/ lb A.I.) (Beauvais et al. 2007)

$AF_{inhalation}$ = inhalation absorption factor

In the absence of chemical-specific data, AF_{dermal} is assumed to be 0.5 (Donahue 1996) and $AF_{inhalation}$ is 1 (Frank and Cochran 2008). For a given population subgroup (e.g., adults), the term "Body Weight (i.e., 70 kg)" entered into the exposure calculation is identical among all products and can be treated as a "constant" (k_1); therefore, STADD

$$STADD_{total} = \frac{\left[UnitExp_{dermal} \times 0.5 + UnitExp_{inhalation}\right] \times Max.APD}{k_1}$$

Where: k_1 = Body Weight (kg)

Therefore, the normalized value of HEI (i.e., HEI_{norm}) for a product is:

$$HEI_{norm} = \frac{\frac{1}{k_1}\left(\left[UnitExp_{dermal} \times 0.5 + UnitExp_{inhalation}\right] \times Max.APD\right)_{individual}}{\frac{1}{k_1}\left(\left[UnitExp_{dermal} \times 0.5 + UnitExp_{inhalation}\right] \times Max.APD\right)_{maximum}}$$

Eliminate the common term, k_1; the final HEI_{norm} equation for use in the ToxPi method is the following:

$$HEI_{norm} = \frac{\left(\left[UnitExp_{dermal} \times 0.5 + UnitExp_{inhalation}\right] \times Max.APD\right)_{individual}}{\left(\left[UnitExp_{dermal} \times 0.5 + UnitExp_{inhalation}\right] \times Max.APD\right)_{maximum}}$$

Based on the equation immediately above, information needed for developing the HEI_{norm} index is the unit exposure rate and the maximum amount of pesticide applied per day. The unit exposure rate is application method dependent and can be obtained from Beauvais et al. (2007), an open access document (https://apps.cdpr.ca.gov/whsrpts/hsrep/hsrep_hsno_action.cfm). The maximum pound applied per day can be derived from the product label and standard value for daily treated acres compiled by the USEPA (2001).

B. Normalized Reentry Exposure Index (REI_{norm}) – Potential for Dermal Exposure from Treated Crop or Turf

Unlike the handlers, inhalation exposure to airborne cyfluthrin (vapor) by reentry workers or bystanders is not expected because of the chemical's low vapor pressure (i.e., 3.3 x 10^{-8} mmHg) (Dotson et al. 2010). Using the aerosol-air partition model of Mackay (2001) and assuming the total suspended particulates (TSP) in ambient air of 40 µg/m^3, the expected fraction of cyfluthrin (vapor pressure of 3 x10^{-8} mmHg at 20ºC) on the particulate is 84%. 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. Accordingly, only the dermal exposure is considered in developing the REI_{norm}

Two types of reentry exposure scenarios are identified: dermal contact with the treated foliage of raw agricultural commodities and treated turf (USEPA 2012, USEPA 2017).

Short-term absorbed daily dose (STADD; mg/kg/day) due to the reentry exposure can be expressed as:

$$\text{STADD} = \frac{R \times TC \times AF_{dermal} \times ET}{BW}$$

Where:
R = residue (µg/cm^2)
TC = transfer coefficient (cm^2/hr)
AF_{dermal} = dermal absorption factor
ET = exposure time (hours/day)
BW = body weight (kg)

Rearrange terms in the above equation; therefore,

$$\text{STADD} = \frac{R \times TC \times ET}{\frac{BW}{AF_{dermal}}}$$

The "Residue" term in the equation above is either dislodgeable foliar residue (DFR) for reentry workers or transferable turf residue (TTR) for residential bystanders. For a given population

subgroup (e.g., adults), the terms "Body weight" (e.g., 70 kg) and "AF_{dermal}" (i.e., 0.5) entered the exposure calculation are identical among all products and can be treated as "constants" (k_2).

$$STADD = \frac{1}{k_2}(R \times TC \times ET)$$

Where: $k_2 = \frac{BW}{AF_{dermal}}$

Therefore, the normalized value of REI (i.e., REI_{norm}) for a product is:

$$REI_{norm} = \frac{\frac{1}{k_2}(R \times TC \times ET)_{individual}}{\frac{1}{k_2}(R \times TC \times ET)_{maximum}}$$

The USEPA 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. Hence, in the absence of chemical specific data, the "Residue" term (i.e., DFR or TTR) can be estimated by the following equations (USEPA 2012, USEPA 2017)

1. DFR ($\mu g/cm^2$) = AF x AppRate ($\mu g/cm^2$) where AF = 0.25
2. TTR ($\mu g/cm^2$) = AF x AppRate ($\mu g/cm^2$) where AF = 0.02 (granule) or 0.01 (liquid)

Where:
AppRate = product application rate ($\mu g/cm^2$)
AF = product formulation specific adjustment factor (USEPA 2012)

Substitute the DFR or TTR expression into the equation of REI_{norm} and eliminate the common term, k_2, the final equation for use in the ToxPi construction is the following:

$$REI_{norm} = \frac{(AF \times AppRate \times TC \times ET)_{individual}}{(AF \times AppRate \times TC \times ET)_{maximum}}$$

Based on the equation immediately above, information needed for developing the REI_{norm} index is the formulation, application rate ($\mu g/cm^2$), transfer coefficient (cm^2/hr), and exposure time (hours/day). The formulation and application rate can be obtained directly from the product label, and exposure time is assumed to be 8 hours/day for agricultural handlers (Beauvais et al. 2007) or 1.5 hours for residential bystanders (i.e., adults) (USEPA 2012). 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. Under the turf reentry scenario, the transfer coefficients are derived from the activities of adults (i.e., 180,000 cm^2/hr for the liquids and 200,000 cm^2/hr for the granules) (USEPA 2012). It is noteworthy that, for a given pesticide formulation, children have a lower transfer coefficient (i.e., 49000 cm^2/hr for liquids and 54000 cm^2/hr for granules). Provided that the same population subgroup is used for determining the REI_{norm}, the relative ranking of indices will not be affected. Under the agricultural setting, the transfer coefficient associated with different post-application activities (e.g., scouting, harvesting, and pruning etc.) can be found in Science Advisory Council for Exposure (ExpoSAC) Policy 3 by the USEPA (2017). The ExpoSAC policy is employed by the Human Health Assessment Branch for assessing post-application exposure of reentry workers (Kwok 2016).

C. Normalized Product Exposure Index (PEI_{norm})

Pesticide products contain both the active and inert ingredients. In the absence of data to suggest otherwise, it is not unreasonable to assume that all products elicit their toxic responses via the same MOA and that the toxicity induced by a product can be attributed to its pesticidal A.I. instead of its co-formulating "inert" ingredient(s). Toxic potency of a pesticide can be characterized by its toxicity threshold (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 a conventional pesticide risk assessment, the POD value is compared directly to the value of anticipated exposures for estimating health risk (i.e., POD/exposure). However, dividing a single POD value by each of the exposure indices would implicitly assume equal toxic response elicited among different population subgroups (i.e., adult, children, and women of childbearing age), an operation that is inconsistent with the known age-dependent susceptibility exhibited in some pyrethroids and other pesticides such as carbamates and organophosphates (Sheets et al. 1994, Moser et al. 2010, Poet et al. 2017).

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

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

Based on the equation above, information needed for calculating the PEI_{norm} index is the percent of A.I.s as specified on the product label. Since β-cyfluthrin is twice as toxic as cyfluthrin, in the equation above, the amount of A.I. in β-cyfluthrin containing products was converted into cyfluthrin (i.e., cyfluthrin-equivalent) using the following equation: cyfluthrin equivalent = 2 x percent of β-cyfluthrin.

D. Normalized Bystander Exposure Index (BEI_{norm}) – Potential for Bystander Exposure

For a given product, multiple use-sites are possible (e.g., recreational areas, schools, fruit crops etc.). These multiple use-sites could translate into a high potential (i.e., probability) of exposure to bystanders who may contact the pesticide residues. Based on this premise, the BEI_{norm} is calculated using the total number of use-sites (TUS) as contained in the DPR open access California Product/Label Database (http://www.cdpr.ca.gov/docs/label/labelque.htm). For example, in the DPR Product/Label Database, product "BCYF264B" has 251 use-sites whereas product "CYF92-H" has only one use-site.

$$BEI_{norm} = \frac{(TUS)_{individual}}{(TUS)_{maximum}}$$

BEI_{norm} is an exposure surrogate instead of a conventional exposure-type calculation. However, the index could be interpreted as an indication of how many bystanders might have been exposed to a product due to the multiple use-sites involved. In other words, products with 251 different use-sites may have more unanticipated bystander contact potential than products with only one use-site. Also, the use-site information is readily available for all products which prevents introduction of bias into the ranking by ToxPi method due to missing use information (e.g., the absence of historical use and sale data on "new" products), lack of bystander exposure data, unpredictability of bystander exposure, and high variability in exposure that occurs for bystanders near pesticide applications. If a single use-site (e.g., citrus) resulted in a high exposure potential to bystanders (e.g., spray drift via aerial and ground applications), the others exposed (i.e., agricultural handlers and reentry workers) would be captured by other indices such as HEI_{norm} and REI_{norm}.

E. Normalized Indoor Exposure Index (IEI_{norm}) – Potential of Post-Application Dermal Exposure from Treated Surfaces

Registered product labels permit a wide of variety of indoor uses. Among all the permissible indoor uses, the hard surface and carpet scenario constitutes the highest estimated post-application exposure (USEPA 2012). Based on a recent publication by Zhou *et al.* (2019), unlike the reentry exposure index calculation, inhalation exposure to airborne cyfluthrin (i.e., vapor and aerosol forms) cannot be ignored. Hence, both the inhalation and dermal exposures are considered in the IEI_{norm} computation.

For characterizing post-application exposure to pesticide via the inhalation of aerosol and vapor, the USEPA (USEPA 2012) derived the following equations:

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

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 (μg/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:

$TR\ (\mu g/cm^2) = AR\ (\mu g/cm^2)\ x\ F_{ai}$
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_3). Hence, the equation above can be rewritten as

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

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

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

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

Replace the product label specific AR by deposited residue (i.e., DepR) as described in the USEPA (2012) (Table 7), the final IEI_{norm} equation for use in the ToxPi method is the following:

$$IEI_{norm} = \frac{(DepR)_{individual}}{(DepR)_{maximum}}$$

Based on the equation immediately above, information needed for developing the IEI_{norm} index is the application rate ($\mu g/cm^2$) as specified on the product label. Table 7 shows different indoor exposure scenarios and their corresponding deposited residue estimation methods by the USEPA (2012). These estimation methods are set to either identical or a fraction of the product application rate. Accordingly, the relative IEI_{norm} ranking based on the scenario of hard surfaces and carpets could be extended to other indoor environment exposure scenarios.

Table 7. Indoor Environments and Deposited Residue Estimation Methods (USEPA 2012)

Indoor Environment	**Deposited Residue Estimation**
Hard Surface and Carpet	DepR = AppR rate ($\mu g/cm^2$)
Broadcast (liquid and fogger formulations)	DepR = AppRate ($\mu g/cm^2$)
Perimeter/Spot/Bedbug (course application)	DepR = 50% × Broadcast-equivalent AppRate ($\mu g/cm^2$)
Perimeter/Spot/Bedbug (pin stream application)	DepR = 50% × Broadcast-equivalent AppRate ($\mu g/cm^2$)
Crack and crevice	DepR = 10% × Broadcast-equivalent AppRate ($\mu g/cm^2$)

Abbreviation: DepR, deposited residue; AppRate, application rate of a product.

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