EPA's Office of Pesticide Programs' Review of the Status of Six PBPK Models in Preparation for the FIFRA SAP for the October 24-27, 2017

Physiologically Based Pharmacokinetic Modeling to Address Pharmacokinetic Differences Between and Within Species

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I. BACKGROUND

The Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) is a licensing program that regulates pesticides in the United States under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). As part of this program, OPP evaluates a substantial body of toxicology, exposure, and other pertinent data to assess the effects of pesticides on human health and the environment in risk assessment (NRC 1983). In human health risk assessment, the most commonly applied default factors are those used to extrapolate animal toxicity data to human health risks (inter-species extrapolation), and those that account for human variability (intra-species extrapolation). In addition, the OPP must consider the 10X Safety Factor required under the Food Quality Protection Act for consideration of toxicology and exposure data for infants and children (often called the FQPA 10X Safety Factor).

The 2009 National Research Council's report "*Science and Decisions, Advancing Risk Assessment*" recommends that the agency to use of the best, most current science to support or revise default assumptions that are applied in risk assessment. In addition, the 2013 Institute of Medicine report on *Environmental Decisions in the Face of Uncertainty* further recommends replacing default uncertainty factors with data-derived extrapolation factors (DDEFs) to decrease uncertainty in risk assessment, especially when sufficient scientific information exists to delineate differences between animals and humans, such as metabolism or mode of action. In 2014, the agency published the "*Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation*", in which uncertainty factors for inter- and intra-species extrapolation are subdivided into pharmacokinetic (PK) and pharmacodynamic (PD) components. The PK component depicts the process of chemicals being absorbed into, distributed to, metabolized within, and eliminated from internal tissues and organs (absorption, distribution, metabolism, excretion [ADME]), and thus, influences the target tissue concentrations of chemicals that enter the body. The PD component describes how chemicals mechanistically bring about tissue responses. The preferred approach for estimating DDEFs is to integrate PK and PD data using computational models, such as physiologically based pharmacokinetic (PBPK) or pharmacokinetic-pharmacodynamic (PBPK-PD) models.

PBPK modeling involves development of mass-balance differential equations to describe the ADME processes of a chemical as functions of relevant physiology, chemistry, and biochemical characteristics. A PBPK model consists of biologically relevant compartments, each representing either a single tissue/organ or a group of tissues/organs with similar blood flow and solubility characteristics. These compartments are connected via blood flows, as they receive chemicals through arterial blood and return the chemical through venous blood. When critical biological determinants of ADME are appropriately described in the model (e.g., tissue volumes, blood flows, metabolism rates), PBPK models have the capability to predict internal dosimetry for a chemical both within and outside of the conditions that are used to calibrate the models. Such capability has rendered PBPK

models to be particularly useful in risk assessment, where modeling approaches have been applied to assist in high-to-low dose, route-to-route, and inter-species extrapolations that are necessary for estimating human health risks under a variety of exposure conditions based on the results of animal toxicity studies. The physiological structure of PBPK models also allows for examining the impact on internal dosimetry from changing physiology, such as aging, early life-stage, pregnancy, or disease progression. Furthermore, the temporal changes of dose metric(s) simulated by a PBPK model can be input into a PD model to predict the temporal changes of responses, such as acetylcholinesterase (AChE) inhibition.

The agency recognizes the value of using PBPK models to predict internal target tissue doses, which can subsequently be used to replace the use of default uncertainty factors on administered/external doses in risk assessment. The scientific basis for such replacement is that equivalent target tissue dose will produce a similar target tissue response across species and exposure conditions. Thus, PBPK models can be used to evaluate uncertainty related to the quantitative relationship between administered dose and target tissue dose across and within species. Specifically, a human PBPK model removes the need for applying default inter-species uncertainty factor for PK, and it also can be used to estimate intra-species DDEF for PK variability in humans. In cases where a PBPK model is coupled with a PD model to predict biological responses, default uncertainty factors for PD can be replaced with DDEFs estimated from the PD model.

Most traditional PBPK (or PBPK/PD) models for environmental chemicals are calibrated using a 'top-down' approach, in which values for some chemical-specific parameters (e.g., hepatic metabolism rates) are determined by adjusting these values until model outputs agree with the available *in vivo* data, such as time course of plasma concentrations of the chemical. To support inter- or intra-species extrapolation, these *in vivo* data-calibrated parameters are either allometrically scaled or assumed to be the same across and within species. While these two extrapolating approaches can be appropriate at times, they do not always sufficiently address the variability in ADME especially when a model parameter represents an agglomeration of ADME processes that are complexly correlated (e.g., using one clearance rate to represent both Phase I and Phase II metabolism may not be appropriate). In these cases, additional empirical fitting of the model is often required for any new conditions (e.g., doses, species, life-stages). When *in vivo* data are not available for a new condition (e.g., no plasma concentrations measured in infants), a modeler usually exercises a parallelogram approach to first identify the variability in ADME using animal data, and then apply the same variability to humans.

Recent advances in *in vitro* to *in vivo* extrapolation (IVIVE) and *in vitro*/*in silico* technologies provide new opportunities to address challenges in inter- and intra-species extrapolations by providing necessary data and methodologies for a 'bottom-up' approach. The ‘bottom-up’ approach incorporates more mechanistic-based parameters (e.g., tissue-specific expression of key enzymes responsible for metabolism) in the model, and thus, species-dependent, gender-dependent, and lifestage-dependent variability of these parameters can be included for the model to evaluate their impact on target tissue doses. Whether it is a top-down or bottom-up PBPK model, the gold standard for evaluating a model’s predictive capacity has always been examining whether the model and

corresponding parameters can adequately simulate the available time course of tissue/plasma concentrations over a range of doses, including those data that are not used to calibrate model parameters (EPA 2006, WHO 2010). When *in vivo* data are not available for a population of interest, the parallelogram approach described above can be used to increase confidence in model predictions.

Recently, OPP employed a PBPK/PD model to enable quantitative incorporation of differing physiological and biochemical properties between animals and humans, as well as within human populations (e.g., as a function of age), in regulatory decision-making in the case of the organophosphate insecticide chlorpyrifos. Specifically, OPP used the PBPK/PD model for chlorpyrifos to examine the impact of exposure routes, frequency, duration, and life-stage on AChE inhibition in red blood cells (RBCs) in humans. This model was used in the 2014 revised human health risk assessment[1] (HHRA) to replace the default inter- and intra-species uncertainty factors, as well as to derive separate human points of departure (PoDs) based on 10% RBC AChE inhibition for both acute and chronic exposures in different scenarios (e.g., worker, residential, food, drinking water). Since then, several registrants, including the Council for the Advancement of Pyrethroid Human Health Risk Assessment (CAPHRA), Tessenderlo Kerley Inc. (TKI), FMC Corporation (FMC), and Syngenta, started developing PBPK and PBPK-PD models with the intention to support a specific HHRA, extrapolate to other chemicals in the same class, or demonstrate a more efficient approach to develop a model.

All scientific products, including PBPK model, that support regulatory decision-making are required to undergo appropriate levels of independent peer review, which are much more rigorous than those required for academic publication (McLanahan et al., 2012). In addition to evaluating how well model simulations reproduce available time-concentration data (as described above), a PBPK model intended for regulatory risk assessment should also be reviewed for model purpose and scope, model structure and biological characterization, mathematical representation of ADME, parameter estimation, computer implementation, documentation, and sensitivity and uncertainty analysis (EPA 2006, WHO 2010). Thus, the purpose of the October 2017 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) review is for the agency to solicit comments from the SAP members on their evaluation of the PBPK (or PBPK/PD) models for deltamethrin (CAPHRA), permethrin (CAPHRA), carbaryl (TKI), malathion (FMC), dimethoate (FMC), and acibenzolar (Syngenta), regarding the capability of each model to predict appropriate internal dose metrics in humans for their intended risk assessment purposes, such as estimating chemical-specific DDEFs or deriving human PoDs for various exposure scenarios. In addition to providing feedback on the model purpose, scope and model predictive capability, the SAP members will also be asked to review other details of the models, including model structure and biological characterization, mathematical representation of ADME, parameter estimation, computer implementation, documentation, and sensitivity and uncertainty analysis (EPA 2006; WHO 2010). Finally, the SAP members will be asked to comment on the potential for using these models as a basis for developing models for other chemicals within the same chemical class.

[1] https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0850-0195

All six models being reviewed during the October 2017 SAP include age-dependent physiological changes from birth to adulthood for predicting dose metrics at different ages. Currently, these models, however, do not include descriptions for gestational and lactational phases, and thus, will not have the capability to predict dose metrics in pregnant women, fetuses, or nursing infants. For dimethoate, malathion, and carbaryl, the PBPK models are coupled with PD models to predict AChE inhibition in red blood cells (RBC) and other tissues, such as brain. The PBPK models for deltamethrin, permethrin, and acibenzolar are developed to predict the time course of plasma concentrations of parent compound and/or metabolites. The carbaryl, deltamethrin, and permethrin models are coded in R[2]; the malathion model is coded in acslX[3] (The AEgis Technologies Group, Huntsville, AL); the dimethoate model is coded in Mathematica[4] (Wolfram Research, Champaign, IL). The acibenzolar model, developed in Simcyp[5] (Certera, Sheffield, UK), is primarily a proof-of-concept study highlighting newer *in vitro* and *in silico* based approaches, and will not be used in a risk assessment by the agency at this time. A brief introduction of each of the six chemicals with PBPK (or PBPK/PD) models being submitted for review is presented in the next section.

II. SUMMARY OF CHEMICAL TOXICITY & USES

A. Carbaryl

Carbaryl is a member of the *N*-methyl carbamate (NMC) class of pesticides. NMCs share the ability to inhibit acetylcholinesterase (AChE) via carbamylation of the active site. NMCs are characterized by rapid onset of AChE inhibition (15-60 minutes) and rapid reactivation of the enzyme leading to half-lives for the time to recovery between 1-4 hours. For NMCs, repeated daily exposure does not result in an increased inhibition of AChE since enzyme recovery is complete before the next acute exposure. Therefore, acute exposure is the only duration of concern for neurotoxic effects.

Carbaryl is a widely used broad spectrum insecticide in agriculture, professional turf management, professional ornamental production, and in the residential lawn and garden markets. Carbaryl formulations include dusts, liquids/emulsifiable concentrates, granules, granule baits, wettable powders (contained in water soluble packets) and ready-to-use products (e.g., shaker cans, hose-end-sprayers, etc.). In addition, carbaryl has a registered specialized use for commercial fishery water systems (24C). Based on the registered use pattern, humans may be exposed to carbaryl via dietary (food and drinking

[2] https://www.r-project.org/
[3] http://acslx.com/
[4] http://www.wolfram.com/mathematica/
[5] https://www.certara.com/software/physiologically-based-pharmacokinetic-modeling-and-simulation/

water), residential, and occupational pathways which can result in oral, dermal, and inhalation exposure.

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B. Synthetic Pyrethroids: Deltamethrin & Cis-Permethrin

Deltamethrin and permethrin are synthetic pyrethroids. This class of pesticides share the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous systems, leading to changes in neuron firing and, ultimately, neurotoxicity. Permethrin is a Type I pyrethroid, which can induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, hyperthermia, and fine tremor progressing to whole-body tremor and prostration (T-syndrome) (Verschoyle and Aldridge 1980; Gammon et al. 1982). Deltamethrin is a Type II pyrethroid, which can produce a toxicity syndrome that includes pawing, burrowing, salivation, hypothermia, and coarse tremors leading to choreoathetosis (CS-syndrome) (Verschoyle and Aldridge 1980; Gammon et al. 1982). The toxicity profiles for pyrethroids are consistently characterized by rapid absorption, metabolism, and time-to-peak effect. The single dose and repeat dosing studies show that repeat exposures do not result in lower PoDs (i.e. there is no evidence of increasing toxicity with an increased duration of exposure). Therefore, for the purpose of exposure assessment, only single day risk assessment need to be conducted for deltamethrin and permethrin.

Permethrin is currently registered in the U.S. with 121 companies on over 590 product labels for a wide variety of indoor and outdoor residential (e.g., hotels, theatres, restaurants, hospitals), industrial settings (e.g., industrial buildings, poultry houses, warehouses), agricultural crops, animal applications, and public health uses. It is formulated as an emulsifiable concentrate (EC), dry flowable (DF), wettable powder (WP) (including water soluble bags), granule (G), dust (D), as well as a number of ready to use (RTU) formulations (e.g., aerosol cans, foggers, trigger pump sprayers, ear tags, hose-end sprayers). Currently, there is also a registered application for military aircraft's cabin, crew, and cargo areas with an aerosol space spray for mosquito control. Based on the registered use pattern, humans may be exposed to permethrin via dietary (food and drinking water), residential, and occupational pathways which can result in oral, dermal, and inhalation exposure.

Deltamethrin is currently formulated as a liquid soluble concentrate (SC), EC, aerosol spray, WP, D, and foam end-use products (EUPs). Deltamethrin is currently registered for use on a wide variety of food/feed crops, stored grains, and was recently registered as a public health adulticide for control of mosquitoes in the vicinity of agricultural crops, as well as outdoor residential and recreational areas. All mosquitocide products are only to be applied by federal, state, tribal, or local government officials responsible for public health and adult mosquito control. It is also registered to control a large variety of indoor and outdoor pests found on turf, pets and in residential and commercial settings (e.g., food handling establishments, warehouses, schools, apartments, auditoriums, grain mills, institutions, schools, supermarkets). Based on these uses, adults and children could be exposed to deltamethrin residues via dietary (food and drinking water), residential, and

occupational exposure resulting in potential oral, dermal, and inhalation exposure. However, systemic toxicity via the dermal route of exposure is not anticipated; therefore, potential for dermal exposure is anticipated to be negligible.

C. Acibenzolar

Acibenzolar is a member of the benzothiadiazole class of compounds used for the control of several fungal, bacterial, and viral plant diseases. It is a plant activator that protects plants against invading pathogens by inducing a natural defense reaction that enhances the plants ability to ward off disease. In subchronic and chronic oral studies in rats, dogs and mice, signs of mild regenerative hemolytic anemia are consistently observed in all three species. Additional toxic effects observed in these studies include decreases in body weight, body weight gain, and/or food consumption.

Acibenzolar is formulated as a water-dispersible granule and a flowable concentrate. In occupational settings, it is used on a number of crops, including leafy and fruiting vegetables, low growing berries, pome fruit, citrus, and tobacco. Agricultural applications may be made using ground (including handheld) or aerial equipment. Acibenzolar is also used in commercial seed treatment operations on cotton to protect against certain early season seed and seed-borne nematodes. In addition, it may be applied via handheld equipment on turf for sod farms, golf courses, professional and collegiate athletic fields, and lawns around commercial and industrial buildings to control turf diseases. In residential settings, acibenzolar is registered for use on lawns and landscape ornamentals, as well as for weed control on non-cropland areas by commercial applicators and homeowners. Exposure to acibenzolar may occur via dietary (food and drinking water), residential, and occupational pathways which can result in oral, dermal, and inhalation exposure.

D. Organophosphate Pesticides (OPs): Malathion & Dimethoate

Like other OPs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for malathion and dimethoate involves inhibition of the enzyme AChE via phosphorylation which leads to an accumulation of acetylcholine and ultimately neurotoxicity in the central and/or peripheral nervous system. Malathion and dimethoate, like some other OPs, require metabolic activation to their oxon metabolite (malaoxon and omethoate, respectively) to inhibit AChE, with subsequent metabolism that leads to detoxification. Clinical signs of neurotoxicity (such as, tremors, salivation, urogenital staining, and decreased motor activity) can be found throughout the database of experimental animal toxicity studies at doses higher than those causing AChE inhibition. Cholinergic toxicity can result from single, acute exposures or from repeated exposures. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme, a phenomenon called steady state.

Malathion is used in the agricultural production of a wide variety of food/feed crops to control insects such as aphids, leafhoppers, and Japanese beetles. Malathion is also used in the Cotton Boll Weevil Eradication Program, Fruit Fly (Medfly) Control Program, and as a public health use for mosquito-borne disease control. It is also available to the home gardener for outdoor residential uses which include vegetable gardens, home orchards, and ornamentals. Malathion is formulated as a technical, a dust, an emulsifiable concentrate (EC), a ready-to-use (RTU) product, a pressurized liquid, and a wettable powder (WP). Several of the 95% liquids are intended for ultra-low-volume (ULV) applications. Malathion can be applied using ground or aerial equipment, thermal and non-thermal fogger, ground boom, airblast sprayer, chemigation, and a variety of hand-held equipment such as backpack sprayers, low pressure handwands, hose-and sprayers, and power dusters. Based on the registered use pattern, humans may be exposed to malathion via dietary (food and drinking water), residential, and occupational exposure resulting in potential oral, dermal, and inhalation exposure.

There are numerous end-use product labels registered with dimethoate as the active ingredient, including liquid and water-soluble packet formulations. The labeled use sites include various agricultural crops, Christmas tree farms, trees grown for pulp, and ornamentals in outdoor nurseries. Most of the registered products are applied via aerial, chemigation, airblast, groundboom, or with handheld equipment. There are currently no registered residential uses of dimethoate. Based on the registered use pattern, humans may be exposed to dimethoate and omethoate via dietary (food and drinking water) and occupational exposure resulting in potential oral, dermal, and inhalation exposure.

III. OVERVIEW OF OPP EXPOSURE ASSESSMENT APPROACHES

A. Typical Exposure Scenarios

In the 2014 chlorpyrifos HHRA, OPP developed an innovative and highly refined approach to using the PBPK/PD model to derive human PoDs[6]. Specifically, OPP coupled peer reviewed and publicly vetted methods for exposure assessment with the PBPK/PD model for chlorpyrifos to derive age, gender, duration, and route specific PoDs (herein called scenario-specific PoDs). OPP intends to use a similar approach for any pesticide with a well-developed, peer reviewed PBPK or PBPK/PD model. Four of the six PBPK or PBPK/PD models developed for the October, 2017 meeting of the FIFRA SAP currently include age-specific variability in physiological and biochemistry. The remaining two (malathion, dimethoate) are expected to refine this information in the future. As such, these PBPK or PBPK/PD models can be used to derive age-, route-, duration-, and frequency-specific PoDs for each chemical based on its relevant internal dose metric (e.g.,

[6] https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0850-0195

10% RBC AChE inhibition for OPs and NMCs). These scenario-specific PoDs can then be used to calculate scenario-specific reference doses (RfDs) by adjusting the PoDs with the respective DDEFs for each chemical. This section provides an overview of the typical exposure assessment approaches conducted at OPP.

As noted in Section II, exposure scenarios are unique for each chemical based on its registered use patterns. The following exposure characteristics are extracted from each scenario to set up the PBPK (or PBPK/PD) models for predicting scenario-specific PoDs: exposure duration [acute; steady state]; route (oral, dermal, inhalation); body weights, which vary by age; ventilation rates for inhalation exposures, which vary by age and activity levels; exposed fraction of skin for dermal exposures, which vary by activities; and exposure frequency [events per day (eating, drinking), hours per day].

The dietary, occupational, and residential exposure assessment methods, algorithms, and inputs used in conjunction with the PBPK (or PBPK/PD) model to derive PoDs are the same as are typically used for risk assessment and are supported by numerous SAPs (details provided below). These peer reviewed methods result in well-documented, transparent, and scientifically supportable methods for assessing the risk of exposures from all pesticides and evaluating the range of population-based exposures that might be expected. The agency has relied on the FIFRA SAP to peer-review guidance documents, methods, approaches, and pilot analyses to ensure that the agency is using appropriate methods and sound science. In addition to the SAP reviews, the agency has sought and considered public comments on these approaches as it developed these assessment methods. Further, the concept of using a "scenario-based" approach to complete exposure assessments is longstanding and outlined in many agency guidance documents and is consistent with federal government risk assessment guidance (NRC, 2009).

The use of a probabilistic exposure approach for assessing food exposure has previously undergone several SAP reviews (1998, 1999, 2000, 2002, 2004, and 2005)[7,8,9,10,11,12,13,14]. Dietary exposure assessment relies upon the Dietary Exposure Evaluation Model (DEEM) with the Food Commodity Intake Database (FCID). DEEM-FCID (version 3.18) incorporates consumption data from the 2003-2008 cycles of USDA's National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA)[15]. The approaches used for modeling drinking water exposures have also undergone extensive SAP review (1997, 1998, 1999, 2000, 2004, 2010, and

[7] https://archive.epa.gov/scipoly/sap/meetings/web/html/032498_mtg.html
[8] https://archive.epa.gov/scipoly/sap/meetings/web/html/052599_mtg.html
[9] https://archive.epa.gov/scipoly/sap/meetings/web/html/022900_mtg.html
[10] https://archive.epa.gov/scipoly/sap/meetings/web/html/092600_mtg.html
[11] https://archive.epa.gov/scipoly/sap/meetings/web/html/120700_mtg.html
[12] https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2002-0228
[13] https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2004-0071
[14] https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2005-0102
[15] http://www.ars.usda.gov/Services/docs.htm?docid=13793

2011.[16,17,18,19,20,21,22,23,24,25,26]). These methods include use of exposure modeling as well as evaluation of available water monitoring data to fully characterize the potential drinking water exposure.

Residential exposures are assessed as recommended in the 2012 Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessment[27] which describes specific algorithms and inputs, on a scenario-specific basis. The 2012 Residential SOPs were subjected to peer review by SAP in October 2009.[28] Occupational exposures are assessed as supported by peer review by SAP of pesticide handler exposures in 1986 and 2007,[29] and field workers in 1998[30] and 2008.[31]

For both residential and occupational exposures, the agency assesses all potential pesticide use scenarios that could lead to exposure. These scenarios include both handler exposures to those individuals who are involved in the pesticide application process, and post-application exposures to those individuals conducting activities in an environment previously treated with a pesticide. Exposure levels can differ based on the population exposed (i.e., adults or children), the amount of active ingredients used, formulation type, the kinds of equipment used to apply the pesticide, exposure duration, use frequency, and for occupational populations, the level of clothing worn and personal protection used (e.g., chemical resistant gloves).

The following dietary, occupational, and residential exposures scenarios have been evaluated for each chemical of interest as appropriate. Differing applicable durations of exposure have also been considered (e.g., acute, steady state). The specific scenarios which have been considered include:

- dietary exposures via drinking water for infants, children, youths, and adults;
- dietary exposures via food for infants, children, youths, and adults;
- non-dietary occupational exposures to active ingredients via skin to adults;
- non-dietary occupational exposure to active ingredients via inhalation for adults;
- non-dietary residential exposures to active ingredients via skin for children, youths, and adults;

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16 https://archive.epa.gov/scipoly/sap/meetings/web/html/121097_mtg.html
17 https://archive.epa.gov/scipoly/sap/meetings/web/html/072998_mtg.html
18 https://archive.epa.gov/scipoly/sap/meetings/web/html/101498_mtg.html
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23 https://archive.epa.gov/scipoly/sap/meetings/web/html/120700_mtg.html
24 https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2004-0005
25 https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2010-0125
26 https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2011-0399
27 http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide
28 http://www.regulations.gov/#!docketBrowser;rpp=50;po=0;D=EPA-HQ-OPP-2009-0516
29 https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2006-0856
30 https://archive.epa.gov/scipoly/sap/meetings/web/html/032498_mtg.html
31 https://www.regulations.gov/docketBrowser?rpp=50&po=0&D=EPA-HQ-OPP-2008-0673

- non-dietary residential exposures to active ingredients via hand-to-mouth ingestion for children 1- 2 years old;
- non-dietary residential exposures to active ingredients via inhalation for children 1 -2 years old and adults.

B. Exposure Inputs Used for PBPK PoD Derivation

1. Dietary Inputs

Dietary exposures for all active ingredients were estimated for varying durations as applicable, including all populations and their respective daily volumes of drinking water. The daily volumes consumed and number of daily consumption events for all populations are mean values by age group based on the NHANES/WWEIA survey data. Infants and children were assumed to consume water six times a day; youths and female adults were assumed to consume water four times a day. For dietary exposures via food, the eating event was set to one meal per day. The daily volumes consumed values are as follow: infants < 1 year old (0.688557 L); children 1-2 years old (0.35 L); children 6-12 years old (0.58 L); and youths 13-19 years old (0.93 L); female adults (1.71062 L). Although the mean daily water consumption inputs for children 1-2 years old and children 6-12 years old, are less than that for infants < 1-year-old, the infant daily water consumption volume was selected to be protective for PBPK/PD PoD derivation for these age groups; the adult daily water consumption was selected to be protective for youths 13-19 years old.

2. Residential Inputs

The values described in this section are based on those recommended in the 2012 Residential SOPs for the scenarios described below. For residential dermal exposures to all active ingredients, the fraction of skin in contact with pesticide active ingredients was set to 50%. A daily shower (i.e., washing off the pesticide) was assumed following exposures. All residential exposures were set to be continuous for OPs to reflect steady state exposures and single day exposures were considered for NMCs and pyrethroids. The following daily exposure periods were used to calculate the residential exposures:

Residential handler exposure duration (adults only):

- Turf or Garden: 1 hour
- Pets: 1 hour

Residential post-application exposure duration following:

- Impregnated Materials: 4 hours (children 1 to < 2 years old)
- Indoor Misting System (barn): 2 hours (children 3 to < 6 years old); 4 hours (adults)

- Outdoor Misting System: 1.5 hours (children 1 to < 2 years old); 2.3 hours (adults)
- Turf: 1.5 hours (adults and children 1 to < 2 years old)
- Gardens: 1.1 hours (children 1 to < 2 years old); 2.2 (adults)
- Pets: 1 hour (children 1 to < 2 years old); 0.77 hours (adults)
- Public Health Mosquitocide: 1.5 hours (adults and children 1 to < 2 years old)
- Spray drift (turf): 1.5 hours (adults and children 1 to < 2 years old)

3. Occupational Inputs

Dermal exposures for occupational handlers (those individuals who are involved in the pesticide application process) and workers (those who enter previously treated areas to perform job functions) assumed even distribution across the entire body surface area. A daily shower (i.e., washing off the pesticide) was assumed following occupational exposures. Female adult workers between the ages of 13 to 49, were assumed to have a mean body weight of 69 kg; male adult workers between the ages of 13 to 49 were assumed to have mean body weight of 80 kg. Occupational handlers were assumed to be exposed either via inhalation or skin for 8 hours/day, 5 days/week, for a total of either 21 days for OPs or single day exposures for NMCs and pyrethroids and post-application workers are exposed via skin for 8 hours/day, 5 days/week, for a total of either 21 days for OPs or single day exposures for NMCs and pyrethroids.

IV. REVIEW OF CURRENT STATUS OF PBPK AND PBPK/PD MODELS & THEIR APPLICATIONS

OPP has regularly met with the registrants and their modelers to review the model structures, assumptions, equations, code implementation, parameterization, and applications during the model development phase.

In January 2017, all relevant registrants submitted their lists of planned documents for the October 2017 SAP review, and the agency provided feedback to the list within one week of receiving the lists.

In February 2017, OPP met with TKI and CAPHRA to review their preliminary model code, initially programmed in acslX, and model simulations. Suggestions to better organize and annotate the code were provided in these meetings. During these meetings, TKI and CAPHRA also presented on their model assumptions and discussed their strategies with the agency to parameterize and evaluate their models. In addition, OPP provided exposure scenarios that are relevant to the human health risk assessments to TKI and CAPHRA for carbaryl, deltamethrin, and permethrin, so that their models can be used to estimate human scenario-specific PoDs.

In early March 2017, TKI, CAPHRA, and Syngenta submitted their draft white papers, and the agency met with each group separately in mid-March to provide feedback to their draft white papers and other supplementary materials.

In mid-March 2017, the second round of code review with TKI and CAPHRA was conducted for the agency to review their changes and run several simulations. In April 2017, TKI and CAPHRA converted their model code from acslX to R, anticipating the challenges with model review since acslX was sunset December, 2015. The agency met with both TKI and CAPHRA in May to review their R code for the carbaryl and pyrethroids models, and was satisfied with the quality and accuracy of the model code.

In mid-March 2017, Syngenta also presented their Simcyp model, as well as their proof-of-concept studies using the acibenzolar model to estimate DDEFs. The agency was satisfied with the study approaches.

In May 2017, TKI and CAPHRA submitted their final documents and model code to OPP for carbaryl, deltamethrin, and permethrin. Syngenta also submitted their final documents, as well as inputs/outputs of the acibenzolar model (no model code). The agency reviewed these documents and provided suggestions for minor revisions to the white papers.

The *in vitro* studies being conducted on behalf of FMC were not complete by June 2017 to provide necessary metabolism and cholinesterase inhibition data for parameterizing the PBPK/PD models for malathion and dimethoate. In addition, the modelers have experienced challenges in fitting some existing *in vivo* data and will benefit from input from the SAP members on the appropriate steps forward. As a result, the

PBPK/PD models for malathion and dimethoate are not fully complete and are not ready for risk assessment applications. In early April 2017, the agency reviewed the preliminary acslX code for the malathion PBPK/PD model and provided suggestions for substantial revision. Beginning in early April, the agency met with FMC and their modelers every two weeks until mid-June to monitor their progress and preliminary modeling results. In mid-June 2017, FMC and their modelers shared with the agency, their Mathematica code for the dimethoate PBPK/PD model, so the code was not thoroughly reviewed prior to the preparation of this white paper. FMC and their modelers are considering converting their model code to a different software language (e.g., R) in the future. In addition to code review, the agency has met with FMC and their modelers multiple times to discuss the key PK behaviors that need to be included in the models based on available *in vivo* and *in vitro* data for malathion, malaoxon, dimethoate, and omethoate. The agency expects to continue the discussions with FMC as they receive additional *in vitro* results and update the models until the life-stage human PBPK/PD models for malathion and dimethoate are completed. In mid-June 2017, FMC submitted their draft white papers for malathion and dimethoate PBPK/PD models to OPP. OPP reviewed the white papers and provided feedback for revisions.

A short summary of each model and the agency's evaluation of the model quality and its applications are listed below.

A. Carbaryl

In preparation for the October 2017 SAP review, TKI submitted a life-stage human PBPK/PD model for that predicts the disposition of carbaryl and the resulting level of AChE inhibition in brain and RBC after oral, inhalation, and dermal exposure to carbaryl at any age from birth to adulthood. The model does not include gestational and lactational components; this does not preclude the agency from using the carbaryl PBPK-PD model. In this model, the age-specific parameters, including body weight, cardiac output, tissue volumes, and tissue blood flows, were obtained from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. Another age-specific parameter, metabolic clearance, was estimated from *in vitro* metabolism data that was collected using human expressed enzymes and the age-dependent changes in the expression profiles of each enzyme. The model structure and biological characterization of the PBPK/PD model for carbaryl appears to be appropriate. Parameter estimation approaches that involved *in vitro* measurements of metabolic clearance, AChE inhibition, tissue-to-plasma partitions, and plasma protein binding; IVIVE; fitting of some chemical-specific parameters to *in vivo* rat or human data; literature sources; and incorporation of age-dependent physiological changes and enzyme ontogeny were thoughtfully conducted for this model. Mathematical representation and computer implementation were accurate and have been carefully documented; sensitivity and uncertainty analyses were performed. Finally, the model performance was evaluated using published data on the time course of plasma concentrations as well as AChE inhibition in RBC, after a single dose of carbaryl in human

volunteers (May et al., 1992)[32]. The model simulations showed general agreement with the observed time course data, providing confidence in the model's capability to predict AChE inhibition in RBC.

The first proposed application of this human PBPK/PD model was to calculate a DDEF to address age-related physiology and PK differences and the resulting PD differences (i.e., AChE inhibition in RBC and in brain) for carbaryl in humans in order to replace the use of the default intra-species uncertainty factor. Specifically, Monte Carlo simulations were conducted for the most sensitive juvenile age, which has the highest AChE inhibition in the brain or in RBCs at a given oral dose, and for the 25-year-old (which are considered adults) to obtain the medians of the simulated distributions of the maximum AChE inhibition in RBCs or in the brain from the two group.

TKI has proposed to use the ratio of the medians from the two age groups in RBCs or in the brain was the proposed intra-species DDEF. The percentile of the population for use in intra-species DDEFs is a science policy decision to be made by the agency following the SAP review of the PBPK-PD model. Since the human PBPK/PD model was used to predict human PD endpoints (i.e., 10% AChE inhibition in RBC and in brain), there was no need for extrapolation from animals to humans, and thus an inter-species uncertainty factor is proposed to be reduced to 1X. The second proposed application of the human PBPK/PD model was to derive PoDs specific to exposure scenarios that are of interest to the agency (Appendix A). These PoDs were estimated based on a maximum of 10% AChE inhibition in RBCs and in the brain. For the typical exposure scenarios that OPP assesses, a body weight is associated with a specific age group (e.g., 4.8 kg for infants less than one year of age). However, these age-body weight combinations did not necessarily match those calculated in the life-stage PBPK/PD model, in which body weight is a function of age and gender. Thus, the approach taken by the registrant was to identify, within the range of ages provided by the agency, the age-gender combination that results in the highest AChE inhibition in RBCs and in the brain at a given dose. This most sensitive age-gender combination was then used to derive a scenario-specific PoD. The model construct was appropriate for these two intended risk assessment applications, and the implementation (e.g., Monte Carlo simulations, reverse dosimetry) was conducted without errors.

The agency has concluded that the life-stage PBPK/PD model for carbaryl can be used to estimate DDEFs, as well as to derive scenario-specific PoDs for risk assessment.

[32] A human study is available that evaluates AChE inhibition resulting from carbaryl exposure (May, D.G., et al., 1992) and the study has been reviewed by the Human Studies Review Board (HSRB) for ethical & scientific considerations and was approved for the proposed use, validation of a carbaryl PBPK model. https://www.epa.gov/osa/january-25-26-2017-meeting-human-studies-review-board https://www.epa.gov/sites/production/files/2017-05/documents/january_2017_hsrb_final_report.pdf

B. Deltamethrin & Cis-Permethrin

CAPHRA submitted, for the October 2017 SAP review, life-stage rat and human PBPK models for both deltamethrin and cis-permethrin that predict the disposition of these two pyrethroids after oral exposure at any age from birth to adulthood. The model does not include gestational and lactational components; this does not preclude the agency from using the deltamethrin and cis-permethrin PBPK models. The two life-stage rat models were developed to investigate and validate the IVIVE approach based on *in vitro* metabolism data measured using microsomes, cytosol, and plasma and enzyme ontogeny to predict time course of plasma and brain concentrations of deltamethrin and permethrin for rats at different ages. Preliminary evaluation of the IVIVE approach showed that *in vitro* estimated metabolic clearance need to be empirically reduced in order for model predictions to fit observed time course data in rats. A single empirical adjustment factor to account for *in vitro* and *in vivo* differences in metabolic clearance for both pyrethroids and for rats at different ages suggested that the differences between *in vitro* and *in vivo* metabolic clearance are independent of age and chemicals. In addition to examining the capability of the model to predict ADME of deltamethrin and permethrin for rats at different ages, the use of a single model structure for both pyrethroids along with chemical-specific parameters demonstrated a read-across strategy to effectively develop PBPK models for chemicals in the same chemical class. The model performance was evaluated by comparing model simulations with time course of brain and plasma concentrations of deltamethrin and permethrin measured in PND15 and PND90 rats given at three single oral doses. The model simulations showed general agreement with the observed time course data, providing confidence in the IVIVE and enzyme ontogeny approaches to account for metabolic variability at different ages, as well as the read across approach to construct the two models using a generic structure.

Similar approaches and modeling strategies were applied to develop the life-stage human PBPK models for deltamethrin and permethrin. The human model structure was based on that of the rat, and inhalation route was added to the human models. In the human models, age-specific parameters, including body weight, cardiac output, tissue volumes, and tissue blood flows, were obtained from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. Another age-specific parameter, metabolic clearance, was estimated from *in vitro* metabolism data that was collected using human expressed enzymes and the age-dependent changes in the expression profiles of each enzyme. The model structure and biological characterization of the life-stage PBPK models for deltamethrin and permethrin appeared to be appropriate. Parameter estimation approaches that involved *in vitro* measurements of metabolic clearance and adjustment made to fit model predictions to *in vivo* rat data; IVIVE; literature sources; and incorporation of age-dependent physiological changes and enzyme ontogeny were thoughtfully conducted for this model. Mathematical representation and computer implementation were accurate and carefully documented; sensitivity and uncertainty analysis were performed.

The first proposed application of the human PBPK models was to calculate a DDEF to address age-related physiology and metabolic clearance differences for deltamethrin and permethrin in humans in order to replace the use of the default intra-species uncertainty factor. Specifically, Monte Carlo simulations were conducted for the most sensitive juvenile age, which has the highest peak plasma or brain concentrations at a given oral dose, and for the adults 20 – 49 year-old (which are considered adults) to obtain the medians of the simulated distributions of the peak plasma or brain concentrations of deltamethrin and cis-permethrin. CAPHRA has proposed to use the ratio of the two medians in peak plasma and brain concentrations as the proposed intra-species DDEF for PK. The percentile of the population for use in intra-species DDEFs is a science policy decision to be made by the agency following the SAP review of the PBPK models. Since the human PBPK model was used to predict human dose metrics, there was no need for extrapolation from animals to humans, and thus an inter-species uncertainty factor for PK is proposed to be reduced to 1X. The second proposed application of the human PBPK models was to derive PoDs specific to exposure scenarios that are of interest to the agency (Appendix B for deltamethrin and Appendix C for permethrin), and these PoDs were estimated based on peak plasma or brain concentrations resulting from rats given an oral dose at a benchmark dose derived from Wolansky (2006). For the typical exposure scenarios that OPP assesses, a body weight is associated with a specific age group (e.g., 4.8 kg for infants less than one year of age). However, these age-body weight combinations did not necessarily match those calculated in the life-stage PBPK models, in which body weight is a function of age and gender. Thus, the approach taken by the registrant was to identify, within the range of age provided by the agency, the age-gender combination that will result in the highest peak concentration of deltamethrin and permethrin in plasma and in brain at a given dose. This most sensitive age-gender combination was then used to derive scenario-specific PoDs, including both oral and inhalation routes. The model construct was appropriate for these two intended risk assessment applications, and the implementation (e.g., Monte Carlo simulations, reverse dosimetry) was conducted without errors.

The agency has concluded that the life-stage PBPK human models for deltamethrin and permethrin can be used to estimate DDEFs, as well as to derive scenario-specific PoDs for risk assessment.

C. Acibenzolar

Syngenta submitted, for the October 2017 SAP review, a proof-of-concept study to demonstrate the use of a population-based PBPK model to predict internal dose metric for different subsets of population, and subsequently compare the outputs to estimate DDEFs for PK uncertainty. The active ingredient used in this proof-of-concept study was acibenzolar. The human PBPK model for acibenzolar, as well as the estimated DDEFs, are not anticipated to be used in a risk assessment by the agency at this time. Using the Simcyp platform, both a rat version and a human version of the acibenzolar PBPK model was constructed using the platform's minimal PBPK model structure, in which the body was

separated into a gut compartment, a liver compartment, and a systemic compartment. Within the human Simcyp Simulator for ADME simulation, virtual individuals can be generated based on distributions of physiological parameters, as well as their covariate relationships (e.g., heart volume is related to gender and body surface area) established from meta-analysis of data in the scientific literature. Since the rat Simcyp Simulator does not include such a built-in function to incorporate population variability, the impact of physiological variability was investigated using the R-Simcyp package. Values of several model parameters for both rats and humans were obtained using *in vitro* studies, such as free fraction of acibenzolar and its primary metabolite, acibenzolar-acid, in rat and human plasma, metabolism rates by hepatocytes, liver microsomes, intestinal microsomes, and plasma. Metabolism rates measured *in vitro* were converted to *in vivo* rates using built-in IVIVE function. Both the oral absorption rate and volume of distribution for rats were calibrated by optimizing model predictions against concentration-time profiles of acibenzolar-acid following either intravenous infusion (1 mg/kg) or oral administration (1, 10, and 100 mg/kg) of acibenzolar. The calibrated rat model was then used to simulate internal dose metrics (e.g., peak plasma concentration, area under the curve [AUC] of plasma concentration) of acibenzolar-acid given an oral PoD from a developmental neurotoxicity (DNT) study (8.2 mg/kg/day).

For the human PBPK model, both the oral absorption rate and volume of distribution were assumed to be equivalent to rat values. In order to simulate an infant population aged between one and two years, enzyme ontogeny data for carboxylesterase 1 (CES1) in liver and CES2 in intestine were applied to adjust the adult metabolism rates. The human model was then used to estimate distributions of human PoDs based on the predicted geometric mean of AUC of acibenzolar-acid concentrations in rat plasma given the oral PoD. Distributions of human PoDs were estimated for both adults and children between one and two years old. The model structure and biological characterization of the life-stage PBPK model for acibenzolar and acibenzolar-acid appeared to be appropriate. Parameter estimation approaches that involved *in vitro* measurements of metabolism rates and other parameters; fitting model predictions to *in vivo* rat data; IVIVE; and age-dependent physiological changes and enzyme ontogeny embedded in the Simcyp platform (but not accessible) are also appropriate. Sensitivity analysis was also performed using Simcyp.

The DDEF to account for interspecies PK differences was calculated as the ratio between rat PoD and estimated human PoD. For this PBPK model, the ratio of AUC is equivalent to the ratio of peak concentration or clearance. Thus, the DDEF to account for intra-species PK differences was calculated as the ratio of the 5th percentile of clearance distributions for children between one and two years of age and adults. In addition, the human PBPK model was also used to predict distributions of AUC of acibenzolar-acid concentrations in plasma for adults and children between one to two years of age at either the human PoD or at estimated intakes from acute and chronic exposure scenarios provided by Syngenta.

The agency concluded that the approaches, including probabilistic PBPK modeling, IVIVE, parallelogram analysis, presented in this proof-of-concept study to derive human PoDs and DDEFs for intra-species PK difference are appropriate. However, OPP does not

have a license for Simcyp and has not been able to review the PBPK model. The code is not available to be posted in the EPA docket for public access, and thus, the Simcyp model does not meet the agency's transparency needs at this time. Finally, a Simcyp model cannot be reproduced using other programming software because of the proprietary data embedded in the Simcyp software (e.g., age-dependent physiological changes). The agency is soliciting input from the SAP on the issues of transparency and accessibility.

The agency has concluded that the approaches presented in this proof-of-concept study to derive human PoDs and DDEFs to account for human PK variability are appropriate.

D. Malathion

For the October 2017 SAP review, FMC submitted their developing rat and human life-stage PBPK/PD models for malathion that predict the disposition of malathion and malaoxon, as well as malaoxon inhibition of AChE in brain and in RBC, at any age from birth to adulthood. The model does not include gestational and lactational components; this does not preclude the agency from using the malathion PBPK-PD model. The rat version of the model includes oral route, and the human version of the model includes oral, inhalation, and dermal routes. While both rat and human versions of the PBPK/PD models have been coded in acslX, values of several chemical-specific parameters will be updated after additional *in vitro* studies are completed. Therefore, the malathion PBPK/PD model will not be reviewed for its readiness to predict tissue/plasma concentrations of malathion and malaoxon, or malaoxon inhibition of AChE. Rather, the key biological characterization included in the model structure, as well as the strategies for parameterizing the model, will be reviewed to determine whether the current model structure can be used to appropriately incorporate age-related physiology, PK, and PD differences in humans exposed to malathion. The ultimate goal is to use the PBPK/PD model to estimate DDEFs and replace the use of default inter- and intra-species uncertainty factors.

The key metabolic processes included in the malathion PBPK/PD model are (1) activation of malathion to malaoxon via P450s; (2) metabolism of malathion by carboxylesterase to mono-carboxylic (MCA) and di-carboxylic acid (DCA); (3) metabolism of malaoxon by carboxylesterase via a catalytic reaction, including inhibition of carboxylesterase by malaoxon; (4) metabolism of malaoxon via a stoichiometric reaction by carboxylesterase, including reactivation of carboxylesterase, as well as stoichiometric reactions of malaoxon with AChE and butyrylcholinesterase. The life-stage human model adopted the approach used in the life-stage PBPK/PD model for chlorpyrifos, which incorporated age-specific body weight prediction and used it to scale other physiological parameters, metabolic constants, and enzyme activity rates. The *in vitro* metabolic constants for malathion activation to malaoxon showed no apparent effect of age. These modeling assumptions and strategies (e.g., selection of literature values, *in vitro* studies designed to estimate model parameters, steps to calibrate model parameters using *in vivo*

studies) appeared to be reasonable, and were appropriately reflected in mathematical representation and computer implementation.

Preliminary simulations from the rat PBPK/PD model were compared to available AChE inhibition and MCA/DCA data measured in urine and blood. Malaoxon metabolic constants were first estimated by fitting model predicted time course of RBC AChE inhibition data from rats exposed to malaoxon in a dietary study. The fitted model overestimated RBC AChE inhibition at high doses and MCA/DCA concentrations in urine; and underestimated MCA/DCA in blood. When simulating malathion exposure, the PBPK/PD underestimated RBC AChE inhibition. Additional *in vitr*o data, which are currently underway, on malathion metabolism rates and malaoxon binding to AChE may improve the model fits to data. If not, the current model assumptions and structure will need to be re-evaluated in order to properly describe the ADME of malathion and malaoxon. Given that refined human health risk assessments will need to be conducted in the near future, the agency is seeking recommendations from the SAP members on the experimental data needed to appropriately parameterizing the model under the current structure, as well as alternative model structure to be considered if no amount of experimental data can be used to improve the model fit. Also, the SAP members will be solicited to provide their evaluation of the model assumptions and parameterization strategies based on literature data, *in vitro* study results, and preliminary model simulations and comparison to *in vivo* data.

The agency has concluded that the additional work needs to be conducted to support the development of a human PBPK/PD model for malathion, as well as the application of the model to derive DDEFs or estimate human PoDs.

E. Dimethoate

FMC submitted, for the October 2017 SAP review, their developing rat PBPK/PD models for dimethoate that predicts the disposition of dimethoate and omethoate, as well as omethoate inhibition of AChE in brain and in RBC, at any age from birth to adulthood. The model does not include gestational and lactational components; this does not preclude the agency from using the dimethoate PBPK-PD model. The rat version of the model includes oral route, and the future human version of the model plans to include oral, inhalation, and dermal routes. The rat PBPK/PD model was coded in Mathematica, and values of several chemical-specific parameters will be updated after additional *in vitro* studies are completed. Therefore, the dimethoate PBPK/PD model will not be reviewed for its readiness to predict tissue/plasma dosimetry of dimethoate and omethoate, or omethoate inhibition of AChE. Rather, the key biological characterization included in the model structure, as well as the strategies for parameterizing the model, will be reviewed to determine whether the current model structure can be used to appropriately incorporate age-related physiology, PK, and PD differences in humans exposed to dimethoate. The ultimate goal is to develop a life-stage human PBPK/PD model for dimethoate to estimate DDEFs and replace the use of default inter- and intra-species uncertainty factors.

The key metabolic processes included in the dimethoate PBPK/PD model are (1) activation of dimethoate to omethoate via P450s; (2) metabolism of dimethoate by carboxyamidase to dimethoate carboxylic acid (DCA); (3) metabolism of omethoate via a catalytic reaction; (4) stoichiometric reactions of omethoate with AChE, butyrylcholinesterase, and carboxylesterase. The *in vitro* study that aimed to quantify metabolic constants for dimethoate to omethoate was not able to detect omethoate. The *in vitro* study that aimed to quantify omethoate metabolism was not able to isolate the enzyme systems, and only showed that omethoate inhibition of AChE for rat and human hepatic microsomes were similar between species. Also, no age, gender or race/ethnicity effects were found for humans based on the *in vitro* results. Since the model was provided in the same week this white paper was prepared and no mathematical equations were provided, the agency cannot comment on whether the mathematical representation and computer implementation were appropriate at this stage. Also, the modeling assumptions and strategies (e.g., selection of literature values, *in vitro* studies designed to estimate model parameters, steps to calibrate model parameters using *in vivo* studies) were not described in detail, and thus the agency cannot comment on the model structure and simulations of the data, even though the rat model simulations appeared to agree with blood and urine data of omethoate, as well as rat brain AChE inhibition data. Given that refined human health risk assessments will need to be conducted in the near future, the agency is seeking recommendations from the SAP members on the experimental data needed to appropriately parameterizing the model under the current structure, as well as alternative model structure to be considered if no amount of experimental data can be used to improve the model fit. Also, the SAP members will be solicited to provide their evaluation of the model assumptions and parameterization strategies based on literature data, *in vitro* study results, and preliminary model simulations and comparison to *in vivo* data.

The agency has concluded that the additional work needs to be conducted to support the development of a human PBPK/PD model for malathion, as well as the application of the model to derive DDEFs or estimate human PoDs.

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VI. APPENDIX A CARBARYL EXPOSURE SCENARIOS AND INPUTS

For carbaryl, Table 1 below presents the exposure scenarios selected for derivation of occupational/residential PoDs with use of the PBPK/PD model.

Table 1. Exposure Inputs Used for Occupational/Residential PoD Derivation

Exposure Scenario	Population	Exposure Route	Exposure Duration	Exposure Frequency (hrs/day)	Body Weight (kg)	Skin Contact	Breathing Rate (m3/hr)
Occupational							
Handler	Adults	Dermal	Single Day (NMC)	8	Adult (NMC): 80	100 %	NA
		Inhalation				NA	Pilots, Tractor Drivers: 0.5 Mixers/Loaders: 1 PHED: 1.74
Post-Application		Dermal				100%	NA
Residential							
Handler: Applying to Turf or Garden	Adults	Dermal	Single Day (NMC)	1.0	Adult (NMC): 80	50 %	NA
		Inhalation				NA	0.64
Post-Application: Garden Exposure	Children 1 to < 2 Years Old	Dermal		1.1	11	50 %	NA
		Incidental Oral				NA	
	Adult	Dermal		2.2	Adult (NMC): 80	50%	NA

VII. APPENDIX B DELTAMETHRIN EXPOSURE SCENARIOS AND INPUTS

For deltamethrin, Table 2 below presents the exposure scenarios selected for derivation of residential PoDs with use of the PBPK/PD model.

Table 2. Exposure Inputs Used for Occupational/Residential PoD Derivation

Exposure Scenario	Population	Exposure Route	Exposure Duration	Exposure Frequency (hrs/day)	Body Weight (kg)	Skin Contact	Breathing Rate (m^3/hr)
Residential							
Post-application Lawn and Turf	Children 1 to < 2 Years Old	Incidental Oral (Hand-to-Mouth)	Series of Acute Exposure (Pyrethroid) Every day is a new day	1.5	11	NA	NA
Post-application Pet				1			
Post-application Public Health Mosquito Adulticide	Adult	Inhalation		1.5	80		
	Children 1 to < 2 Years Old	Incidental Oral (Hand-to-Mouth)			11		

VIII. APPENDIX C PERMETHRIN EXPOSURE SCENARIOS AND INPUTS

For permethrin, Table 3 below presents the exposure scenarios selected for derivation of residential PoDs with use of the PBPK/PD model.

Table 3. Exposure Inputs Used for Occupational/Residential PoD Derivation

Exposure Scenario	Population	Exposure Route	Exposure Duration	Exposure Frequency (hrs/day)	Body Weight (kg)	Skin Contact	Breathing Rate (m^3/hr)
Residential - Handler							
Applying RTU to Pets	Adults	Inhalation	Single Day (pyrethroid)	1.0	Adult (pyrethroid): 80	NA	0.64
Residential – Post-Application							
Indoor Misting System (Barn)	Children 3 to < 6 Years Old	Incidental Oral (HtM)	Single Day (pyrethroid)	2 hrs/day; 4 replenishments/hour (8 replenishments per day)	19	NA	NA
		Inhalation		2.0			0.42
	Adults	Inhalation		4.0	80		0.64
Outdoor Residential Misting system	Children 1 to < 2 Years Old	Incidental Oral (HtM)	Single Day (pyrethroid)	1.5 hrs/day; 4 replenishments/hour (6 replenishments per day)	11		
		Inhalation		2.3			0.33
	Adults	Inhalation		2.3	80		0.64
Impregnated Materials	Children 1 to < 2 Years Old	Incidental Oral (HtM)	Single Day (pyrethroid)	4 hrs/day; 4 replenishments/hour (16 replenishments per day)	11		NA