UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Report on Malathion and Dimethoate Physiologically-Based Pharmacokinetic (PBPK) Model Review and Point of Departure (POD) Calculations

DATE: December 1, 2021

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Report on Malathion and Dimethoate PBPK Model Review and POD Calculations

Prepared by OPP/HED/RAB8 on December 1, 2021

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Introduction

The mode of action of organophosphate (OP) insecticides (i.e., inhibition of carboxyl ester hydrolases, including acetylcholinesterase (AChE), in brain and red blood cells) is well known. The OP insecticides dimethoate and malathion are regulated based on brain AChE inhibition by the toxic metabolites, omethoate and malaoxon, respectively. In an effort to replace the default uncertainty factors associated with interspecies extrapolation from an animal point of departure (POD), the registrant has developed physiologically-based pharmacokinetic (PBPK) models for adult rat, prenatal rat, and human.

OPP Health Effects Division (HED) Risk Assessment Branch 8 (RAB8) reviewed the submitted model code, updated certain POD scenarios, and modified the code to run additional dermal and inhalation exposure scenarios. The estimated exposure for the toxic blood/plasma concentrations associated with a threshold AChE inhibition was determined with the PBPK-PD model to provide a better picture of the associated risk.

Model Code Review

Full Model Code Review

A thorough review of the human PBPK model was conducted. The scenarios employed for dimethoate and malathion use the same core PBPK model and rely on the adjusted parameters to ensure chemical specificity.

In the human dimethoate model, there were typos in the metabolism parameters VMAXparLC_juvenile (993 umol/hr/kg) and KMparoxon_juvenile (399.2 umol/L). The values should have been consistent with the adult parameter values at 933 umol/hr/kg tissue and 339.2 umol/L, respectively, and were thus

updated in the dimethoate_human_parameters.R file. As the scenario files were set up to run the model with user specified body weights and adult metabolic parameters based on the assumption that juvenile and adult values are identical, this edit did not change the POD calculations. However, having the correct juvenile values will allow for more flexibility should a future user choose to run additional juvenile scenarios.

A minor issue was identified related to the age of modeled individuals. In Line 518, the model uses 8766 hr/year to 'age' the modeled individuals. This static value is based on the duration of a Julian year (365.25 days per year; common year being 365 days/year). This was confusing at first because the model parameters set a year equal to 364 days to ensure even divisibility by 7 days/week (line 313 of human_pbpk.R). This will make very little (or no) difference as the amount of time modeled is on the order of days. If the modeled time was 365 days/year, the time difference between the actual value and the utilized value is ~0.000684 yrs, which would contribute negligibly to the overall growth used as this age is only used in the growth curve. Better documentation/annotation of the code would have made this clearer. Also, continuity with the above referenced parameterization (364 days/year) might be nice to ensure internal consistency.

All other concerns during interim review were addressed or corrected in updated model files supplied by the registrant.

Review of Inhalation and Metabolism Differences Across Models

In comparing the POD there were stark differences in the relative values for dimethoate and malathion models for inhalation and dermal exposure routes. There are two primary explanations for this difference. First, 100% of malathion is absorbed via the inhalation route, while only 30% is absorbed in the dimethoate model. Second, metabolism is much faster in the malathion model than the dimethoate model. Since inhalation skips the first pass metabolism observed in oral exposure, the metabolic rate differences likely contribute to the difference.

Table 1. Select inhalation and metabolic parameters in dimethoate and malathion PBPK models.

Model	**Dimethoate**	**Malathion**
Fractional Absorption by Inhalation		
ABS_INH	0.3	1.0
Detoxification (umol/hr/kg tissue)		
VMAXparLC_adult	933	434718.9
VMAXparLC_juvenile	933	92319.48
VMAXparKC_adult	0	260831.3
VMASparKC_juvenile	0	55391.69
VMAXparBRC	0	10000
Oxidation to Oxon (umol/hr/kg tissue)		
VMAXparoxonC_adult	261.6	1624
VMAXparoxonC_juvenile	261.6	1382
Oxon Metabolism (umol/hr/kg tissue)		
VMAXoxonLC	75	0
VMAXoxonKC	0	0
VMAXoxonBRC	0	0

Clearance Rates (L/hr/L plasma)		
CRparLC	0	0
CRparKC	0	0
CRparBRC	0	0
CRparPLC	0	0
CRoxonLC	15	2707
CRoxonKC	0	0
CRoxonBRC	0	500
CRoxonPLC	0.2	386.85

Scenario Code Review

The human exposure scenarios submitted by the registrant were reviewed for to ensure the sex, weight, and dosing matched that of the EPA standards. This review was prompted by the risk assessment team identifying the weight issue with dimethoate scenario 17. The scenarios in Table 2 were identified as needing changes. Updated scripts were submitted by the registrants accordingly and the associated PODs have been updated from the report in the tables in the AED section below.

Table 2. Scenarios updated after the reports were submitted.

Chemical	**ID**	**Scenario Description**	**Issue**
Dimethoate	17	Infant Food (parent)	Weight was 70kg but should be 4.8kg
	33	Occupational worker	Sex was male but should be female
	36	Occupational worker	Sex was male but should be female
	37	Occupational worker	Sex was male but should be female
	38	Occupational worker	Sex was male but should be female
Malathion	43	Dermal (pick your own)	Exposure was 5 hrs/d but should be 1.9 hrs/d
	44	Dermal (mosquitocide aerial) adult	Exposure was 5 d/w but should be 7 d/w
	47	Inhalation (mosquitocide aerial) child	Exposure was 5 d/w but should be 7 d/w

Model Updates

In order to determine the PODs for direct inhalation and dermal exposure to the oxon metabolites, the PBPK models and parameters for dimethoate and malathion were updated. These were subjected to an independent QC review to determine accuracy. The updated models and oxon exposure scenarios are provided in the associated docket package.

Points of Departure (PODs)

Due to the above changes in the initial POD scenarios, as well as requests for additional POD calculations, new POD tables were generated (below). These values may vary slightly from the Exponent reports, due to small updates to the code and version of R used to determine the values. Inhalation based POD values were converted from mg/m3 to mg/kg/day for consistency.

Since the IVIVE values are lower than the *in vitro* human values, there was discussion of the best way to parameterize these models. A committee of toxicologists in HED reviewed the dermal absorption values used for the dimethoate PBPK model and determined that a percent dermal hourly absorption of 5% over

24 hours is appropriate. For malathion, a percent dermal hourly absorption rate of 1% over 8 hours was selected. Therefore, the PODs from these scenarios have been updated to reflect the change. Metabolites were run with the same percent dermal hourly absorption rates are the parent compounds.

Dimethoate Points of Departure (PODs)

Table 3. Dimethoate points of departure (PODs) for acute and subchronic oral exposure.

Exposure Duration	Population Subgroup	Body Weight (kg)	AChE Based POD (mg/kg/day)		
			Food (parent)[a]	Food (oxon)[b]	Drinking water (oxon)[a]
Acute	All infants (<1 year old)	4.8	3.4	0.58	0.69
	Children (1-2 years)	12.6	3.3	0.53	0.62
	Children (3-5 years)	18.7	3.1	0.49	0.58
	Children (6-12 years)	37.1	2.7	0.42	0.50
	Youth (13-19 years)	67.3	2.4	0.37	0.43
	Adults (20-49 years)	81.5	2.4	0.36	0.42
	Female (13-49 years)	72.9	2.4	0.36	0.43
Subchronic	All infants (<1 year old)	4.8	0.88	0.19	0.22
	Children (1-2 years)	12.6	0.80	0.18	0.20
	Children (3-5 years)	18.7	0.75	0.17	0.18
	Children (6-12 years)	37.1	0.64	0.14	0.16
	Youth (13-19 years)	67.3	0.56	0.12	0.14
	Adults (20-49 years)	81.5	0.55	0.12	0.13
	Female (13-49 years)	72.9	0.56	0.12	0.14

[a.] PODs from latest Exponent scripts, rather than report tables.

[b.] PODs from HED/RAB8 scripts available here.

Table 4. Dimethoate points of departure (PODs) for occupational and residential exposures (inhalation and incidental oral).

Population Subgroup	Exposure Route	Exposure Frequency	Weight (kg)	AChE Based POD (mg/kg/day) [a]	
				Parent	Oxon

Occupational Worker	Inhalation: 8.3 L/min	5 days/week 8 hours/day	69	2.1	0.34
Occupational Worker	Inhalation: 16.7 L/min	5 days/week 8 hours/day	69	2.1	0.34
Occupational Worker	Inhalation: 29 L/min	5 days/week 8 hours/day	69	2.1	0.34
Non-Occupational spray drift (children 1 to <2)	Incidental Oral	1.5 hrs/day	11	0.82	0.18

[a.] PODs from latest Exponent scripts, rather than report tables.

Table 5. Dimethoate points of departure (PODs) for occupational and residential exposures (dermal) determined with a percent dermal hourly absorption of 5% over 24 hours.[a]

Population Subgroup	Exposure Route	Exposure Frequency	Weight (kg)	AChE Based POD (mg/kg/day) [b]	
				Parent	Oxon
Occupational Worker	Dermal	5 days/week 8 hours/day	69	38.1	6.1
Non-Occupational spray drift (adult)	Dermal	1.5 hours/day	69	168	26.8
Non-Occupational spray drift (children 1 to <2)	Dermal	1.5 hours/day	11	246	39.3

[a.] Recommendation from HED.

[b.] Reran scenarios 33, 37, and 38 from the Exponent report with new dermal percentage values. All simulations are female (correction from submitted scripts).

Malathion Points of Departure (PODs)

For the malathion model, the metabolism of juveniles (<18) is lower than adults. The use of the juvenile kinetics was considered a conservative assumption for scenarios such as females of childbearing age (13-49). Therefore, the PODs for the food/drinking water adult only scenario (20-49 years) are higher than the PODs for juvenile scenarios, despite the larger body weight.

Additionally, the PODs for inhalation are determined by concentration, such that for a comparable scenario with a longer exposure scenario may have a lower concentration but a higher POD when converted to mg/kg/day. For occupational exposures with different breathing rates and same durations, the concentration was higher for lower breathing rates, but PODs were similar in mg/kg/day.

For occupational scenarios with exposure 5 days/week, exposure begins on day 0 and ends 2 days before the end of the 21 day simulation. The POD is determined based on the maximum percent AChE inhibition across the entire run, so ending the run with 2 days of no exposure does not impact the final result.

Table 6. Malathion points of departure (PODs) for acute and subchronic oral exposure.

Exposure Duration	Population Subgroup	Body Weight (kg)	AChE Based POD (mg/kg/day)		
			Food (parent)[a]	Food (oxon)	Drinking water (oxon)[a]
Acute	All infants (<1 year old)	4.8	34.7	4.8	5.5
	Children	12.6	32.1	4.5	5.2

	(1-2 years)				
	Children (3-5 years)	18.7	30.4	4.3	5
	Children (6-12 years)	37.1	26.7	3.8	4.4
	Youth (13-19 years)	67.3	23.5	3.3	3.8
	Adults (20-49 years)	81.5	87.8	3.2	3.6
	Female (13-49 years)	72.9	24.4[b]	3.4	3.8[b]
Subchronic	All infants (<1 year old)	4.8	7.2	1.5	1.7
	Children (1-2 years)	12.6	6.8	1.5	1.6
	Children (3-5 years)	18.7	6.5	1.4	1.6
	Children (6-12 years)	37.1	5.8	1.2	1.4
	Youth (13-19 years)	67.3	5	1.1	1.2
	Adults (20-49 years)	81.5	17.3	1.0	1.1
	Female (13-49 years)	72.9	5.0[b]	1.1	1.2

[a.] Values from Exponent tables. Confirmed by OPP to be equivalent to 90% AChE inhibition +/- 0.01%.
[b.] Updated from Exponent table (changes of <1.5 mg/kg/day) for optimized PODs.

Table 7. Malathion points of departure (PODs) for occupational and residential exposures. Dermal exposures determined with a percent dermal hourly absorption of 1% over 8 hours.[b]

Exposure Scenario	Exposure Route	Exposure Frequency	Weight (kg)	AChE Based POD (mg/kg/day)	
				Parent[a]	Oxon
Food	Oral (food)	Single dose, 21 days	75	17.7 (male) 18.3 (female)	1.0 (male) 1.1 (female)
Drinking water	Oral (drinking water)	Single dose split into 6 per day, 21 days	4.8	7.6	1.7[a]
Occupational Worker	Inhalation: 16.67 L/min	5 days/week 8 hours/day	69	43.6[b]	NA
Occupational Worker	Inhalation: 8.33 L/min	5 days/week 8 hours/day	69	43.6[b]	NA
Occupational Worker	Inhalation: 26.67 L/min	5 days/week 8 hours/day	69	43.6[b]	NA
Occupational Worker	Inhalation: 28.83 L/min	5 days/week 8 hours/day	69	43.6[b]	NA

Residential handler inhalation	Inhalation: 10.67 L/min	7 days/week 1 hour/day	69	35.2 [b]	NA
Inhalation (mosquitocide aerial) adult	Inhalation: 10.67 L/min	7 days/week 1.5 hours/day	69	36.3 [b]	0.022
Inhalation (mosquitocide aerial) child	Inhalation: 5.5 L/min	7 days/week 1.5 hours/day	11	17.2 [b]	0.029
Oral hand-to-mouth (mosquitocide) child	Oral	7 days/week 1.5 hours/day	11	6.9 [b]	1.5
Non-Occupational Bystander: Ambient Air (Max Concn) adult	Inhalation: 10.67 L/min	Single dose 24 hours	69	255	0.089
Non-Occupational Bystander: Ambient Air (Max Concn) child	Inhalation: 5.5 L/min	Single dose 24 hours	11	500	0.120
Non-Occupational Bystander: Ambient Air (Avg Concn) adult	Inhalation: 10.67 L/min	24 hours/day 21 days	69	47.3	0.024
Non-Occupational Bystander: Ambient Air (Avg Concn) child	Inhalation: 5.5 L/min	24 hours/day 21 days	11	96.7	0.032
Non-Occupational Bystander: Ambient Air (Max Concn) adult	Inhalation: 10.67 L/min	Single dose 2 hours (parent) 8 hours (oxon)	69	244	0.074
Non-Occupational Bystander: Ambient Air (Max Concn) child	Inhalation: 5.5 L/min	Single dose 2 hours (parent) 8 hours (oxon)	11	465	0.099
Occupational Handler & Post-Application	Dermal	5 days/week, 8 hours/day	69	4,401	2.12
Residential Handler	Dermal	7 days/week, 1.1 hours/day	69	25,897	12.2
Residential Post-Application: Gardens	Dermal	7 days/week, 2.2 hours/day	69	13,518	6.40
Residential Post-Application: Gardens	Dermal	7 days/week, 1.1 hours/day	32	39,221	14.3
Residential Post-Application: Pick Your Own	Dermal	7 days/week, 5 hours/day	69	6,151	2.96
Residential Post-Application: Pick Your Own	Dermal	7 days/week, 1.9 hours/day	32	4,706	8.63
Residential Post-Application: Spray Drift, Mosquitocide Aerial and Ground	Dermal	7 days/week, 1.5 hours/day	69	19,424	9.14
Residential Post-Application: Spray Drift,	Dermal	7 days/week, 1.5 hours/day	11	8,261	12.1

Mosquitocide Aerial and Ground					

[a.] Values taken from Tables 21 and 22 of malathion report from Exponent for comparison. All simulations are female.

[b.] Rerun from initial Exponent report to correct exposure and confirm AChE inhibition.

[c.] Recommendation from HED. Reran dermal scenarios from the Exponent report with new dermal percentage values. All simulations are female (correction from submitted scripts).