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This report is a review of existing data. Good Laboratory Practice Standards, 40 CFR Part 160, are not applicable to this submission.

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metabolites are 34.0% and 52.3%, respectively, whereas the corresponding experimentally measured percentages were 34.2% and 52.8%, respectively (Study 8, Table XXIV). The omethoate PBPK-PD model also predicts that 2.5 hours after acute administration of 0.5 mg/kg omethoate in adult rats, Brain AChE is reduced to 73.4% of its baseline level in unexposed rats, consistent with experimental observations shown in Figure 3. The same time after a 10-mg/kg dose to rats the model predicts that Brain AChE is reduced to 0.5% of its baseline level, whereas the data shown in Figure 3 appear to indicate that Brain AChE may not be reduced to quite that extent (as discussed in the Figure 3 legend). 54

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Executive Summary

This report describes the ongoing development of rat and human physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for dimethoate. These models may be useful in the upcoming human health risk assessment for dimethoate by allowing the estimation of data-derived extrapolation factors (DDEFs) in place of standard, default uncertainty factors.

The metabolism of dimethoate is a key process to understand to build a PBPK/PD model. FMC Corporation (FMC) has conducted rat and human metabolism studies that identify levels of key metabolites in urine. The key processes include:

- Activation of dimethoate to omethoate via P450s.
- Metabolism of dimethoate via a catalytic reaction with carboxyamidase including tracking the formation of dimethoate carboxylic acid (DCA).
- Metabolism of omethoate via a catalytic reaction.
- Stoichiometric reactions of omethoate with other esterases including carboxylesterase, (CaE), butrylcholinesterase (BuChE) and acetylcholinesterase (AChE), including esterase reactivation and aging (aging only applicable for BuChE and AChE)

The later process, as it relates to AChE in the brain, is the key indicator of toxicity.

The PBPK/PD models being developed for dimethoate describe all of these processes. The activation of dimethoate to omethoate, and catalytic metabolism of dimethoate and omethoate are described with Michaelis-Menten kinetics. The stoichiometric reactions are modeled using a biomolecular rate constant and by dynamically tracking esterase levels. Metabolism primarily occurs in the liver. Inhibition of esterases in calculated in the model.

To quantify the rates of many of these processes, an *in vitro* testing program is underway at the laboratory of Dr. Janice Chambers at Mississippi State University (MSU), including the estimation of the bimolecular rate constant for inhibition of omethoate with AChE for rats and humans. A parallel program to estimate the kinetics for activation encountered experimental difficulties and we are reevaluating this issue.

The *in vitro* testing program at MSU is not completed yet, thus, a final model has not yet been produced. Therefore, this paper presents a PBPK/PD rat model that is fitted using rat metabolism data for omethoate and dimethoate. A human model has been built but fitting will not be done undtil the *in vitro* testing program is completed. The rat model will also be updated at that time.

Introduction

FMC Corporation (FMC) has undertaken an effort to construct physiologically-based pharmacokinetic/pharmacodynamics PBPK/PD models for dimethoate that may be used to develop pharmacokinetic (PK) and pharmacodynamic (PD) data-derived extrapolation factors (DDEFs) to inform the human health risk assessment of dimethoate. This document describes the model structures, the data used in model development and parameterization, and how the models were used.

The United States (U.S.) Environmental Protection Agency (EPA) has used a human physiologically-based pharmacokinetic/pharmacodynamic (PBPK-PD) model in order to modify uncertainty factors (UFs) using in the human health risk assessment for chlorpyrifos (USEPA 2014). The rat and human PBPK/PD models for dimethoate are similar in structure (compartments, metabolism, and other processes included) to the previously published PBPK/PD model for chlorpyrifos (Timchalk et al. 2002; Smith et al. 2014). Like chlorpyrifos, dimethoate is an organophosphorus (OP) insecticide and exhibits similar pharmacokinetic and pharmacodynamic behavior; both exert toxicity via inhibition of cholinesterase and both must be metabolized to the oxon form in order to inhibit cholinesterase (Timchalk et al. 2002; Buratti and Testai 2007). The rat and human models for dimethoate describe the pharmacokinetics (absorption, distribution, metabolism, excretion) of dimethoate and the oxon metabolite and the subsequent inhibition of acetylcholinesterase (AChE) by the oxon, and they can be used to predict varying levels of AChE inhibition resulting from oral, dermal, or inhalation exposure to dimethoate or the oxon (human model only for dermal and inhalation). Comparison of rat and human PK and PD with use of the models allows for development of interspecies PK and PD DDEFs, which may be used to modify the interspecies 10X uncertainty factor (UF).

In addition to existing PK and PD data for dimethoate, *in vitro* studies are underway at the laboratory of Dr. Janice Chambers at Mississippi State University (MSU) to generate additional data to refine kinetic parameters for the models; these studies will examine both PK and PD parameters and are discussed in more detail below.

At this time, the rat model has been fitted using available rat metabolism data for dimethoate and omethoate. The human model is built but is not yet fitted. After the completion of the *in vitro* testing, additional model development will occur.

We are seeking advice from the SAP on methods to refine the model.

Metabolism

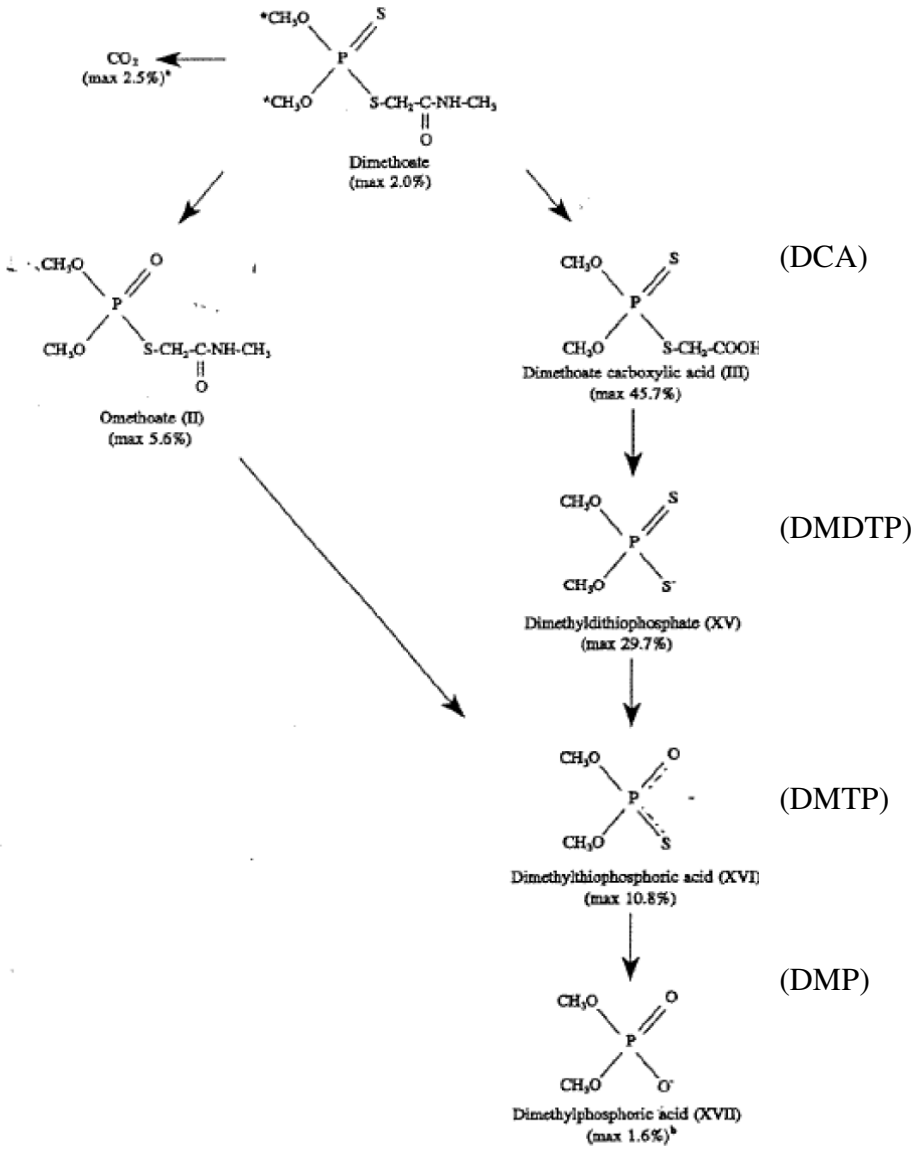
General Metabolism Scheme

Dimethoate metabolism occurs via at least two pathways, of which the dominating pathway involves hydrolytic cleavage of the amide group by carboxyamidases (Figure 1, right, adapted from Kirkpatrick 1995). The cleavage product, dimethoate carboxylic acid, is subsequently metabolized into downstream thiophosphate or phosphate ester intermediates and eventually oxidized to form dimethylphosphoric acid.

To a quantitatively lesser extent, dimethoate undergoes oxidative desulfurization to form the active AChE inhibiting moiety, omethoate (Lucier and Menzer 1970; APVMA 2011). As with other organophosphates, cytochrome P450 isoforms catalyze the reaction to form omethoate in this second pathway (Figure 1, left).

In the rat, dimethoate is metabolized by both a hydrolytic pathway (amidase-dependent) and an oxidative pathway (CYP450 isoforms) (Buratti and Testai 2007). Urine analyses of metabolites in the rat indicate that hydrolysis is the major pathway and involves cleavage of the C-N bond to yield dimethoate carboxylic acid (DCA), which is subsequently metabolized to dimethydithiophosphate (DMDTP), dimethylthiophosphoric acid (DMTP), and dimethylphosphate (DMP). These metabolites are non-toxic and are found to be extensively excreted in urine (Hassan et al. 1969; Lucier and Menzer 1970; Buratti and Testai 2007). Other minor metabolites have been identified, but have been found to be present only in very small amounts in urine. Additionally, other metabolites have been proposed but the structures have not been confirmed (Hassan et al. 1969). In addition to being detoxified by hydrolysis, a minor metabolic pathway is oxidative desulfuration to the toxic oxon form, which is subsequently metabolized to various dialkyl phosphates. Urinary data in both rats and humans indicate that DCA is the major urinary metabolite and that the other phosphates eliminated are present in smaller amounts. The metabolites account for most of the administered dose, while small amounts of the parent dimethoate and the oxon are excreted (Lucier and Menzer 1970; Kirkpatrick 1995; Meuling and Roza 2004). DMDTP, DMTP, and DMP have all been used as biomarkers of dimethoate exposure (Aprea et al. 1998; Buratti and Testai 2007; USEPA 2015); however, these are not specific to dimethoate as other OPs produce these urinary metabolites as well (USEPA 2015).

Figure 1. Metabolism of Dimethoate (adapted from Kirkpatrick 1995). Dimethoate (top molecule) metabolizes via at least two pathways. One pathway subjects dimethoate to hydrolytic cleavage at the amide bond by carboxyamidases; the other, to oxidative desulfurization by cytochrome P450 (CYP) to omethoate. The presence of these enzymes in the liver act as a controlling factor in the metabolism of dimethoate.



Dimethoate and Omethoate Metabolism in Rats

There are available metabolism studies in the rat for both dimethoate and omethoate.

A 1990 study conducted by Bayer AG investigated the metabolism of omethoate in rats (Hoshino 1989). Raw data from the study is in Appendix A. Female and male Wistar rats were administered intravenous or oral doses (with or without a 14-day pretreatment) of 0.5 or 10 mg/kg bw ^{14}C-radiolabeled omethoate. The excretion profile was characterized by observing the metabolites present in urine, feces, expired air, tissues, and remaining carcass, via thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC). The study showed that male and female rats excreted between 25-62% of omethoate unchanged in the urine, following an intravenous dose at 0.5 mg/kg, or oral doses at 0.5 or 10 mg/kg (see Table 1). The study also identified the O-desmethyl and sulphinyl metabolites; however, several other metabolites remained unidentified. The authors concluded that omethoate and its metabolites were quickly and completely absorbed, and that omethoate and its metabolites were rapidly excreted, primarily in the urine.

Table 1. Percent of the omethoate intravenously or orally administered dose excreted in male and female rats by metabolite at 48 hours (adapted from Hoshino 1990 Table XXIV)

Metabolites	i.v. 0.5 mg/kg		p.o. 0.5 mg/kg		p.o. 0.5 mg/kg		p.o. 10 mg/kg		p.o 10 mg/kg
	Test 1 Male	Test 2 Female	Test 3 Male	Test 4 Female	Test 5 Male	Test 6 Female	Test 7 Male	Test 8 Female	Test 9 Male
Omethoate	30.90	43.59	25.86	42.48	32.54	39.01	45.56	62.01	55.52
o-desmethyl	8.51	5.10	6.04	5.55	4.38	4.89	6.18	6.42	6.60
Sulphinyl	35.11	22.86	35.86	26.75	31.11	24.26	17.45	15.53	16.37
Total in Urine	74.53	71.55	67.76	74.78	68.03	68.15	69.19	83.96	78.49

i.v. = intravenous administration
p.o. = oral dose

The urinary excretion profile and time course data for dimethoate metabolism has been characterized in rats (Dauterman et al. 1959). ^{32}P-labeled dimethoate was prepared and administered at 100 mg/kg to 150 g male and female rats. Aside from two unknown hydrolytic metabolites, designated A and B, metabolite identities and proportions were characterized via ion exchange chromatography (Table 2). Over time, the product, $(CH_3O)_2P(O)OH$ (DMPA), increased between 2 and 48 hours post-dose, though the other metabolites did not exhibit as substantial an increase. The carboxy derivative (DCA) was detected as a metabolite for 20-40% of the total detected in the urine, although the amount produced is likely an underestimate

because DCA undergoes further degradation. This suggests that dimethoate is primarily attacked at the amide bond, instead of the dimethoate-P=O bond.

Table 2. Percent of dimethoate metabolites in urine of male rats treated orally at 100 mg/kg (adapted from Dauterman *et al.* 1959 Table 1)

Time (hour post-dose)	$(CH_3O)_2P(O)OH$ (DMPA)	Carboxy (DCA)	Carboxy + $(CH_3O)_2P(S)OH$	$(CH_3O)_2P(S)OH$	Des-methyl	$(CH_3O)_2P(S)SH$	Unknowns A+B
2	6.2	32.4	-	20.5	12.0	23.4	5.5
4	19.6	21.1	-	25.8	5.2	18.3	10.0
12	11.4	42.4	-	20.4	1.2	21.4	3.2
18	12.4	-	63.9[1]		1.2	21.0	1.5
24	17.6	35.2	-	26.6	1.8	17.2	1.6
48	21.7	22.0	-	32.7	5.5	17.4	0.7

[1] Inadequate column resolution prevented differentiation of carboxy and $(CH_3O)_2P(S)OH$ fractions

The urinary excretion profile and distribution within tissues for dimethoate in rats was further characterized in a 1995 study sponsored by the Dimethoate Task Force (Kirkpatrick 1995). Raw data from the study is in Appendix A. Groups of male and female Wistar rats were dosed with ^{14}C-dimethoate at a single oral dose, intravenous dose, or a single dose following 14-day repeated oral doses of unlabeled dimethoate. Most (85-91%) of the dose was excreted in urine as metabolites; relatively small amounts of radioactivity were observed in the feces, tissues, and remaining carcass. Metabolites (omethoate, DMTP, DMDTP, DCA, and unprocessed dimethoate) were identified via HPLC analysis, and data was collected at 48 hours (Table 3). Five metabolites (U1, U2a, U3, U5, and U6) were detected but not identified; however, none of these exceeded 7% of the administered dose.

The distribution of dimethoate and its metabolites within various rat tissues was determined by measuring radioactivity in male and/or female rats sacrificed at 0.5 h after a single oral dose of ^{14}C-dimethoate.

Table 3. Results of HPLC analysis of 48-hour urine samples after single oral, intravenous or dermal doses of dimethoate, expressed as percent of administered dose per metabolite (adapted from Kirkpatrick 1995 Table 23)

Chemical	Oral 10 mg/kg		Oral 10 mg/kg[1]		Oral 100 mg/kg		Intravenous 10 mg/kg		Dermal 10 mg/kg		Dermal 100 mg/kg	
U1	5.2	5.0	6.5	6.0	4.8	3.8	4.3	3.9	-[2]	-	-	-
Omethoate	1.5	2.5	3.2	5.6	3.7	3.7	1.3	1.8	-	-	-	-
U2a	0.3	0.2	0.3	0.3	0.4	0.3	[3]	[3]	-	-	-	-
U3	4.1	4.0	4.2	3.6	2.2	2.0	3.7	3.7	-	-	-	-

Chemical	Oral 10 mg/kg		Oral 10 mg/kg[1]		Oral 100 mg/kg		Intravenous 10 mg/kg		Dermal 10 mg/kg		Dermal 100 mg/kg	
Dimethylthiophosphoric acid (DMTP)	8.3	5.7	10.8	7.3	8.7	4.7	6.5	4.0	-	-	-	-
U5	0.9	0.7	1.2	1.2	1.0	1.3	0.9	0.7	-	-	-	-
U6	2.5	2.1	2.1	1.5	2.3	1.9	3.7	1.8	-	-	-	-
Dimethyldithiophosphate (DMDTP)	26.6	25.2	29.7	27.4	20.3	22.1	22.5	24.1	2.9	3.2	-	-
Dimethoate	1.4	0.7	0.9	0.6	0.7	2.0	0.4	0.5	-	-	-	-
Dicarboxylic acid (DCA)	37.8	35.1	29.1	31.0	43.2	44.4	42.7	45.7	2.5	2.8	-	-
Others	2.3	1.9	2.2	2.1	2.3	2.7	1.7	1.7	-	-	-	-
Total (% of dose identified)	90.9	83.1	90.2	86.6	89.6	88.9	87.7	87.9	5.4	6.0	1.4	1.5

[1]Rats were pretreated once a day for 14 days with unlabeled dimethoate prior to dosing with radiolabeled dimethoate
[2] "-" denotes percentages under 1%
[3]Included in the row: Others

There is a limited amount of dimethoate plasma data in the study. For a dose of 100 mg/kg, dimethoate in plasma was measured for males and females (Kirkpatrick 1995). These data are shown in Table 4. Concentrations after 0.5 hours of exposure were 5.7 mg/L for males and 7.4 mg/L for females. After 24 hours, the concentrations were below 0.051 mg/L.

Table 4. Plasma dimethoate concentrations following a 100 mg/kg exposure

Time (hours)	Males (mg/L)	Females (mg/L)
0.5	5.7	7.4
2	0.87	1.43
6	0.74	1.86
24	<0.051	<0.051

There are also data on the concentration of total radioactivity in plasma after oral doses of 100 mg/kg/day (Tables 5 and 6) and 10 mg/kg/day (Tables 7 and 8).

Table 5. Concentration of radioactivity (mg dimethoate equivalents/L) in plasma of male rats after a single oral dose of 14C-dimethoate at 100 mg/kg/day

Animal number	61	62	63	67	68	69	73	74	75	Mean	Std
Group	1	1	1	2	2	2	3	3	3		
Time (hours)											
0.25	-	-	-	64.0	56.2	32.0	-	-	-	50.7	16.7
0.5	-	-	-	-	-	-	40.6	45.3	45.0	43.6	2.6
1	30.6	38.5	25.3	-	-	-	-	-	-	31.5	6.6
2	-	-	-	14.5	13.1	19.4	-	-	-	15.7	3.3
4	-	-	-	-	-	-	3.61	4.95	5.01	4.52	0.79
6	10.9	12.5	11.3	-	-	-	-	-	-	11.6	0.8
12	-	-	-	7.98	7.53	5.35	-	-	-	6.95	1.41
24	-	-	-	-	-	-	3.09	5.37	4.49	4.32	1.15
48	1.54	5.03	1.94	-	-	-	-	-	-	2.84	1.91
72	-	-	-	1.55	1.26	1.27	-	-	-	1.36	0.16
96	-	-	-	-	-	-	0.75	0.68	0.68	0.70	0.04
120	0.52	2.38	0.61	-	-	-	-	-	-	1.17	1.05
144	-	-	-	0.42	0.38	0.44	-	-	-	0.41	0.03
168	-	-	-	-	-	-	0.22	0.35	0.29	0.29	0.07

Table 6. Concentration of radioactivity (mg dimethoate equivalents/L) in plasma of female rats after a single oral dose of 14C-dimethoate at 100 mg/kg/day

Animal number	64	65	66	70	71	72	76	77	78	Mean	Std
Group	1	1	1	2	2	2	3	3	3		
Time (hours)											
0.25	-	-	-	75.0	59.7	57.2	-	-	-	64.0	9.6
0.5	-	-	-	-	-	-	76.2	109	94.3	93.2	16.4
1	67.9	44.4	30.4	-	-	-	-	-	-	47.6	18.9
2	-	-	-	14.9	16.5	26.1	-	-	-	19.2	6.1
4	-	-	-	-	-	-	6.11	10.6	7.53	8.08	2.29
6	11.7	27.8	15.7	-	-	-	-	-	-	18.4	8.4
12	-	-	-	12.6	6.46	10.7	-	-	-	9.92	3.14
24	-	-	-	-	-	-	5.83	8.31	4.77	6.30	1.82
48	3.71	3.38	5.30	-	-	-	-	-	-	4.13	1.03
72	-	-	-	3.21	2.12	2.91	-	-	-	2.75	0.56
96	-	-	-	-	-	-	2.42	2.77	1.05	2.08	0.91
120	2.47	0.67	2.03	-	-	-	-	-	-	1.72	0.94
144	-	-	-	0.66	0.63	2.01	-	-	-	1.10	0.79
168	-	-	-	-	-	-	0.74	0.99	0.72	0.82	0.15

Table 7. Concentration of radioactivity (mg dimethoate equivalents/L) in plasma of male rats after a single oral dose of 14C-dimethoate at 10 mg/kg/day

Animal number	79	80	81	85	86	87	91	92	93	Mean	Std
Group	1	1	1	2	2	2	3	3	3		
Time (hours)											
0.25	-	-	-	4.98	8.96	5.69	-	-	-	6.54	2.12
0.5	-	-	-	-	-	-	6.55	10.2	9.11	8.62	1.87
1	3.89	4.38	5.47	-	-	-	-	-	-	4.58	0.81
2	-	-	-	3.36	2.77	5.30	-	-	-	3.81	1.32
4	-	-	-	-	-	-	1.83	4.42	2.71	2.99	1.32
6	0.88	0.66	1.37	-	-	-	-	-	-	0.97	0.6
12	-	-	-	0.34	1.13	0.48	-	-	-	0.65	0.42
24	-	-	-	-	-	-	0.20	0.80	0.55	0.52	0.30
48	0.12	0.16	0.14	-	-	-	-	-	-	0.14	0.02
72	-	-	-	0.07	0.23	0.15	-	-	-	0.15	0.08
96	-	-	-	-	-	-	0.06	0.09	0.11	0.09	0.03
120	0.03	0.04	0.04	-	-	-	-	-	-	0.04	0.01
144	-	-	-	0.04	0.11	0.05	-	-	-	0.07	0.04
168	-	-	-	-	-	-	0.03	0.10	0.03	0.05	0.04

Table 8. Concentration of radioactivity in plasma (mg dimethoate equivalents/L) of female rats after a single oral dose of 14C-dimethoate at 10 mg/kg/day

Animal number	82	83	84	88	89	90	94	95	96	Mean	Std
Group	1	1	1	2	2	2	3	3	3		
Time (hours)											
0.25	-	-	-	4.56	6.07	7.26	-	-	-	5.96	1.35
0.5	-	-	-	-	-	-	8.72	7.24	7.07	7.68	0.91
1	4.59	6.30	5.21	-	-	-	-	-	-	5.37	0.87
2	-	-	-	3.18	3.00	3.23	-	-	-	3.14	0.12
4	-	-	-	-	-	-	1.31	1.68	1.37	1.45	0.20
6	0.71	0.81	0.89	-	-	-	-	-	-	0.80	0.09
12	-	-	-	0.30	0.43	0.52	-	-	-	0.42	0.11
24	-	-	-	-	-	-	0.64	0.62	0.24	0.50	0.23
48	0.19	0.19	0.24	-	-	-	-	-	-	0.21	0.03
72	-	-	-	0.11	0.10	0.14	-	-	-	0.12	0.02
96	-	-	-	-	-	-	0.20	0.43	0.19	0.27	0.14
120	0.06	0.09	0.11	-	-	-	-	-	-	0.09	0.03
144	-	-	-	0.04	0.04	0.08	-	-	-	0.05	0.02
168	-	-	-	-	-	-	0.07	0.19	0.07	0.11	0.07

In vitro Metabolism of Dimethoate in Hepatic Microsomes

In a recent study sponsored by FMC and performed by Dr. Janice Chambers at MSU, dimethoate toxication by cytochrome P450 (CYP) to omethoate was measured in hepatic microsomes from rats and humans (Chambers and Meek 2017). Rat hepatic microsomes were obtained from homogenized livers extracted from adult Sprague Dawley-derived rats of both sexes (6 per sex, 70 days old, 250-300 g). Human hepatic microsomes from humans of both sexes, a range of ages, and several races/ethnicities were obtained from XenoTech, LLC (27 total human sources).

The study aimed to first quantify bioactivation via inhibition of purified exogenous AChE (obtained from electric eel) following incubation of hepatic microsomes with dimethoate. Cholinesterase inhibition was used as an analytical tool to serve as an indirect measure omethoate concentration. The hypothesis was that the AChE active metabolite, omethoate, could be quantified with high sensitivity and before appreciable degradation due to its potency against AChE, which acts as a "trap" to remove oxon from the system and measure how much was formed. From this reaction, the study aimed to calculate an affinity constant (K_m) and a maximum rate of metabolism (V_{max}) that could be used in PBPK modeling. However, no omethoate could be detected in the test. The reasons for not detecting omethoate are unclear, but it may be that omethoate detoxication was too fast for the trap system to measure it. Additionally, attempts to find a reliable inhibitor of omethoate detoxication were not successful.

Attempts were also made to measure omethoate detoxication. However, it was not possible to isolate the enzyme systems potentially involved in detoxication. Therefore, only IC_{50} values could be estimated. These IC_{50} values for omethoate inhibition of AChE are given below for rat and human hepatic microsomes in Tables 9 and 10, respectively. While the IC_{50} values cannot be directly used in the PBPK model, the similarily over a 30-minute incubation provides some evidence that rat and human dextoxication is similar. Also, there was no apparent effect of age, gender, or race/ethnicity on the human IC_{50} values.

Table 9. Rat hepatic microsome omethoate detoxication. Hepatic microsomes extracted from livers from adult Sprague Dawley-derived rats.

Subject #	Age (days)	AChE IC_{50} (nM)
Male 1	70	62,999
Male 2	70	62,008
Male 3	70	116,051
Male 4	70	60,638
Male 5	70	60,712
Male 6	70	61,641
Female 1	70	56,196
Female 2	70	53,667
Female 3	70	76,471
Female 4	70	62,680
Female 5	70	74,145
Female 6	70	49,817

Table 10. Human hepatic microsome omethoate detoxication. Hepatic microsomes extracted from livers from adult Sprague Dawley-derived rats.

Subject #	Sex	Race/ Ethnicity	Age (years)	AChE IC_{50} (nM)
354	Female	Caucasian	0.04	42,922
845	Male	Caucasian	0.08	67,870
268	Male	Caucasian	0.343	52,175
395	Male	Caucasian	0.42	54,950
270	Male	Caucasian	0.42	46,146
825	Male	Caucasian	0.92	47,349
322	Male	Hispanic	1	40,642
852	Female	Caucasian	2	48,869
551	Male	Caucasian	2	58,055
57	Male	Hispanic	2	47,676
346	Male	Caucasian	3	74,152
792	Male	American Indian	4	60,745
215	Male	Caucasian	6	59,348
59	Male	Caucasian	9	56,341
485	Male	Caucasian	10	39,810
410	Male	Caucasian	11	60,303
133	Female	Caucasian	17	60,356
236	Male	Asian	17	53,753
25	Female	Caucasian	30	61,869
393	Female	Caucasian	30	51,589
36	Male	African American	37	61,961
420	Male	Caucasian	42	68,945
177	Female	Caucasian	45	58,612
115	Female	Caucasian	48	61,788
201	Male	Hispanic	58	46,051
355	Female	Caucasian	71	67,126
203	Male	Caucasian	75	54,574

Human Urinary Excretion Profile

In a 2004 study sponsored by Cheminova A/S, the urinary excretion profile after an oral dose of dimethoate was characterized in humans (Meuling and Roza 2004). A single 0.03 mg/kg bw oral dose was administered to six healthy men between the ages of 18 and 45 years. The urine was analyzed for the presence of dimethoate, omethoate, dimethoate carboxylic acid (DCA), dimethyldithiophosphate (DMDTP), and dimethylthiophosphoric acid (DMTP). The mean ± s.d. and range for the detected metabolites are given in Table 11.

Table 11. Mean ± s.d. and range of the various excreted amounts of the urinary compounds (mg and µmol) and expressed relative to the administered dose (%).

Compound	Mean ± s.d. (mg)	Range (mg)	Mean ± s.d. (µmol)	% excreted of oral dose
Dimethoate (DM)	0.0019 ± 0.0010	0.0009 - 0.0033	0.0083 ± 0.004	**0.092**
Omethoate (OM)	0.0052 ± 0.0040	0.0013 - 0.0121	0.0244 ± 0.0188	**0.26**
DCA	0.8365 ± 0.1237	0.6570 - 1.1056	3.87 ± 0.57	**42.64**
DMDTP	0.1809 ± 0.0575	0.119 - 0.2645	1.15 ± 0.37	**12.71**
DMTP	0.1540 ± 0.0874	0.0657 - 0.2935	1.09 ± 0.62	**11.70**
			Total	**67.40 ±**

Notably, the study detected DCA as the dominant metabolite at 42.64% excreted of the oral dose. Additionally, DMDTP and DMTP were detected at 12.71% and 11.7% excreted of the oral dose, in support of the metabolism scheme in which carboxyamidases predominantly hydrolyze dimethoate into DCA, DMDTP, and DMTP as in Figure 1.

Cholinesterase activity in red blood cells and plasma was measured before and after the study using a modified Ellman method. Three control blood samples were obtained via finger prick seven days before the study start for each individual. The data showed cholinesterase activity levels did not substantially change from pre-dose levels to post-treatment levels. The EPA thus concluded in a study review in 2004 that a single dose of dimethoate did not significantly inhibit RBC or plasma cholinesterase activities beginning at 4 hours post-dosing.

The study also determined the peak of metabolite urinary excretion (C_{max}), the time at which C_{max} was observed (T_{max}), and the kinetic parameter that describes total drug concentration over time, area under the curve (AUC). These values are listed for each individual in Table 12. PK calculations thus showed primary metabolites (omethoate and DCA) peaked at 2 hours post dosing, and most compounds completed excretion within 24-28 hours, with the exception of DMDTP and DMTP, which completed excretion within 40-60 hours.

Table 12. Pharmacokinetic results of various excreted urinary metabolites for six healthy men

Subject Number	AUC (mg.h/L)					C_{max} (mg/L)					T_{max} (h)		
	DM	OM	DCA	DMDTP	DMTP	DM	OM	DCA	DMDTP	DMTP	DM; OM; and DCA	DMDTP	DMTP
1	0.011	0.1224	5.945	1.716	3.574	0.0035	0.0246	1.50	0.2680	0.4680	2	2	2
2	0.009	0.0232	8.595	2.575	1.230	0.0031	0.0077	2.490	0.4190	0.1920	2	2	2
3	0.011	0.0299	4.460	1.958	2.282	0.0037	0.0073	0.895	0.0972	0.1590	2	2	6
4	0.015	0.0189	7.518	1.307	0.843	0.0048	0.0063	1.820	0.1520	0.1010	2	2	2
5	0.013	0.0151	10.36	4.011	1.222	0.0042	0.0050	2.530	0.5100	0.1520	2	2	2
6	0.012	0.0271	5.159	1.326	1.559	0.0039	0.0065	1.100	0.1660	0.158	2	6	6

Available *In Vivo* Cholinesterase Inhibition Data

There are more than a dozen *in vivo* rat studies that measure cholinesterase inhibition for dimethoate and omethoate. The data are broadly consistent. Therefore, a subset of these studies was selected for model development. The studies were selected to provide a range of ages and exposure durations. Table 13 summarizes the available studies and the raw data (group means and standard deviations) are included in Appendix A. Appendix A includes a numbering system for the studies (also listed on Table 13) and includes columns for the strain, age, sex, weight, and type of dosing. The appendix also numbers the different datasets within each study (for example, a specific dataset could be rats of certain age, sex, and cholinesterase measurement time after doing).

The most important study is the comparative cholinesterase study for dimethoate (Meyers 2001). It includes acute and repeated dose exposures for rat pups and adults. Reiss and Gaylor (2004) estimated benchmark doses for these data. For acute exposures, the brain AChE BMD_{10}s for PND11 males and females were 1.8 and 1.5 mg/kg, respectively, whereas the BMD_{10} for adult males and females were 2.6 and 2.1 mg/kg, respectively. For repeated dose exposures, the brain AChE BMD_{10}s for PND11-21 pups was 0.64 mg/kg (combined sexes), and 0.47 mg/kg for adult males and 0.36 mg/kg for adult females. These data show no evidence for age-related sensitivity, consistent with EPA's prior conclusion.

There are also long-term dietary exposure studies for both dimethoate (Kaspers et al. 2004) and omethoate (Schladt 1995). Several studies provide time course data to show peak effects and recovery, including Brennan (2001) for dimethoate and Barnett (2012) for omethoate.

Table 13. Cholinesterase data for dimethoate and omethoate

Study	Chemical	Ages	Doses	Cholinesterase Compartments	Datasets
Myers (2001) Study No. 1	Dimethoate	Adults, fetuses, dams and pups[1]	Gavage (0.1, 0.5, 3 mg/kg)	Plasma, RBC, and brain	• Single exposures to PND11, dams, and adult rats • Repeated exposures to

[1] The fetus data were not used for model validation. The dams were not more sensitive than non-pregnant females. Therefore, the data for dams was not used either.

Study	Chemical	Ages	Doses	Cholinesterase Compartments	Datasets
					PND11-21 and adults
Kaspers et al. (2003) Study No. 2	Dimethoate	Adults	Diet (1.0, 3.0, and 7.5 mg/kg/day)	Plasma, RBC, and brain	• Repeat exposures for 2, 8, and 29 days
Brennan (2001) Study No. 3	Dimethoate	Adults	Gavage (30 mg/kg/day)	RBC	• Measurements at 2.5 and 24 hours after a single dose
Mellert et al. (2003) Study No. 4	Omethoate	Adults	Gavage (0, 0.2, 0.35, and 5 mg/kg)	RBC, Plasma, and Brain	• Measurements at 2.5 hours and 15 days after a single dose
Schladt (1995) Study No. 5	Omethoate	Adults	Diet (0, 0.05, 0.44, and 3.93 mg/kg/day)	RBC, Plasma, and Brain	• Repeated exposures for 182, 265, and 735 days
Barnett (2012) Study No. 6	Omethoate	Adults and pups[2]	Gavage	RBC	• Time of peak effect study with measurements at 0.5, 1, 2, 3, 4, and 8 hours)

[2] The data for pups and adults were similar; thus only the adult data were used for model validation.

Age-Specific PBPK/PD Models for Rats

General Model Structure

The general model structure for the adult rat and human PBPK/PD model is shown in Figure 2. This section describes the general model structure, which is based on the Timchalk et al. (2002) model. A few additional model components were needed to successfully fit the available data. These are described in the next section which reviews the model fitting process.

The models describe the time course of absorption, distribution, metabolism, and excretion of dimethoate (parent) and omethoate (oxon form) and the inhibition of target B-esterases by the oxon. Data suggest that both pharmacokinetic and pharmacodynamics responses are independent of sex in the rat and human (Edson et al. 1967; Kirkpatrick 1995). The human model is a life stage model, which allows for simulation and evaluation of PK and PD from birth to adulthood, and is based on the human life stage PBPK/PD model for chlorpyrifos (Poet et al. 2014; Smith et al. 2014). Briefly, body weight is a function age, calculated using a modified Gompertz growth function for both males and females. Tissue volumes, blood flows, rates of metabolism, cholinesterase enzyme activities, and external doses are then calculated as a function of body weight from birth to adulthood.

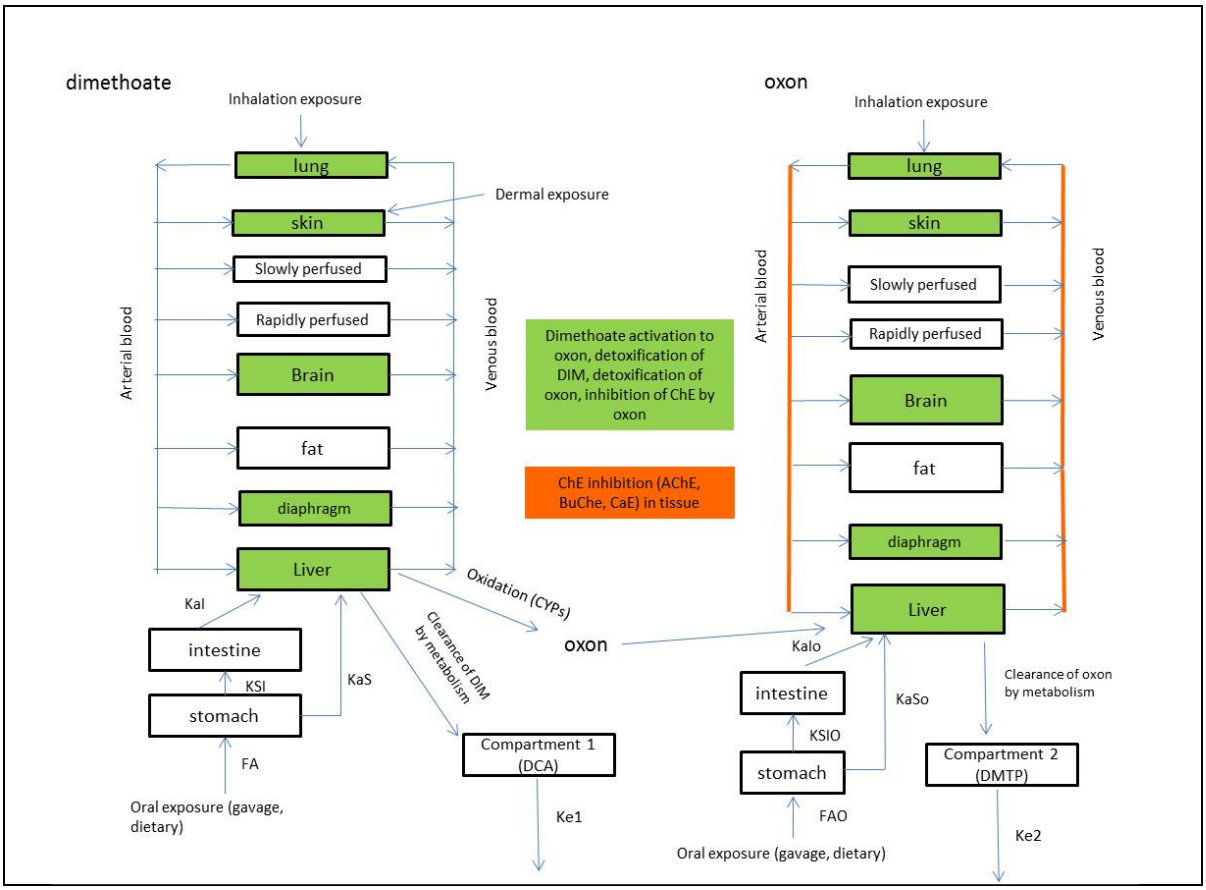
Both the rat and human models (for both parent and oxon) include compartments for fat, brain, liver, lung, skin, and lumped compartments for slowly and rapidly perfused tissues. Exposure to dimethoate is through the oral, dermal, and inhalation routes; direct exposure to the oxon is through the oral and inhalation routes. The absorption of dimethoate or the oxon following oral administration required a two-compartment model (stomach and intestine), which uses first-order rate constants to describe transfer between compartments and systemic uptake into the liver. The rate of change in the stomach is modeled as:

$$\frac{dStom}{dt} = -K_aS * Stom - K_sI * Stom$$

where *Stom* is the mass of dimethoate in the stomach, K_aS is the transfer rate from the stomach to the liver and K_sI is the transfer rate from the stomach to the intestine. In the intestine, the rate of change is modeled as:

$$\frac{dInst}{dt} = K_sI * Stom - K_aI * Inst$$

Figure 2. Dimethoate PBPK model structure. Metabolizing tissues include lung, skin, diaphragm, liver and brain.



where *Inst* is the mass of dimethoate in the intestine, K_aI is the transfer rate from the intestine to liver. The total rate of oral absorption is:

$$\frac{dOral}{dt} = K_aS * Stom + K_aI * Inst$$

Carboxyamidase-mediated (hydrolysis) metabolism to the inactive metabolite dimethoate carboxylic acid (DCA) and CYP450-mediated (oxidative) metabolism to the active oxon form are described for the liver, lung, diaphragm, brain, and skin, and detoxification (oxon to dimethyldithiophosphoric acid (DMTP)) is described in the each tissue, though primary detoxication is in the liver and other tissues are scaled to liver detoxication. All metabolism processes are described as saturable processes (i.e., Michaelis-Menten kinetics). The dimethoate model is linked to the oxon model through the liver, lung, diaphragm, brain, and

skin compartments. Kinetics of DCA and DMTP resulting from hydrolysis of dimethoate or oxon are modeled using simple one-compartment models to describe urinary elimination. As the other dialkyl phosphate metabolites are found to be excreted in smaller amounts than DCA and are not specific to dimethoate exposure, these are not explicitly described in the current models.

Metabolism occurs primarily in the liver. In the model, small fractions of total liver metabolism were assumed to occur in the lung, diaphragm, brain, and skin as was assumed to be the case in a similar model for chlorpyrifos (Poet et al., 2014), consistent with observations that extrahepatic tissues do not degrade dimethoate appreciably (Uchida et al. 1964; Uchida and O'Brien 1967). Data suggest that pharmacokinetics and metabolism are similar in both species.

A kinetic study in rats administered omethoate found that it is partially metabolized (~50% of the parent omethoate was found in urine) (Hoshino 1989), and detoxification of the oxon was hypothesized to occur through hydrolysis and dealkylation with subsequent degradation to dialkyl phosphate metabolites (Aharoni and O'Brien 1968; Hassan et al. 1969; Hoshino 1989). The loss of the methoxy groups from dimethoate to form carbon dioxide is a minor metabolic pathway (Kirkpatrick 1995; Leibold and Hoffmann 2001) and is not described in the current models. Although A-esterases (i.e., PON1) play an important role in the detoxification of several OPs, such as chlorpyrifos and paraoxonase, PON1 does not appear to appreciably detoxify omethoate and this pathway is not described in these models.

A study with sheep liver amidase indicated that several OP oxons, including omethoate, inhibited this enzyme but were not substrates for hydrolysis (Chen and Dauterman 1971). As carboxyamidase in the liver is thought to be the main metabolic pathway for dimethoate to DCA, inhibition of this pathway will limit detoxification of the parent compound. However, Kirkpatrick (1995) accounted for about 90% of the dimethoate mass via the metabolites in the rat metabolism study, including 70-80% from the known products of the substrate reactions and omethoate. Therefore, it is likely that the inhibition of carboxyamidase is not a substantial factor at doses that are relevant. Thus, it is not considered in the model.

In the liver, the rate of change of dimethoate is modeled as:

$$\frac{dDim_{liver}}{dt} = QH * (CAM - CVM) + \frac{dOral}{dt} - \frac{dAct}{dt} - \frac{dDetox_{parent}}{dt}$$

where DIM_{liver} is the mass of dimethoate in the liver, QH is the blood flow to the liver, CAM is the dimethoate concentration in arterial blood, CVM is the dimethoate concentration in

venous blood leaving the liver, *dACt* is the rate of dimethoate activation to omethoate, and $dDetox_{parent}$ is the rate of dimethoate detoxication.
dAct/dt is the rate of dimethoate activation to omethoate:

$$\frac{dAct}{dt} = \frac{V_{max,act}[Dim]}{[Dim] + K_{m,act}}$$

where $V_{max,act}$ is the V_{max} for dimethoate activation to omethoate, [Dim] is the concentration of dimethoate in the liver, and $K_{m,act}$ is the K_m for activation to the oxon. $dDetox_{parent}/dt$ is the rate of catalytic dimethoate detoxication via carboxyamidase:

$$\frac{dDetox_{parent}}{dt} = \frac{V_{max,parent}[Dim]}{[Dim] + K_{m,parent}}$$

where $V_{max,parent}$ is the V_{max} for dimethoate detoxication, and $K_{m,parent}$ is the K_m for parent detoxication.

Similarly, the rate of change of omethoate in the liver is modeled as:

$$\frac{dOxon_{liver}}{dt} = QH * (CAO - CVO) + \frac{dAct}{dt} - \frac{dDetxox_{oxon}}{dt} - \sum_{i=1}^{3}\left(\frac{dInhibition_i}{dt}\right)$$

Where $Oxon_{liver}$ is the mass of omethoate in the liver, *CAO* is the omethoate concentration in arterial blood, *CVO* is the omethoate concentration in venous blood leaving the liver, $dDetox_{oxon}$ is the rate of omethoate detoxication:

$$\frac{dDetox_{oxon}}{dt} = \frac{V_{max,oxon}[Oxon]}{[Oxon] + K_{m,oxon}}$$

where $V_{max,}$oxon is the V_{max} for oxon detoxication, [Oxon] is the concentration in the liver, and $K_{m,oxon}$ is the K_m for oxon detoxication

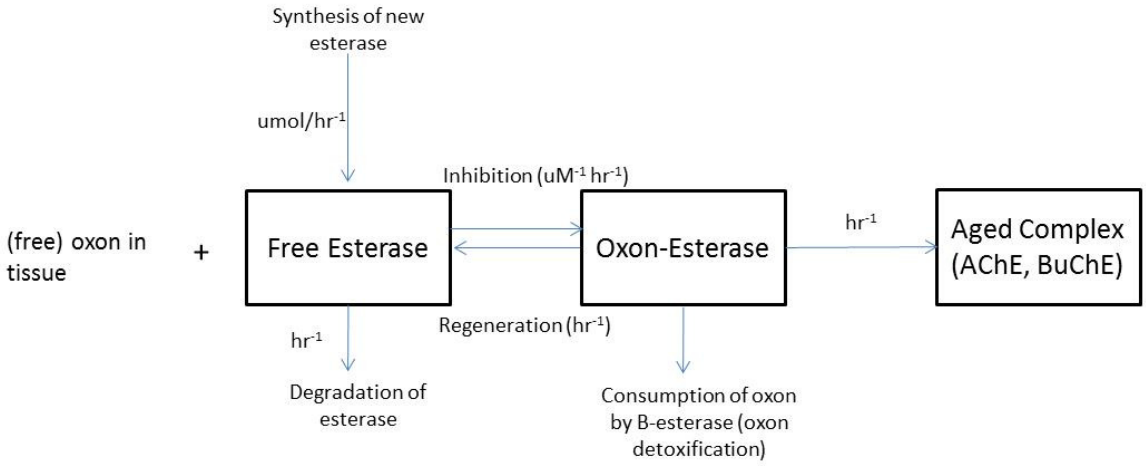
$dInhibition_i$ is the rate of the esterase inhibition reaction with the oxon, and *i*=1 is AChE, *i*=2 is BuChE and *i*=3 is CaE. Esterase reactions are modeled as:

$$\frac{dInhibition}{dt} = Esterase * k_i * C_{oxon,liver}$$

where *Esterase* is the esterase available mass, k_i is the bimolecular rate constant, and $C_{oxon,liver}$ is the concentration of oxon in the liver.

In in addition to describing the pharmacokinetics of dimethoate and omethoate, the models include a description of AChE inhibition by omethoate, as this is the toxicity endpoint of interest. AChE inhibition as well as inhibition of other B-esterases (butylcholinesterase; BuChE and carboxylesterase (CaE) by the oxon is included in these models. B-esterases can detoxify the oxon by hydrolysis; however, the oxon becomes irreversibly bound, inhibiting and thus inactivating the enzyme. The esterases can be reactivated, with the oxon being consumed. AChE and BuChE can age, whereby the enzyme cannot be reactivated. Figure 3 illustrates the model description of oxon binding and subsequent enzyme inhibition.

Figure 3. B-esterase (AChE, BuChE, and CaE) inhibition in the omethoate model. Note only AChE and BuChE are assumed to age; CaE is not assumed to age



Esterase levels are modeled as:

$$\frac{dEsterase}{dt} = K_s - Esterase * \left(K_d + K_i * C_{oxon,tissue}\right) + InActive * K_r$$

where *Esterase* is the mass of esterase, K_s is the zero-order synthesis rate, K_d is the enzyme degradation rate, *InActive* is the mass of inactive enzyme, and K_r is enzyme reactivation rate. The inactive enzyme is modeled as:

$$\frac{dInActive}{dt} = Esterase * K_i * C_{oxon,tissue} - InActive * (K_a + K_r)$$

where K_a is the enzyme aging rate.

In the current human model, exposure to dimethoate can occur through the oral, dermal, and inhalation routes (dermal and inhalation are in the human model only; these routes are not described for the rat). For omethoate, the model only includes direct exposure through the oral route only. Both the rat and human models include a model for the parent dimethoate and a submodel for the metabolite omethoate; both describe absorption, distribution, metabolism, and excretion of the parent and oxon. The model structure includes compartments for fat, kidney, brain, liver, and lumped compartments for slowly and rapidly perfused tissues. A two-compartment model (stomach and intestine) is used in order to model uptake and absorption from the oral route (gavage and dietary exposure).

Dermal uptake is modeled using a skin compartment that uses information on the surface area exposed and the skin permeability coefficient of dimethoate. A standard K_p-based formulation is used (e.g., Corley et al. 1994).

Inhalation exposure is modeled similarly to that described for chromium (O'Flaherty et al. 2001) and CPF (Poet et al. 2014; Smith et al. 2014), where a fraction of inhaled chemical reaches the deep (alveolar region) lung and is absorbed into systemic circulation, while the remainder is assumed to be cleared in the upper airways by mucociliary clearance and then transferred to the GI tract as an oral dose.

Available Data for Model Parameterization

Several types of data were needed to develop these models, which included physiological constants, partition coefficients, biochemical parameters to describe metabolism, and parameters to describe B-esterase inhibition by the oxon. Data were obtained from the literature, from experiments, or by fitting (optimization) to available kinetic or inhibition data. The models were coded originally in AcslX. After it became clear that kinetic data would not be available from the MSU in vitro study and that fitting would need to be done using the rat and human metabolism studies (i.e., urinary metabolite levels, radioactivity in plasma), the rat model was rebuilt in Mathematica.

Parameter values, sources, and assumptions are provided in Appendix B. The basis for these values is reviewed in this section. Additional information is provided in the next section which describes the model fitting process.

Physiological Constants and Partition Coefficients

Physiological parameters (tissue volumes, blood flows) for both the rat and human were adapted from the chlorpyrifos rat and human models (Timchalk et al. 2002; Poet et al. 2014) or obtained from the literature (Brown et al. 1997). Tissue:blood partition coefficients for dimethoate and omethoate have not been experimentally measured in rat or human tissues. In the current models, tissue:blood partition coefficients for both the parent and oxon were derived using the Poulin and Krishnan algorithm (Poulin and Krishnan 1995), which is based on the lipid and water content of tissues. The same values are used in both the rat and human models as partition coefficients are generally thought to be consistent across species.

Plasma Protein Binding

Although some organophosphorus insecticides, such as chlorpyrifos, exhibit a high degree of plasma protein binding, studies with rat and human albumin did not indicate that OPs with a thioester linkage bind albumin to an appreciable extent (Tarhoni et al. 2008); thus, both dimethoate and the oxon are assumed to be largely unbound in plasma in both the human and rat models.

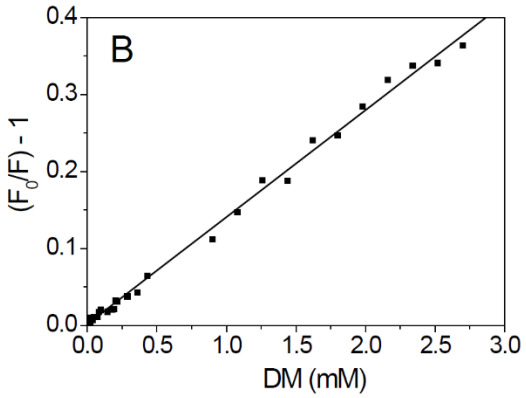
Dimethoate interaction with bovine serum albumin (BSA) was assessed via fluorescence titration (Yan et al. 2017). Intrinsic fluorescence spectra of 2 μM BSA (excitation wavelength = 295 nm) was recorded with increasing concentrations of quencher (Q; dimethoate). These

data were fitted to the Stern Volmer equation, in which F and F_0 are fluorescence intensities with or without quencher, respectively:

$$F_0 = F\ x\ (1 + K_A\ x\ Q)$$

The equation gave a linear plot, demonstrating the existence of one type of binding site for dimethoate in BSA (Figure 4). The apparent association constant for the fluorophore and quencher, K_A, equals the slope of the plot ($1.39\ x\ 10^2\ M^{-1}$).

Figure 4. Stern-Volmer plot for fluorescence titration of BSA by dimethoate (adapted from Yan *et al.* 2016).



The determination of K_A by Yan *et al.* 2016 allows for determination of the fraction unbound between BSA (as a receptor) and dimethoate (as a ligand). Because the linear Stern-Volmer plot indicates one type of dimethoate binding site in BSA, B_{max} (total number of ligand binding sites) equals the known total concentration of receptor molecules (2µM). Thus, fraction unbound may be approximated from the following equation (Toutain and Bousquet-Melou 2002),

$$fraction\ unbound = \frac{K_D}{B_{max} + K_D}$$

assuming that K_D, the dissociation constant between dimethoate and BSA, is much lower than the free plasma concentration of dimethoate. Using B_{max} and K_A (because $K_A = 1/K_D$), the fraction unbound between BSA and dimethoate is calculated to be 0.9997, suggesting that dimethoate is typically unbound to BSA. However, as we fit the data, we found that there may be a small amount (3.5%) of plasma protein binding (hypothesized to be omethoate) as described below.

Biochemical Constants

Bioactivation of Dimethoate to Omethoate by Cytochrome P450 (CYP)

The bioactivation of dimethoate to omethoate has been investigated previously *in vitro* using c-DNA expressed human cytochrome P450 isoforms (CYPs) (Buratti and Testai 2007). Kinetic parameters were determined from a plot of omethoate formation against the concentration of dimethoate incubated with each CYP. Acetylcholinesterase inhibition provided the basis for tracking omethoate formation. Five out of the nine recombinant human CYPs tested gave typical saturation curves, with which both K_m and V_{max} were determined (Table 14). V_{max} ranged from 0.11 to 0.28 nmol omethoate per nmol P450 min; K_m ranged from 15 to 85 µM. Three of the nine CYPs, 2C8, 2C9, and 2A6, exhibited less activity and gave linear plots. One CYP, CYP2D6, was unable to catalyze omethoate formation. Each isoform was ranked by intrinsic clearance (CL_i), or the V_{max}/K_m ratio; thus, CYP2C19 exhibited the highest CL_i, due to its high affinity for dimethoate (with a low K_m at 15 ± 4) and its high V_m (0.28 ± 0.02) for omethoate production. Normalized to the average abundance of each CYP (determined in humans in Inoue *et al*. 2006), the percent contribution of each CYP at low or high dimethoate concentrations was estimated. Estimates for percent contribution at low dimethoate concentration were determined using intrinsic clearance values. Estimates for percent contribution at high dimethoate concentrations were determined using V_{max} only, because reaction velocity ν approaches V_{max} as substrate (dimethoate) concentration greatly exceeds K_m.

Table 14. Kinetic parameters and percent contribution of five cytochrome P450 isoforms to bioactivation of dimethoate to omethoate (adapted from Buratti and Testai 2007; Inoue, *et al.* 2006).

CYP	V_{max} (nmol omethoate/ nmol / P450 / min)	K_m (µM)	CL_i (pmol omethoate/nmol P450 min µM)	Relative concentration in human hepatic content (%)	% Contribution[1]	
					Low dimethoate concentration	High dimethoate concentration
2C19	0.28 ± 0.02	15 ± 4	19	4	28	15
1A2	0.12 ± 0.01	15 ± 4	8	14	44	25
2B6	0.07 ± 0.01	44 ± 11	1.6	3	2	3
3A4	0.13 ± 0.02	85 ± 18	1.5	30	17	57
1A1	0.11 ± 0.02	85 ± 23	1.3	traces	n.d.	n.d.

[1]Percent contribution is calculated by taking the product of relative concentration and either CL_i (low dimethoate concentration) or V_{max} (high dimethoate concentration). This value is then expressed as a percent of the total products (for each CYP).

Apparent kinetic parameters were also determined for dimethoate desulfuration by human liver microsomes (HLMs) (Buratti and Testai 2007). Three liver microsomes were selected based on varying content of CYPs, following examination of the recombinant CYPs. HLM_1

and HLM_3 predominantly exhibited greater levels of CYP1A2 activity compared to the other CYPs; HLM_2 exhibited higher levels of CYPP2B6, CYP3A4, and CYP2C19 activity. While all HLMs catalyzed dimethoate desulfuration, only plots of HLM_3 CYP activity versus dimethoate concentration gave a curve typical of Michaelis-Menten kinetics, suggesting that one or more CYPs exhibit comparable kinetics, or that one CYP dominates omethoate formation. HLM_1 and HLM_2 activities plotted against dimethoate concentration gave sigmoidal curves, and $K_{0.5}$ (analogous to K_m) was determined from the corresponding Hill plots. Each of these parameters are listed below in Table 15. K_{mapp} (or $K_{0.5}$) for each HLM is quantitatively larger than those observed in recombinant CYPs; however, this is expected due to the combination of various CYP affinities present in HLMs.

Table 15. Apparent kinetic parameters for the bioactivation of dimethoate by three human liver microsome preparations.

HLM	V_{maxapp} (nmol omethoate / mg / prot / min)	K_{mapp} (µM)	$K_{0.5}$ (µM)
HLM_1	2.65	N/A	448
HLM_2	0.12	N/A	416
HLM_3	0.041	742	N/A

Dimethoate Hydrolysis

The hydrolysis of dimethoate to dimethoate carboxylic acid has been examined *in vitro* for the rat and several other species (Uchida et al. 1964; Uchida and O'Brien 1967). Although a V_{max} was not reported, the average amount of dimethoate hydrolyzed by liver tissue homogenate and microsomes (ug/30 min/g liver) was reported for the rat; this *in vitro* measurement was extrapolated to estimate the *in vivo* value for the rat and used as the V_{max} for this metabolic pathway. While the K_m for hydrolysis was not reported for the rat by Uchida et al., the K_m was reported for male sheep liver amidase (which is thought to be responsible for hydrolysis) in both whole liver and microsomes. Although the K_m was measured for sheep, K_m is generally considered to be species-invariant, and in the absence of rat or human data, the sheep K_m was used. Metabolic parameters for the detoxification of the oxon have not been reported. Thus, the V_{max} and K_m for the rat were estimated by fitting the model to available kinetic and inhibition data.

Esterase inhibition

Inhibition of AChE, BuChE, and CaE by the oxon is described by the same methods used in the chlorpyrifos PBPK/PD model (Timchalk et al. 2002; Smith et al. 2014); both chemical-specific and non-chemical specific parameters are needed. Non-chemical specific parameters

include baseline B-esterase activity levels in tissues, enzyme turnover rates, and degradation rates, which were based on Maxwell et al and Timchalk et al (Maxwell et al. 1987; Timchalk et al. 2002).

The bimolecular rate constant, K_i has been calculated for omethoate in a study screening for various organophosphate pesticides (Herzsprung et al. 1992). An AChE inhibition reaction, combined with the following scheme, allowed for determination of the bimolecular rate constant, K_i:

$$EH + IB \overset{Ki}{\rightarrow} EI + BH$$

$$K_i = \frac{ln2}{t_{0.5} \times [IB]}$$

Using the preceding formulae, in which [EH] is active enzyme concentration and [IB] is active inhibitor concentration, K_i and $t_{0.5}$ (the reaction half time) were calculated via a plot of relative activity (activity after inhibition time / initial inhibited activity) versus time and via linear regression analysis to give:

$$K_i = \frac{ln2 \times b}{log2 \times [IB]}$$

in which b is the coefficient to the slope of the plot of relative activity versus time. An example plot for the reaction of 20 µg/L aldicarb sulfoxide with bovine erythrocyte AChE is given in Figure 5. Omethoate was subjected to similar mathematical treatment in reactions with eel AChE, bovine AChE, human BuChE, and horse BuChE; bimolecular rate constants are given in Table 16.

Figure 5. Inactivation of bovine erythrocyte acetylcholinesterase over time by 20 µg/L aldicarb sulfoxide (adapted from Herzsprung *et al.* 1992 Figure 1).

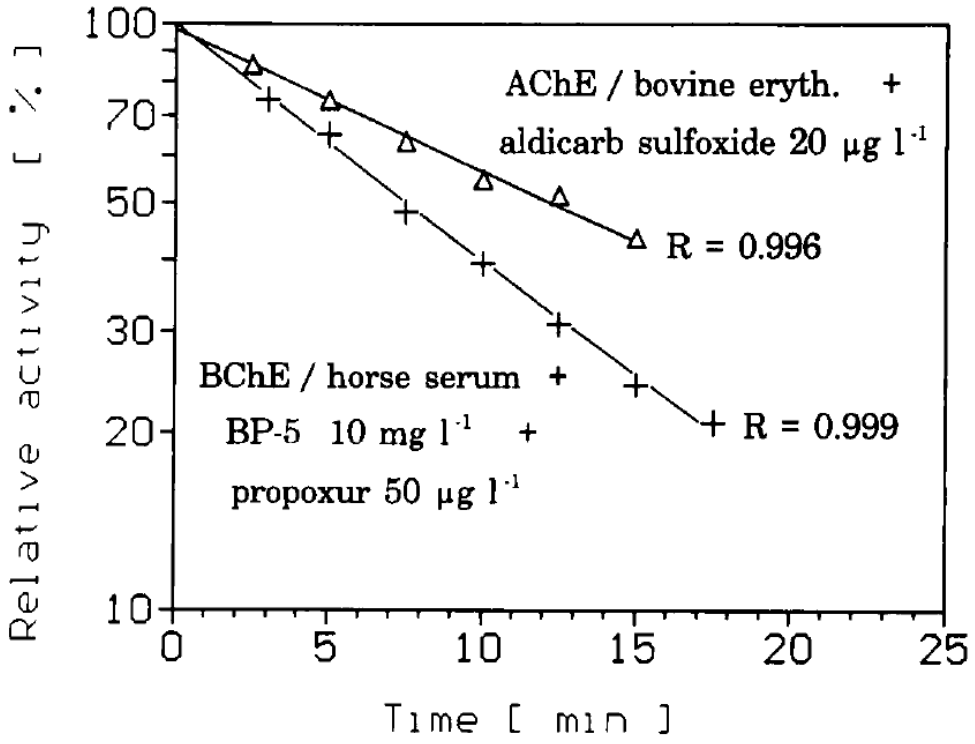


Table 16. Bimolecular rate constant K_i for omethoate and four cholinesterases (adapted from Herzsprung *et al.* 1992 Table 3)

K_i [L * mol^{-1} * min^{-1}] ± ($\Delta k_i/k_i$) * 100% (n)			
AChE eel	AChE bovine	BuChE human	BuChE horse
2.6*10^3 ± 3%	0.9*10^3 ± 3%	0.8*10^2 ± 5%	1.0*10^2 ± 4%

Δk_i: Confidence interval (0.95, n)
n: Number of determination of ΔE min^{-1} as a function of inhibition time *t*

Aging (K_a) and reactivation (K_r) rate constants for AChE, BuChE, or CaE were not available; however, these values have been reported for rat brain AChE, human RBC AChE, and human plasma BuChE for other dimethoxy OP oxon-cholinesterase complexes (Skrinjaric-Spoljar et al. 1973; Wallace and Herzberg 1988; Worek et al. 1999; Mason et al. 2000). The part of the OP compound that remains bound to the enzyme is the same for dimethoxy OPs, so the dimethoxy OP-oxon complexes would be expected to behave similarly with respect to

aging and reactivation (Carr and Chambers 1996; Poet et al. 2004). The values from Mason et al. (2000) were considered the most reliable.

There is no available inhibition constant for CaE for omethoate; therefore, it was estimated proportionally to the AChE inhibition constant for chlorpyrifos. The rate constants for spontaneous reactivation for CaE have not been measured; thus, these were assumed to be the same as those for AChE or BuChE, which was the same assumption used in the CPF model (Poet et al. 2014; Smith et al. 2014). Aging for CaE is assumed to be negligible (Maxwell et al. 1987).

Additionally, *in vitro* studies are being conducted by Dr. Janice Chambers at MSU to determine the K_i for the inhibition of human and rat RBC AChE for omethoate. Rat AChE was obtained from pooled blood samples taken from adult rats. Human AChE was obtained from both adult and pediatric blood samples (ages 8-65 years) from both sexes and various ethnic groups. The measured K_is will be incorporated into the respective models and used for AChE in all tissues for which AChE inhibition occurs. Although mammalian AChE exists in multiple oligomeric forms, RBC AChE and the forms found in other tissues (such as brain and muscle) differ only at the C-terminus; the catalytic site remains the same. Thus, the use of values measured for RBC AChE would be expected to be the same for other tissues.

In Vitro to *In Vivo* Extrapolation

In order to use *in vitro* metabolism measurements in PBPK models, the values obtained *in vitro* must be scaled to describe an *in vivo* system. Scaling factors for IVIVE are based on knowledge about the concentrations of various compartments (such as microsomes and hepatocytes) of the intact liver. For microsomes, which was the *in vitro* system used in the metabolism studies for dimethoate activation, metabolic rates (V_{max}) are expressed as metabolic product formed/time/mg microsomal protein (MSP). Thus, the appropriate scaling factor is the concentration of MSP per gram liver (mg MSP/g liver).

For dimethoate activation to omethoate, *in vitro* V_{max} values were extrapolated to *in vivo* values for use in the model by using the MSP scaling factor. The model requires units for V_{max} to be in µmol/hr/kg tissue. For the rat, 45 mg MSP/g liver was used (Lipscomb and Poet 2008). For dimethoate hydrolysis in liver, V_{max} was reported as µg dimethoate hydrolyzed/30 min/g tissue; thus, conversions were needed only for µg to µmol, min to hr, and g to kg tissue (i.e., no scaling factors were required). The following equation is an example of how the extrapolations for V_{max} were performed.

$$Vmax_{in\ vivo}\left(\frac{\frac{\mu mol}{hr}}{kg\ tissue}\right) = Vmax_{in\ vitro}\left(\frac{nmol/min}{mg\ MSP}\right) * \frac{60\ min}{1\ hr} * \frac{1\ \mu mol}{1000\ nmol} * \frac{45\ mg\ MSP}{g\ liver} * \frac{1000\ g}{1\ kg}$$

For K_m, no extrapolation was performed from the *in vitro* values, which is standard practice (Lipscomb and Poet 2008). Values are summarized in Table 17.

Table 17. *In vitro* and extrapolated *in vivo* values for dimethoate metabolism

Dimethoate bioactivation to oxon in liver		
Parameter	**Rat *in vitro* (nmol/min/mg MSP)[a]**	**Rat *in vivo* (µmol/hr/kg liver)**
V_{max}	0.937	2530
K_m (all in µmol/L)	535	535
Dimethoate hydrolysis in liver		
Parameter	**Rat *in vitro* (µg/30 min/g liver)**	**Rat *in vivo* (µmol/hr/kg liver)**
V_{max}	4.9	42.7
K_m (all in µmol/L)—from sheep liver microsomes	155	155

[a] For rat, a conversion factor of 45 mg MSP/g liver was used (Lipscomb and Poet 2008)

Rate Constants and Uptake Parameters

Dermal Uptake

In vivo rat data and *in vitro* rat and human data suggest that dimethoate is not well-absorbed dermally (Davies 1999; Leibold and Hoffmann 2001); however, this is still considered a potential exposure route for occupational handlers (USEPA 2015). In the current models, dermal absorption is modeled as a one-compartment structure as was done in the CPF model

(Poet et al. 2014; Smith et al. 2014). The volume of skin exposed to dimethoate is defined as the fraction of skin surface area exposed compared with total skin surface area, which assumes that diffusion in the skin is limited to the skin immediately below the application area. Thus, the dermal compartment consists of the volume of skin under the application site. The dose is assumed to be evenly spread over the application area, and absorption is based on the skin permeability coefficient (K_p), which has been determined experimentally for dimethoate using human skin *in vitro* (Holmgaard and Nielsen 2008). The K_p value was $4.9x10^{-5}$ cm/hr.

Oral Uptake

Oral (gavage and dietary exposure) absorption of dimethoate or oxon from the stomach, transfer from the stomach to the intestine, and transfer from the intestine to the liver were all modeled as first-order processes. From rat and human PK data, dimethoate is well absorbed orally; in the model, 100% of the dose is assumed to be absorbed. There are no existing data from which the oral absorption rate or transfer rates have been determined; thus, the rate constants for the rat and human were estimated by fitting the model to the available PK and PD data.

Inhalation Exposure

Due to low volatility, inhalation is not a significant route of exposure; however, inhalation of spray or mist is still anticipated to occur during occupational use (al-Jaqhbir et al. 1992). Inhaled exposures to dimethoate and omethoate are described in the same way as in the chlorpyrifos model, where a fraction of what is inhaled reaches the lung tissue and is absorbed while the remaining chemical is eliminated by mucociliary clearance and transferred to the GI tract and gets absorbed as an oral dose. Uptake by inhalation is based on alveolar ventilation rate, the concentration of chemical in the air, and the fraction available to the deep lung. The fraction available to the deep lung can be estimated using the Multiple Path Particle Dosimetry Model (MPPD) software (Price et al.) as was done with the chlorpyrifos model. The lung:air partition coefficient can be estimated using the Poulin and Krishnan (1995) methods. The rate constant for transfer from the lung to the GI tract will be fitted using rat data.

Elimination Rate

Urinary elimination of the dimethoate DCA metabolite and oxon DMTP metabolite are modeled as first-order processes. There are no existing data from which the urinary excretion rate constants have been determined; thus, the rate constants for the rat were estimated by fitting the model to the available data.

Model Testing and Validation

Overview

PBPK/PD models for dimethoate were developed based very closely on the perfusion-driven PBPK and integrated PD structures incorporated into a similar model developed previously for the organophosphate pesticide chlorpyrifos as described above.

A total of eight dimethoate-mass-conserving compartments were modeled as indicated in Appendix C, with respect to each of five distributed chemicals: (1) dimethoate, (2) omethoate, (3) dimethoate dicarboxylic acid (DCA), dimethylthioiphosphoric acid (DMTP), and one or more other metabolites (Other). Two additional auxiliary tissue compartments were also modeled as indicated in Appendix C, conserving cholin/carboxyl esterase (CE) activity of three types: (1) AChE, (2) BuChE, and (3) CaE. The following five dimethoate metabolic pathways were modeled:

- Dimethoate to omethoate
- Dimethoate to DCA
- Omethoate to DMTP
- DCA to Other
- Omethoate to Other

These metabolic pathways were each assumed to follow Michaelis-Menten (1st-to-zero-order) saturation kinetics governed by parameters V_{max} and K_m, used to specify pathway- and tissue-specific 1st-order reaction rates (in micromoles per hour, or µmol/hour) each defined (using matrix notation) in tissue i, precursor j, and metabolite k, as $V_{max}[i][j,k]$ $C[i,j]/(K_m[i][j,k] + C[i,j])$, where $C[i,j] = M[i,j]/V[i]$ = concentration of chemical j in tissue i (µmol/L in tissue i), $M[i,j]$ = mass of chemical j in tissue i (µmol), and $V[i]$ = volume of tissue i (L). Metabolizing tissue compartments were assumed to include the liver, lung, diaphragm, brain and skin using tissue:liver metabolic activity assumptions described by Poet et al. (2014). Specifically, relative rates per liter in lung, brain, diaphragm, and skin per liter were assumed to be 100%, 10%, 10%, and 10% of those in liver. There are not specific data to assign metabolism rates in the brain, diaphragm, and the skin, so nominal levels were chosen consistent with small amounts of extrahepatic metabolism (Uchida et al., 1966). The complete set of assumed and estimated model parameters used in the dimethoate PBPK-PD model are listed in Appendix B. All input data, including cholinesterase and metabolism study data, are provided in a separate spreadsheet.

The PBPK-PD model was implemented using *Mathematica*® 11.0 symbolic, programming, numerical, and graphic software (Wolfram Research 2017). Complete annotated documentation of the model and its applications described herein appear in Appendix C,. A few auxiliary (e.g., data-manipulation and plotting) functions contained in a copyrighted *Mathematica* package called *RiskQ* (cited in Appendix C) were also used to facilitate model development, parameter adjustment, and model applications; code for these *RiskQ* functions used can be supplied upon request. The advanced *Mathematica* programming language supports highly efficient functional programming that takes full advantage of that platform's symbolic and numeric calculation abilities. Importantly, in the context of numeric calculations, *Mathematica* implements infinite-precision integer arithmetic as well as numeric calculations (including, e.g., numeric solution of linked sets of ordinary differential equations or ODEs) that adhere to any arbitrary level of user-specified accuracy and/or precision, with accuracy/precision violations reported by the program when/if they are encountered. This allows numeric ODE solutions to avoid numerical instabilities if/as required, simply by increasing the requested working precision used by numeric calculation (e.g., retaining a default of 16, but on request up to 20 to 50 or more digits for any real calculations involved if/as required). Linked sets of ODEs are each expressed symbolically using similar-to-standard mathematical notation, but they can include functionally/symbolically expressed numeric, logical, or other inputs or constraints, including discontinuous ones, which can be solved using highly sophisticated default methods or (sometimes more efficiently) using many alternative user-specified methods.

The PBPK-PD model expressed in *Mathematica* involves a total of 113 linked ordinary differential equations (ODEs), of which 75 are dimethoate/omethoate-mass-conserving, each defining a rate of change in a symbolically expressed function of time t for corresponding variables representing compartment-specific masses at time t (these functions are all listed symbolically in Appendix C). The model allows either dimethoate or omethoate to be specified as the chemical to which a rat of a user-specified weight is exposed to a user-specified input mass (in mg) by one or more specified exposure routes and exposure patterns (only the oral route is fully implemented presently). Each solution of the PBPK-PD model run over a user-specified period of time is returned in the form of a (lengthy) set or list of "rules" named symbolically, e.g., as "R". Each rule in set R assigns a symbolic interpolating function of time t to each model variable (i.e., each compartment). Any particular variable at time t can then be evaluated conditional on both the (entire) set R and on any specified value of t. For example, the value of accumulated mass of DCA in liver or urine at time t (denoted MM[2,3][t] or U[3][t], respectively) for a particular time t = 10 hours is generated by evaluating the expressions MM[2,3][t]/.R/.t→10 or U[3][t]/.R/.t→10, respectively, where the notation "/." means "conditional on" and the set R of rules. Conveniently, there is never a requirement to view the complex, symbolically expressed interpolating-function contents of rule set R; rather, R was defined and applied symbolically.

Model Fitting and Results

The model was fit first for omethoate by modifying chlorpyrifos-PBPK model parameters and initial dimethoate/omethoate physico-chemical property estimates to (jointly) fit urinary ^{14}C-radiolabel and urinary metabolite fraction (Hoshino 1989; Kirkpatrick 1995), and brain AChE data (Meyers et al. 2001, Study No. 1), as described below. A corresponding PBPK model for dimethoate was then developed using the same approach conditioned on the model developed for omethoate, as described below.

Before proceeding to the omethoate fitting, an initial discussion of the brain AChE inhibition data to which PD components of the dimethoate and omethoate models developed is discussed.

Figures 6 and 7 (which appear at the end of this section together with all other figures cited in this section) show brain AChE inhibition for acute and repeated doses of dimethoate, together with a linear fit to those data that was used to modify our original estimate of the V_{max} governing dimethoate metabolism to omethoate in liver, which was scaled as described in the previous section. The cholinesterase data are from Mayers et al. (2001) (Study No. 1 in Appendix A) and includes doses of 0, 0.1, 0.5, and 3.0 mg/kg for PND11 rats (acute) or PND11-21 rats (repeated dose). The inhibition levels for the acute doses were 1.8%, 3.6%, and 12.0% at 0.1, 0.5, and 3.0 mg/kg for males, and 3.7%, 2.1%, and 14.4% at 0.1, 0.5, and 3.0 mg/kg for females. The inhibition levels for repeated doses were 0.79%, 9.92, and 47.0% at 0.1, 0.5, and 3.0 mg/kg for males, and 6.4%, 13.4%, and 58.4% at 0.1, 0.5, and 3.0 mg/kg for females.

The brain AChE level one hour after an acute dose of 10 mg/kg expected according to the approximately linear relationship shown in Figure 6 was used to modify an initial estimate of the maximum rate of dimethoate metabolism to omethoate in liver, such that resulting predicted concentrations of omethoate in all metabolizing tissues suffice to have the model generate this predicted brain AChE level. The brain AChE reactivation rate of 0.0088/hr incorporated into the PBPK/PD model was estimated by fitting the repeat-dose brain-AChE response data as shown in Figure 7 (see footnote 3 cited in the legend of that figure). The latter estimate is a bit less than a corresponding value of 0.019/hr measured in vitro that was reported by Mason et al. (2000). Also (see Appendix B, Table A1.2), the AChE bimolecular rate constant was adjusted from 0.054 L/µmol/hr to 0.065 L/µmol/hr to better fit the data.

Figure 8 shows brain AChE inhibition for omethoate in relation to acute orally administered dose. The fits are based on study in Mellert et al. (2003) study with adult rats (Study No. 4). The doses were 0, 0.2, 0.25, 0.35, and 5.0 mg/kg of omethoate. The brain AChE inhibition levels were 6.5%, 7.8%, 18.9%, and 80.6% at doses of 0.2, 0.25, 0.35, and 5.0 mg/kg for

males, and 14.3%, 9.8%, 27.3%, and 80.1% at doses of 0.2, 0.25, 0.35, and 5.0 mg/kg for females. The exhibited pattern of reduced brain AChE exhibits a saturation-like effect at the 5-mg/kg dose, whereby residual/reserve activity is maintained above the effective 0%-AChE level that is implied by simple linear extrapolation. This pattern is described well by the complementary hyperbolic-saturation relationship shown (%AChE = 100(K/[K + Dose]) with K (±1 SE) = 1.377 ± 0.126 mg/kg of acutely administered omethoate; solid curve, R^2 = 0.977), which was fit numerically by nonlinear inverse-variance weighted least squares regression. Such a relationship suggests that systemically circulated AChE (e.g., in RBCs where AChE activity shows a similar pattern in relation to dose) can to some extent continuously replenish brain AChE levels and thus prevent their depletion *in situ*. Such a pattern is not reflected the PD component of the PBPK/PD model structure developed for chlorpyrifos and was applied here for dimethoate/omethoate, which assumes static tissue-specific baseline cholinesterase levels. The saturation model plotted estimates that, relative to control levels, mean brain AChE levels of 73.4% and 12.1% will occur in rats 2.5 hours after acute gavage omethoate doses of 0.5 and 10 mg/kg, respectively.

For omethoate detoxication, the V_{max} was fit to the data (475 µmol/hr/kg) and the K_m estimated from Uchida et al. (1964) of 155 µM for sheep liver microsomes for dimethoate was used. For dimethoate activation to omethoate, an average K_m of 267.5 µM for sheep liver microsomes estimated from in vitro human liver microsome data of Buratti & Testai (2007) was retained, but a corresponding rat-scaled V_{max} of 2,530 µmol/hr/kg liver was increased ~1.49-fold to 3,765 µmol/hr/kg liver to better fit available rat data discussed below. For dimethoate detoxication to DCA, the K_m estimated from Uchida et al. (1964) of 155 µM for sheep liver microsomes was retained, but the V_{max} from Uchida et al. (1964) (43 µmol/hr/kg liver) was increased 21.7-fold to 2,322 µmol/hr/kg liver to better fit the data. (Metabolic parameters used are summarized in Table A1.3.) As discussed further below, the resulting fits obtained were generally consistent with the data (see Figures 9–13 and corresponding legends).

Figure 9 shows the fit to the relative percentage of dose in plasma in groups of adult rats at omethoate doses of 0.5 and 10 mg/kg from the Hoshino (1990) dataset. The fit is generally consistent with the data. Our original fits underestimated the percentage dose in plasma at the end of the 50-hour measurement period. It was suspected that a relatively small amount of omethoate (orange in Figure 9, note that Y-axis is on a log scale) bound to one or more plasma proteins with an elimination rate reflecting the albumin turnover rate in rats (~3.3 days; Funabiki et al. 1984). This somewhat contradicts the *in vitro* data from Yan et al. (2017) which suggested little plasma protein binding, but the situation *in vivo* could be different, or some other process explains these data. Nonetheless, only 3.5% plasma protein binding was needed to explain the data.

Figure 10 shows the fit for omethoate recovered in urine at 0.5 and 10 mg/kg (Hoshino, 1990) and Figure 11 shows a similar fit for dimethoate recovered in urine at 10 mg/kg (Kirkpatrick, 1995). A key problem encountered in developing this set of PBPK-PD models is the rapidity with which dimethoate, omethoate, and other metabolites of dimethoate and omethoate have been observed experimentally to be excreted in urine (nearly all within a few hours). Such rapid excretion kinetics appear to violate the perfusion-limited modeling approach used assuming urinary excretion limited by blood flow to the kidney (represented in the model by the Rapidly perfused compartment). The observed urinary excretion patterns could be explained using the current model structure only by substantially increasing the assumed partition of dimethoate metabolites into the Rapid compartment, beyond starting default partition values estimated by Poulin and Krishnan (1995). The increased partition coefficient for the rapid compartment had the effect of increasing predicted blood concentrations to levels inconsistent with reported experimental plasma levels, without applying estimated scaling factors to reconcile predicted and observed plasma loss patterns shown in Figures 9, 11, and 12. However, using this approach, the resulting predicted and observed plasma loss patterns, urinary excretion, and brain AChE inhibition patterns, and relative amounts of DCA in urine, and the fraction of omethoate in urine after omethoate exposure, match fairly well (Figures 7–13), at least at relatively low doses of administered dimethoate and omethoate yielding brain AChE levels within 25% of control levels.

Table 18 provides a tabular summary of the observed vs. predicted urinary metabolite and brain AChE inhibition for dimethoate, which shows the generally good agreement. However, the model significantly overpredicts urine levels of omethoate following a dimethoate exposure. It is difficult to reconcile the very large amounts of omethoate that are excreted following omethoate exposure (up to 60%) with the much smaller amounts (2-4%) after a dimethoate exposure. Figure 11 shows the percentage of dose in plasma for a 10 mg/kg dose of dimethoate and Figure 12 shows the same figure for 100 mg/kg dose (both from Kirkpatrick, 1995). The fits were excellent, showing that the model correctly apportions the mass of dimethoate into plasma.

Figure 13 shows the fit for the recovery ^{14}C-radiolabel in urine at 10 and 100 mg/kg (Kirkpatrick, 1995). The PBPK model fits are consistent with the data.

Key discrepancies, however, remain between model predictions and experimental data concerning (1) a far lower relative amount of observed than predicted omethoate in urine following dimethoate exposure (despite much greater urinary fractions of omethoate after omethoate exposure, but nevertheless predicted brain AChE reductions following either low-dose omethoate or dimethoate exposure close to those observed), and (2) apparent saturation-type nonlinearity in brain AChE reduction after exposure to relatively high dose of

omethoate (Figure 8). Resolution of such discrepancies will require further model development perhaps supplemented by additional experimental data.

Table 18. Comparison of DIM urinary metabolite and Brain AChE data with PBPK-PD model predictions

Study	DataSet	DIM						DIM				
7	1	Dose	Measure	Ave %	Adjusted%	Predicted		Dose	Measure	Ave %	Adjusted%	Predicted
7	1	10	Omethoate	2.25	2.59	20.5		100	Omethoate	3.7	4.15	35.8
7	1	10	DMPT	7	8.05	7.8		100	DMPT	6.7	7.51	3.7
7	1	10	DMDPT	25.9	29.77	28.2		100	DMDPT	21.2	23.75	16.4
7	1	10	Dimethoate	1.05	1.21	2.4		100	Dimethoate	1.35	1.51	15.6
7	1	10	DCA	36.45	41.90	41.1		100	DCA	43.8	49.08	29
7	1	10	DCA+DMDPT	62.35	71.67	69.3		100	DCA+DMDPT	65	72.83	45.4
7	1	10	TotalRecover	87	100	95.9		100	TotalRecovere	89.25	100	97.2
1	1, 2, 5, 6	10	Br AChE**	45.4*		45.5		100	Br AChE**	No data		0.5
		Dose in mg/kg acute										
		*Estimated by linear extrapolation from study data at 3.0 mg/kg acute gavage										
		** Brain AChE data (% control AChE level) & prediction at 1 hr post dose										

Study: Kirkpatrick (1995).

Figure 6. Brain AChE inhibition exhibited in groups of 8–10 M (open points) and F (solid points) adult (200- to 300-g) rats (circles) and postnatal day-11 (~25-g) rat pups (inverted triangles) 1 hour after they were administered a single acute gavage dose of 0, 0.1, 0.5, or 3.0 mg/kg dimethoate (Study 1, DataSets 1, 2, 5, and 6, involving a total of 144 rats; Meyers et al. 2001). Data points and error bars denote averages ±1 SD. The mean responses at 0.5 and 3.0 mg/kg were 97.8% and 84.7% of control levels, respectively, which for a similarly administered dose of 10 mg/kg implies an estimated 45.4% level relative to controls based on the plotted inverse-variance weighted linear regression fit to these data (solid line, $R^2 = 0.922$). The expected 45.4% brain AChE level 1 hour after an acute dose of 10 mg/kg was used to modify an initial estimate of the maximum rate of dimethoate metabolism to omethoate in liver, such that resulting predicted concentrations of omethoate in all metabolizing tissues suffice to have the model generate this predicted brain AChE level.

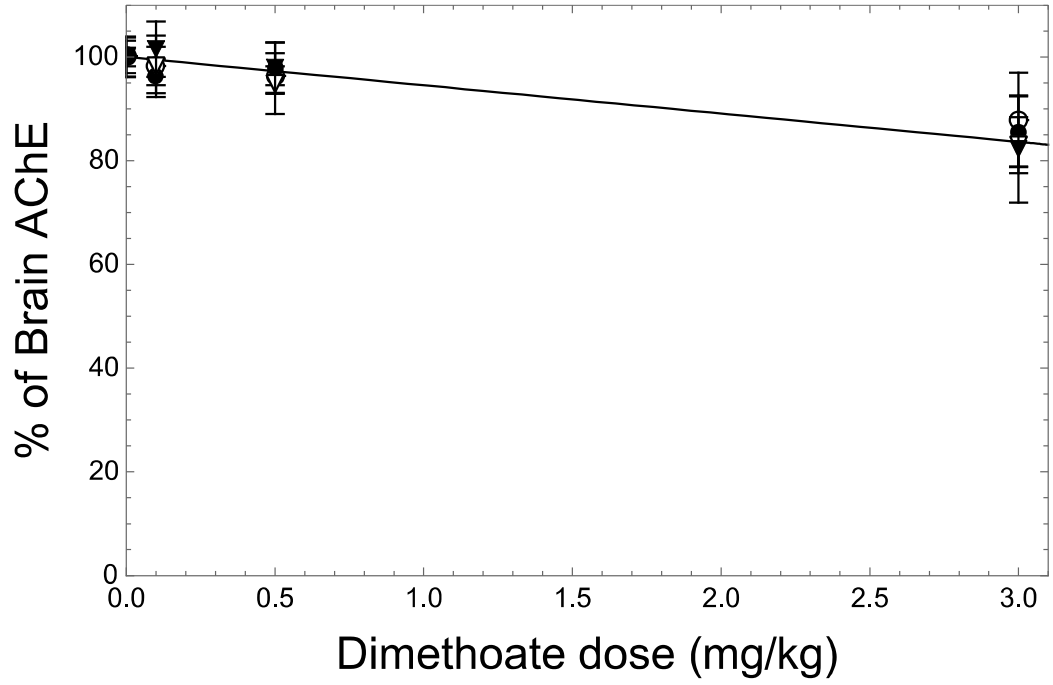
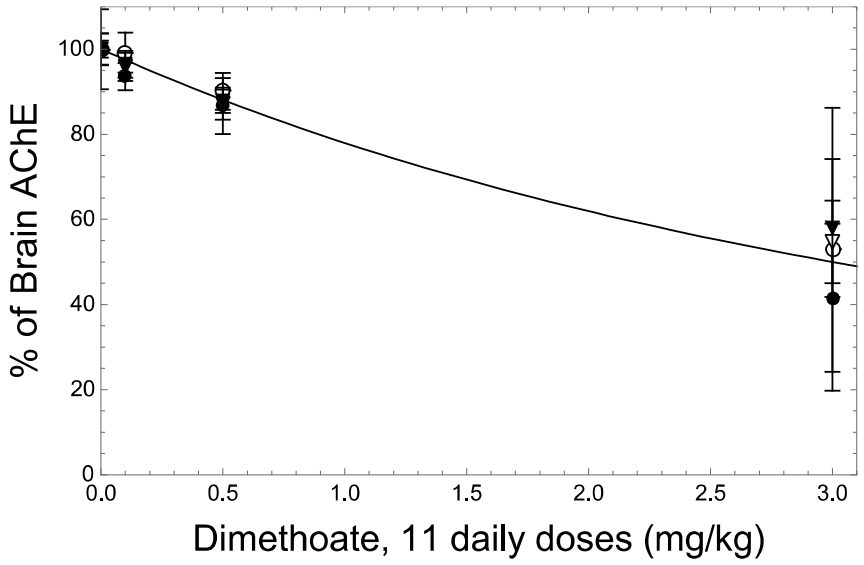


Figure 7. Brain AChE inhibition exhibited in groups of 8–10 M (open points) and F (solid points) adult (200- to 300-g) rats (circles) and postnatal day-11 (~25-g) rat pups (inverted triangles) 1 hour after they were administered 11 consecutive daily acute gavage doses of 0, 0.1, 0.5, or 3.0 mg/kg dimethoate (Study 1, DataSets 3, 4, 7, and 8, involving a total of 144 rats; Meyers et al. 2001). Data points and error bars denote averages ±1 SD. The solid curve shows predicted mean response (R^2 = 0.968) assuming sawtooth recovery from repeated dose-induced daily %AChE reductions to dose-related a percentage $100f\%$ = 100(1 – b Dose)% of the level after the preceding dose, with b = 0.05457 kg/mg estimated from the fit to corresponding acute-response data shown in Figure 6,[3] assuming an estimated AChE recovery (reactivation) rate of k = 0.00880/hour (corresponding to a reactivation half-time of 78.7 hours or 3.28 days), which is close to the rate k = ~0.019/hour reported by Mason (2000) for a dimethoxy organophosphate at 37 ºC (the latter value was at this point incorporated into the PBPK-PD model Exponent developed for dimethoate/omethoate). The reactivation rate of k = 0.00880/hour was estimated by fitting the recovery model to the data by inverse-variance weighted least-squares regression.



[3] The response model applied reflects the recursive relationship $f_n = f - (1 - f_{n-1})\exp(-k\,t)$ assuming $f_1 = f$, in which k is a 1st-oirder recovery rate and t is the re-dosing interval (24 hours). This response model has the solution $f_n = f - (1-f)\sum_{i=1}^{n-1} f^i \exp(-i\,k\,t)$. This model was fit to the data shown in Figure 7 by numerically fitting the reactivation parameter k conditional on n = 11 and the estimated value of f discussed, by nonlinear inverse-variance-weighted regression (Wolfram Research 2017).

Figure 8. Brain AChE inhibition exhibited in groups of 10 M (circles) and F (triangles) adult (~150- to 200-g) rats 2.5 hours after they were administered a single acute gavage dose of 0, 0.2, 0.25, 0.35, or 5.0 mg/kg omethoate (Study 4, DataSets 2 and 4, involving a total of 40 rats; Mellert et al. 2003). Data points and error bars denote averages ±1 SD. Corresponding mean responses were 100%, 89.6%, 91.2%, 76.9%, and 19.6% of control levels, respectively. The exhibited pattern of reduced Brain AChE exhibits a saturation-like effect at the 5-mg/kg dose, whereby residual/reserve activity is maintained above the effective 0%-AChE level that is implied by simple linear extrapolation. This pattern is described well by the complementary hyperbolic-saturation relationship shown (%AChE = 100(K/[K + Dose]) with K (±1 SE) = 1.377 ± 0.126 mg/kg of acutely administered omethoate; solid curve, R^2 = 0.977), which was fit numerically by nonlinear inverse-variance weighted least squares regression. Such a relationship suggests that systemically circulated AChE (e.g., in plasma where AChE activity shows a similar pattern in relation to dose) can to some extent continuously replenish Brain AChE levels and thus prevent their depletion *in situ*. Such a pattern is not reflected the PBPK-PD model developed for omethoate, which assumes static tissue-specific baseline cholinesterase levels presented in the similar model previously developed for chlorpyrifos (Timchalk et al. 2002; Poet et al. 2003, 2014). The saturation model plotted estimates that, relative to control levels, mean Brain AChE levels of 73.4% and 12.1% will occur in rats 2.5 hours after acute gavage omethoate doses of 0.5 and 10 mg/kg, respectively.

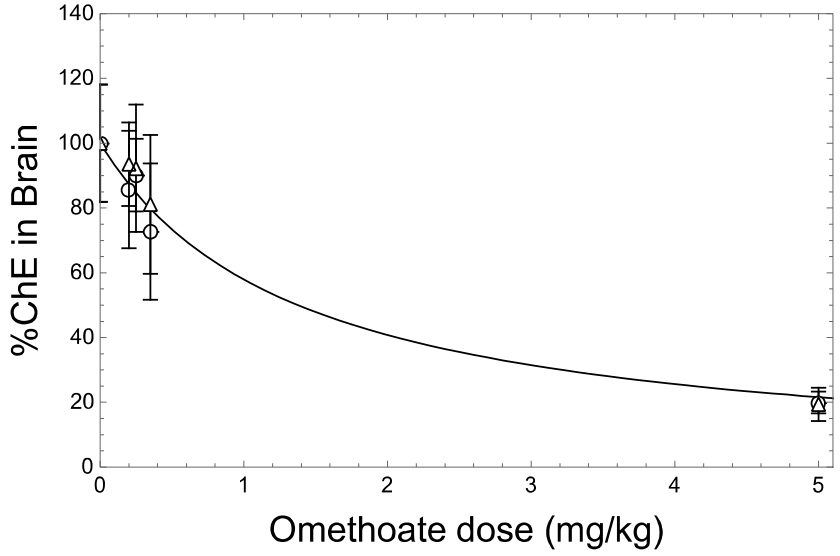


Figure 9. Relative percentage of dose in plasma in groups of 8 adult (~200-g) M and F rats administered an acute gavage dose of 0.5 or 10 mg/kg omethoate (OME) (Study 8, DataSets 1, 2, 3, and 4, involving a total of 278 rats; Hoshino 1989). Data points and error bars denote averages ±1 (estimated group-wise) SD. Data are compared to corresponding fits by the PBPK-PD model for the following: total predicted radiolabel (Black), omethoate (Blue), DMDT (Red), one or more DMDT metabolites (Green), and suspected omethoate (Orange) bound to one or more plasma proteins with an elimination rate reflecting the albumin turnover rate in rats (~3.3 days; Funabiki et al. 1984). These data were estimated to reflect radioactivity associated with sample representing ~3.5% of total rat plasma.

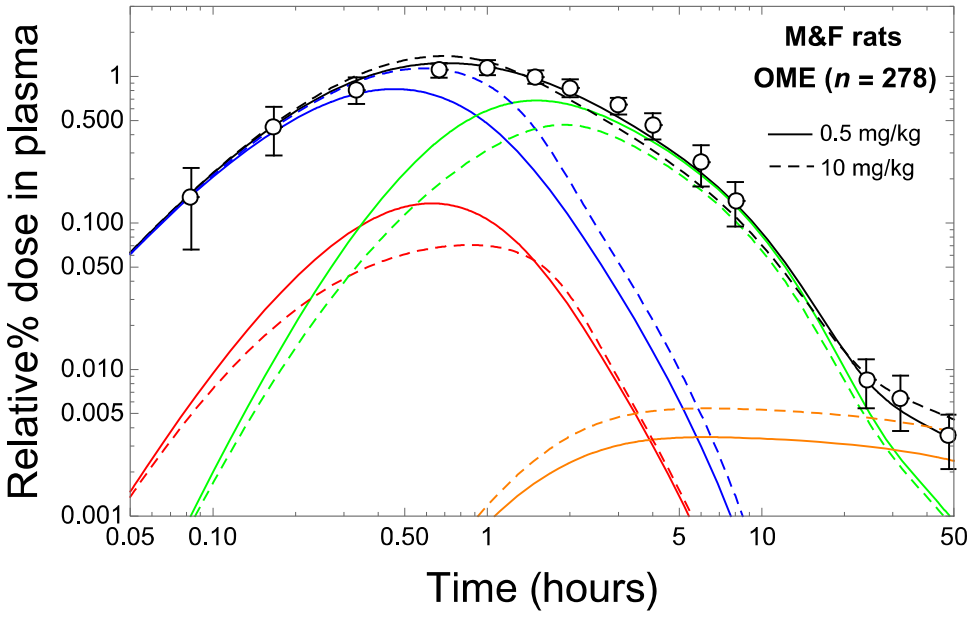


Figure 10. Percentage of ^{14}C-radiolabel recovered in urine, and corresponding PBPK-PD model fits, after groups of 8 adult (~200-g) M and F rats administered an acute gavage dose of 0.5 or 10 mg/kg omethoate (OME) (Study 8, DataSets 1, 2, 3, and 4, involving a total of 120 rats; Hoshino 1989). Data points and error bars denote averages ±1 (estimated group-wise) SD. Data are compared to corresponding fits by the PBPK-PD model. The PBPK-PD model predicts that 48 hours after gavage administration of 0.5 or 10 mg/kg OME to adult rats, the percentage that OME represents among all recovered urinary metabolites are 34.0% and 52.3%, respectively, whereas the corresponding experimentally measured percentages were 34.2% and 52.8%, respectively (Study 8, Table XXIV; Hoshino 1989). The omethoate PBPK-PD model also predicts that 2.5 hours after acute administration of 0.5 mg/kg omethoate in adult rats, Brain AChE is reduced to 73.4% of its baseline level in unexposed rats, consistent with experimental observations shown in Figure 6. The same time after a 10-mg/kg dose to rats the model predicts that brain AChE is reduced to 0.5% of its baseline level, whereas the data shown in Figure 6 appear to indicate that brain AChE may not be reduced to quite that extent (as discussed in the Figure 6 legend).

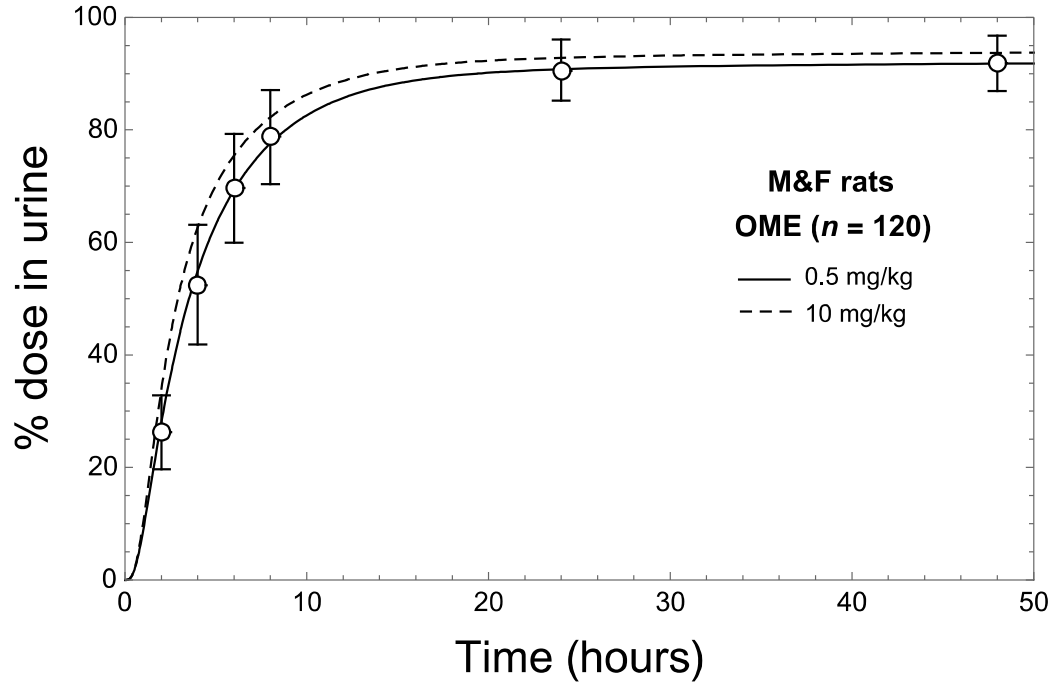
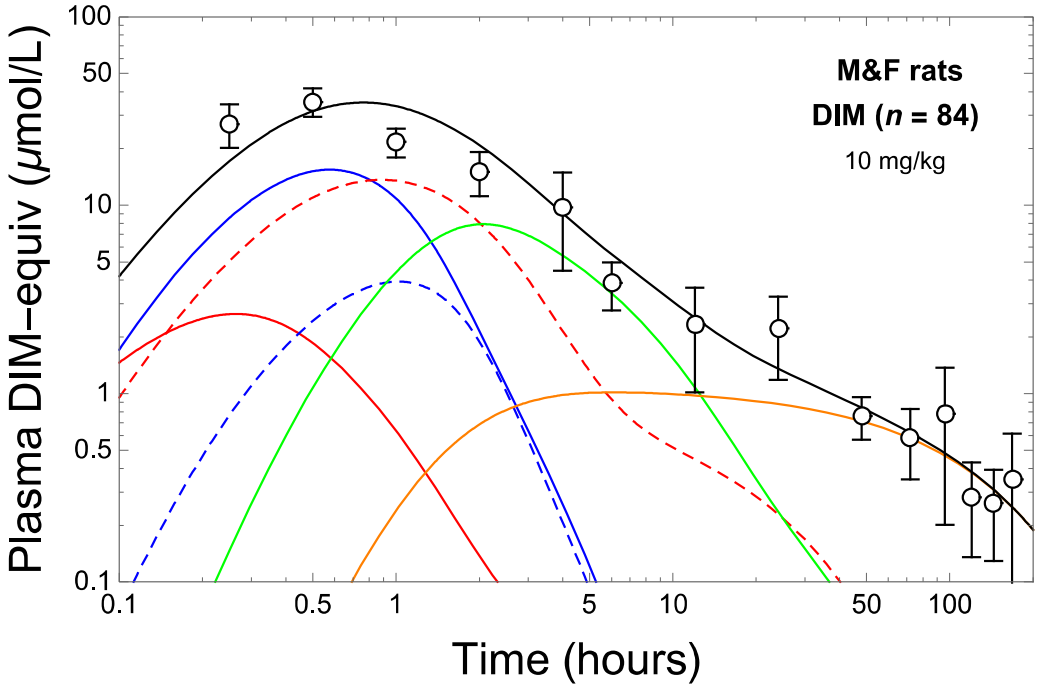


Figure 11. Relative percentage of dose in plasma in groups of 3 adult (~215–220-g) M and F rats administered an acute gavage dose of 10 mg/kg dimethoate (DIM) (Study 7, DataSets 8 and 9, 10, and 11, involving a total of 84 rats; Kirkpatrick 1995). Data points and error bars denote averages ±1 (estimated group-wise) SD for total radiolabel (open points) and dimethoate (solid points) in plasma. Data are compared to corresponding fits by the dimethoate PBPK-PD model (which was conditioned on a corresponding model developed for omethoate) for the following: total predicted radiolabel (Black), dimethoate (Red), omethoate (Blue), DCA (Red dashed), DMDT (Blue dashed), one or more DCA/DMDT metabolites (Green), and suspected omethoate (Orange) bound to one or more plasma proteins with an elimination rate reflecting the albumin turnover rate in rats (~3.3 days; Funabiki et al. 1984). The model predictions shown reflect an unexplained scaling factor of 16% applied in relation to the reported and plotted plasma data.



Model-predicted values of dimethoate and metabolite fractions expected in urine are compared to experimentally observed values in Table 1. Notably, observed urinary fractions of omethoate are substantially less than those predicted by the PBPK-PD model, which successfully predicts omethoate fractions measured in urine excreted from rats 48 hours after exposures to either 0.5 or 10 mg/mg of omethoate. We are so far unable to identify plausible explanations for this substantial discrepancy.

Figure 12. Relative percentage of dose in plasma in groups of 3 adult (~215–220-g) M and F rats administered an acute gavage dose of 100 mg/kg dimethoate (DIM) (Study 7, DataSets 10 and 11, involving a total of 84 rats; Kirkpatrick 1995). Data points and error bars denote averages ±1 (estimated group-wise) SD for total radiolabel (open points) and dimethoate (solid points) in plasma. Data are compared to corresponding fits by the PBPK-PD model for the following: total predicted radiolabel (Black), dimethoate (Red), omethoate (Blue), DCA (Red dashed), DMDT (Blue dashed), one or more DCA/DMDT metabolites (Green), and suspected omethoate (Orange) bound to one or more plasma proteins with an elimination rate reflecting the albumin turnover rate in rats (~3.3 days; Funabiki et al. 1984). The model predictions shown reflect an unexplained scaling factor of 16% applied in relation to the reported and plotted plasma data.

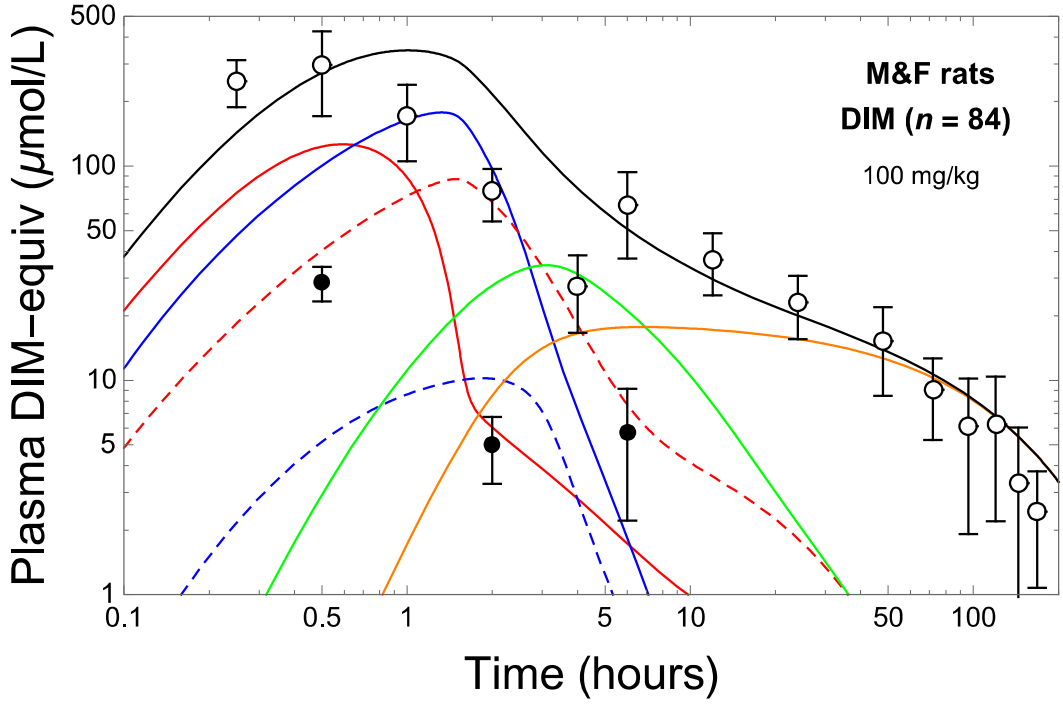
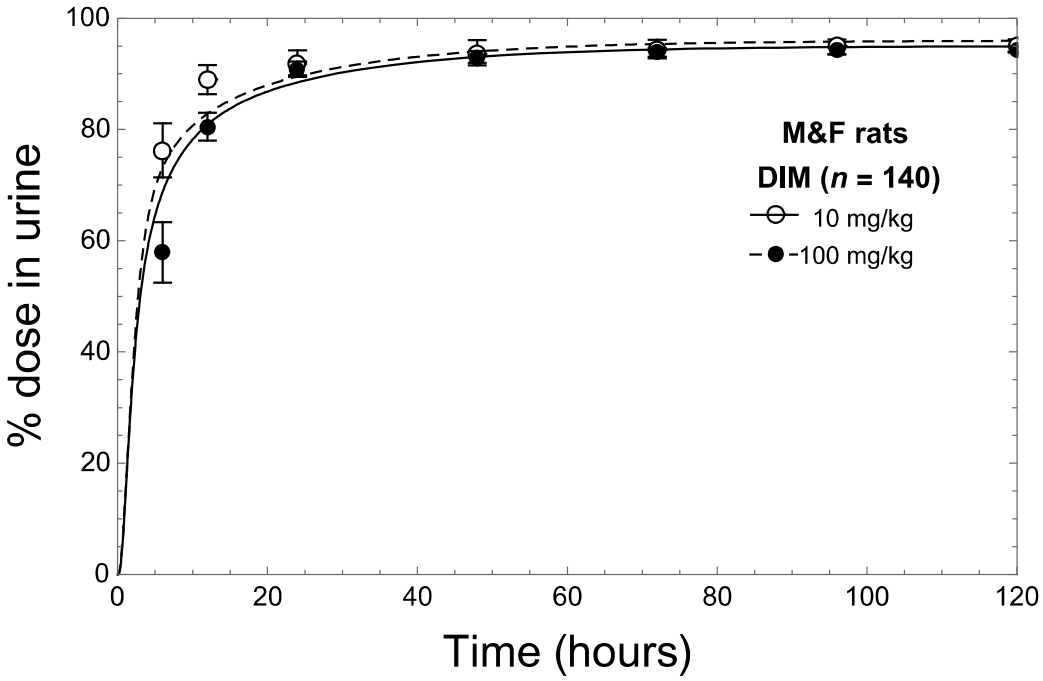


Figure 13. Percentage of ^{14}C-radiolabel recovered in urine, and corresponding PBPK-PD model fits, after groups of 5 adult (~210-g) M and F rats administered an acute gavage dose of 10 or 100 mg/kg dimethoate (DIM) (Study 7, DataSets 2, 3, 4, and 5, involving a total of 140 rats; Kirkpatrick 1995). Data points and error bars denote averages ±1 (estimated group-wise) SD.



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Appendix A – Raw Data Used in Model Fitting and Validation

See Excel sheet

Appendix B – Parameters Values Used in PBPK Model

Table A1.1. Dimethoate rat PBPK model parameters

		PBPK parameters*		Partition coefficients (metabolite:blood)			
Index	Tissue	Vf	Qf	Pdim	Pome	Pdca, etc.	Pdmpt
1	Fat	0.07	0.09	0.464	0.197	0.197	0.197
2	Liver	0.04	0.25	1.05	0.5	0.868	0.868
3	Rapid	0.04	0.37625	1.25	30	0.868	30
4	Slow	0.456	0.136	0.945	0.001	0.868	0.01
5	Brain	0.012	0.03	1.25	0.868	0.868	0.868
6	Skin	0.197	0.058	1.06	0.001	0.868	0.868
7	Diaphr	0.03	0.006	0.945	0.868	0.868	0.868
8	Lung	0.005	0.05375	0.874	0.864	0.864	0.864
9	RBC	0.0276	0.46	1	0.868	0.868	0.868
10	Plasma	0.0324	0.54	1	0.868	0.868	0.868

* Vf = volume fraction of BW assuming 1 L per kg BW

Qf = Blood flow fraction of cardiac blood flow Qc, where Qc = 0.14 x BW^0.75

Hematocrit	46%		
MW values:	DIM	229.26 g/mol	dimthoate
	OME	213.19 g/mol	omethoate
	DCA	216.21 g/mol	dimethoate carbaoxylic acid

Table A1.2. Dimethoate rat PBPK model metabolic rate parameters

		Metabolic parameters*					
		DIM to OME		DIM to DCA**		OME to DMTP**	
Index	Tissue	Vmax	Km	Vmax	Km	Vmax	Km
1	Fat	0.0	1	0.0	1	0	1
2	Liver	3764.6	267.5	2321.9	155	475.1	155
3	Rapid	0.0	1	0.0	1	0	1
4	Slow	0.0	1	0.0	1	0	1
5	Brain	75.3	267.5	46.4	155	9.502	155
6	Skin	75.3	267.5	46.4	155	9.502	155
7	Diaphr	75.3	267.5	46.4	155	9.502	155
8	Lung	3764.6	267.5	2321.9	155	475.1	155
9	RBC	0.0	1	0.0	1	0	1
10	Plasma	0.0	1	0.0	1	0	1

* Vmax in umol/hour/L tisssue

Km in umol/L

Metabolites: 1 = DIM, 2 = OME, 3 = DCA, 4 = DMTP, 5 = Other

** Metabolism to Other assumed to be K35 times these rates

*** Metabolism to Other assumed to be K45 times these rates

Table A1.3a. Dimethoate rat PD model parameters

		Baseline CE activity (umol/hour/L)			CE Bimolecular inhibition (L/umol/hour)				
Index	Tissue	AChE	BChE	CaE	AChE*	BChE	CaE	Refs CE	Refs Inhib
1	Fat	0	0	0	0	0	0	Maxwell87=M;M;M	Herzsprung92=H;H
2	Liver	10200	30000	1.94E+06	0.06507	0.0048	0.005		
3	Rapid	0	0	0	0	0	0		
4	Slow	0	0	0	0	0	0	M;M;Hojring76	H;H
5	Brain	440000	46800	288000	0.06507	0.0048	0.005		
6	Skin	0	0	0	0	0	0		
7	Diaphr	0	0	0	0	0	0	M;M;M	H;H
8	Lung	22800	86400	1.40E+06	0.06507	0.0048	0.005	Zheng2000	H;H
9	RBC	33900	0	0	0.06507	0	0	Timchalk02;Carr01;Li05	
10	Plasma	23300	7850	84000	0.06507	0.0048	0.005		

*Re-estimated using omethoate Brain AChE response data

Table A1.2b. Dimethoate rat PD model parameters (continued)

		CE Reactivation (1/hour)			CE Degradation (1/hour)				
Index	Tissue	AChE*	BChE	CaE	AChE	BChE	CaE	Refs Reactivation	Refs Degadation
1	Fat	0	0	0	0	0	0	Mason2000=M;M	Timchalk02=T;T;T
2	Liver	0.0088	0.03	5.00E-03	0.054	0.0048	0.005		
3	Rapid	0	0	0	0	0	0		
4	Slow	0	0	0	0	0	0	M;M	T;T;T
5	Brain	0.0088	0.03	0.005	0.054	0.0048	0.005		
6	Skin	0	0	0	0	0	0		
7	Diaphr	0	0	0	0	0	0	M;M	T;T;T
8	Lung	0.0088	0.03	5.00E-03	0.054	0.0048	0.005	M;M	T;T;T
9	RBC	0.0088	0	0	0.054	0	0	M;M	T;T;T
10	Plasma	0.0088	0.03	0.005	0.054	0.0048	0.005		

*Re-estimated using dimethoate Brain AChE response data

Table A1.2c. Dimethoate rat PD model parameters (continued)

		CE Aging (1/hour)			
Index	Tissue	AChE	BChE	CaE	Refs Aging
1	Fat	0	0	0	Mason2000=M;M
2	Liver	0.022	0.12	0	
3	Rapid	0	0	0	
4	Slow	0	0	0	M;M
5	Brain	0.022	0.12	0	
6	Skin	0	0	0	
7	Diaphr	0	0	0	M;M
8	Lung	0.022	0.12	0	M;M
9	RBC	0.022	0	0	M;M
10	Plasma	0.022	0.12	0	

Table A1.4. Additional parameters used in the dimethoate rat PBPK-PD model

Parameter	Definition	Value(s)	Unit
Foral	Fraction of oral dose absorbed	1	unitless
Fplasma OME	Scaling factor to fit plasma data	0.035	unitless
Fplasma DIM	Scaling factor to fit plasma data	0.16	unitless
Kstom2intes	Transfer rate constant	2	1/hour
Kstom2liv	Transfer rate constant	0.125	1/hour
Kintes2liv	Transfer rate constant	11	1/hour
Kintes2feces	Transfer rate constant	0.0833333	1/hour
FKfecar	Fraction of Kurx to feces/carcass	0.06	unitless
Kturn AChE*	Turnover rate	1.17E+07	umol/hour
Kturn BChE*	Turnover rate	3.66E+06	umol/hour
Kturn CaE*	Turnover rate	108600	umol/hour
Kurx[1]	Urinary excretion rate , DIM	10	1/hour
Kurx[2]	Urinary excretion rate, OME	1	1/hour
Kurx[3]	Urinary excretion rate, DCA	10	1/hour
Kurx[4]	Urinary excretion rate, DMPT	1	1/hour
Kurx[5]	Urinary excretion rate, Other	0.35	1/hour
K35**	Fractional DCA to Other metab	0.00505	unitless
K45**	Fractional TMPT to Other metab	0.65	unitless
Kalb	Plasma protein turnover rate	0.00875	1/hour
KalbX***	Plasma protein OME binding rate	100	
Malb****	Bindable plasma protein mass	0.00023	

* umol/L CE = Baseline CE activity (umol/hour/L) divided by Kturn (see table A1.3a)

** See Table A1.2 notes

*** Assumed analogous to albumin

**** Estimated by fitting DIM-study plasma data

Appendix C – Mathematica Model Code

Rat PBPK/PD Model for Malathion

Ken Bogen, DrPH DABT Exponent 14June2017 1200734.002 S0T0

```
<< RiskQ11`;
```

References

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Metabolic & Inhibition Data

Input

```
in = Import[
   "/Volumes/Macintosh HD/Users/kbogen/Desktop/Dimethoate-Omethoate PBPK Culled Data_6-13-17 -KB.txt", "TSV"];
in = Prepend[Rest[in], ToExpression[in[[1]]]];
{DataQ[in], Dimensions[in], in[[1]]}
```

```
{True, {594, 20}, {Report, Strain, Study, DataSet, Age, Sex, Grams,
  Chemical, DoseType, Dose, DoseUnit, Days, Hours, Measure, Unit, Tissue, Average, SD, N, Page}}
```

```
tx[x_] := ToExpression[x];
in = Data[in, Replace → {{Age, tx[Age]}, {Sex, tx[Sex]}, {DoseType, tx[DoseType]}, {Tissue, tx[Tissue]}}];
DataQ[in]
```

```
True
```

```
TBL[Union[Transpose[Data[in, Select → Measure == "Brain", Return → {Chemical, Study, DataSet}]]]]
```

```
Omethoate 4 2
Omethoate 4 4
Omethoate 4 6
Omethoate 4 8
```

```
TBL[Union[Transpose[Data[in, Select → Study != 7, Return → {Chemical, Measure, Tissue}]]]]
```

```
14C-Omethoate Recovered 14C Carcass
14C-Omethoate Recovered 14C Feces
14C-Omethoate Recovered 14C Plasma
14C-Omethoate Recovered 14C Urine
Dimethoate    Brain AChE    Brain
Dimethoate    Plasma AChE   Plasma
Dimethoate    Plasma BuChe  Plasma
Dimethoate    RBC AChE      RBC
Omethoate     Brain         Brain
Omethoate     Brain AChE    Brain
Omethoate     Plasma AChE   Plasma
Omethoate     Plasma BuChe  Plasma
Omethoate     RBC AChE      RBC
```

```
TBL[Union[Transpose[Data[in, Select → Study == 7, Return → {Chemical, Measure, Tissue}]]]]
```

```
14C-Dimethoate DCA             Urine
14C-Dimethoate Dimethoate      Plasma
14C-Dimethoate Dimethoate      Urine
14C-Dimethoate DMDPT           Urine
14C-Dimethoate DMPT            Urine
14C-Dimethoate Omethoate       Urine
14C-Dimethoate Recovered 14C   CageWash
14C-Dimethoate Recovered 14C   Carcass
14C-Dimethoate Recovered 14C   ExpiredAir
14C-Dimethoate Recovered 14C   Feces
14C-Dimethoate Recovered 14C   TotalRecovered
14C-Dimethoate Recovered 14C   Urine
14C-Dimethoate TotalRecovered  Urine
```

```
{tissues = Union[Data[in, Tissue]], Union[Head /@ tissues]}
```

```
{{Brain, CageWash, Carcass, ExpiredAir, Feces, Plasma, RBC, TotalRecovered, Urine}, {Symbol}}
```

```
{measures = Union[Data[in, Measure]], Union[Head /@ measures]}
```

```
{{Brain, Brain AChE, DCA, Dimethoate, DMDPT, DMPT, Omethoate,
  Plasma AChE, Plasma BuChe, RBC AChE, Recovered 14C, TotalRecovered}, {String}}
```

DIM data

```
dataDIM = Data[in, Select → MemberQ[{"14C-Dimethoate", "Dimethoate", Dimethoate}, Chemical]];
take = Data[dataDIM,
  Take → {Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical, DoseType, Dose, Measure, Tissue, Average, SD, N}];
Union[Transpose[Data[take, {Report, Strain}]]]
```

```
{{BASF (1983); Report No. 25698n 5M 7107 (22/20441), Rat (Wistar)},
 {Brennan (2001) Report No. SCI 058/004733, Rat (SD, Crl:CD IGS BR)},
 {Huntungdon Life Sciences 1995 - Kirkpatric (14C Dimethoate - The Biokinetics and Metabolism in the Rat) ,
  Rat (Wistar)}, {Meyers, D. (2001), Rat (Crl:CD BR)}}
```

```
dataDIM[[1]]
```

```
{Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical,
 DoseType, Dose, DoseUnit, Days, Hours, Measure, Unit, Tissue, Average, SD, N, Page}
```

```
TBL[summary = Data[take, Drop → {Report, Strain}, Union → {{Study, DataSet, Age, Sex, Measure},
      {{Grams, Mean}, {{Chemical, Dose, DoseType, Tissue, Average}, First}, {N, Sum}}}]]
```

DIM metabolism data

```
chems = Union[Data[in, Chemical]]
```

```
{14C-Dimethoate, 14C-Omethoate, Dimethoate, Omethoate}
```

```
dataDIM[[1]]
```

```
{Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical,
 DoseType, Dose, DoseUnit, Days, Hours, Measure, Unit, Tissue, Average, SD, N, Page}
```

```
TBL[metabDIM = Data[dataDIM, Drop → {Report, Chemical, Strain, Days, DoseType, DoseUnit, Page}, Select → Study > 5]]
```

Metab

```
TBL[metsum = Data[metabDIM, Select → DataSet == 1]]
```

Study	DataSet	Age	Sex	Grams	Dose	Hours	Measure	Tissue	Average	SD	N
7	1	Adults	MF	206.8	10	48	Omethoate	Urine	2.25	NC	10
7	1	Adults	MF	206.8	10	48	DMPT	Urine	7.	NC	10
7	1	Adults	MF	206.8	10	48	DMDPT	Urine	25.9	NC	10
7	1	Adults	MF	206.8	10	48	Dimethoate	Urine	1.05	NC	10
7	1	Adults	MF	206.8	10	48	DCA	Urine	36.45	NC	10
7	1	Adults	MF	206.8	10	48	TotalRecovered	Urine	87	NC	10
7	1	Adults	MF	214.	100	48	Omethoate	Urine	3.7	NC	10
7	1	Adults	MF	214.	100	48	DMPT	Urine	6.7	NC	10
7	1	Adults	MF	214.	100	48	DMDPT	Urine	21.2	NC	10
7	1	Adults	MF	214.	100	48	Dimethoate	Urine	1.35	NC	10
7	1	Adults	MF	214.	100	48	DCA	Urine	43.8	NC	10
7	1	Adults	MF	214.	100	48	TotalRecovered	Urine	89.25	NC	10

```
TBL /@ (Transpose[dd = Data[metsum, Select → Dose == #, Return → {Measure, Average}]] & /@ {10, 100})
```

```
{ Omethoate       2.25    , Omethoate       3.7
  DMPT            7.        DMPT            6.7
  DMDPT           25.9      DMDPT           21.2
  Dimethoate      1.05      Dimethoate      1.35
  DCA             36.45     DCA             43.8
  TotalRecovered  87        TotalRecovered  89.25 }
```

```
Stats[Data[metsum, Grams], R]
```

Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n
210.4	3.76008	0.515894	208.011	212.789	206.8	214.	12

Plasma

```
1. {mwD(*mg/mmol*), mwD / 1000(*mg/umol*)}
```

```
{229.26, 0.22926}
```

```
TBL[plasmasum =
  Data[metabDIM, Select → DataSet > 5, Append → {{AVumol, Average / (mwD / 1000.)}, {SDumol, SD / (mwD / 1000.)}}]]
```

Study	DataSet	Age	Sex	Grams	Dose	Hours	Measure	Unit	Tissue	Average	SD	N	AVumol	SDumol
7	6	Adults	M	210	100	0.5	Dimethoate	mg/L	Plasma	5.7	8.2	3	24.8626	35.7673
7	6	Adults	M	210	100	2	Dimethoate	mg/L	Plasma	0.87	6.6	3	3.79482	28.7883
7	6	Adults	M	210	100	6	Dimethoate	mg/L	Plasma	0.74	6.7	3	3.22778	29.2245
7	7	Adults	F	210	100	0.5	Dimethoate	mg/L	Plasma	7.4	11.	3	32.2778	47.9805
7	7	Adults	F	210	100	2	Dimethoate	mg/L	Plasma	1.43	11.4	3	6.23746	49.7252
7	7	Adults	F	210	100	6	Dimethoate	mg/L	Plasma	1.86	14.	3	8.11306	61.066
7	8	Adults	M	215	10	0.25	Recovered 14C	mg/L	Plasma	6.54	2.12	3	28.5266	9.24714
7	8	Adults	M	215	10	0.5	Recovered 14C	mg/L	Plasma	8.62	1.87	3	37.5992	8.15668
7	8	Adults	M	215	10	1	Recovered 14C	mg/L	Plasma	4.58	0.81	3	19.9773	3.53311
7	8	Adults	M	215	10	2	Recovered 14C	mg/L	Plasma	3.81	1.32	3	16.6187	5.75766

7	8	Adults	M	215	10	4	Recovered	14C	mg/L	Plasma	2.99	1.32	3	13.042	5.75766
7	8	Adults	M	215	10	6	Recovered	14C	mg/L	Plasma	0.97	0.36	3	4.231	1.57027
7	8	Adults	M	215	10	12	Recovered	14C	mg/L	Plasma	0.65	0.42	3	2.83521	1.83198
7	8	Adults	M	215	10	24	Recovered	14C	mg/L	Plasma	0.52	0.3	3	2.26817	1.30856
7	8	Adults	M	215	10	48	Recovered	14C	mg/L	Plasma	0.14	0.02	3	0.61066	0.0872372
7	8	Adults	M	215	10	72	Recovered	14C	mg/L	Plasma	0.15	0.08	3	0.654279	0.348949
7	8	Adults	M	215	10	96	Recovered	14C	mg/L	Plasma	0.09	0.03	3	0.392567	0.130856
7	8	Adults	M	215	10	120	Recovered	14C	mg/L	Plasma	0.04	0.01	3	0.174474	0.0436186
7	8	Adults	M	215	10	144	Recovered	14C	mg/L	Plasma	0.07	0.04	3	0.30533	0.174474
7	8	Adults	M	215	10	168	Recovered	14C	mg/L	Plasma	0.05	0.04	3	0.218093	0.174474
7	9	Adults	F	220	10	0.25	Recovered	14C	mg/L	Plasma	5.96	1.35	3	25.9967	5.88851
7	9	Adults	F	220	10	0.5	Recovered	14C	mg/L	Plasma	7.68	0.91	3	33.4991	3.96929
7	9	Adults	F	220	10	1	Recovered	14C	mg/L	Plasma	5.37	0.87	3	23.4232	3.79482
7	9	Adults	F	220	10	2	Recovered	14C	mg/L	Plasma	3.14	0.12	3	13.6962	0.523423
7	9	Adults	F	220	10	4	Recovered	14C	mg/L	Plasma	1.45	0.2	3	6.3247	0.872372
7	9	Adults	F	220	10	6	Recovered	14C	mg/L	Plasma	0.8	0.09	3	3.48949	0.392567
7	9	Adults	F	220	10	12	Recovered	14C	mg/L	Plasma	0.42	0.11	3	1.83198	0.479805
7	9	Adults	F	220	10	24	Recovered	14C	mg/L	Plasma	0.5	0.23	3	2.18093	1.00323
7	9	Adults	F	220	10	48	Recovered	14C	mg/L	Plasma	0.21	0.03	3	0.915991	0.130856
7	9	Adults	F	220	10	72	Recovered	14C	mg/L	Plasma	0.12	0.02	3	0.523423	0.0872372
7	9	Adults	F	220	10	96	Recovered	14C	mg/L	Plasma	0.27	0.14	3	1.1777	0.61066
7	9	Adults	F	220	10	120	Recovered	14C	mg/L	Plasma	0.09	0.03	3	0.392567	0.130856
7	9	Adults	F	220	10	144	Recovered	14C	mg/L	Plasma	0.05	0.02	3	0.218093	0.0872372
7	9	Adults	F	220	10	168	Recovered	14C	mg/L	Plasma	0.11	0.07	3	0.479805	0.30533
7	10	Adults	M	215	100	0.25	Recovered	14C	mg/L	Plasma	50.7	16.7	3	221.146	72.8431
7	10	Adults	M	215	100	0.5	Recovered	14C	mg/L	Plasma	43.6	2.6	3	190.177	11.3408
7	10	Adults	M	215	100	1	Recovered	14C	mg/L	Plasma	31.5	6.6	3	137.399	28.7883
7	10	Adults	M	215	100	2	Recovered	14C	mg/L	Plasma	15.7	3.3	3	68.4812	14.3941
7	10	Adults	M	215	100	4	Recovered	14C	mg/L	Plasma	4.52	0.79	3	19.7156	3.44587
7	10	Adults	M	215	100	6	Recovered	14C	mg/L	Plasma	11.6	0.8	3	50.5976	3.48949
7	10	Adults	M	215	100	12	Recovered	14C	mg/L	Plasma	6.95	1.41	3	30.3149	6.15022
7	10	Adults	M	215	100	24	Recovered	14C	mg/L	Plasma	4.32	1.15	3	18.8432	5.01614
7	10	Adults	M	215	100	48	Recovered	14C	mg/L	Plasma	2.84	1.91	3	12.3877	8.33115
7	10	Adults	M	215	100	72	Recovered	14C	mg/L	Plasma	1.36	0.16	3	5.93213	0.697898
7	10	Adults	M	215	100	96	Recovered	14C	mg/L	Plasma	0.7	0.04	3	3.0533	0.174474
7	10	Adults	M	215	100	120	Recovered	14C	mg/L	Plasma	1.17	1.05	3	5.10338	4.57995
7	10	Adults	M	215	100	144	Recovered	14C	mg/L	Plasma	0.41	0.03	3	1.78836	0.130856
7	10	Adults	M	215	100	168	Recovered	14C	mg/L	Plasma	0.29	0.07	3	1.26494	0.30533
7	11	Adults	F	220	100	0.25	Recovered	14C	mg/L	Plasma	64	9.6	3	279.159	41.8739
7	11	Adults	F	220	100	0.5	Recovered	14C	mg/L	Plasma	93.2	16.4	3	406.525	71.5345
7	11	Adults	F	220	100	1	Recovered	14C	mg/L	Plasma	47.6	18.9	3	207.625	82.4392
7	11	Adults	F	220	100	2	Recovered	14C	mg/L	Plasma	19.2	6.1	3	83.7477	26.6073
7	11	Adults	F	220	100	4	Recovered	14C	mg/L	Plasma	8.08	2.29	3	35.2438	9.98866
7	11	Adults	F	220	100	6	Recovered	14C	mg/L	Plasma	18.4	8.4	3	80.2582	36.6396
7	11	Adults	F	220	100	12	Recovered	14C	mg/L	Plasma	9.92	3.14	3	43.2697	13.6962
7	11	Adults	F	220	100	24	Recovered	14C	mg/L	Plasma	6.3	1.82	3	27.4797	7.93859
7	11	Adults	F	220	100	48	Recovered	14C	mg/L	Plasma	4.13	1.03	3	18.0145	4.49272
7	11	Adults	F	220	100	72	Recovered	14C	mg/L	Plasma	2.75	0.56	3	11.9951	2.44264
7	11	Adults	F	220	100	96	Recovered	14C	mg/L	Plasma	2.08	0.91	3	9.07267	3.96929
7	11	Adults	F	220	100	120	Recovered	14C	mg/L	Plasma	1.72	0.94	3	7.5024	4.10015
7	11	Adults	F	220	100	144	Recovered	14C	mg/L	Plasma	1.1	0.79	3	4.79805	3.44587
7	11	Adults	F	220	100	168	Recovered	14C	mg/L	Plasma	0.82	0.15	3	3.57673	0.654279

```
Data[plasmasum, Select → DataSet > 7, Return → Plus @@ N]
```

```
168
```

```
Data[plasmasum, Select → DataSet < 8, Return → AVumol]
```

```
Data[plasmasum, Select → 5 < DataSet < 8, Return → AVumol]
```

```
{24.8626, 3.79482, 3.22778, 32.2778, 6.23746, 8.11306}
```

```
xyPlasmaMF = Transpose[{time6, #}] & /@ Partition[Data[plasmasum, Select → 5 < DataSet < 8, Return → AVumol], 3]
```

```
{{{0.5, 24.8626}, {2, 3.79482}, {6, 3.22778}}, {{0.5, 32.2778}, {2, 6.23746}, {6, 8.11306}}}
```

```
pctDIM = Partition[Data[plasmasum, Select → 5 < DataSet < 8, Return → SD], 3]
```

```
{{8.2, 6.6, 6.7}, {11., 11.4, 14.}}
```

```
1. EV[Data[plasmasum, Select → DataSet > 7, Return → Grams]]
```

```
217.5
```

```
timeP = Union[Data[plasmasum, Select → DataSet > 7, Return → Hours]]
```

```
{0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168}
```

```
yP = Data[plasmasum, Select → DataSet == #, Return → AVumol] & /@ {8, 9, 10, 11}
```

```
sP = Data[plasmasum, Select → DataSet == #, Return → SDumol] & /@ {8, 9, 10, 11}
```

```
{yP10, yP100} = (EV /@ Transpose[yP[[#]]]) & /@ {{1, 2}, {3, 4}}
```

```
{{27.2616, 35.5492, 21.7003, 15.1575, 9.68333, 3.86025, 2.3336, 2.22455, 0.763325,
  0.588851, 0.785135, 0.283521, 0.261712, 0.348949}, {250.153, 298.351, 172.512, 76.1145,
  27.4797, 65.4279, 36.7923, 23.1615, 15.2011, 8.96362, 6.06299, 6.30289, 3.2932, 2.42083}}
```

```
ina = Append[Transpose /@ (#[[{1, 2}]] & /@ {yP, sP}), Table[{3, 3}, {14}]];
sP10 = MapThread[SD[{#1, #2, #3}] &, ina]
```

```
{7.07063, 6.16101, 3.7836, 3.9915, 5.20588, 1.10132,
 1.31776, 1.04393, 0.19458, 0.23851, 0.583903, 0.147918, 0.132302, 0.264604}
```

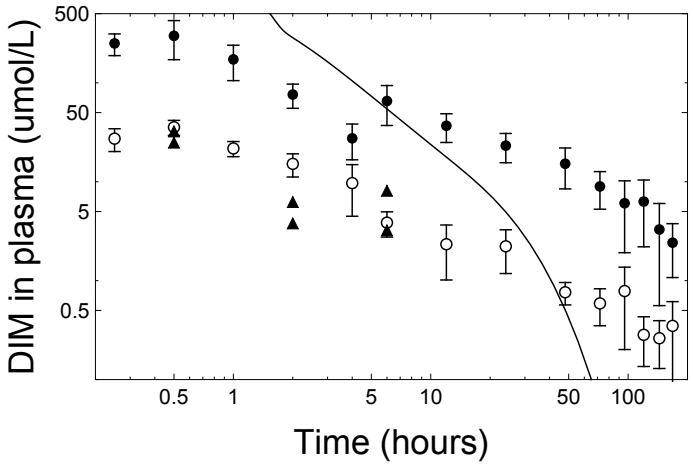
```
ina = Append[Transpose /@ (#[[{3, 4}]] & /@ {yP, sP}), Table[{3, 3}, {14}]];
sP100 = MapThread[SD[{#1, #2, #3}] &, ina]
```

```
{61.9149, 127.044, 67.3015, 20.8801, 10.8165, 28.3863,
 11.8538, 7.59274, 6.73315, 3.68909, 4.14537, 4.10384, 2.73385, 1.34604}
```

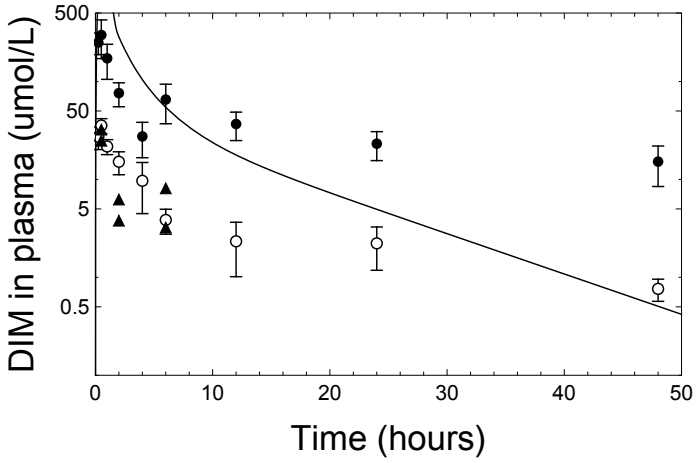
```
xyPlasma10 = Transpose[{timeP, #}] & /@ {yP10 - sP10, yP10 + sP10, yP10}
```

```
xyPlasma100 = Transpose[{timeP, #}] & /@ {yP100 - sP100, yP100 + sP100, yP100}
```

```
PlotData[Join[Join[xyPlasma10, xyPlasma100], xyPlasmaMF], Style → {M, J, M, OO, M, J, M, O, A, A},
 FitTo → {Plasma[1][t] //. sol, t}, Labels → {"Time (hours)", "DIM in plasma (umol/L)"},
 X → {0.2, 200}, Y → {0.1, 500}, PlotType → LogLog, PlotStyle → Black]
```



```
PlotData[Join[Join[xyPlasma10, xyPlasma100], xyPlasmaMF], Style → {M, J, M, OO, M, J, M, O, A, A},
 FitTo → {Plasma[1][t] //. sol, t}, Labels → {"Time (hours)", "DIM in plasma (umol/L)"},
 X → {0, 50}, Y → {0.1, 500}, PlotType → LinearLog, PlotStyle → Black]
```



Urine

```
TBL[takeU = Data[metabDIM, Select → 1 < DataSet < 6]]
```

Study	DataSet	Age	Sex	Grams	Dose	Hours	Measure	Unit	Tissue	Average	SD	N
7	2	Adults	M	202.	10	6	Recovered	14C % admin dose	Urine	69.3	8.3	5
7	2	Adults	M	202.	10	12	Recovered	14C % admin dose	Urine	17.1	5.7	5
7	2	Adults	M	202.	10	24	Recovered	14C % admin dose	Urine	2.64	0.58	5
7	2	Adults	M	202.	10	48	Recovered	14C % admin dose	Urine	1.72	1.84	5
7	2	Adults	M	202.	10	72	Recovered	14C % admin dose	Urine	0.26	0.08	5
7	2	Adults	M	202.	10	96	Recovered	14C % admin dose	Urine	0.17	0.11	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	Urine	0.07	0.02	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	CageWash	0.1	0.04	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	ExpiredAir	2.1	0.59	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	Feces	1.15	0.18	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	Carcass	0.67	0.2	5
7	2	Adults	M	202.	10	120	Recovered	14C % admin dose	TotalRecovered	95.3	2.9	5
7	3	Adults	F	210.	10	6	Recovered	14C % admin dose	Urine	71.9	3.5	5
7	3	Adults	F	210.	10	12	Recovered	14C % admin dose	Urine	6.67	1.52	5
7	3	Adults	F	210.	10	24	Recovered	14C % admin dose	Urine	2.97	1.19	5
7	3	Adults	F	210.	10	48	Recovered	14C % admin dose	Urine	1.6	0.58	5
7	3	Adults	F	210.	10	72	Recovered	14C % admin dose	Urine	1.02	0.64	5
7	3	Adults	F	210.	10	96	Recovered	14C % admin dose	Urine	0.56	0.47	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	Urine	0.36	0.27	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	CageWash	0.29	0.14	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	ExpiredAir	2.17	0.28	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	Feces	1.56	1.34	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	Carcass	1.45	0.59	5
7	3	Adults	F	210.	10	120	Recovered	14C % admin dose	TotalRecovered	90.6	3.8	5
7	4	Adults	M	204.4	100	6	Recovered	14C % admin dose	Urine	59	6.8	5
7	4	Adults	M	204.4	100	12	Recovered	14C % admin dose	Urine	19.6	2.2	5
7	4	Adults	M	204.4	100	24	Recovered	14C % admin dose	Urine	9.12	5.21	5
7	4	Adults	M	204.4	100	48	Recovered	14C % admin dose	Urine	1.89	0.97	5
7	4	Adults	M	204.4	100	72	Recovered	14C % admin dose	Urine	0.58	0.21	5
7	4	Adults	M	204.4	100	96	Recovered	14C % admin dose	Urine	0.2	0.08	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	Urine	0.15	0.06	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	CageWash	0.27	0.16	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	ExpiredAir	2.44	0.38	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	Feces	1.45	0.25	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	Carcass	1.14	0.2	5
7	4	Adults	M	204.4	100	120	Recovered	14C % admin dose	TotalRecovered	95.9	0.9	5
7	5	Adults	F	211.4	100	6	Recovered	14C % admin dose	Urine	52	8.3	5
7	5	Adults	F	211.4	100	12	Recovered	14C % admin dose	Urine	23.7	6.	5
7	5	Adults	F	211.4	100	24	Recovered	14C % admin dose	Urine	10.7	4.8	5
7	5	Adults	F	211.4	100	48	Recovered	14C % admin dose	Urine	2.37	0.7	5
7	5	Adults	F	211.4	100	72	Recovered	14C % admin dose	Urine	0.97	0.37	5
7	5	Adults	F	211.4	100	96	Recovered	14C % admin dose	Urine	0.35	0.1	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	Urine	0.26	0.11	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	CageWash	0.45	0.32	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	ExpiredAir	2.53	0.48	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	Feces	1.45	0.55	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	Carcass	1.88	0.73	5
7	5	Adults	F	211.4	100	120	Recovered	14C % admin dose	TotalRecovered	96.6	2.	5

```
Data[take, Select → Tissue == Urine, Return → Plus @@ N]
```

```
140
```

```
Stats[Data[take, Grams], R]
```

```
Mean    SD        CVM%      95%LCL   95%UCL   Min   Max    n
206.95  3.91755   0.27323   205.812  208.088  202.  211.4  48
```

```
time = Union[Data[take, Hours]]
```

```
{6, 12, 24, 48, 72, 96, 120}
```

```
sets = Union[Transpose[Data[take, {DataSet, Sex, Dose}]]]
```

```
{{2, M, 10}, {3, F, 10}, {4, M, 100}, {5, F, 100}}
```

```
avi = Data[take, Select → {DataSet, Sex, Dose} == #, Return → Average] & /@ sets;
avi = Drop[#, -1] & /@ avi;
ftot = Plus @@ # & /@ avi / 100;
TBL[avi = avi / ftot]
```

```
72.733   17.9471  2.77078  1.80521  0.27288   0.178421  0.0734677  0.104954  2.20403  1.20697  0.703191
79.4036  7.3661   3.27996  1.76698  1.12645   0.618443  0.39757    0.320265  2.39647  1.72281  1.60133
61.5609  20.4508  9.51586  1.97204  0.605175  0.208681  0.156511   0.28172   2.54591  1.51294  1.18948
53.7968  24.5189  11.0697  2.45189  1.00352   0.362094  0.268984   0.465549  2.61742  1.5001   1.94496
```

```
Plus @@ # & /@ avi
```

```
{100., 100., 100., 100.}
```

```
{cw, air, fec, carc} = Transpose[avi][[Range[8, 11]]];
nu = Take[#, 7] & /@ avi;
ur = Accumulate /@ MapThread[(#1 + (#1 / #2) #3) &, {nu, tot, cw}];
TBL[ur]
```

```
72.8166  90.7844  93.5584  95.3656  95.6388  95.8175  95.891
79.7025  87.0964  90.3887  92.1623  93.293   93.9138  94.3128
61.7525  82.2669  91.8123  93.7905  94.3976  94.6069  94.7639
54.074   78.7193  89.8461  92.3106  93.3193  93.6832  93.9536
```

```
sd10 = SD /@ Transpose[tt = ur[[{1, 2}]]];
av10 = Plus @@ tt / 2;
sd100 = SD /@ Transpose[tt = ur[[{3, 4}]]];
av100 = Plus @@ tt / 2;
TBL[1. {ave10, ave100}]
```

```
70.6  11.885  2.805  1.66  0.64   0.365  0.215  0.195  2.135  1.355  1.06  92.95
55.5  21.65   9.91   2.13  0.775  0.275  0.205  0.36   2.485  1.45   1.51  96.25
```

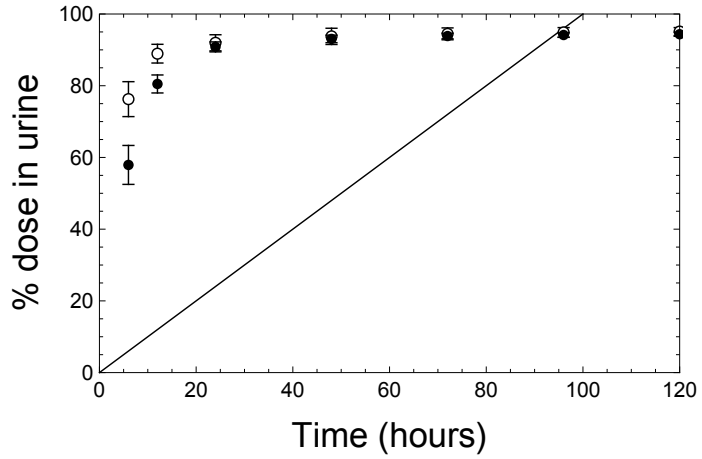
```
{EV[#[[{1, 2}]]] & /@ {cw, air, carc}, EV[#[[{3, 4}]]] & /@ {cw, air, carc}}
```

```
{{0.212609, 2.30025, 1.15226}, {0.373634, 2.58167, 1.56722}}
```

```
TBL[{sd10, sd100}]
```

```
4.86907  2.60782  2.24131  2.2651   1.65876  1.34612  1.11594
5.4295   2.50852  1.39037  1.04647  0.762473 0.653134 0.572967
```

```
xy10 = Transpose[{time, #}] & /@ {av10 - sd10, av10 + sd10, av10};
xy100 = Transpose[{time, #}] & /@ {av100 - sd100, av100 + sd100, av100};
PlotData[Join[xy10, xy100], Style → {M, J, M, OO, M, J, M, O}, X → {0, 120},
 Y → {0, 100}, FitTo → {x, x}, Labels → {"Time (hours)", "% dose in urine"}, PlotStyle → Black]
```



DIM CE data

```
dataDIM[[1]]
```

```
{Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical,
 DoseType, Dose, DoseUnit, Days, Hours, Measure, Unit, Tissue, Average, SD, N, Page}
```

```
Union[Data[dataDIM, Tissue]]
```

```
{Brain, CageWash, Carcass, ExpiredAir, Feces, Plasma, RBC, TotalRecovered, Urine}
```

```
TBL[ceDIMr = Data[dataDIM, Drop → {Report, Chemical, Strain, Unit, DoseUnit, Page}, Select → Tissue == Plasma]]
```

```
TBL[ceDIMr = Data[dataDIM, Drop → {Report, Chemical, Strain, Unit, DoseUnit, Page}, Select → Tissue == RBC]]
```

```
TBL[ceDIM = Data[dataDIM, Drop → {Report, Chemical, Strain, Unit, DoseUnit, Page}, Select → Tissue == Brain]]
```

```
Stats[Data[ceDIM, Select → {Age, Sex} == #, Return → Grams], R] & /@ {{Adult, M}, {Adult, F}, {PND11, M}, {PND11, F}}
```

```
{{Mean  SD        CVM%       95%LCL   95%UCL   Min   Max    n , Mean     SD        CVM%       95%LCL   95%UCL   Min   Max    n ,
 287.  3.90969  0.481633  283.731  290.269  283.  292.5  8 , 206.125  2.76134  0.473636  203.816  208.434  204.  210.5  8 ,
 Mean    SD        CVM%       95%LCL   95%UCL   Min   Max   n , Mean  SD        CVM%       95%LCL   95%UCL   Min   Max   n}
 25.525  0.205287  0.284349  25.3534  25.6966  25.2  25.7  8 , 24.5  0.130931  0.188943  24.3905  24.6095  24.4  24.7  8}}
```

```
take = Data[ceDIM, Select → Age == PND11 || Age == Adult];
doses = Union[Data[take, Dose]]
```

```
{0, 0.1, 0.5, 3}
```

```
sets = Union[Transpose[Data[take, Return → {Sex, Age, Days}]]]
```

```
{{F, Adult, 11 days}, {F, Adult, Acute}, {F, PND11, 11 days}, {F, PND11, Acute},
 {M, Adult, 11 days}, {M, Adult, Acute}, {M, PND11, 11 days}, {M, PND11, Acute}}
```

```
TBL[dat = Data[take, Group → {{Sex, Age, Days}, {{Pct, 100. * Average / Average[[1]]}, {SDpct, 100. * SD / Average}}}]]
```

```
nrats = 2 (4 * 8 + 4 * 10) (* in the acute studies, and in the 11-day studies *)
```

```
144
```

```
setsAll = Union[Transpose[Data[dat, {Study, DataSet, Age, Sex, Days}]]]
```

```
{{1, 1, Adult, M, Acute}, {1, 2, Adult, F, Acute}, {1, 3, Adult, M, 11 days}, {1, 4, Adult, F, 11 days},
 {1, 5, PND11, M, Acute}, {1, 6, PND11, F, Acute}, {1, 7, PND11, M, 11 days}, {1, 8, PND11, F, 11 days}}
```

```
sets = Union[Transpose[Data[dat, {Study, DataSet}]]]
```

```
{{1, 1}, {1, 2}, {1, 3}, {1, 4}, {1, 5}, {1, 6}, {1, 7}, {1, 8}}
```

```
xi = Data[dat, Select → {Study, DataSet} == #, Return → Pct] & /@ sets;
si = Data[dat, Select → {Study, DataSet} == #, Return → SDpct] & /@ sets;
```

```
xi
```

```
{{100., 98.1876, 96.3752, 87.944}, {100., 96.2898, 97.8799, 85.5548},
 {100., 99.2057, 90.0709, 52.9716}, {100., 93.5705, 86.6299, 41.6168}, {100., 98.2703, 94.888, 83.0116},
 {100., 101.503, 97.906, 82.2251}, {100., 95.8458, 87.1711, 54.6988}, {100., 96.4088, 87.7762, 57.9659}}
```

```
si
```

```
{{1.79063, 5.92439, 1.81435, 9.038}, {3.92085, 3.26459, 4.96101, 6.82719},
 {3.75319, 4.72977, 4.3126, 33.2628}, {9.41354, 3.20707, 6.56083, 17.4144}, {3.76062, 3.70423, 5.85938, 5.40093},
 {3.1234, 5.32441, 4.85878, 10.3441}, {1.99518, 3.32965, 3.75498, 9.70925}, {3.66034, 3.16273, 2.74753, 16.2005}}
```

```
xy = Table[Transpose[{doses, #}] & /@ {xi[[i]] - si[[i]], xi[[i]] + si[[i]], xi[[i]]}, {i, Length[xi]}]
```

```
setsAll[[#]] & /@ {{1, 2}, {5, 6}}
```

```
{{{1, 1, Adult, M, Acute}, {1, 2, Adult, F, Acute}}, {{1, 5, PND11, M, Acute}, {1, 6, PND11, F, Acute}}}
```

```
(* at 0.5-mg/kg acute dose*)
Stats[#[[3]] & /@ xi[[{1, 2, 5, 6}]], R]
```

Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n
96.7623	1.43987	0.744027	94.4711	99.0534	94.888	97.906	4

```
(* at 3.0-mg/kg acute dose*)
Stats[#[[4]] & /@ xi[[{1, 2, 5, 6}]], R]
```

Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n
84.6839	2.59675	1.53321	80.5518	88.8159	82.2251	87.944	4

```
{eq = LQ[{{0, 100}, {3, 84.68}}], eq /. x → 10}
```

```
{100.00000000000000000000 - 5.106666666666643929299 x, 48.933333333333356070701}
```

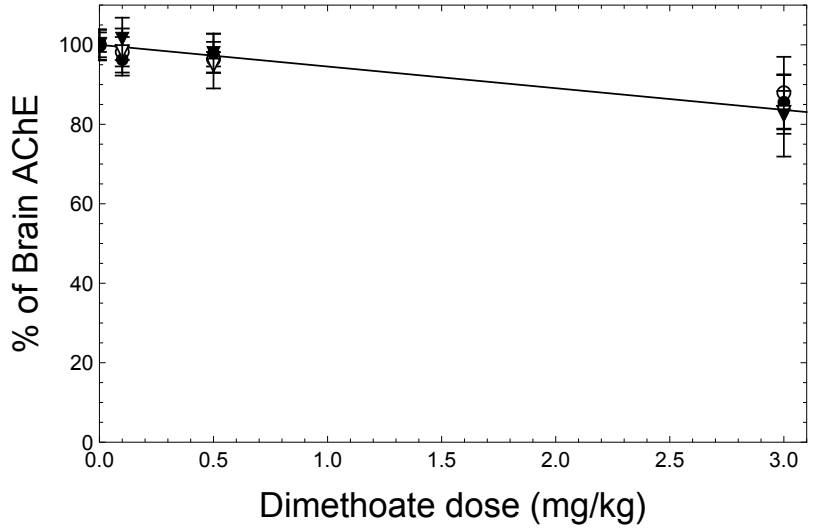
```
wi = (Join @@ si[[{1, 2, 5, 6}]]) ^ -2
```

```
{0.311879, 0.0284913, 0.303778, 0.0122421, 0.0650489, 0.0938304, 0.0406312, 0.0214544,
 0.0707101, 0.0728794, 0.0291271, 0.0342817, 0.102505, 0.0352742, 0.0423591, 0.00934578}
```

```
xyD = Join @@ (Last /@ xy[[{1, 2, 5, 6}]]);
{out = NonlinearModelFit[xyD, 100 - B * x, {{B, 10}}, x, Weights → wi];
 fit = Normal[out], out["ParameterTable"], RSQ[xyD, fit, x]}
```

$$\left\{100 - 5.45724\,x,\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline \text{B} & 5.45724 & 0.409328 & 13.3322 & 1.01248\times10^{-9} \end{array},\ 0.921891\right\}$$

```
PlotData[Join @@ xy[[{1, 2, 5, 6}]], Style → {M, J, M, OO, M, J, M, O, M, J, M, OV, M, J, M, V}, X → {0, 3.1},
 Y → {0, 110}, FitTo → {fit, x}, Labels → {"Dimethoate dose (mg/kg)", "% of Brain AChE"}, PlotStyle → Black]
```



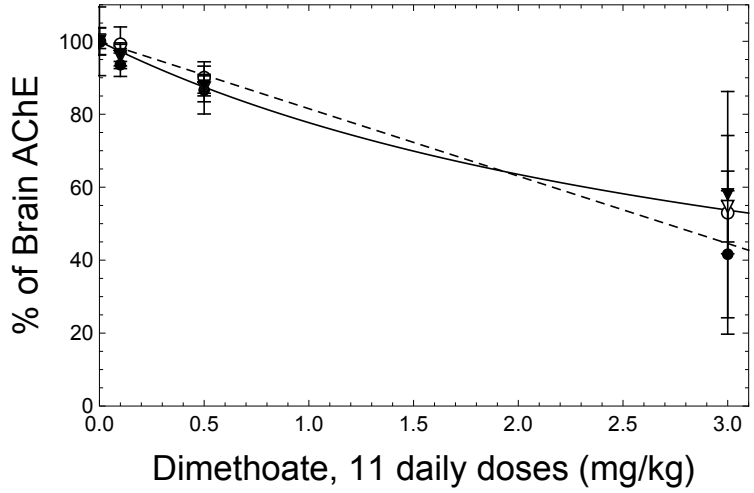

```
(100 - 5.457237399720463` x) /. x → # & /@ {1, 3, 10, 100}
```

```
{94.5428, 83.6283, 45.4276, -445.724}
```

```
setsAll[[#]] & /@ {{3, 4}, {7, 8}}
```

```
{{{1, 3, Adult, M, 11 days}, {1, 4, Adult, F, 11 days}}, {{1, 7, PND11, M, 11 days}, {1, 8, PND11, F, 11 days}}}
```

```
PlotData[Join @@ xy[[{3, 4, 7, 8}]], Style → {M, J, M, OO, M, J, M, O, M, J, M, OV, M, J, M, V},
 X → {0, 3.1}, Y → {0, 110}, FitTo → {{fit, fit2}, x},
 Labels → {"Dimethoate, 11 daily doses (mg/kg)", "% of Brain AChE"}, PlotStyle → {{Black, Dashed}, Black}]
```




```
wi = (Join @@ si[[{3, 4, 7, 8}]]) ^ -2
```

```
{0.0709902, 0.0447013, 0.0537678, 0.00090382, 0.0112848, 0.097226, 0.0232318, 0.0032975,
 0.251209, 0.0901994, 0.0709228, 0.0106079, 0.0746375, 0.0999714, 0.132469, 0.00381017}
```

```
xyD = Join @@ (Last /@ xy[[{3, 4, 7, 8}]]);
{out = NonlinearModelFit[xyD, 100 - B * x, {{B, 10}}, x, Weights → wi];
 fit = Normal[out], out["ParameterTable"], RSQ[xyD, fit, x]}
```

$$\left\{100 - 18.4795\, x,\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline \text{B} & 18.4795 & 1.41681 & 13.043 & 1.37265\times 10^{-9} \end{array},\ 0.928117\right\}$$

```
xyD = Join @@ (Last /@ xy[[{3, 4, 7, 8}]]);
{out = NonlinearModelFit[xyD, 100 K/(K + x), {{K, 3.3}}, x, Weights → wi];
 fit2 = Normal[out], out["ParameterTable"], RSQ[xyD, fit2, x]}
```

$$\left\{\frac{348.197}{3.48197 + x},\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline K & 3.48197 & 0.21238 & 16.395 & 5.49772\times 10^{-11} \end{array},\ 0.96778\right\}$$

```
D[348.1970467642377`/(3.4819704676423773` + x), x] /. x → 0
```

$$-28.7194$$

```
{28.719370520023233`/5.457237399720463`, 1 - 0.28719370520023233`}
```

$$\{5.26262,\ 0.712806\}$$

Analytic Solution of Impact of Sawtooth Recovery from Repeated Reductions

```
Remove[f, fxn]
fxn[n_] := fxn[n] = f (1 - (1 - fxn[n - 1]) E^(-k * t))
fxn[1] = f
```

$$f$$

```
sim = FullSimplify[fxn[10], k > 0 && t > 0]
```

$$e^{-9kt} f \left(e^{9kt} + e^{8kt}(-1+f) + e^{7kt}(-1+f) f + e^{6kt}(-1+f) f^2 + e^{5kt}(-1+f) f^3 + e^{4kt}(-1+f) f^4 + e^{3kt}(-1+f) f^5 + e^{2kt}(-1+f) f^6 + e^{kt}(-1+f) f^7 + (-1+f) f^8\right)$$

```
f - (1 - f) (f e^(-kt) + f^2 e^(-2kt) + f^3 e^(-3kt) + f^4 e^(-4kt) + f^5 e^(-5kt) + f^6 e^(-6kt) + f^7 e^(-7kt) + f^8 e^(-8t) + f^9 e^(-9kt))
ff[n_] := f - (1 - f) Sum[f^i e^(-ikt), {i, 1, n-1}]
ff[1]
```

$$f$$

```
1 - 0.9454276260027953`
```

```
0.0545724
```

```
(Log[2] / ({1, 24} 0.00508936)) {hours, days}
```

```
{136.195 hours, 5.67481 days}
```

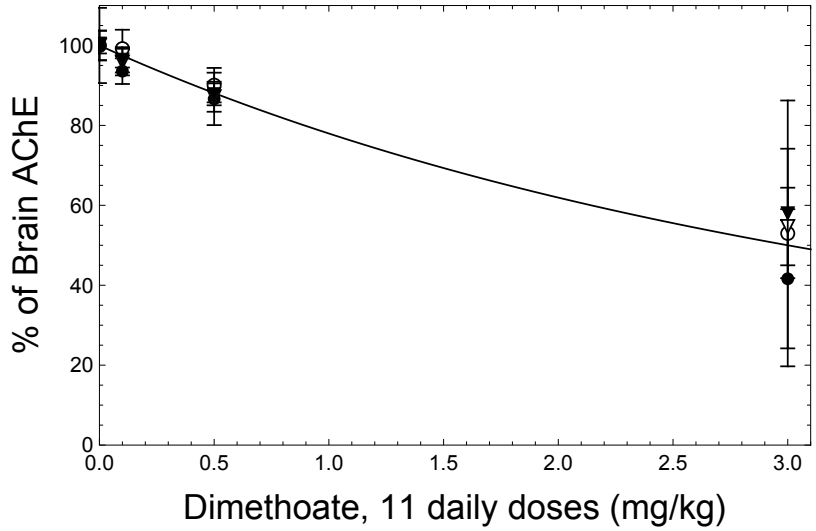
```
{f11 = ff[11] /. {k → 0.00508936, t → 24, f → (f1 = 0.9454276260027953`)}, (1 - f11) / (1 - f1)}
```

```
{0.712806, 5.26262}
```

```
{f11 = ff[11] /. {k → 0.00508936, t → 24, f → (f1 = 0.836282878008386`)}, (1 - f11) / (1 - f1)}
```

```
{0.393009, 3.70756}
```

```
PlotData[Join @@ xy[[{3, 4, 7, 8}]], Style → {M, J, M, OO, M, J, M, O, M, J, M, OV, M, J, M, V}, X → {0, 3.1}, Y → {0, 110},
 FitTo → {fit4, x}, Labels → {"Dimethoate, 11 daily doses (mg/kg)", "% of Brain AChE"}, PlotStyle → {Black}]
```




```
ff[11]
```

$$f - (1 - f)\ \left(e^{-k\,t}\,f + e^{-2\,k\,t}\,f^2 + e^{-3\,k\,t}\,f^3 + e^{-4\,k\,t}\,f^4 + e^{-5\,k\,t}\,f^5 + e^{-6\,k\,t}\,f^6 + e^{-7\,k\,t}\,f^7 + e^{-8\,k\,t}\,f^8 + e^{-9\,k\,t}\,f^9 + e^{-10\,k\,t}\,f^{10}\right)$$

```
Clear[zz]

zz[K_] := 100 ff[11] /. {k → K, t → 24, f → 0.9454276260027953}

zz[.02]
```

```
86.8857
```

```
{out = NonlinearModelFit[xyD, 100 ff[11] /. {k → K, t → 24, f → 1 - 0.054572373997204715` x}, {{K, 0.02}}, x, Weights → wi];
 fit4 = Normal[out], out["ParameterTable"], RSQ[xyD, fit4, x]}
```

$$\{100 \left(1 - 0.0545724\, x - 0.0545724 \left(0.80956 \left(1 - 0.0545724\, x\right) + 0.655388 \left(1 - 0.0545724\, x\right)^2 + 0.530576 \left(1 - 0.0545724\, x\right)^3 + 0.429534 \left(1 - 0.0545724\, x\right)^4 + 0.347733 \left(1 - 0.0545724\, x\right)^5 + 0.281511 \left(1 - 0.0545724\, x\right)^6 + 0.2279 \left(1 - 0.0545724\, x\right)^7 + 0.184499 \left(1 - 0.0545724\, x\right)^8 + 0.149363 \left(1 - 0.0545724\, x\right)^9 + 0.120919 \left(1 - 0.0545724\, x\right)^{10}\right) x\right),$$

	Estimate	Standard Error	t-Statistic	P-Value
K	0.00880266	0.00081831	10.7571	1.89713×10^{-8}

$$, 0.967785\}$$

OME CE data

```
ceOME = Data[in,
   Select → Chemical === ("Omethoate" || Chemical === "14C-Omethoate") && MemberQ[{Brain, Plasma, RBC}, Tissue]];
tissues = Union[Data[ceOME, Tissue]]
```

```
{Brain, Plasma, RBC}
```

```
takeA = Data[ceOME, Take →
    {Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical, DoseType, Days, Hours, Dose, Measure, Average, SD, N}];
Union[Transpose[Data[take, {Report, Strain}]]]
```

```
{{BASF (2003); Report No. 20C0709/01098, Rat (Wistar CrlGlxBrlHan:WI)},
 {Bayer AG (1995); Report No. T 2030748, Rat (BOR:WISW)},
 {Charles River Labs (2012); Report No. 20010314, Rat (Crl:CD(SD))}}
```

```
TBL[Data[takeA, Drop → {Report, Strain}]]

Union[Data[ceOME, Select → Hours =!= "Pre-dosing", Return → Days]]
```

```
{15 Days Post-Dosing, 182 Days, 196 Days, 2.5 hours post-dose Subset A, 364 Days, 546 Days, 735 Days, Post-dosing}
```

```
TBL[
 ceo = Data[ceOME, Select → MemberQ[{"2.5 hours post-dose Subset A", "Post-dosing"}, Days] && Hours =!= "Pre-dosing",
   Take → {Strain, Study, DataSet, Age, Grams, Sex, Days, Hours, Dose, DoseUnit, Measure, Unit, Tissue, Average, SD, N}]]
```

```
TBL[ceo2 = Data[ceOME, Select → Days === "2.5 hours post-dose Subset A",
    Take → {Study, DataSet, Age, Grams, Sex, Hours, Dose, Measure, Tissue, Average, SD, N},
    Group → {{Sex, Tissue}, {{Pct, 100 Average / Average[[1]]}, {SDpct, 100 (SD / Average[[1]])}}}]];
```

```
wt = Stats[Data[ceo2, Select → Sex == #, Return → Grams], R] & /@ {M, F}
```

	Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n
{	190.4	3.19441	0.43319	188.631	192.169	185.4	194.9	15 ,
	Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n }
	141.08	2.1903	0.40086	139.867	142.293	138.5	144.4	15 }

```
set = Union[Transpose[Data[ceo2, {Sex, Tissue}]]]
```

```
{{F, Brain}, {F, Plasma}, {F, RBC}, {M, Brain}, {M, Plasma}, {M, RBC}}
```

```
dose = Union[Data[ceo2, Dose]]
```

```
{0, 0.2, 0.25, 0.35, 5}
```

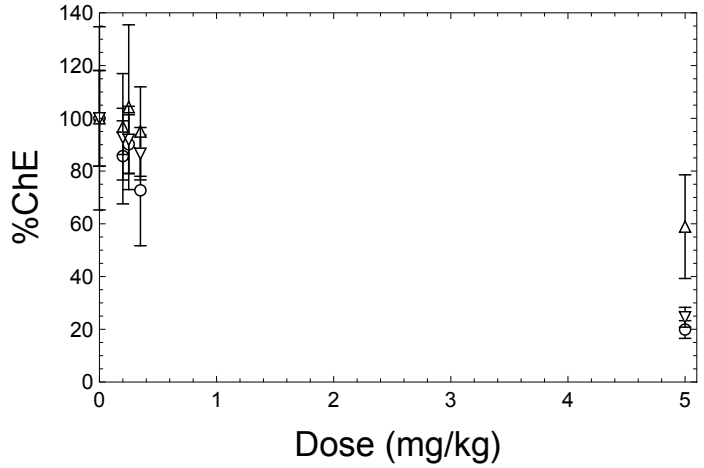
```
xyij = Data[ceo2, Select → {Sex, Tissue} == #, Return → {Pct, SDpct}] & /@ set;
yi = First /@ xyij;
si = Last /@ xyij;
xyi = Join @@ Table[Transpose[{dose, #}] & /@ {yi[[i]] - si[[i]], yi[[i]] + si[[i]], yi[[i]]}, {i, 6}]
```

```
Length[xyi]
```

```
18
```

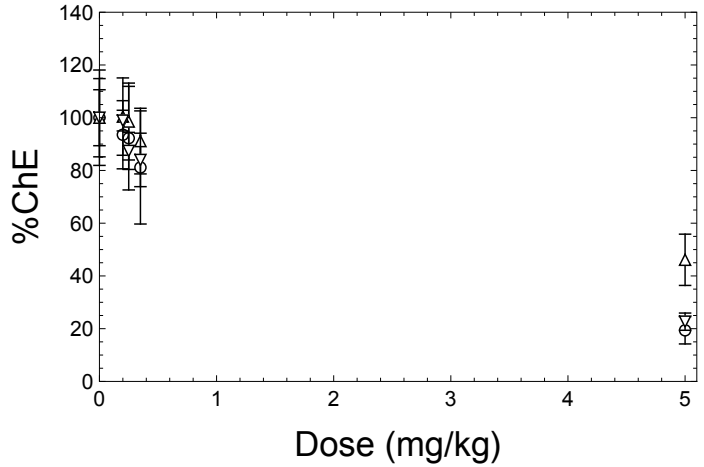
Female ○ = Brain, △ = Plasma, ▽ = sRBC,

```
PlotData[xyi[[Range[9]]], Style → {M, J, M, OO, M, J, M, OA, M, J, M, OV},
 Labels → {"Dose (mg/kg)", "%ChE"}, X → {0, 5.1}, Y → {0, 140}]
```



Male ○ = Brain, △ = Plasma, ▽ = sRBC,

```
PlotData[xyi[[Range[10, 18]]], Style → {M, J, M, OO, M, J, M, OA, M, J, M, OV},
 Labels → {"Dose (mg/kg)", "%ChE"}, X → {0, 5.1}, X → {0, 5.1}, Y → {0, 140}]
```

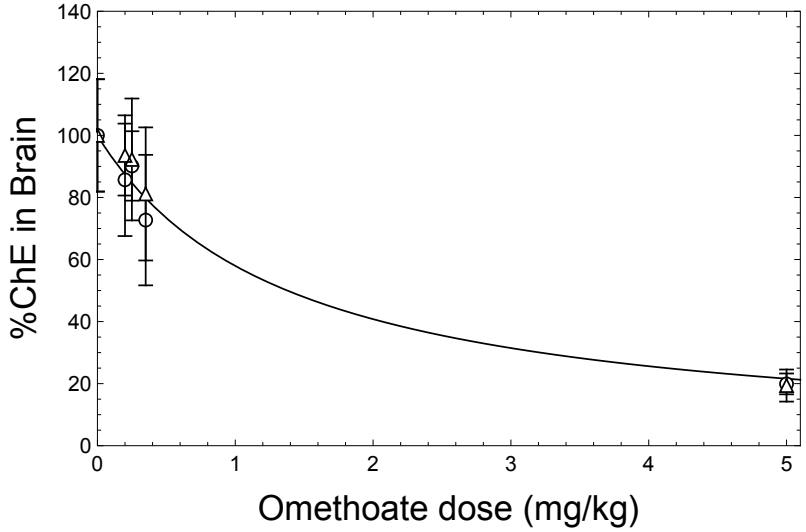


```
set
```

```
{{F, Brain}, {F, Plasma}, {F, RBC}, {M, Brain}, {M, Plasma}, {M, RBC}}
```

Brain in Female ○ , and Male △

```
PlotData[take = xyi[[{1, 2, 3, 10, 11, 12}]], Style → {M, J, M, OO, M, J, M, OA}, FitTo → {fit, x}, PlotStyle → Black,
 Labels → {"Omethoate dose (mg/kg)", "%ChE in Brain"}, X → {0, 5.1}, Y → {0, 140}]
```




```
xyfit = Join @@ take[[{3, 6}]]
```

```
{{0, 100.}, {0.2, 85.6823}, {0.25, 90.1566}, {0.35, 72.7069},
 {5, 19.9105}, {0, 100.}, {0.2, 93.5401}, {0.25, 92.2481}, {0.35, 81.137}, {5, 19.3798}}
```

```
wi = (Join @@ si[[{3, 6}]]) ^ -2
```

```
{0.00303576, 0.0245299, 0.00621855, 0.0101374, 0.0709572, 0.00888501, 0.0649638, 0.02023, 0.00972941, 0.093848}
```

```
{out = NonlinearModelFit[xyfit, 100 K/(K + x), {{K, 1.4}}, x, Weights → wi];
 fit = Normal[out], out["ParameterTable"], RSQ[xyfit, fit, x]}
```

$$\left\{\frac{137.724}{1.37724 + x},\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline \text{K} & 1.37724 & 0.126126 & 10.9196 & 1.71268\times10^{-6} \end{array},\ 0.977522\right\}$$

```
fit /. x → # & /@ {0.5, 10}
```

```
{73.3651, 12.1052}
```

```
TBL[rr = Last /@ # & /@ xyi[[{3, 12}]]]
```

```
100.  85.6823  90.1566  72.7069  19.9105
100.  93.5401  92.2481  81.137   19.3798
```

```
(Plus @@ rr) / 2
```

```
{100., 89.6112, 91.2023, 76.9219, 19.6452}
```

```
Stats[#[[4]] & /@ rr, R]
```

```
Mean     SD       CVM%     95%LCL   95%UCL   Min      Max     n
76.9219  5.96092  5.47959  23.3652  130.479  72.7069  81.137  2
```

OME metabolism data

```
metabOME = Data[in, Select → Study == 8];
take = Data[metabOME, Take → {Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical, DoseType, Dose, Measure}];
Union[Transpose[Data[take, {Report, Strain}]]]
```

```
{{Bayer AG [Hoshino T]. 1990. Report No. DMT-506, Rat (Wistar BOR WISW (Spf Cbp))}}
```

```
TBL[Data[take, Drop → Report,
  Union → {{Study, DataSet, Age, Sex}, {{Grams, Mean}, {{Chemical, Dose, DoseType, Measure}, First}}}]]
```

```
Strain  Study  DataSet  Age     Sex  Grams  Chemical       DoseType  Dose  Measure
22      8      1        Adults  M    200.   14C-Omethoate  Gavage    0.5   Recovered 14C
22      8      2        Adults  F    182.   14C-Omethoate  Gavage    0.5   Recovered 14C
22      8      3        Adults  M    211.   14C-Omethoate  Gavage    10    Recovered 14C
22      8      4        Adults  F    199.   14C-Omethoate  Gavage    10    Recovered 14C
```

```
in[[1]]
```

```
{Report, Strain, Study, DataSet, Age, Sex, Grams, Chemical,
 DoseType, Dose, DoseUnit, Days, Hours, Measure, Unit, Tissue, Average, SD, N, Page}
```

```
TBL[dat = Data[metabOME, Take → {DataSet, Sex, Grams, Dose, Hours, Tissue, Average, SD, N},
   Append → {{GM, ByMoments[Average, SD][[1]]}, {GSD, ByMoments[Average, SD][[2]]}}]]
```

DataSet	Sex	Grams	Dose	Hours	Tissue	Average	SD	N	GM	GSD
1	M	200.	0.5	2	Urine	24.3	14.337	5	24.3	14.337
1	M	200.	0.5	4	Urine	33.7	13.143	5	33.7	13.143
1	M	200.	0.5	6	Urine	18.8	6.016	5	18.8	6.016
1	M	200.	0.5	8	Urine	8.69	3.3022	5	8.69	3.3022
1	M	200.	0.5	24	Urine	8.17	1.3889	5	8.17	1.3889
1	M	200.	0.5	48	Urine	0.583	0.07579	5	0.583	0.07579
1	M	200.	0.5	48	Feces	2.26	0.859	5	2.26	0.859
1	M	200.	0.5	48	Carcass	0.318	0.007	5	0.318	0.007
1	M	200.	0.5	0.0833	Plasma	0.14883	0.0401841	5	0.14883	0.0401841
1	M	200.	0.5	0.1667	Plasma	0.58084	0.0813176	5	0.58084	0.0813176
1	M	200.	0.5	0.3333	Plasma	0.92771	0.102048	5	0.92771	0.102048
1	M	200.	0.5	0.6667	Plasma	1.18323	0.0354969	4	1.18323	0.0354969
1	M	200.	0.5	1	Plasma	1.17211	0.0234422	4	1.17211	0.0234422
1	M	200.	0.5	1.5	Plasma	1.0495	0.052475	5	1.0495	0.052475
1	M	200.	0.5	2	Plasma	0.88659	0.0709272	5	0.88659	0.0709272
1	M	200.	0.5	3	Plasma	0.64234	0.0899276	5	0.64234	0.0899276
1	M	200.	0.5	4	Plasma	0.46806	0.15914	5	0.46806	0.15914
1	M	200.	0.5	6	Plasma	0.19848	0.039696	5	0.19848	0.039696
1	M	200.	0.5	8	Plasma	0.09806	0.024515	5	0.09806	0.024515
1	M	200.	0.5	24	Plasma	0.00602	0.000301	5	0.00602	0.000301
1	M	200.	0.5	32	Plasma	0.00497	0.000497	5	0.00497	0.000497
1	M	200.	0.5	48	Plasma	0.00308	0.0001848	5	0.00308	0.0001848
2	F	182.	0.5	2	Urine	24.886	6.2215	5	24.886	6.2215
2	F	182.	0.5	4	Urine	33.452	2.67616	5	33.452	2.67616
2	F	182.	0.5	6	Urine	15.888	2.3832	5	15.888	2.3832
2	F	182.	0.5	8	Urine	8.175	0.89925	5	8.175	0.89925
2	F	182.	0.5	24	Urine	9.194	1.28716	5	9.194	1.28716
2	F	182.	0.5	48	Urine	0.951	0.26628	5	0.951	0.26628
2	F	182.	0.5	48	Feces	2.85	1.253	5	2.85	1.253
2	F	182.	0.5	48	Carcass	0.34	0.04	5	0.34	0.04
2	F	182.	0.5	0.0833	Plasma	0.20888	0.15666	5	0.20888	0.15666
2	F	182.	0.5	0.1667	Plasma	0.57456	0.19535	5	0.57456	0.19535
2	F	182.	0.5	0.3333	Plasma	0.93392	0.177445	5	0.93392	0.177445
2	F	182.	0.5	0.6667	Plasma	1.16707	0.105036	5	1.16707	0.105036
2	F	182.	0.5	1	Plasma	1.27604	0.178646	5	1.27604	0.178646
2	F	182.	0.5	1.5	Plasma	1.08102	0.0216204	5	1.08102	0.0216204
2	F	182.	0.5	2	Plasma	0.95528	0.0764224	5	0.95528	0.0764224
2	F	182.	0.5	3	Plasma	0.68399	0.0820788	5	0.68399	0.0820788
2	F	182.	0.5	4	Plasma	0.46148	0.0553776	5	0.46148	0.0553776
2	F	182.	0.5	6	Plasma	0.21324	0.0298536	5	0.21324	0.0298536
2	F	182.	0.5	8	Plasma	0.11157	0.0167355	5	0.11157	0.0167355
2	F	182.	0.5	24	Plasma	0.0084	0.002184	5	0.0084	0.002184
2	F	182.	0.5	32	Plasma	0.00626	0.0011268	5	0.00626	0.0011268
2	F	182.	0.5	48	Plasma	0.00386	0.0005018	5	0.00386	0.0005018
3	M	211.	10	2	Urine	20.159	2.62067	5	20.159	2.62067
3	M	211.	10	4	Urine	16.376	7.20544	5	16.376	7.20544
3	M	211.	10	6	Urine	18.843	2.63802	5	18.843	2.63802
3	M	211.	10	8	Urine	11.178	2.7945	5	11.178	2.7945
3	M	211.	10	24	Urine	16.162	2.4243	5	16.162	2.4243
3	M	211.	10	48	Urine	1.974	1.32258	5	1.974	1.32258
3	M	211.	10	48	Feces	4.195	1.087	5	4.195	1.087
3	M	211.	10	48	Carcass	0.301	0.046	5	0.301	0.046

3	M	211.	10	0.0833	Plasma	0.11726	0.046904	5	0.11726	0.046904
3	M	211.	10	0.1667	Plasma	0.30676	0.0705548	5	0.30676	0.0705548
3	M	211.	10	0.3333	Plasma	0.65337	0.12414	5	0.65337	0.12414
3	M	211.	10	0.6667	Plasma	1.00074	0.140104	5	1.00074	0.140104
3	M	211.	10	1	Plasma	1.11141	0.0666846	5	1.11141	0.0666846
3	M	211.	10	1.5	Plasma	0.94646	0.047323	5	0.94646	0.047323
3	M	211.	10	2	Plasma	0.78747	0.0472482	5	0.78747	0.0472482
3	M	211.	10	3	Plasma	0.62212	0.0497696	5	0.62212	0.0497696
3	M	211.	10	4	Plasma	0.50954	0.0662402	5	0.50954	0.0662402
3	M	211.	10	6	Plasma	0.36143	0.0831289	5	0.36143	0.0831289
3	M	211.	10	8	Plasma	0.199	0.03582	5	0.199	0.03582
3	M	211.	10	24	Plasma	0.00879	0.0021975	5	0.00879	0.0021975
3	M	211.	10	32	Plasma	0.00727	0.0047982	5	0.00727	0.0047982
3	M	211.	10	48	Plasma	0.00284	0.000284	5	0.00284	0.000284
4	F	199.	10	2	Urine	35.597	2.84776	5	35.597	2.84776
4	F	199.	10	4	Urine	21.418	6.21122	5	21.418	6.21122
4	F	199.	10	6	Urine	14.909	1.78908	5	14.909	1.78908
4	F	199.	10	8	Urine	8.403	2.18478	5	8.403	2.18478
4	F	199.	10	24	Urine	14.285	4.2855	5	14.285	4.2855
4	F	199.	10	48	Urine	1.238	0.42092	5	1.238	0.42092
4	F	199.	10	48	Feces	2.271	0.26	5	2.271	0.26
4	F	199.	10	48	Carcass	0.291	0.042	5	0.291	0.042
4	F	199.	10	0.0833	Plasma	0.13103	0.0183442	5	0.13103	0.0183442
4	F	199.	10	0.1667	Plasma	0.35004	0.017502	5	0.35004	0.017502
4	F	199.	10	0.3333	Plasma	0.75062	0.075062	5	0.75062	0.075062
4	F	199.	10	0.6667	Plasma	1.05118	0.0840944	5	1.05118	0.0840944
4	F	199.	10	1	Plasma	1.04884	0.115372	5	1.04884	0.115372
4	F	199.	10	1.5	Plasma	0.89046	0.133569	5	0.89046	0.133569
4	F	199.	10	2	Plasma	0.7213	0.100982	5	0.7213	0.100982
4	F	199.	10	3	Plasma	0.57964	0.086946	5	0.57964	0.086946
4	F	199.	10	4	Plasma	0.42418	0.0763524	5	0.42418	0.0763524
4	F	199.	10	6	Plasma	0.25775	0.036085	5	0.25775	0.036085
4	F	199.	10	8	Plasma	0.16095	0.0241425	5	0.16095	0.0241425
4	F	199.	10	24	Plasma	0.01115	0.0045715	5	0.01115	0.0045715
4	F	199.	10	32	Plasma	0.00725	0.0019575	5	0.00725	0.0019575
4	F	199.	10	48	Plasma	0.00425	0.0027625	5	0.00425	0.0027625

Feces & Carcass

```
TBL[fc = Data[dat, Select → Tissue =!= Urine && Tissue =!= Plasma]]
```

DataSet	Sex	Grams	Dose	Hours	Tissue	Average	SD	GM	GSD
1	M	200.	0.5	48	Feces	2.26	0.859	2.26	0.859
1	M	200.	0.5	48	Carcass	0.318	0.007	0.318	0.007
2	F	182.	0.5	48	Feces	2.85	1.253	2.85	1.253
2	F	182.	0.5	48	Carcass	0.34	0.04	0.34	0.04
3	M	211.	10	48	Feces	4.195	1.087	4.195	1.087
3	M	211.	10	48	Carcass	0.301	0.046	0.301	0.046
4	F	199.	10	48	Feces	2.271	0.26	2.271	0.26
4	F	199.	10	48	Carcass	0.291	0.042	0.291	0.042

Mean BW: ~200 g

```
Stats[Data[dat, Grams], R]
```

Mean	SD	CVM%	95%LCL	95%UCL	Min	Max	n
198.	10.5341	0.940499	194.202	201.798	182.	211.	32

Mean Fecal & Carcass % at 48 h:

```
Stats[#, R] & /@ Transpose[Partition[Data[fc, Average], 2]]
```

```
{Mean   SD        CVM%     95%LCL   95%UCL   Min   Max    n , Mean    SD         CVM%     95%LCL   95%UCL   Min    Max   n}
{2.894  0.910059  15.7232  1.44589  4.34211  2.26  4.195  4 , 0.3125  0.0214554  3.43286  0.27836  0.34664  0.291  0.34  4}
```

```
pfc48 = 2.894 + 0.3125
```

```
3.2065
```

Urine

Bayer AG (Hoshino T). 1990. Methylene-14-C-Omethoate: General Metabolism Study in the Rat. August 8, 1990. Report DMT 506. Table XXIV. Distribution of omethoate and its metabolites in urine [48 hours] after administration to male and female rats.

TstGrp	Dose*	Sex	%OME	%Urin	~AveMF	%OMEinUrine
3	0.5	M	25.86	67.75		
4	0.5	F	42.48	74.78	0.342	
7	10	M	44.56	69.19		
8	10	F	62.01	83.96	0.528	
7	10	M	45.77	71.60		
8	10	F	62.22	84.92	0.540**	

*5 rats/group

** Urine + Feces

```
pctOMEinU = {25.86, 42.48, 44.56, 62.01, 45.77, 62.22};
EV /@ Partition[pctOMEinU, 2]
```

```
{34.17, 53.285, 53.995}
```

```
TBL[udat = Data[dat, Select → Tissue == Urine]]
```

DataSet	Sex	Grams	Dose	Hours	Tissue	Average	SD	N	GM	GSD
1	M	200.	0.5	2	Urine	24.3	14.337	5	24.3	14.337
1	M	200.	0.5	4	Urine	33.7	13.143	5	33.7	13.143
1	M	200.	0.5	6	Urine	18.8	6.016	5	18.8	6.016
1	M	200.	0.5	8	Urine	8.69	3.3022	5	8.69	3.3022
1	M	200.	0.5	24	Urine	8.17	1.3889	5	8.17	1.3889
1	M	200.	0.5	48	Urine	0.583	0.07579	5	0.583	0.07579
2	F	182.	0.5	2	Urine	24.886	6.2215	5	24.886	6.2215
2	F	182.	0.5	4	Urine	33.452	2.67616	5	33.452	2.67616
2	F	182.	0.5	6	Urine	15.888	2.3832	5	15.888	2.3832
2	F	182.	0.5	8	Urine	8.175	0.89925	5	8.175	0.89925
2	F	182.	0.5	24	Urine	9.194	1.28716	5	9.194	1.28716
2	F	182.	0.5	48	Urine	0.951	0.26628	5	0.951	0.26628
3	M	211.	10	2	Urine	20.159	2.62067	5	20.159	2.62067
3	M	211.	10	4	Urine	16.376	7.20544	5	16.376	7.20544
3	M	211.	10	6	Urine	18.843	2.63802	5	18.843	2.63802
3	M	211.	10	8	Urine	11.178	2.7945	5	11.178	2.7945
3	M	211.	10	24	Urine	16.162	2.4243	5	16.162	2.4243
3	M	211.	10	48	Urine	1.974	1.32258	5	1.974	1.32258
4	F	199.	10	2	Urine	35.597	2.84776	5	35.597	2.84776
4	F	199.	10	4	Urine	21.418	6.21122	5	21.418	6.21122
4	F	199.	10	6	Urine	14.909	1.78908	5	14.909	1.78908
4	F	199.	10	8	Urine	8.403	2.18478	5	8.403	2.18478
4	F	199.	10	24	Urine	14.285	4.2855	5	14.285	4.2855
4	F	199.	10	48	Urine	1.238	0.42092	5	1.238	0.42092

```
Data[udat, Plus @@ N]
```

```
120
```

```
time = Union[Data[dat, Select → Tissue == Urine, Return → Hours]]
```

```
{2, 4, 6, 8, 24, 48}
```

```
{μij, sdij} = Transpose[Partition[Data[dat, Select → Tissue == Urine, Return → #], 6]] & /@ {Average, SD};
TBL /@ {μij, sdij}
```

$$\left\{\begin{pmatrix} 24.3 & 24.886 & 20.159 & 35.597 \\ 33.7 & 33.452 & 16.376 & 21.418 \\ 18.8 & 15.888 & 18.843 & 14.909 \\ 8.69 & 8.175 & 11.178 & 8.403 \\ 8.17 & 9.194 & 16.162 & 14.285 \\ 0.583 & 0.951 & 1.974 & 1.238 \end{pmatrix}, \begin{pmatrix} 14.337 & 6.2215 & 2.62067 & 2.84776 \\ 13.143 & 2.67616 & 7.20544 & 6.21122 \\ 6.016 & 2.3832 & 2.63802 & 1.78908 \\ 3.3022 & 0.89925 & 2.7945 & 2.18478 \\ 1.3889 & 1.28716 & 2.4243 & 4.2855 \\ 0.07579 & 0.26628 & 1.32258 & 0.42092 \end{pmatrix}\right\}$$

```
nij = {5, 5, 5, 5};
μj = MapThread[EV[#1, Weights → #2] &, {μij, Table[nij, Length[μij]]}];
sumμj = Accumulate[μj];
sumμij = Accumulate /@ Transpose[μij];
TBL[{sumμj, sdj = SD /@ Transpose[sumμij]}]
```

```
26.2355  52.472  69.582  78.6935  90.6463  91.8327
6.58607  10.6395  9.67652  8.36511  5.43345  4.94795
```

```
sdj
```

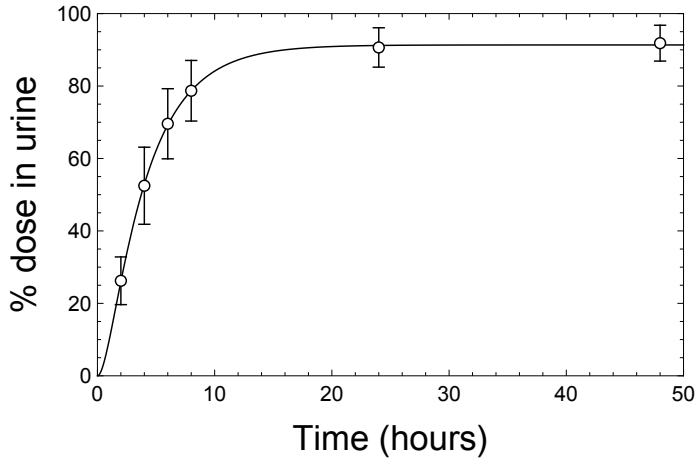
```
{6.58607, 10.6395, 9.67652, 8.36511, 5.43345, 4.94795}
```

```
fit2 = 96.1878 (-0.2794968423175797` (1 - ℯ^(-1.229091615817655` x)) + 1.229091615817655` (1 - ℯ^(-0.2794968423175797` x)));
```

```
xyi = Transpose[{time, #}] & /@ {sumμj - sdj, sumμj + sdj, sumμj}
```

```
{{{2, 19.6494}, {4, 41.8325}, {6, 59.9055}, {8, 70.3284}, {24, 85.2128}, {48, 86.8848}},
 {{2, 32.8216}, {4, 63.1115}, {6, 79.2585}, {8, 87.0586}, {24, 96.0797}, {48, 96.7807}},
 {{2, 26.2355}, {4, 52.472}, {6, 69.582}, {8, 78.6935}, {24, 90.6463}, {48, 91.8327}}}
```

```
PlotData[xyi, Style → {M, J, M, OO}, X → {0, 50}, Y → {0, 100},
 FitTo → {fit2, x}, Labels → {"Time (hours)", "% dose in urine"}, PlotStyle → Black]
```



```
xyi
```

```
{{{2, 19.6494}, {4, 41.8325}, {6, 59.9055}, {8, 70.3284}, {24, 85.2128}, {48, 86.8848}},
 {{2, 32.8216}, {4, 63.1115}, {6, 79.2585}, {8, 87.0586}, {24, 96.0797}, {48, 96.7807}},
 {{2, 26.2355}, {4, 52.472}, {6, 69.582}, {8, 78.6935}, {24, 90.6463}, {48, 91.8327}}}
```

```
sol = FullSimplify[
  DSolve[{Stomach'[t] == -King * Stomach[t], Body'[t] == King * Stomach[t] - Kur * Body[t], Urine'[t] == Kur * Body[t],
    Stomach[0] == 1, Body[0] == 0, Urine[0] == 0}, {Stomach[t], Body[t], Urine[t]}, t][[1]]]
```

$$\left\{\text{Body}[t] \to -\frac{\left(e^{-\text{King}\,t} - e^{-\text{Kur}\,t}\right)\text{King}}{\text{King} - \text{Kur}},\ \text{Stomach}[t] \to e^{-\text{King}\,t},\ \text{Urine}[t] \to \frac{\text{King} - e^{-\text{Kur}\,t}\,\text{King} + \left(-1 + e^{-\text{King}\,t}\right)\text{Kur}}{\text{King} - \text{Kur}}\right\}$$

```
Limit[Urine[t] /. sol, King → Kur]
```

$$e^{-\text{Kur}\,t}\left(-1 + e^{\text{Kur}\,t} - \text{Kur}\,t\right)$$

$$\frac{\text{King}\left(1 - e^{-\text{Kur}\,t}\right) - \text{Kur}\left(1 - e^{-\text{King}\,t}\right)}{\text{King} - \text{Kur}}$$

```
xy = Last[xyi];
{out = NonlinearModelFit[xy, A (1 - E^(-b * x)), {{A, 90}, {b, 0.08}}, x, Weights → sdj^-2];
 fit1 = fit = Normal[out], out["ParameterTable"], RSQ[xy, fit, x]}
```

$$\left\{92.0673\left(1 - e^{-0.208646\,x}\right),\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline \text{A} & 92.0673 & 1.89353 & 48.6221 & 1.07052\times10^{-6} \\ \text{b} & 0.208646 & 0.0174516 & 11.9557 & 0.000280453 \end{array},\ 0.981725\right\}$$

```
{out = NonlinearModelFit[xy, {A (King (1 - E^(-Kur x)) - Kur (1 - E^(-King x)))/(King - Kur)}, {{A, 92}, {King, 1.4}, {Kur, 0.21}}, x];
 fit2 = fit = Normal[out], out["ParameterTable"], RSQ[xy, fit, x]}
```

$$\left\{96.1878\left(-0.279497\left(1 - e^{-1.22909\,x}\right) + 1.22909\left(1 - e^{-0.279497\,x}\right)\right),\ \begin{array}{c|cccc} & \text{Estimate} & \text{Standard Error} & \text{t-Statistic} & \text{P-Value} \\ \hline \text{A} & 91.3394 & 0.381202 & 239.609 & 1.603\times10^{-7} \\ \text{King} & 1.22909 & 0.100713 & 12.2039 & 0.00118461 \\ \text{Kur} & 0.279497 & 0.00796324 & 35.0984 & 0.0000508559 \end{array},\ 0.99973\right\}$$

```
tHalf = (Log[2] / #) & /@ {0.2795, 1.22909}
```

```
{2.47995, 0.563952}
```

```
{pu48 = fit /. x → 48, pu48 + pfc48}
```

```
{92.5343, 95.7408}
```

Plasma

```
{time = Union[Data[dat, Select → Tissue == Plasma, Return → Hours]], Length[time]}
```

```
{{0.0833, 0.1667, 0.3333, 0.6667, 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48}, 14}
```

```
TBL[pdat = Data[dat, Select → Tissue == Plasma]]
```

DataSet	Sex	Grams	Dose	Hours	Tissue	Average	SD	N	GM	GSD
1	M	200.	0.5	0.0833	Plasma	0.14883	0.0401841	5	0.14883	0.0401841
1	M	200.	0.5	0.1667	Plasma	0.58084	0.0813176	5	0.58084	0.0813176
1	M	200.	0.5	0.3333	Plasma	0.92771	0.102048	5	0.92771	0.102048
1	M	200.	0.5	0.6667	Plasma	1.18323	0.0354969	4	1.18323	0.0354969
1	M	200.	0.5	1	Plasma	1.17211	0.0234422	4	1.17211	0.0234422
1	M	200.	0.5	1.5	Plasma	1.0495	0.052475	5	1.0495	0.052475
1	M	200.	0.5	2	Plasma	0.88659	0.0709272	5	0.88659	0.0709272
1	M	200.	0.5	3	Plasma	0.64234	0.0899276	5	0.64234	0.0899276
1	M	200.	0.5	4	Plasma	0.46806	0.15914	5	0.46806	0.15914
1	M	200.	0.5	6	Plasma	0.19848	0.039696	5	0.19848	0.039696
1	M	200.	0.5	8	Plasma	0.09806	0.024515	5	0.09806	0.024515
1	M	200.	0.5	24	Plasma	0.00602	0.000301	5	0.00602	0.000301
1	M	200.	0.5	32	Plasma	0.00497	0.000497	5	0.00497	0.000497
1	M	200.	0.5	48	Plasma	0.00308	0.0001848	5	0.00308	0.0001848
2	F	182.	0.5	0.0833	Plasma	0.20888	0.15666	5	0.20888	0.15666
2	F	182.	0.5	0.1667	Plasma	0.57456	0.19535	5	0.57456	0.19535
2	F	182.	0.5	0.3333	Plasma	0.93392	0.177445	5	0.93392	0.177445
2	F	182.	0.5	0.6667	Plasma	1.16707	0.105036	5	1.16707	0.105036
2	F	182.	0.5	1	Plasma	1.27604	0.178646	5	1.27604	0.178646
2	F	182.	0.5	1.5	Plasma	1.08102	0.0216204	5	1.08102	0.0216204
2	F	182.	0.5	2	Plasma	0.95528	0.0764224	5	0.95528	0.0764224
2	F	182.	0.5	3	Plasma	0.68399	0.0820788	5	0.68399	0.0820788
2	F	182.	0.5	4	Plasma	0.46148	0.0553776	5	0.46148	0.0553776
2	F	182.	0.5	6	Plasma	0.21324	0.0298536	5	0.21324	0.0298536
2	F	182.	0.5	8	Plasma	0.11157	0.0167355	5	0.11157	0.0167355
2	F	182.	0.5	24	Plasma	0.0084	0.002184	5	0.0084	0.002184
2	F	182.	0.5	32	Plasma	0.00626	0.0011268	5	0.00626	0.0011268
2	F	182.	0.5	48	Plasma	0.00386	0.0005018	5	0.00386	0.0005018
3	M	211.	10	0.0833	Plasma	0.11726	0.046904	5	0.11726	0.046904
3	M	211.	10	0.1667	Plasma	0.30676	0.0705548	5	0.30676	0.0705548
3	M	211.	10	0.3333	Plasma	0.65337	0.12414	5	0.65337	0.12414
3	M	211.	10	0.6667	Plasma	1.00074	0.140104	5	1.00074	0.140104
3	M	211.	10	1	Plasma	1.11141	0.0666846	5	1.11141	0.0666846
3	M	211.	10	1.5	Plasma	0.94646	0.047323	5	0.94646	0.047323
3	M	211.	10	2	Plasma	0.78747	0.0472482	5	0.78747	0.0472482
3	M	211.	10	3	Plasma	0.62212	0.0497696	5	0.62212	0.0497696
3	M	211.	10	4	Plasma	0.50954	0.0662402	5	0.50954	0.0662402
3	M	211.	10	6	Plasma	0.36143	0.0831289	5	0.36143	0.0831289
3	M	211.	10	8	Plasma	0.199	0.03582	5	0.199	0.03582
3	M	211.	10	24	Plasma	0.00879	0.0021975	5	0.00879	0.0021975
3	M	211.	10	32	Plasma	0.00727	0.0047982	5	0.00727	0.0047982
3	M	211.	10	48	Plasma	0.00284	0.000284	5	0.00284	0.000284
4	F	199.	10	0.0833	Plasma	0.13103	0.0183442	5	0.13103	0.0183442
4	F	199.	10	0.1667	Plasma	0.35004	0.017502	5	0.35004	0.017502
4	F	199.	10	0.3333	Plasma	0.75062	0.075062	5	0.75062	0.075062
4	F	199.	10	0.6667	Plasma	1.05118	0.0840944	5	1.05118	0.0840944
4	F	199.	10	1	Plasma	1.04884	0.115372	5	1.04884	0.115372
4	F	199.	10	1.5	Plasma	0.89046	0.133569	5	0.89046	0.133569
4	F	199.	10	2	Plasma	0.7213	0.100982	5	0.7213	0.100982
4	F	199.	10	3	Plasma	0.57964	0.086946	5	0.57964	0.086946
4	F	199.	10	4	Plasma	0.42418	0.0763524	5	0.42418	0.0763524
4	F	199.	10	6	Plasma	0.25775	0.036085	5	0.25775	0.036085
4	F	199.	10	8	Plasma	0.16095	0.0241425	5	0.16095	0.0241425
4	F	199.	10	24	Plasma	0.01115	0.0045715	5	0.01115	0.0045715
4	F	199.	10	32	Plasma	0.00725	0.0019575	5	0.00725	0.0019575
4	F	199.	10	48	Plasma	0.00425	0.0027625	5	0.00425	0.0027625

```
Data[pdat, Plus @@ N]
```

```
278
```

```
{μij, sdij} = Transpose[Partition[Data[dat, Select → Tissue == Plasma, Return → #], 14]] & /@ {Average, SD};
TBL /@ {μij, sdij}
```

```
  0.14883  0.20888  0.11726  0.13103   0.0401841  0.15666   0.046904   0.0183442
  0.58084  0.57456  0.30676  0.35004   0.0813176  0.19535   0.0705548  0.017502
  0.92771  0.93392  0.65337  0.75062   0.102048   0.177445  0.12414    0.075062
  1.18323  1.16707  1.00074  1.05118   0.0354969  0.105036  0.140104   0.0840944
  1.17211  1.27604  1.11141  1.04884   0.0234422  0.178646  0.0666846  0.115372
  1.0495   1.08102  0.94646  0.89046   0.052475   0.0216204 0.047323   0.133569
{ 0.88659  0.95528  0.78747  0.7213  , 0.0709272  0.0764224 0.0472482  0.100982  }
{ 0.64234  0.68399  0.62212  0.57964 , 0.0899276  0.0820788 0.0497696  0.086946  }
  0.46806  0.46148  0.50954  0.42418   0.15914    0.0553776 0.0662402  0.0763524
  0.19848  0.21324  0.36143  0.25775   0.039696   0.0298536 0.0831289  0.036085
  0.09806  0.11157  0.199    0.16095   0.024515   0.0167355 0.03582    0.0241425
  0.00602  0.0084   0.00879  0.01115   0.000301   0.002184  0.0021975  0.0045715
  0.00497  0.00626  0.00727  0.00725   0.000497   0.0011268 0.0047982  0.0019575
  0.00308  0.00386  0.00284  0.00425   0.0001848  0.0005018 0.000284   0.0027625
```

```
nij = Table[{5, 5}, 14]; nn = 10;
{xi, sdi} = Transpose[MapThread[(avex2i = Plus @@ ((#1 - 1) #3^2 + #1 * #2^2)) / (nn - 1);
      μ = EV[#2, Weights → #1];
      {μ, Sqrt[avex2i - nn (μ^2) / (nn - 1)]}) &, {nij, Take[#, 2] & /@ μij, Take[#, 2] & /@ sdij}]];
xyLo = Transpose[{time, #}] & /@ {xi - sdi, xi + sdi, xi};
nij = Table[{5, 5}, 14]; nn = 10;
{xi, sdi} = Transpose[MapThread[(avex2i = Plus @@ ((#1 - 1) #3^2 + #1 * #2^2)) / (nn - 1);
      μ = EV[#2, Weights → #1];
      {μ, Sqrt[avex2i - nn (μ^2) / (nn - 1)]}) &, {nij, Take[#, -2] & /@ μij, Take[#, -2] & /@ sdij}]];
xyHi = Transpose[{time, #}] & /@ {xi - sdi, xi + sdi, xi};
nij = Table[{5, 5, 5, 5}, 14]; nn = 20;
{xi, sdi} = Transpose[MapThread[(avex2i = Plus @@ ((#1 - 1) #3^2 + #1 * #2^2)) / (nn - 1);
      μ = EV[#2, Weights → #1];
      {μ, Sqrt[avex2i - nn (μ^2) / (nn - 1)]}) &, {nij, μij, sdij}]];
xy = Transpose[{time, #}] & /@ {xi - sdi, xi + sdi, xi}
```

```
{{{0.0833, 0.0658971}, {0.1667, 0.28829}, {0.3333, 0.648239}, {0.6667, 0.980407}, {1, 1.01808},
  {1.5, 0.886409}, {2, 0.721893}, {3, 0.550045}, {4, 0.370453}, {6, 0.17696}, {8, 0.0946518},
  {24, 0.00544002}, {32, 0.00380995}, {48, 0.0020838}}, {{0.0833, 0.237103}, {0.1667, 0.61781},
  {0.3333, 0.984571}, {0.6667, 1.2207}, {1, 1.28612}, {1.5, 1.09731}, {2, 0.953427}, {3, 0.714},
  {4, 0.561177}, {6, 0.33849}, {8, 0.190138}, {24, 0.01174}, {32, 0.00906505}, {48, 0.0049312}},
 {{0.0833, 0.1515}, {0.1667, 0.45305}, {0.3333, 0.816405}, {0.6667, 1.10056}, {1, 1.1521}, {1.5, 0.99186}, {2, 0.83766},
  {3, 0.632023}, {4, 0.465815}, {6, 0.257725}, {8, 0.142395}, {24, 0.00859}, {32, 0.0064375}, {48, 0.0035075}}}
```

```
sdi
```

```
{0.0856029, 0.16476, 0.168166, 0.120148, 0.134024, 0.105451, 0.115767,
 0.081978, 0.0953622, 0.0807649, 0.0477432, 0.00314998, 0.00262755, 0.0014237}
```

```
XYdata = Last[xy]
```

```
{{0.0833, 0.1515}, {0.1667, 0.45305}, {0.3333, 0.816405}, {0.6667, 1.10056}, {1, 1.1521}, {1.5, 0.99186}, {2, 0.83766},
 {3, 0.632023}, {4, 0.465815}, {6, 0.257725}, {8, 0.142395}, {24, 0.00859}, {32, 0.0064375}, {48, 0.0035075}}
```

```
{BW = 0.2, umol = 1000. (dose = 0.5 * BW / mw0)}
```

```
{0.2, 0.469065}
```

Partitioned sample variance (from Ken Bogen)

```
x1 = {3, 2.5, 6, 8, 1, 4, 3};
x2 = {13, 2.5, 16, 5, 10};
x3 = {3.4, 25, 16, 8.5, 1, 4, 3, 5, 6, 1, 11, 13, 3};
xall = Join[x1, x2, x3];
{ni = Length /@ {x1, x2, x3}, nn = Length[xall]}
```

```
{{7, 5, 13}, 25}
```

```
{μi = Mean /@ {x1, x2, x3}, μ = Mean[xall],
 σ2i = CentralMoment[#, 2] & /@ {x1, x2, x3},
 {σ2 = CentralMoment[xall, 2], Var[xall]},
 s2i = Variance /@ {x1, x2, x3},
 {s2 = Variance[xall], SD[xall]^2}}
```

```
{{3.92857, 9.3, 7.68462}, 6.956, {4.7449, 24.76, 44.9321},
 {33.5865, 33.5865}, {5.53571, 30.95, 48.6764}, {34.9859, 34.9859}}
```

```
{Variance[xall],
 avex2i = Plus @@ ((ni - 1) s2i + ni * μi^2) / (nn - 1),
 avex2i - nn (μ^2) / (nn - 1)}
```

```
{34.9859, 85.3879, 34.9859}
```

OME Data Fit

Define data {XYdata =Last[xy] = Plasma , Udata = Last[xyu] = Urine}, & variance data

```
xyP = {{{0.0833`, 0.06589705842185338`}, {0.1667`, 0.28829045197736447`}, {0.3333`, 0.6482390986351865`},
     {0.6667`, 0.9804068912283939`}, {1, 1.0180762802225924`}, {1.5`, 0.8864086338975363`}, {2, 0.7218926049002709`},
     {3, 0.550044525108011`}, {4, 0.3704527820035404`}, {6, 0.17696014676065688`}, {8, 0.09465176456512947`},
     {24, 0.0054400183626266245`}, {32, 0.0038099511931019123`}, {48, 0.0020838013121856833`}},
    {{0.0833`, 0.2371029415781466`}, {0.1667`, 0.6178095480226355`}, {0.3333`, 0.9845709013648134`},
     {0.6667`, 1.220703108771606`}, {1, 1.2861237197774074`}, {1.5`, 1.0973113661024638`}, {2, 0.9534273950997293`},
     {3, 0.714000474891989`}, {4, 0.5611772179964595`}, {6, 0.3384898532393431`}, {8, 0.19013823543487052`},
     {24, 0.011739981637373376`}, {32, 0.00906504880689809`}, {48, 0.004931198687814317`}},
    {{0.0833`, 0.1515`}, {0.1667`, 0.45305`}, {0.3333`, 0.8164049999999999`}, {0.6667`, 1.100555`},
     {1, 1.1521`}, {1.5`, 0.9918600000000001`}, {2, 0.8376600000000001`}, {3, 0.6320225`}, {4, 0.465815`},
     {6, 0.257725`}, {8, 0.142395`}, {24, 0.00859`}, {32, 0.0064375000000000005`}, {48, 0.0035075`}}};
XYPdata = Last[xy];
vXYPdata =
  {0.08560294157814662`, 0.16475954802263557`, 0.1681659013648134`, 0.12014810877160603`, 0.13402371977740743`,
   0.1054513661024637`, 0.1157673950997292`, 0.08197797489198902`, 0.09536221799645954`, 0.0807648532393431`,
   0.047743235434870517`, 0.0031499816373733763`, 0.0026275488068980882`, 0.0014236986878143 17`};

xyi = xyu = {{{2, 19.649432761756326`}, {4, 41.83252072076206`}, {6, 59.905484787038944`}, {8, 70.32838997880681`},
     {24, 85.21279999869634`}, {48, 86.88479962467622`}}, {{2, 32.821567238243674`}, {4, 63.11147927923794`},
     {6, 79.25851521296104`}, {8, 87.05861002119319`}, {24, 96.07970000130365`}, {48, 96.78070037532376`}},
    {{2, 26.235500000000002`}, {4, 52.472`}, {6, 69.582`}, {8, 78.6935`}, {24, 90.64625`}, {48, 91.83274999999999`}}};
Udata = Last[xyu];
vUdata = {6.586067238243675`, 10.639479279237936`,
    9.676515212961052`, 8.365110021193185`, 5.43345000130366`, 4.947950375323778`}^2;
```

Test & Final fits

```
{1. BW, umol = 1000. (dose = 0.5 * BW / mw0)}
```

$$\left\{1.\ BW,\ \frac{500.\ BW}{mw0}\right\}$$

Rest

Define plasma function

```
Remove[plasma]
```

$$\text{plasma}[T\_, \text{umol}\_, \text{sol}\_, i\_: \{1, 2, 3, 4, 5\}] := \frac{100 * \text{Fplasma}}{\text{umol}} \text{Append}\left[\left(\text{Blood}[\#][t]\ \&\ /@\ i\right) \text{vBlood}, \text{AlbX}[t]\right] /.\ \text{sol} /.\ t \to T$$

Test & Final fits

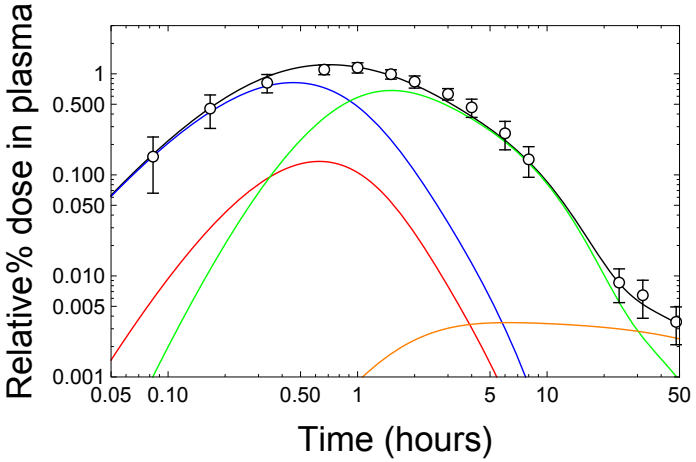
```
pino = {5.5, 22, 1.2, 1.2,  1.3, 0.07,  4, 4,  0.24, 25, 80,  0.1, 1.2};

adjo = {};

ponew

adj = adjNew
```

Dose = 0.5 mg/kg

```
TBL[RateTable]
```

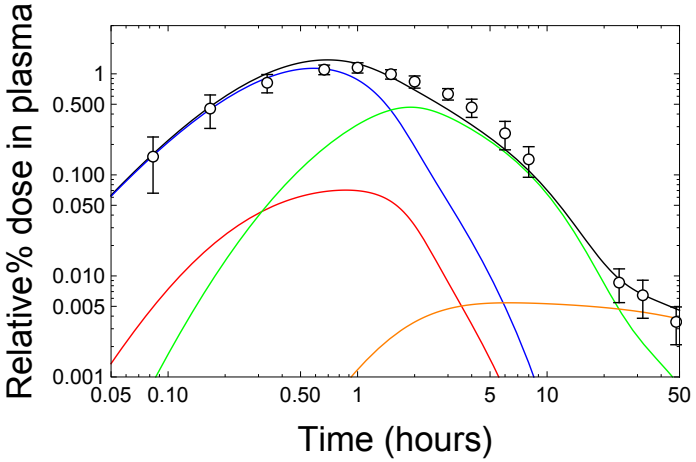
```
adj = {{Rate, {"Kstom2liv", "Kstom2intes", "Kintes2liv",
      "Kurx[2]", "Kurx[4]", "Kurx[5]",
      "FKfecar", "Fplasma",  "K35", "K45",   "Kalb", "KalbX", "Malb"},
     {0.25,  4,  22,
      1,  1 ,  0.35,
      3,    0.035,           0,  25,          1, 1, 1.4}},
    {Met, {{V24, 2}}, {0.475}},
    {Inhib, {AChE, #} & /@ {2, 5, 8, 9, 10}, 1.2065 {1, 1, 1, 1, 1}},
    {React, {AChE, #} & /@ {2, 5, 8, 9, 10}, (0.0088 / 0.019) {1, 1, 1, 1, 1}},
    {PPset, Join[  {#, 2} & /@ {2, 3, 4, 6},  {3, #} & /@ {4, 5},  {#, 4} & /@ {4}, {#, 5} & /@ {4, 6}],
       Join[{0.5,  30, 0.001, 0.001}, {30, 5},  Table[0.01, {2}], Table[0.01, {1}] ] }
   };

{BW = 0.2, umol = 1000. (dose = 0.5 * BW / mw0)};
sol = DimethoateModel[BW, 0.5 * BW, 0, 0, 50,
   Scenario → Oral, Chemical → Omethoate, Adjust → adj, Precision → 22, Goal → 7];
{PCE[5, 1][t] /. sol /. t → 2.5, utot = 1. Plus @@ (U[#][t] & /@ Range[5]) /. sol /. t → 48;
 U[2][t] / utot /. sol /. t → 48, 100 * utot / umol, 100 SUM[t] //. sol / umol /. t → # & /@ {1 / 60, 1, 2, 50}}
{73.4012, 0.33968, 91.7666, {100., 100.039, 100.079, 100.199}}

pceHat = 73.4
```

```
PlotData[xyP, Style → {M, J, M, OO}, X → {0.05, 50}, Y → {0.001, 3},
 FitTo → {Join[{Plus @@ plasma[t, umol, sol]}, plasma[t, umol, sol][[{2, 4, 5, 6}]]], t},
 Labels → {"Time (hours)", "Relative% dose in plasma"},
 PlotStyle → {Black, Blue, Red, Green, Orange}, PlotType → LogLog]
```

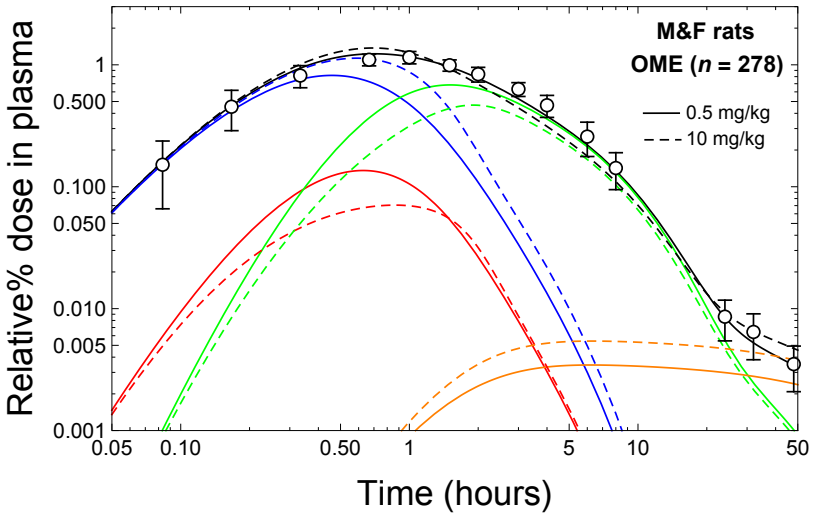



```
{BW = 0.2, umol2 = 1000. (dose = 10 * BW / mwO)};
sol2 = DimethoateModel[BW,     10 * BW, 0, 0, 50,
   Scenario → Oral, Chemical → Omethoate, Adjust → adj, Precision → 22, Goal → 7];
{PCE[5, 1][t] /. sol2 /. t → 2.5, utot2 = 1. Plus @@ (U[#][t] & /@ Range[5]) /. sol2 /. t → 48;
 U[2][t] / utot2 /. sol2 /. t → 48, 100 * utot2 / umol2, 100 SUM[t] //. sol2 / umol2 /. t → # & /@ {1 / 60, 1, 2, 50}}
{0.485958, 0.522829, 93.6798, {100., 100.05, 100.097, 100.184}}

pceHat = 12.9 (* see hyperbolic saturation fit in OME CE data section *)
```

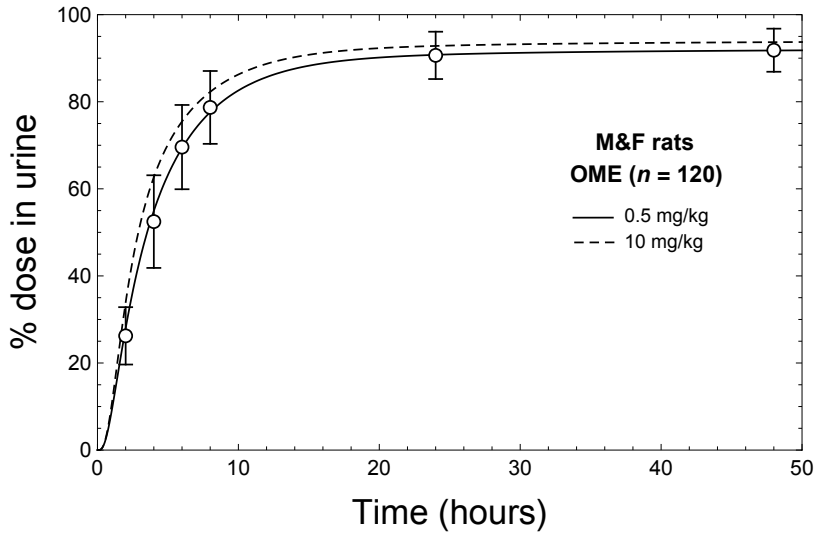
```
PlotData[xyP, Style → {M, J, M, OO}, X → {0.05, 50}, Y → {0.001, 3},
 FitTo → {Join[{Plus @@ plasma[t, umol2, sol2]}, plasma[t, umol2, sol2][[{2, 4, 5, 6}]]], t},
 Labels → {"Time (hours)", "Relative% dose in plasma"},
 PlotStyle → {Black, Blue, Red, Green, Orange}, PlotType → LogLog]
```




```
PlotData[xyP, Style → {M, J, M, OO}, X → {0.05, 50}, Y → {0.001, 3},
 FitTo → {Join[{Plus @@ plasma[t, umol, sol]}, plasma[t, umol, sol][[{2, 4, 5, 6}]],
    {Plus @@ plasma[t, umol2, sol2]}, plasma[t, umol2, sol2][[{2, 4, 5, 6}]]], t},
 Labels → {"Time (hours)", "Relative% dose in plasma"}, PlotStyle → {Black, Blue, Red, Green, Orange,
   {Black, Dashed}, {Blue, Dashed}, {Red, Dashed}, {Green, Dashed}, {Orange, Dashed}}, PlotType → LogLog]
```




```
PlotData[xyi, Style → {M, J, M, OO}, X → {0, 50}, Y → {0, 100},
 FitTo → {100/{umol, umol2} {Plus @@ (U[#][t] & /@ Range[5]) //. sol, Plus @@ (U[#][t] & /@ Range[5]) //. sol2}, t},
 Labels → {"Time (hours)", "% dose in urine"}, PlotStyle → {Black, {Black, Dashed}}]
```



Optimization: OME (not used)

DIM Data Fit

Define data {XYdata =Last[xy] = Plasma , Udata = Last[xyu] = Urine}, & variance data

```
xy10 = {{{6, 71.39052814649087`}, {12, 86.33255192227215`}, {24, 89.73220513825032`},
    {48, 91.49886680378454`}, {72, 92.80714978596468`}, {96, 93.51949168045422`}, {120, 93.98597497363033`}},
   {{6, 81.1286581668977`}, {12, 91.54820191911541`}, {24, 94.21481860555252`}, {48, 96.02906970874518`},
    {72, 96.1246702337741`}, {96, 96.21172587003286`}, {120, 96.21786171268363`}},
   {{6, 76.25959315669428`}, {12, 88.94037692069378`}, {24, 91.97351187190142`}, {48, 93.76396825626486`},
    {72, 94.46591000986939`}, {96, 94.86560877524354`}, {120, 95.10191834315698`}}};
Udata10 = Last[xy10];
vUdata10 = {4.869065010203413`, 2.607824998421636`, 2.241306733651104`,
    2.265101452480327`, 1.6587602239047003`, 1.3461170947893255`, 1.115943369526648`}^2;
```

```
xy100 = {{{6, 52.48375082613771`}, {12, 77.98455738543913`}, {24, 89.43882352500917`},
    {48, 92.00407799590975`}, {72, 93.09594663666378`}, {96, 93.49193111432515`}, {120, 93.78578134232318`}},
   {{6, 63.34274799661159`}, {12, 83.00159800897745`}, {24, 92.21956898252641`}, {48, 94.09701450900339`},
    {72, 94.62089253296698`}, {96, 94.79819822242604`}, {120, 94.9317159075499`}},
   {{6, 57.91324941137465`}, {12, 80.49307769720829`}, {24, 90.82919625376779`}, {48, 93.05054625245657`},
    {72, 93.85841958481538`}, {96, 94.1450646683756`}, {120, 94.35874862493654`}}};
Udata100 = Last[xy100];
vUdata100 = {5.429498585236945`, 2.508520311769155`, 1.390372728758624`,
    1.0464682565468229`, 0.7624729481515955`, 0.6531335540504436`, 0.57296728261336`}^2;
xyPlasmaMF = {{{0.5`, 24.862601413242604`}, {2, 3.7948181104422924`},
    {6, 3.2277763238244783`}, {24, 0.10904649742650266`}},
   {{0.5`, 32.27776323824479`}, {2, 6.237459652795952`}, {6, 8.113059408531798`}, {24, 0.10904649742650266`}}};
xyPlasma10 = {{{0.25`, 20.190996992206586`}, {0.5`, 29.38814878918402`}, {1, 17.91665693807343`},
    {2, 11.16596807339923`}, {4, 4.477453295848179`}, {6, 2.758930369628143`}, {12, 1.0158368151370654`},
    {24, 1.180614128821315`}, {48, 0.5687454591014969`}, {72, 0.3503406941552417`}, {96, 0.2012317707168626`},
    {120, 0.13560302749879463`}, {144, 0.12940983260836508`}, {168, 0.08434526933432612`}},
   {{0.25`, 34.33225172104475`}, {0.5`, 41.710167532895724`}, {1, 25.48384903767463`},
    {2, 19.14895821116852`}, {4, 14.889204647098698`}, {6, 4.961561648168246`}, {12, 3.6513532747172492`},
    {24, 3.2684829661799943`}, {48, 0.9579055048695406`}, {72, 0.8273614780509871`}, {96, 1.369037792224776`},
    {120, 0.4314387591190193`}, {144, 0.39401335503884777`}, {168, 0.613552314195291`}},
   {{0.25`, 27.261624356625667`}, {0.5`, 35.54915816103987`}, {1, 21.70025298787403`},
    {2, 15.157463142283873`}, {4, 9.683328971473438`}, {6, 3.8602460088981947`}, {12, 2.3335950449271574`},
    {24, 2.2245485475006546`}, {48, 0.7633254819855188`}, {72, 0.5888510861031144`}, {96, 0.7851347814708194`},
    {120, 0.28352089330890695`}, {144, 0.2617115938236064`}, {168, 0.3489487917648086`}}};
xyPlasma100 = {{{0.25`, 188.23775776968193`}, {0.5`, 171.3067777656402`}, {1, 105.21002542018522`},
    {2, 55.23439999144827`}, {4, 16.663219428962492`}, {6, 37.04160593210611`}, {12, 24.938497582846523`},
    {24, 15.568732016920407`}, {48, 8.4679324878851`}, {72, 5.274535404158911`}, {96, 1.9176116651778`},
    {120, 2.199051886275236`}, {144, 0.559358293446433`}, {168, 1.0747902649362517`}},
   {{0.25`, 312.0675724231123`}, {0.5`, 425.3956561521825`}, {1, 239.81309243726923`},
    {2, 96.99451041594946`}, {4, 38.29621527399486`}, {6, 93.81419097969709`}, {12, 48.64607888055748`},
```

```
    {24, 30.75422008985793`}, {48, 21.934230994623846`}, {72, 12.652708772758128`}, {96, 10.208358848649297`},
    {120, 10.406723216228471`}, {144, 6.027050151114329`}, {168, 3.7668742208004664`}},
   {{0.25`, 250.15266509639713`}, {0.5`, 298.3512169589113`}, {1, 172.51155892872723`},
    {2, 76.11445520369887`}, {4, 27.479717351478676`}, {6, 65.4278984559016`}, {12, 36.792288231702`},
    {24, 23.16147605338917`}, {48, 15.201081741254473`}, {72, 8.96362208845852`}, {96, 6.0629852569135485`},
    {120, 6.302887551251854`}, {144, 3.293204222280381`}, {168, 2.420832242868359`}}};
```

Test & Final fits

```
plasmaD[T_, umol_, sol_, i_: {1, 2, 3, 4, 5}] := Append[Blood[#][t] & /@ i, AlbX[t]/vBlood] /. sol /. t → T
```

Rest

```
varsMassConserving
```

```
{1. BW, umol = 1000. (dose = 0.5 * BW / mw0)}
```

```
{0.2, 0.469065}
```

Dose = 10 mg/kg

```
TBL[PDTableReact]
```

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.019	0.03	0.005	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.019	0.03	0.005	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.019	0.03	0.005	M;M;?
9	RBC	0.019	0	0	M;M;?
10	Plasma	0.019	0.03	0.005	M;M;?

```
1. mwD
```

```
229.26
```

In[5149]:=
```
adj = {{Rate, {"Kstom2liv", "Kstom2intes", "Kintes2liv",
      "Kurx[2]", "Kurx[4]", "Kurx[5]",      "Kurx[1]", "Kurx[3]",
      "FKfecar", "Fplasma", "K35", "K45",   "Kalb", "KalbX", "Malb"},
     {0.25,  4,  22,
      1,  1 ,  0.35,     10, 10,
      3,    1,           0.0505,  0.26 * 25,         1, 1, 23}},
    {Met, {{V12, 2}, {Km12, 2}, {V13, 2},  {V24, 2}},  {1.488, 0.5, 21.7,   0.475}},
    {Inhib, {AChE, #} & /@ {2, 5, 8, 9, 10}, 1.205 {1, 1, 1, 1, 1}},
    {React, {AChE, #} & /@ {2, 5, 8, 9, 10}, (0.0088 / 0.019) {1, 1, 1, 1, 1}},
    {PPset, Join[ {#, 2} & /@ {2, 3, 4, 6},  {3, #} & /@ {4, 5},  {#, 4} & /@ {4}, {#, 5} & /@ {4, 6}],
      Join[{0.5,  30, 0.001, 0.001}, {30, 5},  Table[0.01, {2}], Table[0.01, {1}] ] }
   };
{BW = 0.2175, umol = 1000. (dose = 10 * BW / mwD)};
sol = DimethoateModel[BW, 10 * BW, 0, 0, 200,
  Scenario → Oral, Chemical → Dimethoate, Adjust → adj, Precision → 21, Goal → 7];
o = {PCE[5, 1][t] /. sol /. t → 1, uri[T_] := ((U[#][t] & /@ Range[5] /. sol) /. t → T);
  utot = 1. Plus @@ (uu = uri[48]);
  ur = 100 * uu / utot, uTot = 100. * Plus @@ uri[120] / umol, 100 SUM[t] //. sol / umol /. t → # & /@ {1 / 60, 1, 2, 5, 50, 120}}
```

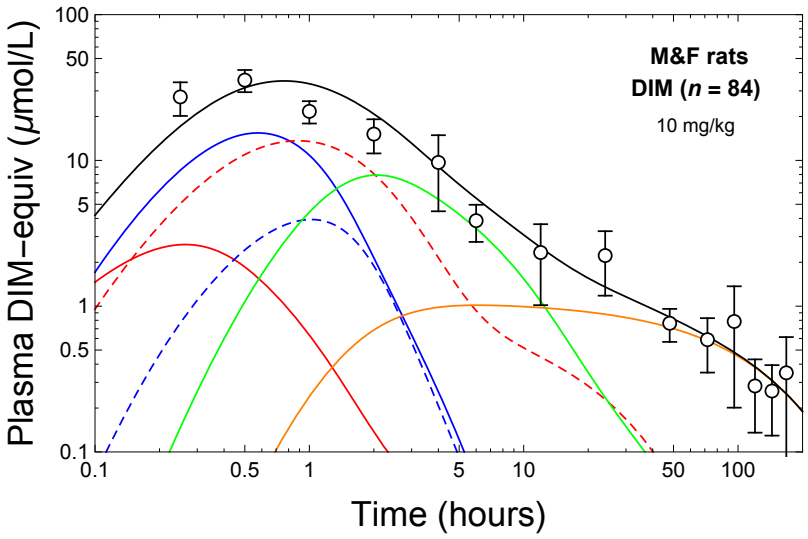
Out[5151]=
```
{45.344772674873440625, {2.42296, 20.4811, 41.0582, 7.81461, 28.2232},
 94.9417, {100., 100.022, 100.045, 100.064, 100.101, 100.139}}
```

```
pceHat = 45.4
```

In[5001]:=
```
umol {1, 1 / BW}
```

Out[5001]=
```
{9.48705, 43.6186}
```

```
PlotData[xyPlasma10, Style → {M, J, M, OO}, FitTo → {Append[xx = 0.16 * plasmaD[t, umol, sol], Plus @@ xx] //. sol, t},
 Labels → {"Time (hours)", "Plasma DIM-equiv (μmol/L)"}, X → {0.1, 200}, Y → {0.1, 100},
 PlotType → LogLog, PlotStyle → {Red, Blue, {Red, Dashed}, {Blue, Dashed}, Green, Orange, Black}]
```



In[5152]:=

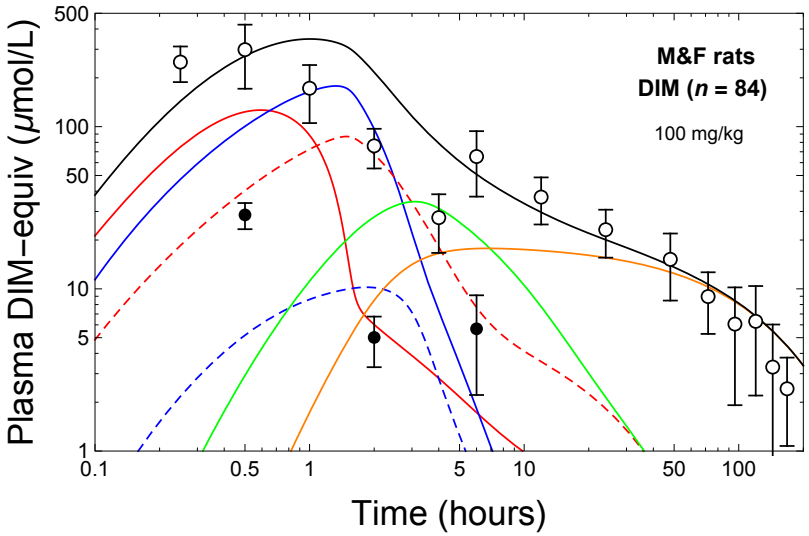
```
{BW = 0.2175, umol2 = 1000. (dose = 100 * BW / mwD)};
sol2 = DimethoateModel[BW, 100 * BW, 0, 0, 200,
   Scenario → Oral, Chemical → Dimethoate, Adjust → adj, Precision → 21, Goal → 7];
o = {PCE[5, 1][t] /. sol2 /. t → 1, uri[T_] := ((U[#][t] & /@ Range[5]) /. sol2) /. t → T};
   utot2 = 1. Plus @@ (uu2 = uri[48]);
   ur2 = 100 * uu2 / utot2, uTot2 = 100. * Plus @@ uri[120] / umol2, 100 SUM[t] //. sol2 / umol2 /. t → # & /@ {1 / 60, 1, 2, 5, 50, 120}}
```

Out[5153]= {0.4355134562821032307, {15.5607, 35.7538, 28.9606, 3.71045, 16.0145}, 95.931, {100., 100.015, 100.022, 100.023, 100.031, 100.039}}

```
xyPlasmaMF
```

```
{{{0.5, 24.8626}, {2, 3.79482}, {6, 3.22778}, {24, 0.109046}},
 {{0.5, 32.2778}, {2, 6.23746}, {6, 8.11306}, {24, 0.109046}}}
```

```
tt = Drop[First /@ xyPlasmaMF[[1]], -1];
yyt = Last /@ # & /@ xyPlasmaMF;
yy = Drop[EV /@ Transpose[yyt], -1];
sy = Drop[SD /@ Transpose[yyt], -1];
xyD = Transpose[{tt, #}] & /@ {yy - sy, yy + sy, yy};

PlotData[Join[xyPlasma100, xyD], Style → {M, J, M, OO, M, J, M, O},
 FitTo → {Append[xx = 0.16 plasmaD[t, umol, sol2], Plus @@ xx], t},
 Labels → {"Time (hours)", "Plasma DIM-equiv (μmol/L)"}, X → {0.1, 200}, Y → {1, 500},
 PlotType → LogLog, PlotStyle → {Red, Blue, {Red, Dashed}, {Blue, Dashed}, Green, Orange, Black}]
```




```
TBL /@ (tr =
    Prepend[Transpose[dd = Data[metsum, Select → Dose == #, Return → {Measure, Average}]], {Measure, Ave}] & /@ {10, 100})
```

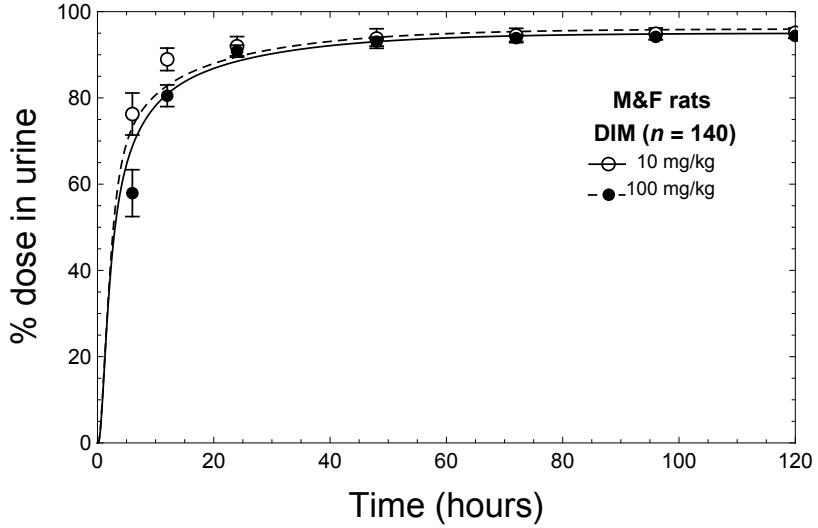
```
TBL /@ (tr2 = Data[#, Append → {Adj, Ave / (Last[Ave] / 100.), 1}] & /@ tr)
```

Measure	Ave	Adj	Measure	Ave	Adj
Omethoate	2.25	2.58621	Omethoate	3.7	4.14566
DMPT	7.	8.04598	DMPT	6.7	7.507
DMDPT	25.9	29.7701	DMDPT	21.2	23.7535
Dimethoate	1.05	1.2069	Dimethoate	1.35	1.51261
DCA	36.45	41.8966	DCA	43.8	49.0756
TotalRecovered	87	100.	TotalRecovered	89.25	100.

```
o = Data[#, Select → Measure == "DMDPT" || Measure == "DCA", Return → Adj] & /@ tr2
```

```
{{29.7701, 41.8966}, {23.7535, 49.0756}}
```

In[4996]:=
```
PlotData[Join[xy10, xy100], Style → {M, J, M, OO, M, J, M, O},
 X → {0, 120}, Y → {0, 100}, FitTo → {{100 * Plus @@ (U[#][t] & /@ Range[5]) / umol /. sol,
    100 * Plus @@ (U[#][t] & /@ Range[5]) / umol2 /. sol2}, t},
 Labels → {"Time (hours)", "% dose in urine"}, PlotStyle → {Black, {Black, Dashed}}]
```



DIM PBPK-PD model parameter summary

In[5055]:=
```
NN[x_] := Map[If[NumericQ[#] && Not[IntegerQ[#]], 1. #, #] &, x, Infinity]
```

Unscaled parameters

In[5056]:=
```
TBL[NN[RateTableScaled]]
```

Out[5056]//TableForm=

Foral	1
Finhal	0.047
Kmuc	0.02
Fplasma	1
Kstom2intes	2.
Kstom2liv	0.125
Kintes2liv	11.
Kintes2feces	0.0833333
FKfecar	0.06
Kp	0.00005
Kturn	1.17×10^7 3.66×10^6 108 600. 760 000
Pair	1 000 000 000 1 000 000 000 1 000 000 000
Kurx[1]	10
Kurx[2]	1
Kurx[3]	10
Kurx[4]	1
Kurx[5]	0.35
K35	0.00505
K45	0.65
Kair	0.0001
Kalb	0.00875
KalbX	100
Malb	0.00023

In[5111]:=
```
TBL[ParTable]
```

Out[5111]//TableForm=

Index	Tissue	Vf	Qf	Pdim	Pome
1	Fat	0.07	0.09	0.464	0.197
2	Liver	0.04	0.25	1.05	0.868
3	Rapid	0.04	0.37625	1.25	0.868
4	Slow	0.456	0.136	0.945	0.868
5	Brain	0.012	0.03	1.25	0.868
6	Skin	0.197	0.058	1.06	0.868
7	Diaphr	0.03	0.006	0.945	0.868
8	Lung	0.005	0.05375	0.874	0.864
9	RBC	0.0276	0.46	1	0.868
10	Plasma	0.0324	0.54	1	0.868

In[5115]:= TBL[MetTable]

Out[5115]//TableForm=

Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1	Fat	0	1	0	1	0	1
2	Liver	2530	535	107	155	1000	155
3	Rapid	0	1	0	1	0	1
4	Slow	0	1	0	1	0	1
5	Brain	0	1	0	1	0	1
6	Skin	0	1	0	1	0	1
7	Diaphr	0	1	0	1	0	1
8	Lung	0	1	0	1	0	1
9	RBC	0	1	0	1	0	1
10	Plasma	0	1	0	1	0	1

In[5114]:= TBL[PDTableCE]

Out[5114]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	10 200	30 000	1.94×10^6	Maxwell87=M;M;M
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	440 000	46 800	288 000	M;M;Hojring76
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	22 800	86 400	1.4×10^6	M;M;M
9	RBC	33 900	0	0	Zheng2000
10	Plasma	23 300	7850	84 000	Timchalk02;Carr01;Li05

In[5116]:= TBL[PDTableInhib]

Out[5116]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.054	0.0048	0.005	Herzsprung92=H;H;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.054	0.0048	0.005	H;H;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.054	0.0048	0.005	H;H;?
9	RBC	0.054	0	0	H;H;?
10	Plasma	0.054	0.0048	0.005	H;H;?

In[5154]:= `TBL[PDTableReact]`

Out[5154]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.019	0.03	0.005	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.019	0.03	0.005	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.019	0.03	0.005	M;M;?
9	RBC	0.019	0	0	M;M;?
10	Plasma	0.019	0.03	0.005	M;M;?

In[5162]:= `TBL[PDTableDegr]`

Out[5162]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.003	0.01	0.001	Timchalk02=T;T;T
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.003	0.01	0.000754	T;T;T
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.003	0.01	0.001	T;T;T
9	RBC	0.003	0	0	T;T;T
10	Plasma	0.003	0.01	0.001	T;T;T

In[5161]:= `TBL[PDTableAge]`

Out[5161]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.022	0.12	0	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.022	0.12	0	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.022	0.12	0	M;M;?
9	RBC	0.022	0	0	M;M;?
10	Plasma	0.022	0.12	0	M;M;?

Scaled parameters for a 217.5-g rat

In[5104]:=
```
{ii, tis} = Data[ParTable, {Index, Tissue}];
scaled[XX_, head_List] := Module[{hh = Join[{Index, Tissue}, head], nn},
  nn = Prepend[NN[Table[XX[i, j], {i, 10}, {j, Length[head]}]], head];
  Data[nn, Append → {{Index, ii, 1}, {Tissue, tis, 1}}, Take → hh]
 ]
```

In[5057]:=
```
TBL[NN[ParTableScaled]]
```

Out[5057]//TableForm=

Index	Tissue	Vf	Qf	Pdim	Pome
1	Fat	0.015225	0.00401296	0.464	0.197
2	Liver	0.0087	0.0111471	1.05	0.5
3	Rapid	0.0087	0.0167764	1.25	30
4	Slow	0.09918	0.00606403	0.945	0.001
5	Brain	0.00261	0.00133765	1.25	0.868
6	Skin	0.0428475	0.00258613	1.06	0.001
7	Diaphr	0.006525	0.000267531	0.945	0.868
8	Lung	0.0010875	0.00239663	0.874	0.864
9	RBC	0.006003	0.0205107	1	0.868
10	Plasma	0.007047	0.0240778	1	0.868

In[5097]:=
```
TBL[scaled[PP, {Pdim, Pome, Pdca, Ptmpt, Pother}]]
```

Out[5097]//TableForm=

Index	Tissue	Pdim	Pome	Pdca	Ptmpt	Pother
1	Fat	0.464	0.197	0.197	0.197	0.197
2	Liver	1.05	0.5	0.868	0.868	0.868
3	Rapid	1.25	30	0.868	30	5
4	Slow	0.945	0.001	0.868	0.01	0.01
5	Brain	1.25	0.868	0.868	0.868	0.868
6	Skin	1.06	0.001	0.868	0.868	0.01
7	Diaphr	0.945	0.868	0.868	0.868	0.868
8	Lung	0.874	0.864	0.864	0.864	0.864
9	RBC	1	0.868	0.868	0.868	0.868
10	Plasma	1	0.868	0.868	0.868	0.868

In[5167]:=
```
TBL[Data[scaled[CE0, {AChE, BChE, CaE}],
  Replace → {{AChE, AChE * Kturn[[1]]/VV[Index]}, {BChE, BChE * Kturn[[2]]/VV[Index]}, {CaE, CaE * Kturn[[3]]/VV[Index]}}]]
```

Out[5167]//TableForm=

Index	Tissue	AChE	BChE	CaE
1	Fat	0	0	0
2	Liver	10 200.	30 000.	1.94×10^6
3	Rapid	0	0	0
4	Slow	0	0	0
5	Brain	440 000.	46 800.	288 000.
6	Skin	0	0	0
7	Diaphr	0	0	0
8	Lung	22 800.	86 400.	1.4×10^6
9	RBC	33 900.	0	0
10	Plasma	23 300.	7850.	84 000.

In[5156]:=
```
TBL[Data[scaled[Kinhib, {AChE, BChE, CaE}],
  Replace → {{AChE, AChE * VV[Index]}, {BChE, BChE * VV[Index]}, {CaE, CaE * VV[Index]}}]]
```

Out[5156]//TableForm=

Index	Tissue	AChE	BChE	CaE
1	Fat	0	0	0
2	Liver	0.06507	0.0048	0.005
3	Rapid	0	0	0
4	Slow	0	0	0
5	Brain	0.06507	0.0048	0.005
6	Skin	0	0	0
7	Diaphr	0	0	0
8	Lung	0.06507	0.0048	0.005
9	RBC	0.06507	0	0
10	Plasma	0.06507	0.0048	0.005

In[5157]:=
```
TBL[scaled[Kreact, {AChE, BChE, CaE}]]
```

Out[5157]//TableForm=

Index	Tissue	AChE	BChE	CaE
1	Fat	0	0	0
2	Liver	0.0088	0.03	0.005
3	Rapid	0	0	0
4	Slow	0	0	0
5	Brain	0.0088	0.03	0.005
6	Skin	0	0	0
7	Diaphr	0	0	0
8	Lung	0.0088	0.03	0.005
9	RBC	0.0088	0	0
10	Plasma	0.0088	0.03	0.005

In[5110]:=
```
TBL[scaled[Kage, {AChE, BChE, CaE}]]
```

Out[5110]//TableForm=

Index	Tissue	AChE	BChE	CaE
1	Fat	0	0	0
2	Liver	0.022	0.12	0
3	Rapid	0	0	0
4	Slow	0	0	0
5	Brain	0.022	0.12	0
6	Skin	0	0	0
7	Diaphr	0	0	0
8	Lung	0.022	0.12	0
9	RBC	0.022	0	0
10	Plasma	0.022	0.12	0

Rat PBPK/PD model

References

Model definition

RBC vs Plasma

Mass M in Blood is divided into free (F) and plasma-bound (1–F) fractions, yielding masses M F and M(1–F), respectively. Blood is divided into RBC and Plasma fractions, approximated by h (hematocrit) and (1-h), respectively (a better approximation would reduce h by 5–10% to account for incomplete RBC packing). Thus, the fraction of M in RBCs is h F M, and that in RBCs is (1–h)F M [free] + (1–F)M [bound] = (1–h F)M, respectively. The corresponding fraction of all M contained in Plasma that is free (unbound) is (1–h)F M/(F M) = 1–h = the fraction of Blood that is Plasma.

Model parameter notation

GENERIC
BW = body weight
C = BW-correction factor
K = 1st-order mass-transfer rate
Px = tissue:blood partition coeff. for chemical x; OR = blood:air partition coeff. if x = Blood
Vfc = volume (liters = kg; entered as fraction BW)
Qf = flow (L/hour; entered as fraction of QC, except for Blood)
QCc = scaled Qcardiac = Q[Blood] in L/hr/[(kg BW)**0.75]

MVc = scaled minute volume in L/hr/[(kg BW)**0.75]
…

TISSUES
C = Cardiac
F = fat
R = richly perfused
L = liver
BR or Br = brain
S = slowly perfused
BL = blood
L = lung
Sk = skin
D = diaphragm
hematocrit = [red blood cell (RBC)]:TotalBlood volume ratio; rest = Plasma
SP = ?? (Central SC = what? Subcutaneous?)
PS = ?? (Peripheral SC = what?)
PL = plasma? (what is KPL?)

ENZYMES
AChE = CE = acetylcholinesterase
BuChE = BE = butyrylcholinesterase
CaE = CR = carboxylesterase

CONSTANTS
VCHA = rat inhalation chamber volume correction factor
vX = volume (mL) of X = Blood, Plasma, or RBC (estimated for blood per Lee and Blaufox 1985)
wBlood = blood weight (kg)
VV[i] = volume (V)of the ith compartment, i = 1,...,9 (liters, L)
PP[i,j] = tissue:blood coefficient (P) for metabolite j in compartment i = 1,...,9 (L blood per L tissue)
except: PP[9,j] = blood:air partition coeff. for metab j
QQ[i] = flow rate (Q) of the ith compartment, i = 1,...,9 (L/hour)
Qc = QQ[All] = cardiac output (L/hour)
Qresp = inhalation rate or minute volume (L/hour)

Qalv = 0.67*Qresp (L/hour) (see U.S. EPA 2006, Table 3-3)

Vmax = maximum rate of Michaelis-Menten metabolism (mmol/hour) = Vmaxc x BW
Vmaxc = maximum rate of Michaelis-Menten metabolism (mmol/hr/kg)
Km = Michaelis (affinity) constant (mmol per L venous blood exiting liver)
Kp = dermal “permeability constant” (cm/hour)
Kf = rate of loss from GI to feces (per hour)
Foral= fraction of ingested DIM and OME absorbed (=1 by default)
Finhal = fraction deposited in mucus transported to Stomach

DimethoateModel[BW, DOSE, 0, 0, 0, 75, Scenario→Oral, Foral→a, TOralPulse→1]

DimethoateModel notation

BW = body weight (kg)
PP[i,m] = tissue:blood partition coef for metabolite j in compartment i
MM[i,m][t] = mass (mmol) of metabolite j in compartment i at time t measured in hours
i=1,...,10 = mmol metab m in {Fat, Liver, Rich/Rapid, Slow, Brain, Skin, Diaphr, Lung, Blood}
m=1,...,4 = {Dimethoate, Omethoate, DCA, DMPT}
CA[t] = arterial (assumed also to be average venous) blood concentration at time t (umol/L)
CV[t] = arterial (assumed also to be average venous) blood concentration at time t (umol/L)
Ingest= oral dose (mg)
AS: 1 Tp-length pulse to Stomach (mg) (Oral), or 1 such pulse per hour for 12 hours/day (OralDaily)
Tp = 1/3 by default, reset using OralPulseDuration → Tp
Cair = air concentration (ug/L)
Dermal = dermally applied dose (in mg, at a known [but not specified] initial dermal load L in mg/cm2)
Kcar = carcas accumulation rate
Kfec = fecal elimination rate
NOralPulses = # oral pulses/Trep/day using Scenario → OralDaily;
Trep = duration of each replicated pulse/off-cycle = 1 hour*, or specify via NOralPulses→{Npulses, Trep}
* Trep is constrained to be ≥ TOralPulse
TOralPulse = duration of each daily oral pulse using Scenario →Oral or →OralDaily

MakePars (define DEFAULT model parameters) (Evaluate this & SetPars together) <---------- Pars

```
skinVolrat = EV[{15.8, 23.6}] (* EPA 2006 *)
19.7

Remove[MakePars]

MakePars[ss_: 1] := Module[{o},
  Clear[ParTable, RateTable, MetTable, PDTableCE, PDTableDegr,
                        PDTableInhib, PDTableReact, PDTableAge, o];
  Clear[Index, Tissue, CA,
   Fat, Liver, Rapid, Slow, Brain, Skin, Diaphr, Lung,
   Mucous, Stomach, Intest, Feces, Carcass, Exhaled, Air,
    V12,  Km12,  V13, Km13,  V34, Km34,
   AChE,  BChE,  CE, CEX, CE0, PCE, CERefs, Kdegr,  Kinhib,
   par, vBlood, vPlasma, vRBC, wBlood, Qresp, Qalv, Qc, VV, QQ, MM,
   Foral, Finhal, Kmuc, Kstom2intes, Kstom2liv, Kintes2liv, Kintes2feces,
   Pair, Kurx, K35, K45, FKfecar, Fplasma, Kalb, KalbX, Malb,
   Kp, Kage,  Kreact, RdegrBu2A, RdegrCa2A, RinhibBu2A, RinhibCa2A, Kturn,
   Kair
  ];
  o = {vBlood, vPlasma, vRBC, wBlood, Qresp, Qalv, Qc};
  PkPars = TBL[Transpose[{ToString /@ o, 1. o}]];

(* MW of Dimethoate, Omethoate, DCA in g/mol; Free = unbound fraction *)
  {mwD, mwO, mwDCA} = {22 926, 21 319, 21 621} / 100;
  {MVc,  Vdca, Vdmpt, Free} = {114,  427, 584,  997} / 1000;
  {QCc, hematocrit} = {14, 46} / 100 ;
  hc = hematocrit;
  fLungAllRapid = 0.005 / .04;
  {qLung, qRapid} = {fLungAllRapid, 1 - fLungAllRapid} * 0.43;
```

```
ParTable =
 {Index, Tissue,     Vf,       Qf,     Pdim,   Pome,
  1,     Fat,       0.070,    0.090,   0.464,   0.197,
  2,     Liver,     0.040,    0.250,   1.050,   0.868,
  3,     Rapid,     0.040,    qRapid, 1.250,   0.868,
  4,     Slow,      0.456,    0.000,   0.945,   0.868,
  5,     Brain,     0.012,    0.030,   1.250,   0.868,
  6,     Skin,      0.197,    0.058,   1.060,   0.868,
  7,     Diaphr,   0.030,    0.006,   0.945,   0.868,
  8,     Lung,      0.005,     qLung,   0.874,  0.864,
  9,     RBC,       0.060 hc,    hc,       1,   0.868,
  10,    Plasma,   0.060 (1 - hc), (1 - hc), 1,  0.868
 };
ParTable = Partition[ParTable, 6];
QfSlow = Data[ParTable, 1 - Plus @@ Take[Qf, 8]];
TBL[
 ParTable = Data[ParTable, Replace → {{Qf, If[Tissue === Slow, QfSlow, 1. Qf]}, {Pome, If[Index > 1, ss, 1] Pome}}]];
(* Assumes dry rat bone = 100% - ~91% = ~9% of BW <--- EPA 2006 *)

(* F = fraction, K = rate (1/hr)  *)
RateTable = {
  {Foral, 1}, {Finhal, 0.047`}, {Kmuc, 2 / 100}, {Fplasma, 1},
  {Kstom2intes, 0.5}, {Kstom2liv, 0.5}, {Kintes2liv, 0.5}, {Kintes2feces, 1 / 12},
  {FKfecar, 1 / 50},
  {Kp, 1 / 20 000},
  (* Turnover rates = substrate hydrolysis/hr/active {AChE,BChE,CaE} site) (Maxwell 1987)*)
  {Kturn, {11.7, 3.66, 0.1086} 10^6},
  (* Metab-specific blood:air partition coefs & Urinary excretion rates [see MetTable] *)
  {Pair, {760 000, 10^9, 10^9, 10^9}},
  (* DIM, OME, DCA, DMPT+DMDPT, Other *)
  {Kurx[1], 1}, {Kurx[2], 1}, {Kurx[3], 1}, {Kurx[4], 1}, {Kurx[5], 1},
```

```
  {K35, 1/10}, {K45, 1/10},
  {Kair, 10^-4}, {Kalb, 0.00875}, {KalbX, 100}, {Malb, 10^-5}
 };
RateTable = {ToString[#[[1]]], #[[2]]} & /@ RateTable;
RatePars = First /@ RateTable;

MetTable =
 (* METABOLITES m=1...5 = {DIM, OME, DCA, DMPT, Other}                *)
 (* Vmaxc = umol/hr/kg ; Blood = RBC activity                         *)
 (* Km = umol/L venous blood exiting tissue                           *)
 (* 1 to 2: DIM oxidation  to OME in liver; Burratti et al 2007       *)
 (* 1 to 3: DIM hydrolysis to DCA in liver; Uchida et al 1964         *)
 (* 2 to 4: OME hydrolysis to DMPT; to be estimated                   *)
 (* MPPGL=45500 mg MSP/kg liver (Lipscomb& Poet 2008;45 mg/g for rat) *)
(* MPHOML=122040 mg protein/kg liver (for homogenate;Beyer 1983)     *)
 {Index, Tissue,   V12, Km12,   V13,   Km13,  V24, Km24,
  1,     Fat,      0,      1,     0,    1,    0,     1,
  2,     Liver,   2530,  535,   107,  155, 1000,  155,
  3,     Rapid,    0,      1,     0,    1,    0,     1,
  4,     Slow,     0,      1,     0,    1,    0,     1,
  5,     Brain,    0,      1,     0,    1,    0,     1,
  6,     Skin,     0,      1,     0,    1,    0,     1,
  7,     Diaphr,   0,      1,     0,    1,    0,     1,
  8,     Lung,     0,      1,     0,    1,    0,     1,
  9,     RBC,      0,      1,     0,    1,    0,     1,
  10,    Plasma,   0,      1,     0,    1,    0,     1
 };
MetTable = Partition[MetTable, 8];

PDTableCE = (* ChE activities (umol/hr/kg tissue):                    *)
  (* AChE = acetylcholinesterase; "Blood" means RBC here             *)
```

```
    (* BChE = BuChE = butyrylcholinesterase                                    *)
    (* CaE = carboxylesterase                                                  *)
   {Index, Tissue,  AChE,   BChE,   CaE,      Refs,
    1,     Fat,     0,      0,     0,         "",
    2,     Liver,   10200,  30000, 1.94 * 10^6, "Maxwell87=M;M;M",
    3,     Rapid,   0,      0,      0,         "",
    4,     Slow,    0,      0,      0,         "",
    5,     Brain,   440000, 46800, 288000,    "M;M;Hojring76",
    6,     Skin,    0,      0,      0,         "",
    7,     Diaphr,  0,      0,      0,         "",
    8,     Lung,    22800,  86400, 1.4 * 10^6, "M;M;M",
    9,     RBC,     33900,  0,     0 ,        "Zheng2000",
    10,    Plasma,  23300,  7850,  84000,     "Timchalk02;Carr01;Li05"
   };

PDTableInhib = (* Kinhib bimolecular inhibition constants (L tissue/[umol hr]) *)
   {Index, Tissue,  AChE,   BChE,    CaE,      Refs,
    1,     Fat,     0,      0,       0,         "",
    2,     Liver,   0.054,  0.0048,  0.005,    "Herzsprung92=H;H;?",
    3,     Rapid,   0,      0,       0,         "",
    4,     Slow,    0,      0,       0,         "",
    5,     Brain,   0.054,  0.0048,  0.005,    "H;H;?",
    6,     Skin,    0,      0,       0,         "",
    7,     Diaphr,  0,      0,       0,         "",
    8,     Lung,    0.054,  0.0048,  0.005,    "H;H;?",
    9,     RBC,     0.054,  0,       0 ,        "H;H;?",
    10,    Plasma,  0.054,  0.0048,  0.005,    "H;H;?"
   };

PDTableReact = (* Kreact reactivation rates (1/hr) *)
   {Index, Tissue,  AChE,   BChE,    CaE,      Refs,
```

```
   1,     Fat,     0,      0,       0,        "",
   2,     Liver,   0.019,  0.030,   0.005,    "Mason2000=M;M;?",
   3,     Rapid,   0,      0,       0,        "",
   4,     Slow,    0,      0,       0,        "",
   5,     Brain,   0.019,  0.030,   0.005,    "M;M;?",
   6,     Skin,    0,      0,       0,        "",
   7,     Diaphr,  0,      0,       0,        "",
   8,     Lung,    0.019,   0.030,   0.005,    "M;M;?",
   9,     RBC,     0.019,   0,       0 ,       "M;M;?",
   10,    Plasma,  0.019,   0.030,   0.005,    "M;M;?"
  };

 PDTableDegr = (* Kdegr degradation (1/hr)                          *)
  {Index, Tissue,  AChE,   BChE,   CaE,      Refs,
   1,     Fat,     0,      0,     0,        "",
   2,     Liver,   0.003,  0.01,   0.001,    "Timchalk02=T;T;T",
   3,     Rapid,   0,      0,     0,        "",
   4,     Slow,    0,      0,     0,        "",
   5,     Brain,   0.003,  0.01,   0.000754, "T;T;T",
   6,     Skin,    0,      0,     0,        "",
   7,     Diaphr,  0,      0,     0,        "",
   8,     Lung,    0.003,   0.01,  0.001,    "T;T;T",
   9,     RBC,     0.003,   0,     0 ,       "T;T;T",
   10,    Plasma,  0.003,   0.01,  0.001,    "T;T;T"
  };

PDTableAge = (* Kage bimolecular inhibition constants (1/hr) *)
   {Index, Tissue,  AChE,   BChE,    CaE,   Refs,
    1,     Fat,     0,      0,       0,     "",
    2,     Liver,   0.022,  0.120,   0,     "Mason2000=M;M;?",
    3,     Rapid,   0,      0,       0,     "",
```

```
    4,     Slow,    0,      0,       0,     "",
    5,     Brain,   0.022,  0.120,   0,    "M;M;?",
    6,     Skin,    0,      0,       0,    "",
    7,     Diaphr,  0,      0,       0,    "",
    8,     Lung,    0.022,  0.120,   0,    "M;M;?",
    9,     RBC,     0.022,  0,       0 ,   "M;M;?",
    10,    Plasma,  0.022,  0.120,   0,    "M;M;?"
   };

{PDTableCE, PDTableDegr, PDTableInhib, PDTableReact, PDTableAge} =
   Partition[#, 6] & /@ {PDTableCE, PDTableDegr, PDTableInhib, PDTableReact, PDTableAge};
 ]

MakePars[];
(* Assumes dry rat bone = 100% - ~91% = ~9% of BW <--- EPA 2006 *)
{(vf = Data[ParTable, Vf]), Plus @@ vf, Plus @@ Data[ParTable, Qf]}
{{0.07, 0.04, 0.04, 0.456, 0.012, 0.197, 0.03, 0.005, 0.0276, 0.0324}, 0.91, 2.}

(* Assumes dry rat bone = 100% - ~91% = ~9% of BW <--- EPA 2006 *)
Plus @@ Data[ParTable, Qf] - 1
1.

{fLungAllRapid = 0.005 / .04, {qLung, qRapid} = {fLungAllRapid, 1 - fLungAllRapid} * 0.43}
{0.125, {0.05375, 0.37625}}
```

```
ShowPars := TBL /@ {ParTable, MetTable, PDTableCE, PDTableDegr, PDTableInhib, PDTableReact, PDTableAge, RateTable};
TBL[tissues = Transpose[Data[PDTableCE, {Index, Tissue}]]]
```

```
1  Fat
2  Liver
3  Rapid
4  Slow
5  Brain
6  Skin
7  Diaphr
8  Lung
9  RBC
10 Plasma
```

```
ShowPars
```

Index	Tissue	Vf	Of	Pdim	Pome	Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1	Fat	0.07	0.09	0.464	0.197	1	Fat	0	1	0	1	0	1
2	Liver	0.04	0.25	1.05	0.868	2	Liver	2530	535	107	155	1000	155
3	Rapid	0.04	0.37625	1.25	0.868	3	Rapid	0	1	0	1	0	1
4	Slow	0.456	0.136	0.945	0.868	4	Slow	0	1	0	1	0	1
5	Brain	0.012	0.03	1.25	0.868	5	Brain	0	1	0	1	0	1
6	Skin	0.197	0.058	1.06	0.868	6	Skin	0	1	0	1	0	1
7	Diaphr	0.03	0.006	0.945	0.868	7	Diaphr	0	1	0	1	0	1
8	Lung	0.005	0.05375	0.874	0.864	8	Lung	0	1	0	1	0	1
9	RBC	0.0276	0.46	1	0.868	9	RBC	0	1	0	1	0	1
10	Plasma	0.0324	0.54	1	0.868	10	Plasma	0	1	0	1	0	1

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	10 200	30 000	1.94×10^6	Maxwell87=M;M;M
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	440 000	46 800	288 000	M;M;Hojring76
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	22 800	86 400	1.4×10^6	M;M;M
9	RBC	33 900	0	0	Zheng2000
10	Plasma	23 300	7850	84 000	Timchalk02;Carr01;Li05

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.003	0.01	0.001	Timchalk02=T;T;T
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.003	0.01	0.000754	T;T;T
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.003	0.01	0.001	T;T;T
9	RBC	0.003	0	0	T;T;T
10	Plasma	0.003	0.01	0.001	T;T;T

,

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.054	0.0048	0.005	Herzsprung92=H;H;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.054	0.0048	0.005	H;H;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.054	0.0048	0.005	H;H;?
9	RBC	0.054	0	0	H;H;?
10	Plasma	0.054	0.0048	0.005	H;H;?

,

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.019	0.03	0.005	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.019	0.03	0.005	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.019	0.03	0.005	M;M;?
9	RBC	0.019	0	0	M;M;?
10	Plasma	0.019	0.03	0.005	M;M;?

,

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.022	0.12	0	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.022	0.12	0	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.022	0.12	0	M;M;?
9	RBC	0.022	0	0	M;M;?
10	Plasma	0.022	0.12	0	M;M;?

,

Foral	1
Finhal	0.047
Kmuc	$\frac{1}{50}$
Fplasma	1
Kstom2intes	0.5
Kstom2liv	0.5
Kintes2liv	0.5
Kintes2feces	$\frac{1}{12}$
FKfecar	$\frac{1}{50}$
Kp	$\frac{1}{20\,000}$
Kturn	1.17×10^7 3.66×10^6
Pair	$\frac{108\,600.}{760\,000}$ $1\,000\,000\,000$ $1\,000\,000\,000$ $1\,000\,000\,000$
Kurx[1]	1
Kurx[2]	1
Kurx[3]	1
Kurx[4]	1
Kurx[5]	1
K35	$\frac{1}{10}$
K45	$\frac{1}{10}$
Kair	$\frac{1}{10\,000}$
Kalb	0.00875
KalbX	100
Malb	$\frac{1}{100\,000}$

SetPars (Initialize & [if/as needed] adjust DEFAULT model parameters) <---------- Set

```
Remove[SetPars]
```

In[5134]:=
```
TBL[PDTableReact]
```

Out[5134]//TableForm=

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.019	0.03	0.005	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.019	0.03	0.005	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.019	0.03	0.005	M;M;?
9	RBC	0.019	0	0	M;M;?
10	Plasma	0.019	0.03	0.005	M;M;?

```
Options[SetPars] = {Adjust → {{False}}, PPome → 1, Species → Rat};

SetPars[bwKG_, options___Rule] := Module[
       {bw, Rz, xx, fix, ρ = 1058 / 1000 (*g/mL for blood*), species,
        par, o, o1, adjust, sel, fadj, com, tr, new, adj, ii, adJ,
        rateTable, parTable, metTable, pdTableCE, pdTableDegr, pdTableInhib,
        pdTableReact, pdTableAge, ppome},

   adjust =  Adjust /. {options} /. Options[SetPars];
   ppome =   PPome /. {options} /. Options[SetPars];
   species = Species /. {options} /. Options[SetPars];

   ClearAll[BW, Index, Tissue, Vmax, Km, vPlasma, vRBC, wBlood, CA,
    Fat, Liver, Rapid, Slow, Brain, Skin, Diaphr, Lung, Feces, Intest, Exhaled,
    Mucous, Stomach, Intest, Feces, Carcass, Exhaled, Air,
    V12, Km12, V13, Km13, V34, Km34,
    CE, CEX, CE0, PCE, AChE, BChE, CaE, ChERefs, Kdegr, Kinhib,
    Qresp, Qalv, Qc, VV, QQ, PP, MM,
    Foral, Finhal, Kmuc, Kstom2intes, Kstom2liv, Kintes2liv, Kintes2feces,
    Pair, Kurx, K35, K45, FKfecar, Fplasma, Kalb, KalbX, Malb,
    Kp, Kage, Kreact, RdegrBu2A, RdegrCa2A, RinhibBu2A, RinhibCa2A, Kturn,
    Kair, ParTableScaled, MetTableScaled, RateTableScaled, sumQQ
   ];

   adJ = {Rate, PPset, Par, Met, CE, Degr, Inhib, React, Age};
   If[Not[adjust === {{False}}],
    If[Length[adjust] == 3, If[MemberQ[adJ, adjust[[1]]], adjust = {adjust}]];
    o1 = First /@ adjust;
    If[Not[SubsetQ[adJ, o1]] || Max[Last /@ Tally[o1]] > 1,
     Return["DimethoateModel: Bad Adjust option"]]
   ];
```

```
MakePars[ppome];

(*********************************************************************)
(***NOTE: Human Blood vol=~54.5% plasma,45% red blood cells (RBCs), ***)
(***and 0.7% white blood cells (WBCs)                               ***)
(*  CE[i,j]: tissue i, AChE,BuChE,CaE (j=1,2,3);  Kdegr[j],Kinhib[j] *)
(*********************************************************************)
(* QQ rates here defined in L/hour, Vmax in mmol/h, Km in mmol/L     *)
Rz[x_] := Rationalize[x, 0];
xx[s_Symbol] := ToExpression[StringJoin @@ (ToString /@ {s, s})];
fix[rate_, k_] := Module[{n = Length[rate], r = rate},
  If[n == 0, r = {r}; n = 1];
  If[n ≤ k, Join[r, Table[Last[r], {k - n}]], Take[r, k]]
 ];
bw = BW = Rz[bwKG];

Qc =    Rz[QCc * bw^(3/4)];
Qresp = Rz[MVc * bw^(3/4)];
Qalv =  Rz[(67/100) Qresp];

(* Define rates and other constants (e.g., RdegrBu2A & RdegrCa2A) *)
rateTable = RateTable;
sel = Select[adjust, #[[1]] === Rate &];
If[Length[sel] == 1, adj = sel[[1]];
 o = Data[Prepend[RateTable, {Rate, Value}]];
 tr = Transpose[adj[[{2, 3}]]];
 com = {#, 1} & /@ Complement[rates = Data[o, Rate], adj[[2]]];
 new = Prepend[If[com === {}, rates, Join[tr, com]], {Rate, Fadj}];
 fadj[rate_] := Data[new, Select → Rate === rate, Return → Fadj][[1]];
 new = Data[o, Append → {{Fadj, fadj[Rate]}, {Vadj, Fadj * Value}}];
 rateTable = Rest[Data[new, Take → {Rate, Vadj}]]
```

```
];
RateTableScaled = rateTable;
Set @@ {ToExpression[Transpose[rateTable][[1]]], Rz[Transpose[rateTable][[2]]]};
(*Print[Transpose[rateTable]];
Print[ToExpression[Transpose[rateTable][[1]]]];
Return[rateTable];*)

(* Define PBPK parameters *)
parTable = ParTable;
sel = Select[adjust, #[[1]] === Par &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
  o = {par, If @@ {Index == ii, fadj * par, par}};
  parTable = Data @@ {parTable, Replace → o}, {i, Length[tr]}]
];
par = Rz[parTable];
Set @@ Data[par, {VV /@ Index, Vf * bw}];

Set @@ Data[par, {QQ /@ Index, Qf * Qc}];
sumQQ = Plus @@ Table[QQ[i], {i, 8}];
Do[QQ[i] = QQ[i] (Qc / sumQQ), {i, 8}];
sumQQ = Plus @@ Table[QQ[i], {i, 9, 10}];
Do[QQ[i] = QQ[i] (Qc / sumQQ), {i, 9, 10}];

Set @@ Data[par, {PP[#, 1] & /@ Index, Pdim}];
Set @@ Data[par, {PP[#, 2] & /@ Index, Pome}];
(* Assume PP_TCA & PP_DMPT = PP_OME *)
(PP[#, 3] = PP[#, 4] = PP[#, 5] = PP[#, 2]) & /@ Range[10];
sel = Select[adjust, #[[1]] === PPset &];
If[Length[sel] == 1, adj = sel[[1]];
```

```
 tr = Transpose[Rest[adj]];
 o = Table[sel = Select[tr, #[[1]] == {i, j} &];
   If[sel === {}, PP[i, j], Rz[sel[[1, 2]]]], {i, 10}, {j, 5}];
 ClearAll[PP];
 Do[PP[i, j] = o[[i, j]], {i, 10}, {j, 5}]
];
ParTableScaled = Data[par, Replace → {{Vf, VV /@ Range[10], 1},
    {Qf, QQ /@ Range[10], 1}, {Pdim, PP[#, 1] & /@ Range[10], 1}, {Pome, PP[#, 2] & /@ Range[10], 1}}];

{vRBC, vPlasma} = VV /@ {9, 10};
{vBlood, wBlood} = {1, ρ} (vRBC + vPlasma);
If[species === RatLeeBlaufox85, (* bw(kg), vBlood (L), Lee & Blaufox 1985 *)
 vBlood = If[bw < 1 / 10, 677 bw / 10 000, (6 bw + 77 / 1000) / 100];
 vRBC = (2083 / 100 000) bw;
 {vPlasma, wBlood} = {vBlood - vRBC, ρ * vBlood};
 {VV[9], VV[10]} = {vRBC, vPlasma};
 hematocrit = hc = vRBC / vBlood;
 {{VV[9], QQ[9]}, {VV[10], QQ[10]}} = {{6 / 100, Qc} hc, {6 / 100, Qc} (1 - hc)};
];


(* Define metabolic parameters                                          *)
(* METABOLITE m = 1...5 = {DIM, OME, DCA, DMPT+DMDPT, Other}            *)
(* Vmax (umol/hr/kg-tissue), Km (umol/Liter)  from/to metabolite j/k    *)
(* i=1...8 :   {Fat,Liver,Rapid,Slow,Brain,Skin,Diaphr,Lung}            *)
Do[Vmax[i][j, k] = 0; Km[i][j, k] = 1, {i, 10}, {j, 4}, {k, 4}];
metTable = MetTable;
sel = Select[adjust, #[[1]] === Met &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
```

```
  o = {par, If @@ {Index == ii, fadj * par, par}};
  metTable = Data @@ {metTable, Replace → o}, {i, Length[tr]}]
];
par = Rz[metTable];
(* Assume Vmax for Brain[5] & Skin[6] =2%, Lung[8] =100% of Liver[2]
    Vmax tissue (Poet et al 2014); rescale tissue-specific Vmax to umol/hr *)
o =  Flatten[Data[par, Select → Tissue == Liver, Return → {V12, V13, V24}]];
o1 = Flatten[Data[par, Select → Tissue == Liver, Return → {Km12, Km13, Km24}]];
par = Data[par, Replace → {
    {V12, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o[[1]] / 50,
      If[Tissue === Lung, o[[1]], V12]]},
    {V13, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o[[2]] / 50, If[Tissue === Lung, o[[2]], V13]]},
    {V24, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o[[3]] / 50, If[Tissue === Lung, o[[3]], V24]]},
    {Km12, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o1[[1]] / 50, If[Tissue === Lung, o1[[1]], Km12]]},
    {Km13, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o1[[2]] / 50, If[Tissue === Lung, o1[[2]], Km13]]},
    {Km24, If[MemberQ[{Brain, Skin, Diaphr}, Tissue], o1[[3]] / 50, If[Tissue === Lung, o1[[3]], Km24]]}
   }];
(o = First /@ Data[par, Select → Index === #, Return → {V12, V13, V24, Km12, Km13, Km24}];
   {Vmax[#][1, 2], Vmax[#][1, 3], Vmax[#][2, 4]} = o[[{1, 2, 3}]] * VV[#];
   {Km[#][1, 2], Km[#][1, 3], Km[#][2, 4]} =       o[[{4, 5, 6}]]
  ) & /@ Range[10];
o = Table[MapThread[#1[i] @@ #2 &,
   {{Vmax, Km, Vmax, Km, Vmax, Km}, {{1, 2}, {1, 2}, {1, 3}, {1, 3}, {2, 4}, {2, 4}}}], {i, 10}];
o1 = Data[par, Take → {Index, Tissue}];
MetTableScaled = Join @@ # & /@ Transpose[{o1, Prepend[o, Drop[par[[1]], 2]]}];

(* Define pharmacodynamic (PD) parameters: ChE activities                    *)
(* Kturn = rxns per {AChE,BChE,CaE} enzyme per hour            (Maxwell 1987)  *)
(* CE0[i,j] = {j=AChE,BChE,CaE} activity in tissue i (umol substr/h)           *)
(* CE[i,j] enzyme (umol enz) = CE0/Kturn; Kdegr = degradation rate (umol/h)    *)
(* RCE = CE synthesis rate (umol/hr) = Kdegr x (umol Binding Sites)            *)
```

```
pdTableCE = PDTableCE;
sel = Select[adjust, #[[1]] === CE &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
  o = {par, If @@ {Index == ii, fadj * par, par}};
  pdTableCE = Data @@ {pdTableCE, Replace → o}, {i, Length[tr]}]
];
par = Rz[pdTableCE];
o = Data[par, {Index, #}] & /@ {AChE, BChE, CaE};
Do[MapThread[(Set @@ {CE0[#1, j], #2 * VV[#1] / Kturn[[j]]}) &, o[[j]]], {j, 3}];

(* Kdegr= CE degredation rate (1/h)  *)
pdTableDegr = PDTableDegr;
sel = Select[adjust, #[[1]] === Degr &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
  o = {par, If @@ {Index == ii, fadj * par, par}};
  pdTableDegr = Data @@ {pdTableDegr, Replace → o}, {i, Length[tr]}]
];
par = Rz[pdTableDegr];
o = Data[par, {Index, #}] & /@ {AChE, BChE, CaE};
Do[MapThread[(Set @@ {Kdegr[#1, j], #2}) &, o[[j]]], {j, 3}];

(* Kinhib = bi-molec inhibition rate L/(umol/h), here comverted to 1/(umol/h)  *)
pdTableInhib = PDTableInhib;
sel = Select[adjust, #[[1]] === Inhib &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
```

```
  o = {par, If @@ {Index == ii, fadj * par, par}};
  pdTableInhib = Data @@ {pdTableInhib, Replace → o}, {i, Length[tr]}]
];
par = Rz[pdTableInhib];
o = Data[par, {Index, #}] & /@ {AChE, BChE, CaE};
Do[MapThread[(Set @@ {Kinhib[#1, j], #2 / VV[#1]}) &, o[[j]]], {j, 3}];

(* Kreact = CE reactivation rate (1/h)  *)
pdTableReact = PDTableReact;
sel = Select[adjust, #[[1]] === React &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
  o = {par, If @@ {Index == ii, fadj * par, par}};
  pdTableReact = Data @@ {pdTableReact, Replace → o}, {i, Length[tr]}]
];
par = Rz[pdTableReact];
o = Data[par, {Index, #}] & /@ {AChE, BChE, CaE};
Do[MapThread[(Set @@ {Kreact[#1, j], #2}) &, o[[j]]], {j, 3}];

(* Kage = CE aging rate (1/h)  *)
pdTableAge = PDTableAge;
sel = Select[adjust, #[[1]] === Age &];
If[Length[sel] == 1, adj = sel[[1]];
 tr = Transpose[Rest[adj]];
 Do[{par, ii, fadj} = Flatten[tr[[i]]];
  o = {par, If @@ {Index == ii, fadj * par, par}};
  pdTableAge = Data @@ {pdTableAge, Replace → o}, {i, Length[tr]}]
];
par = Rz[pdTableAge];
o = Data[par, {Index, #}] & /@ {AChE, BChE, CaE};
```

```
   Do[MapThread[(Set @@ {Kage[#1, j], #2}) &, o[[j]]], {j, 3}];

  ];
```

Tests:

```
SetPars[0.425];
{K34, zz = QQ /@ {9, 10}, Plus @@ zz, Qc, Plus @@ zz == Qc,
 {{vBlood, vv = {vRBC, vPlasma}, vBlood == Plus @@ vv}, {zz = VV /@ {9, 10}, zz == vv}},
 TBL[ParTableScaled], TBL[PDTableInhib], TBL[RateTableScaled]}
```

$$\left\{1, \left\{\frac{161\left(\frac{17}{5}\right)^{3/4}}{10\,000\times 2^{1/4}}, \frac{189\left(\frac{17}{5}\right)^{3/4}}{10\,000\times 2^{1/4}}\right\}, \frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}, \frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}, \text{True},\right.$$

$$\left.\left\{\left\{\frac{51}{2000}, \left\{\frac{1173}{100\,000}, \frac{1377}{100\,000}\right\}, \text{True}\right\}, \left\{\left\{\frac{1173}{100\,000}, \frac{1377}{100\,000}\right\}, \text{True}\right\}\right\},\right.$$

Index	Tissue	Vf	Qf	Pdim	Pome
1	Fat	$\frac{119}{4000}$	$\frac{463\,605\,843\,994\,279\left(\frac{17}{5}\right)^{3/4}}{147\,176\,458\,410\,882\,240\times 2^{1/4}}$	$\frac{58}{125}$	$\frac{197}{1000}$
2	Liver	$\frac{17}{1000}$	$\frac{463\,605\,843\,994\,279\left(\frac{5}{2}\right)^{1/4} 17^{3/4}}{264\,917\,625\,139\,588\,032}$	$\frac{21}{20}$	$\frac{217}{250}$
3	Rapid	$\frac{17}{1000}$	$\frac{139\,545\,359\,042\,277\,979\left(\frac{17}{5}\right)^{3/4}}{10\,596\,705\,005\,583\,521\,280\times 2^{1/4}}$	$\frac{5}{4}$	$\frac{217}{250}$
4	Slow	$\frac{969}{5000}$	$\frac{1\,167\,599\,903\,393\left(\frac{5}{2}\right)^{1/4} 17^{3/4}}{1\,226\,470\,486\,757\,352}$	$\frac{189}{200}$	$\frac{217}{250}$
5	Brain	$\frac{51}{10\,000}$	$\frac{463\,605\,843\,994\,279\left(\frac{17}{5}\right)^{3/4}}{441\,529\,375\,232\,646\,720\times 2^{1/4}}$	$\frac{5}{4}$	$\frac{217}{250}$
6	Skin	$\frac{3349}{40\,000}$	$\frac{13\,444\,569\,475\,834\,091\left(\frac{17}{5}\right)^{3/4}}{6\,622\,940\,628\,489\,700\,800\times 2^{1/4}}$	$\frac{53}{50}$	$\frac{217}{250}$
7	Diaphr	$\frac{51}{4000}$	$\frac{463\,605\,843\,994\,279\left(\frac{17}{5}\right)^{3/4}}{2\,207\,646\,876\,163\,233\,600\times 2^{1/4}}$	$\frac{189}{200}$	$\frac{217}{250}$
8	Lung	$\frac{17}{8000}$	$\frac{19\,935\,051\,291\,753\,997\left(\frac{17}{5}\right)^{3/4}}{10\,596\,705\,005\,583\,521\,280\times 2^{1/4}}$	$\frac{437}{500}$	$\frac{108}{125}$
9	RBC	$\frac{1173}{100\,000}$	$\frac{161\left(\frac{17}{5}\right)^{3/4}}{10\,000\times 2^{1/4}}$	1	$\frac{217}{250}$
10	Plasma	$\frac{1377}{100\,000}$	$\frac{189\left(\frac{17}{5}\right)^{3/4}}{10\,000\times 2^{1/4}}$	1	$\frac{217}{250}$

,

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	

Foral	1
Finhal	0.047
Kmuc	$\frac{1}{50}$
Fplasma	1
Kstom2intes	0.5
Kstom2liv	0.5
Kintes2liv	0.5
Kintes2feces	$\frac{1}{12}$
FKfecar	$\frac{1}{50}$
Kp	$\frac{1}{20\,000}$

2	Liver	0.054	0.0048	0.005	Herzsprung92=H;H;?		1.17×10^7
3	Rapid	0	0	0		Kturn	3.66×10^6
4	Slow	0	0	0			108 600.
5	Brain	0.054	0.0048	0.005	H;H;?		760 000 }
6	Skin	0	0	0		, Pair	1 000 000 000
7	Diaphr	0	0	0			1 000 000 000
8	Lung	0.054	0.0048	0.005	H;H;?		1 000 000 000
9	RBC	0.054	0	0	H;H;?	Kurx[1]	1
10	Plasma	0.054	0.0048	0.005	H;H;?	Kurx[2]	1
						Kurx[3]	1
						Kurx[4]	1
						Kurx[5]	1
						K35	$\frac{1}{10}$
						K45	$\frac{1}{10}$
						Kair	$\frac{1}{10\,000}$
						Kalb	0.00875
						KalbX	100
						Malb	$\frac{1}{100\,000}$

```
SetPars[0.2]; (1. Kinhib[#, 1] * VV[#]) & /@ Range[10]
```

```
{0., 0.054, 0., 0., 0.054, 0., 0., 0.054, 0.054, 0.054}
```

In[5145]:=
```
adJ = {{Rate, {"Kstom2liv", "Kstom2intes", "Kintes2liv",
     "Kurx[2]", "Kurx[4]", "Kurx[5]",      "Kurx[1]", "Kurx[3]",
     "FKfecar", "Fplasma", "K35", "K45",   "Kalb", "KalbX", "Malb"},
    {0.25,  4,  22,
     1,  1 ,  0.35,     10, 10,
     3,    1,           0.0505,  0.26 * 25,         1, 1, 23}},
   {Met, {{V12, 2}, {Km12, 2}, {V13, 2},  {V24, 2}},  {1.488, 0.5, 21.7,   0.475}},
   {Inhib, {AChE, #} & /@ {2, 5, 8, 9, 10}, 1.205 {1, 1, 1, 1, 1}},
   {React, {AChE, #} & /@ {2, 5, 8, 9, 10}, (0.0088 / 0.019) {1, 1, 1, 1, 1}},
   {PPset, Join[ {#, 2} & /@ {2, 3, 4, 6},  {3, #} & /@ {4, 5},  {#, 4} & /@ {4}, {#, 5} & /@ {4, 6}],
      Join[{0.5,  30, 0.001, 0.001}, {30, 5},  Table[0.01, {2}], Table[0.01, {1}] ] }
  };
SetPars[0.2, Adjust → adJ];
{(1. Kinhib[#, 1] * VV[#]) & /@ Range[10], TBL[RateTableScaled], TBL[PDTableInhib], TBL[PDTableReact]}
```

Out[5147]=

Foral	1
Finhal	0.047
Kmuc	$\frac{1}{50}$
Fplasma	1
Kstom2intes	2.
Kstom2liv	0.125
Kintes2liv	11.
Kintes2feces	$\frac{1}{12}$
FKfecar	$\frac{3}{50}$
Kp	$\frac{1}{20\,000}$
Kturn	1.17×10^7
	3.66×10^6
	$\frac{108\,600.}{760\,000}$
Pair	$1\,000\,000\,000$
	$1\,000\,000\,000$
	$1\,000\,000\,000$
Kurx[1]	10
Kurx[2]	1
Kurx[3]	10
Kurx[4]	1
Kurx[5]	0.35
K35	0.00505
K45	0.65
Kair	$\frac{1}{10\,000}$
Kalb	0.00875
KalbX	100
Malb	$\frac{23}{100\,000}$

{{0., 0.06507, 0., 0., 0.06507, 0., 0., 0.06507, 0.06507, 0.06507},

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.054	0.0048	0.005	Herzsprung92=H;H;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.054	0.0048	0.005	H;H;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.054	0.0048	0.005	H;H;?
9	RBC	0.054	0	0	H;H;?
10	Plasma	0.054	0.0048	0.005	H;H;?

,

Index	Tissue	AChE	BChE	CaE	Refs
1	Fat	0	0	0	
2	Liver	0.019	0.03	0.005	Mason2000=M;M;?
3	Rapid	0	0	0	
4	Slow	0	0	0	
5	Brain	0.019	0.03	0.005	M;M;?
6	Skin	0	0	0	
7	Diaphr	0	0	0	
8	Lung	0.019	0.03	0.005	M;M;?
9	RBC	0.019	0	0	M;M;?
10	Plasma	0.019	0.03	0.005	M;M;?

}

```
o = SetPars[0.2, Adjust → {{Rate, {"Foral",  "Kstom2liv", "Kstom2intes", "Kintes2liv", "Kintes2feces",
        "Kurx[2]", "Kurx[4]",  "FKfecal", "FKcarcas", "Fplasma"}, {1,  .2, 5, .5, 0.5,  0.25, 0.25,  .15, .15,  0.1}},
      {Met, {{V24, 2}, {Km24, 2}}, {.03, 1}}, {PPset, {{4, 4}, {2, 2}}, {10, 20}},
      {Inhib, {{AChE, 2}, {AChE, 5}, {AChE, 8}, {AChE, 9}, {AChE, 10}}, 12 {1, 1, 1, 1, 1}}}];
If[StringQ[o], o,
TBL[N[#]] & /@ {Table[CE0[i, j], {i, 10}, {j, 3}],
   Table[PP[i, j], {i, 10}, {j, 5}], ParTable, RateTableScaled, MetTable, MetTableScaled}]
```

```
{{0.,              0.,             0.,            0.464, 0.197, 0.197, 0.197, 0.197},
 {6.97436*^-6,     0.0000655738,   0.14291,       1.05,  20.,   0.868, 0.868, 0.868},
 {0.,              0.,             0.,            1.25,  0.868, 0.868, 0.868, 0.868},
 {0.,              0.,             0.,            0.945, 0.868, 0.868, 10.,   0.868},
 {0.0000902564,    0.0000306885,   0.00636464,    1.25,  0.868, 0.868, 0.868, 0.868},
 {0.,              0.,             0.,            1.06,  0.868, 0.868, 0.868, 0.868},
 {0.,              0.,             0.,            0.945, 0.868, 0.868, 0.868, 0.868},
 {1.94872*^-6,     0.0000236066,   0.0128913,     0.874, 0.864, 0.864, 0.864, 0.864},
 {0.0000159938,    0.,             0.,            1.,    0.868, 0.868, 0.868, 0.868},
 {0.0000129046,    0.0000138984,   0.00501215,    1.,    0.868, 0.868, 0.868, 0.868}}
```

Index	Tissue	Vf	Qf	Pdim	Pome
1.	Fat	0.07	0.09	0.464	0.197
2.	Liver	0.04	0.25	1.05	0.868
3.	Rapid	0.04	0.37625	1.25	0.868
4.	Slow	0.456	0.136	0.945	0.868
5.	Brain	0.012	0.03	1.25	0.868
6.	Skin	0.197	0.058	1.06	0.868
7.	Diaphr	0.03	0.006	0.945	0.868
8.	Lung	0.005	0.05375	0.874	0.864
9.	RBC	0.0276	0.46	1.	0.868
10.	Plasma	0.0324	0.54	1.	0.868

Foral	1.
Finhal	0.047
Kmuc	0.02
Fplasma	0.1
Kstom2intes	2.5
Kstom2liv	0.1
Kintes2liv	0.25
Kintes2feces	0.0416667
FKfecar	0.02
Kp	0.00005
Kturn	1.17×10^7 3.66×10^6 108 600. 760 000.
Pair	$1. \times 10^9$ $1. \times 10^9$ $1. \times 10^9$
Kurx[1]	1.
Kurx[2]	0.25
Kurx[3]	1.
Kurx[4]	0.25
Kurx[5]	1.
K35	0.1
K45	0.1
Kair	0.0001
Kalb	0.00875
KalbX	100.
Malb	0.00001

Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1.	Fat	0.	1.	0.	1.	0.	1.
2.	Liver	2530.	535.	107.	155.	1000.	155.
3.	Rapid	0.	1.	0.	1.	0.	1.
4.	Slow	0.	1.	0.	1.	0.	1.
5.	Brain	0.	1.	0.	1.	0.	1.
6.	Skin	0.	1.	0.	1.	0.	1.
7.	Diaphr	0.	1.	0.	1.	0.	1.
8.	Lung	0.	1.	0.	1.	0.	1.
9.	RBC	0.	1.	0.	1.	0.	1.
10.	Plasma	0.	1.	0.	1.	0.	1.

Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1.	Fat	0.	1.	0.	1.	0.	1.
2.	Liver	20.24	535.	0.856	155.	0.24	155.
3.	Rapid	0.	1.	0.	1.	0.	1.
4.	Slow	0.	1.	0.	1.	0.	1.
5.	Brain	0.12144	10.7	0.005136	3.1	0.00144	3.1
6.	Skin	1.99364	10.7	0.084316	3.1	0.02364	3.1
7.	Diaphr	0.3036	10.7	0.01284	3.1	0.0036	3.1
8.	Lung	2.53	535.	0.107	155.	0.03	155.
9.	RBC	0.	1.	0.	1.	0.	1.
10.	Plasma	0.	1.	0.	1.	0.	1.

```
SetPars[0.2];
{1. {Kurx /@ Range[5], Kturn, Kstom2intes, Kintes2feces, FKcarcas, FKfecal},
 TBL[N[#]] & /@ {Table[CE0[i, j], {i, 10}, {j, 3}], Table[PP[i, j], {i, 10}, {j, 5}], MetTable, MetTableScaled}}
```

$$\left\{\left\{\{1.,\ 1.,\ 1.,\ 1.,\ 1.\},\ \left\{1.17\times10^{7},\ 3.66\times10^{6},\ 108\,600.\right\},\ 0.5,\ 0.0833333,\ 0.01,\ 0.01\right\},\right.$$

$$\left\{\begin{array}{ccc} 0. & 0. & 0. \\ 6.97436\times10^{-6} & 0.0000655738 & 0.14291 \\ 0. & 0. & 0. \\ 0. & 0. & 0. \\ 0.0000902564 & 0.0000306885 & 0.00636464 \\ 0. & 0. & 0. \\ 0. & 0. & 0. \\ 1.94872\times10^{-6} & 0.0000236066 & 0.0128913 \\ 0.0000159938 & 0. & 0. \\ 0.0000129046 & 0.0000138984 & 0.00501215 \end{array}\right.,\ \left\{\begin{array}{ccccc} 0.464 & 0.197 & 0.197 & 0.197 & 0.197 \\ 1.05 & 0.868 & 0.868 & 0.868 & 0.868 \\ 1.25 & 0.868 & 0.868 & 0.868 & 0.868 \\ 0.945 & 0.868 & 0.868 & 0.868 & 0.868 \\ 1.25 & 0.868 & 0.868 & 0.868 & 0.868 \\ 1.06 & 0.868 & 0.868 & 0.868 & 0.868 \\ 0.945 & 0.868 & 0.868 & 0.868 & 0.868 \\ 0.874 & 0.864 & 0.864 & 0.864 & 0.864 \\ 1. & 0.868 & 0.868 & 0.868 & 0.868 \\ 1. & 0.868 & 0.868 & 0.868 & 0.868 \end{array}\right\},$$

Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1.	Fat	0.	1.	0.	1.	0.	1.
2.	Liver	2530.	535.	107.	155.	1000.	155.
3.	Rapid	0.	1.	0.	1.	0.	1.
4.	Slow	0.	1.	0.	1.	0.	1.
5.	Brain	0.	1.	0.	1.	0.	1.
6.	Skin	0.	1.	0.	1.	0.	1.
7.	Diaphr	0.	1.	0.	1.	0.	1.
8.	Lung	0.	1.	0.	1.	0.	1.
9.	RBC	0.	1.	0.	1.	0.	1.
10.	Plasma	0.	1.	0.	1.	0.	1.

Index	Tissue	V12	Km12	V13	Km13	V24	Km24
1.	Fat	0.	1.	0.	1.	0.	1.
2.	Liver	20.24	535.	0.856	155.	8.	155.
3.	Rapid	0.	1.	0.	1.	0.	1.
4.	Slow	0.	1.	0.	1.	0.	1.
5.	Brain	0.12144	10.7	0.005136	3.1	0.048	3.1
6.	Skin	1.99364	10.7	0.084316	3.1	0.788	3.1
7.	Diaphr	0.3036	10.7	0.01284	3.1	0.12	3.1
8.	Lung	2.53	535.	0.107	155.	1.	155.
9.	RBC	0.	1.	0.	1.	0.	1.
10.	Plasma	0.	1.	0.	1.	0.	1.

```
adjNewD = {{Rate, {"Kstom2liv", "Kstom2intes", "Kintes2liv",
      "Kurx[1]", "Kurx[2]", "Kurx[3]", "Kurx[4]", "Kurx[5]", "FKfecar", "K35"},
     {0.04302287018713838`, 6.447287881297196`, 24.892688718635217`,
      0.05, 0.743263161909309`, 0.5, 0.8729947391421071`, .3, .3, .3}},
    {Met, {{V12, 2}, {V13, 2}, {V24, 2}}, {1, 22.5, 0.19014207349320744`}},
    {PPset, {{6, 1}, {1, 4}}, {1, 1.781863130336682`}}, {Inhib, {{AChE, 2}, {AChE, 5}, {AChE, 8}, {AChE, 9}, {AChE, 10}}},
     {0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`}}};
SetPars[0.2, Adjust → adjNewD];
{1. {Kurx /@ Range[4], Kstom2intes, Kintes2feces, FKcarcas, FKfecal},
 TBL[N[#]] & /@ {Table[CE0[i, j], {i, 10}, {j, 3}], Table[PP[i, j], {i, 10}, {j, 5}], MetTable, MetTableScaled}}
```

```
{{{0.05, 0.743263, 0.5, 0.872995}, 3.22364, 0.0833333, 0.01, 0.01},

  0.                0.            0.           0.464  0.197  0.197  1.78186  0.197
  6.97436 × 10^-6   0.0000655738  0.14291      1.05   0.868  0.868  0.868    0.868
  0.                0.            0.           1.25   0.868  0.868  0.868    0.868
  0.                0.            0.           0.945  0.868  0.868  0.868    0.868
 {0.0000902564      0.0000306885  0.00636464 , 1.25   0.868  0.868  0.868    0.868 ,
  0.                0.            0.           1.     0.868  0.868  0.868    0.868
  0.                0.            0.           0.945  0.868  0.868  0.868    0.868
  1.94872 × 10^-6   0.0000236066  0.0128913    0.874  0.864  0.864  0.864    0.864
  0.0000159938      0.            0.           1.     0.868  0.868  0.868    0.868
  0.0000129046      0.0000138984  0.00501215   1.     0.868  0.868  0.868    0.868


  Index  Tissue  V12    Km12  V13   Km13  V24    Km24   Index  Tissue  V12      Km12  V13      Km13  V24         Km24
  1.     Fat     0.     1.    0.    1.    0.     1.     1.     Fat     0.       1.    0.       1.    0.          1.
  2.     Liver   2530.  535.  107.  155.  1000.  155.   2.     Liver   20.24    535.  19.26    155.  1.52114     155.
  3.     Rapid   0.     1.    0.    1.    0.     1.     3.     Rapid   0.       1.    0.       1.    0.          1.
  4.     Slow    0.     1.    0.    1.    0.     1.     4.     Slow    0.       1.    0.       1.    0.          1.
  5.     Brain   0.     1.    0.    1.    0.     1.   , 5.     Brain   0.12144  10.7  0.11556  3.1   0.00912682  3.1  }}
  6.     Skin    0.     1.    0.    1.    0.     1.     6.     Skin    1.99364  10.7  1.89711  3.1   0.149832    3.1
  7.     Diaphr  0.     1.    0.    1.    0.     1.     7.     Diaphr  0.3036   10.7  0.2889   3.1   0.022817    3.1
  8.     Lung    0.     1.    0.    1.    0.     1.     8.     Lung    2.53     535.  2.4075   155.  0.190142    155.
  9.     RBC     0.     1.    0.    1.    0.     1.     9.     RBC     0.       1.    0.       1.    0.          1.
  10.    Plasma  0.     1.    0.    1.    0.     1.     10.    Plasma  0.       1.    0.       1.    0.          1.
```

```
2530 * .2 * .04 * 4
```

```
80.96
```

```
SetPars[0.425, Species → RatLeeBlaufox85];
{{{vBlood, vRBC, vPlasma}, Kturn, Kstom2intes, Kintes2feces, FKcarcas, FKfecal},
 TBL /@ {Table[CE0[i, j], {i, 10}, {j, 3}], Table[Kinhib[i, j], {i, 10}, {j, 3}], Table[PP[i, j], {i, 10}, {j, 5}]}}
```

$$\left\{\left\{\frac{2627}{100\,000}, \frac{35\,411}{4\,000\,000}, \frac{69\,669}{4\,000\,000}\right\}, \{11\,700\,000, 3\,660\,000, 108\,600\}, \frac{1}{2}, \frac{1}{12}, \frac{1}{100}, \frac{1}{100}\right\},$$

$$\left\{\begin{pmatrix} 0 & 0 & 0 \\ \frac{289}{19\,500\,000} & \frac{17}{122\,000} & \frac{1649}{5430} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \frac{187}{975\,000} & \frac{1989}{30\,500\,000} & \frac{306}{22\,625} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \frac{323}{78\,000\,000} & \frac{153}{3\,050\,000} & \frac{119}{4344} \\ \frac{4\,001\,443}{68\,302\,000\,000} & 0 & 0 \\ \frac{5\,410\,959}{68\,302\,000\,000} & \frac{10\,938\,033}{128\,197\,600\,000} & \frac{1\,463\,049}{47\,548\,700} \end{pmatrix}, \begin{pmatrix} 0 & 0 & 0 \\ \frac{54}{17} & \frac{24}{85} & \frac{5}{17} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \frac{180}{17} & \frac{16}{17} & \frac{50}{51} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \frac{432}{17} & \frac{192}{85} & \frac{40}{17} \\ \frac{94\,572}{35\,411} & 0 & 0 \\ \frac{10\,508}{7741} & \frac{42\,032}{348\,345} & \frac{26\,270}{209\,007} \end{pmatrix}, \begin{pmatrix} \frac{58}{125} & \frac{197}{1000} & \frac{197}{1000} & \frac{197}{1000} & \frac{197}{1000} \\ \frac{21}{20} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{5}{4} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{189}{200} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{5}{4} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{53}{50} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{189}{200} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ \frac{437}{500} & \frac{108}{125} & \frac{108}{125} & \frac{108}{125} & \frac{108}{125} \\ 1 & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \\ 1 & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} & \frac{217}{250} \end{pmatrix}\right\}$$

```
TBL[ParTable]
```

Index	Tissue	Vf	Qf	Pdim	Pome
1	Fat	0.07	0.09	0.464	0.197
2	Liver	0.04	0.25	1.05	0.868
3	Rapid	0.04	0.37625	1.25	0.868
4	Slow	0.456	0.136	0.945	0.868
5	Brain	0.012	0.03	1.25	0.868
6	Skin	0.197	0.058	1.06	0.868
7	Diaphr	0.03	0.006	0.945	0.868
8	Lung	0.005	0.05375	0.874	0.864
9	RBC	0.0276	0.46	1	0.868
10	Plasma	0.0324	0.54	1	0.868

```
Plus @@ QQ /@ {9, 10}
```

$$\frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}$$

```
{Qc, Plus @@ Table[QQ[i], {i, 8}] == Qc, zz = Plus @@ (QQ /@ {9, 10}), Qc, zz == Qc}
```

$$\left\{\frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}, \text{True}, \frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}, \frac{7\left(\frac{17}{5}\right)^{3/4}}{200\times 2^{1/4}}, \text{True}\right\}$$

```
Rationalize[10 200 * 0.425 * 0.04](* umol/hr ACHE in liver *)
```

$$\frac{867}{5}$$

```
{aa = #[2, 1] & /@ {CE0, Kdegr}, 1. aa}
```

$$\left\{\left\{\frac{289}{19\,500\,000}, \frac{3}{1000}\right\}, \{0.0000148205, 0.003\}\right\}$$

Define DimethoateModel (8/10 compartment) <---------- Code

```
Remove[DimethoateModel];

ClearAll[R, S, vM, CA, CE, CEX, CEXX, PCE, Blood, Plasma, SUM];

Options[DimethoateModel] = {Adjust → {{False}}, Chemical → Dimethoate, Goal → Automatic, Input → {},
    Method → Automatic, NOralPulses → 1, Occluded → True, Output → Automatic,
    PPome → 1, Precision → MachinePrecision, Scenario → Automatic, Species → Rat,
    Time → Automatic, Toff → Automatic, TOralPulse → 1 / 60 (*gavage*), Verbose → False};

DimethoateModel[bwKg_, Ingest_, Dermal_, CAir_, tmax_, options___Rule] := Module[{
        method, out, region, scenario, v, time, tadd, toff, prec, goal,
        ingest, dermal, Cair, Calv, Kp, foral, occlude,
        tPulse, nPulse, tRep = 1, tpi,
        eqn, eqn0, OnOff, ndsolveArgs,
        gainMet, lossMet, lossPDcex, lossPD, ΔMbinding,
        t0, t1, t2, t3, vars, r, nweeks, varsMassConserving, varsRest,
        sol, join, onskin, sum, chem, min, mw, pce, KinCEM2,
        species, input, o, oo, adjust, bx = 3,
        ppome, K34rate, bloodmt},

    (* time & tmax (hours); skin area (cm2); Cair (mg/m3) *)
    adjust =    Adjust /. {options} /. Options[DimethoateModel];
    chem =     Chemical /. {options} /. Options[DimethoateModel];
```

```
goal =        Goal /. {options} /. Options[DimethoateModel];
nPulse =     NOralPulses /. {options} /. Options[DimethoateModel];
occlude =   Occlude /. {options} /. Options[DimethoateModel];
out =         Output /. {options} /. Options[DimethoateModel];
prec =    Precision /. {options} /. Options[DimethoateModel];
ppome =       PPome /. {options} /. Options[DimethoateModel];
scenario = Scenario /. {options} /. Options[DimethoateModel];
species =   Species /. {options} /. Options[DimethoateModel];
time =        Time /. {options} /. Options[DimethoateModel];
toff =       Toff /. {options} /. Options[DimethoateModel];
tPulse = TOralPulse /. {options} /. Options[DimethoateModel];
v =       Verbose /. {options} /. Options[DimethoateModel];

Clear[MM, CVfree, MBrbc, MBpls, Blood, Plasma];

SetPars[bwKg, Species → RatLeeBlaufox85, Adjust → adjust, PPome → ppome];

{mw, min} = If[chem === Dimethoate, {mwD, 1}, {mwO, 2}];
{ingest, dermal, cAir} = Rationalize[{1000 * Ingest / mw, Dermal, CAir}, 10^-12];

If[Not[Head[t] === Symbol], Return["DimethoateModel: t must be a symbol"]];
If[Not[TrueQ[0 < toff <= tmax]], toff = tmax];

Which[
     time === Automatic,    time = {0, tmax},
 VectorQ[time, NumericQ],  time = Select[time, (0 < # < tmax) &],
 True,                     Return["DimethoateModel: Bad Time-option value list"]
];
time = Join[Select[{10^-4, 10^-2, 1/10, 1/2, 1, 4}, # < tmax &], Rest[time]];

Which[
```

```
      NumericQ[CAir], Cair[t_] := CAir,
      VectorQ[{CAir[0], CAir[tmax]}, NumericQ], Cair = CAir,
      True, Return["DimethoateModel: Bad CAir (must be a number or function)"]
];

Which[
 scenario === Automatic,
      onskin[t_] := 0;
      OnOff[t_] := 1,
 scenario === Oral,          (* one pulse  lasting TOralPulse hours *)
      OnOff[t_] := If[t ≤ tPulse, 1, 0] / tPulse;
      onskin[t_] := 0;
      time = Union[Join[time, Range[0, toff, 24], {tPulse}]],
 scenario === OralDaily,     (* NOralPulses pulses/trep/day each for TOralPulse hours *)
      If[VectorQ[nPulse, NumericQ] && Length[nPulse] == 2, {nPulse, tRep} = nPulse];
      tRep = Max[tRep, tPulse];
      OnOff[t_] := If[Mod[t, tRep] ≤ tPulse && Mod[t, 24] < nPulse * tRep && t < toff,
             1, 0] / (tPulse * nPulse);
      Clear[onOff];
      onOff[t_] := OnOff[t];
      onskin[t_] := 0;
      tpi = Table[24 * i {1, 1} + {j, j + tPulse},
          {i, 0, Floor[toff / 24] - If[Mod[toff, 24] == 0, 1, 0]}, {j, 0, tRep (nPulse - 1), tRep}];
      time = Union[  Join[time, rr = Range[0, toff, 24], Flatten[tpi]] ],
 scenario === DermalPatch,
      occlude = 0;
      OnOff[t_] := 1;           (* continuous dermal uptake *)
      onskin[t_] := dermal / mwD,
 scenario === Wash24,
      occlude = If[TrueQ[occlude], 1, 0];
      OnOff[t_] := If[t ≤ 24, 1, 0];
```

```
    If[Min[tmax, toff] ≥ 24, time = Union[time, {24}]];
    onskin[t_] := OnOff[t] * (dermal / mwD) * E^(- (Kp + occlude * Kair) t), (* in mmol *)
 scenario === Occupational || scenario === DermalDaily,
    occlude = If[TrueQ[occlude], 1, 0];
    OnOff[t_] := If[Mod[t, 24] ≤ 8 && Mod[t, 168] ≤ 120 && t ≤ toff, 1, 0];
    nweeks = Floor[toff / 168];
    If[scenario === DermalDaily,
        onskin[t_] := OnOff[t] * (dermal / mw) * E^(- (Kp + occlude * Kair) t) (* in mmol *)
     ];
    time =  If[toff > 24,
      tadd = Flatten[Table[168 * j + Table[{0, 8} + 24 i, {i, 0, 4}], {j, 0, nweeks}]];
       Union[Join[time, tadd, {toff}]],
      time = If[toff ≥ 8, AppendTo[time, 8], time];
       Union[time, {toff}]
    ],
 True, Return["MalathionModel: Bad Scenario"]
];

Which[
 out === TIME, Return[Prepend[Union[{0, tmax}, time], t]],
 out === ONOFF, Return[OnOff[t]]
];

(*** DEFINE ODE SYSTEM ***)
(* MM[i,m] (i=1,...,8) = umol in tissue i and metab m                        *)
(* CE/CEX[i,j] (i=1,...,10) = umol in tissue i for CEj (j=1,2,3)             *)
(* i=1...8 :   {Fat,Liver,Rapid,Slow,Brain,Skin,Diaphr,Lung,RBC,Plasma       *)
(*             m=1...5 = {Dimethoate, Omethoate, DCA, DMTP, DMP,  DTDTandDTP}  *)
(*             j=1...3 = {AChE, BChE, CaE}                                   *)
(*             where DTD = DTDT + DTP                                        *)
```

```
(* Mixed venous and arterial blood concentrations of metab m (umol/L)  *)
CVfree[m_][t_] := Simplify[Plus @@ (((QQ[#] * MM[#, m][t])/(VV[#] * PP[#, m] * Qc)) & /@ Range[8])];
(*CVfree[5][t_]:=MBLR[t]/VPLR;*)
CA[m_][t_] := (*(Qalv(Cair[t]/mw)+Qc*CVfree[m][t])/(Qalv/Pair[[m]]+Qc)*)CVfree[m][t];

(* Initialize Gain & loss to/from tissue i *)

Do[gainMet[i_, m_][t_] := 0;  lossMet[i_, m_][t_] := 0,  {i, 10}, {m, 5}]; (*Metabolism *)

(* Rates of tissue i metabolism from j to k = Vmax[i][j,k]*Ctissue/(Kmi][j,k]+Ctissue)  *)
dmet[i_, j_, k_] := If[k < 5, (Vmax[i][j, k] * MM[i, j][t])/(Km[i][j, k] * VV[i] + MM[i, j][t]), Switch[j,
    3, K35 (Vmax[i][1, 3]/Km[i][1, 3]) (MM[i, 3][t]/VV[i]),
    4, K45 (Vmax[i][2, 4]/Km[i][2, 4]) (MM[i, 4][t]/VV[i]), _, 0]];
(*QLR=(QQ[2]+QQ[3])/2;
VPLR=(VV[2]+VV[3])PP[2,2]*FPPLR5;*)

(* Gain & Loss definitions: *)
(* Metabolism & Excretion *)
(gainMet[#, 2][t_] := dmet[#, 1, 2]) & /@ {2, 6, 7, 8};
(gainMet[#, 3][t_] := dmet[#, 1, 3]) & /@ {2, 6, 7, 8};
(gainMet[#, 4][t_] := dmet[#, 2, 4]) & /@ {2, 6, 7, 8};
(gainMet[#, 5][t_] := dmet[#, 3, 5] + dmet[#, 4, 5]) & /@ {2, 6, 7, 8};
(lossMet[#, 1][t_] := dmet[#, 1, 2] + dmet[#, 1, 3]) & /@ {2, 6, 7, 8};
(lossMet[#, 2][t_] := dmet[#, 2, 4]) & /@ {2, 6, 7, 8};
(lossMet[#, 3][t_] := dmet[#, 3, 5]) & /@ {2, 6, 7, 8};
(lossMet[#, 4][t_] := dmet[#, 4, 5]) & /@ {2, 6, 7, 8};
(* loss: DCA,DMP,Other (m=3,4,5) Rapid+Other→Urine, Slow→Feces, Slow→Carcass *)
```

```
(* Pharmacodynamic *)
KinCEM2[i_, j_][t_] := Kinhib[i, j] * CE[i, j][t] * MM[i, 2][t];
lossPDcex[t_] := Plus @@ Flatten[Table[
    (Kreact[i, j] + Kdegr[i, j] + Kdegr[i, j]) CEX[i, j][t], {i, 8}, {j, 3}]];
(lossPD[#][t_] := Plus @@ Table[KinCEM2[#, j][t], {j, 3}]) & /@ Range[10];

(* Binding *)
(*Do[ΔMbinding[i_,m_][t_]:=10^bx Qc(Free*If[i==9,MBrbc,MBpls][m][t]-(1-Free)MM[i,m][t])
  ,{i,9,10},{m,4}
 ];*)

If[out === GainLoss, Return[{
   GainM →  Table[gainMet[i, m][t], {i, 10}, {m, 5}],
   LossM →  Table[lossMet[i, m][t], {i, 10}, {m, 5}],
   (*ΔMbind→   Table[ΔMbinding[i,m][t],{i,9,10},{m,4}],*)
   LossPD → Table[lossPD[i][t], {i, 10}],
   LossPDcex → lossPDcex[t]}]
];

(* ODE system for masses MM[i,m] *)

t0 = Flatten[{Table[  MM[i, m]'[t] ==
      gainMet[i, m][t] + Switch[{i, m}, (*{6,min},Kp*onskin[t],*)
        {2, min}, Kstom2liv * Stomach[t] + Kintes2liv * Intest[t], _, 0] +
       (*If[i>8,ΔMbinding[i,m][t],0] +*)

       QQ[i] (CA[m][t] - MM[i, m][t] / (VV[i] * PP[i, m])) -

       lossMet[i, m][t] -
```

```
      If[{i, m} == {2, 2}, lossPD[i][t] + KalbX * Malb * MM[10, 2][t], 0] -
      If[i == 3,  Kurx[m] * MM[3, m][t], 0] -
      If[1 < i < 4 && m == 5, FKfecar * Kurx[5] * MM[i, 5][t], 0]
    , {i, 8}, {m, 5}],
   Table[ MM[i, 2]'[t] == Qc (CA[2][t] - MM[i, 2][t] / (VV[i] * PP[i, 2])), {i, 9, 10}]}
 ];

(* Miscellaneous *)
t1 = Flatten[{
   (*Mucous'[t]==OnOff[t](1-Finhal)Qalv(Cair[t]/mw)-Kmuc*Mucous[t],*)
   Stomach'[t] == OnOff[t] * Foral * ingest(*+ Kmuc*Mucous[t]*) -
        (Kstom2intes + Kstom2liv) Stomach[t],
   Intest'[t] == Kstom2intes * Stomach[t] - (Kintes2liv + Kintes2feces) Intest[t],
   StomachUnAbs'[t] == OnOff[t] (1 - Foral) ingest(*+ Kmuc*Mucous[t]*) - Kstom2intes * StomachUnAbs[t],
   IntestUnAbs'[t] == Kstom2intes * StomachUnAbs[t] - Kintes2feces * IntestUnAbs[t],
   (*(MBrbc[#]'[t]==10^bx Qc((1-Free)MM[9,#][t]  -Free*MBrbc[#][t]))&/@{1,2,3,4},
   (MBpls[#]'[t]==10^bx Qc((1-Free)MM[10,#][t]-Free*MBpls[#][t]))&/@{1,2,3,4},*)
   FeCar'[t] ==   Plus @@ (FKfecar * Kurx[5] (MM[#, 5][t] & /@ {2, 3})) +
     Kintes2feces (Intest[t] + IntestUnAbs[t]) + Kalb * AlbX[t] + lossPDcex[t]
   (*,          (*from Slow*)Exhaled'[t]==Qalv*Plus@@Table[If[j<3,Free,1]*CA[j][t]/Pair[[j]],{j,4}],
   Air'[t]==occlude*Kair*onskin[t]*)
  }];

(* Urinary     U[m] = metab m in Urine,    and    Alb && AlbX *)
t2 = Append[Table[U[m]'[t] == Kurx[m] * MM[3, m][t], {m, 5}] ,
  AlbX'[t] == KalbX * Malb * MM[10, 2][t] - Kalb * AlbX[t]];

(* CE,CEX (Acetylcholine, Butyrylcholine, and Carboxy esterase umol-active sites) *)
t3 = Flatten[{
   Table[CEX[i, j]'[t] == KinCEM2[i, j][t] - (Kreact[i, j] + Kage[i, j] + Kdegr[i, j]) CEX[i, j][t], {i, 10}, {j, 3}],
```

```
    (*Table[CEXX[i,j]'[t]==Kage[i,j]*CEX[i,j]'[t]-Kdegr[i,j]*CEXX[i,j][t],
                    {i,10},{j,3}],*)
    Table[ CE[i, j]'[t] ==
      Kdegr[i, j] (CE0[i, j] - CE[i, j][t]) + Kreact[i, j] * CEX[i, j][t] - KinCEM2[i, j][t], {i, 10}, {j, 3}]
   }];

(************************)

eqn = Evaluate[Join[t0, t1, t2, t3]];
vars = #[[1, 0, 1]][t] & /@ eqn;
varsMassConserving = vars[[Join[Range[40], Range[43, 77]]]];
varsRest = Complement[vars, varsMassConserving];
sum[t_] := Plus @@ varsMassConserving + onskin[t]; (* all but CEX,CE *)
Table[pce[j][t_] := (100 (Plus @@ (CE[#, j][t] / CE0[#, j])) & /@ Range[10]), {j, 3}];
eqn0 = (# == 0) & /@ (Drop[vars, -30] /. t → 0);
t1 = Flatten[Table[CE0[i, j], {i, 10}, {j, 3}]];
t2 = (#[[1]] == #[[2]]) & /@ Transpose[{Take[vars, -30] /. t → 0, t1}];
eqn0 = Evaluate[Join[eqn0, t2]];
ndsolveArgs = {Join[eqn, eqn0], vars, Prepend[Union[{0, tmax}, time], t],
  WorkingPrecision → prec, MaxSteps → 10^5, Method → {"DiscontinuityProcessing" → False }};
If[TrueQ[goal > 0], ndsolveArgs = Join[ndsolveArgs, {AccuracyGoal → goal, PrecisionGoal → goal}]];

If[MemberQ[{ODE, VAR, VARmass, VARrest, ALL, NDSolveArgs}, out],
 Return[Switch[out,  ODE, {eqn, eqn0},  VAR, vars,  VARmass, varsMassConserving,
   VARrest, varsRest,  ALL, {VAR → vars, VARmass → varsMassConserving, VARrest → varsRest,
    EQ0 → eqn0, EQ → eqn}, NDSolveArgs, ndsolveArgs]]
];

sol = (NDSolve @@ ndsolveArgs)[[1]];
(* PCE[i,j][t] = 100% CE[j][t]/CE0[j]  (non-inhibited CE) at time t   *)
PCE[i_, j_][T_] := If[CE0[i, j] ≤ 0, 0, 100 CE[i, j][t] / CE0[i, j] /. sol /. t → T];
```

```
    (* Blood[m][t] = Blood concentrations of metab m at time t *)
    bloodmt = Table[Blood[m][t] → (Plus @@ ((QQ[#] * MM[#, m][t]) / (VV[#] * PP[#, m] * Qc) & /@ Range[8])) /. sol, {m, 5}];
    Join[sol, {SUM[t] → sum[t]}, bloodmt]
  ] /; FreeQ[Head /@ {bwKg, Ingest, Dermal, CAir, tmax}, Rule]
```

"DiscontinuityProcessing"→False , Method→"StiffnessSwitching"

Optimize (not used) <----------

Test 1

Verify that eq, eq0, and all ODEs contain functions of time _[t] that each is also an ODE (left-side) variable:

In[5011]:=
```
BW = 1 / 5; dd = mwO / 1000; Clear[vars, varsMassConserving, eq, eq0];
vars = DimethoateModel[BW, dd, 0, 0, 78, Scenario → Oral, Chemical → Omethoate, Output → VAR];
varsMassConserving =
  varM = DimethoateModel[BW, dd, 0, 0, 78, Scenario → Oral, Chemical → Omethoate, Output → VARmass];
{eq, eq0} = ode = DimethoateModel[BW, dd, 0, 0, 78, Scenario → Oral, Chemical → Omethoate, Output → ODE];
Length /@ {vars, varM}
```

Out[5015]= {113, 75}

In[5023]:=
```
{var, Length[var]}
```

Out[5023]=
```
{{MM[1, 1][t], MM[1, 2][t], MM[1, 3][t], MM[1, 4][t], MM[1, 5][t], MM[2, 1][t], MM[2, 2][t], MM[2, 3][t], MM[2, 4][t],
  MM[2, 5][t], MM[3, 1][t], MM[3, 2][t], MM[3, 3][t], MM[3, 4][t], MM[3, 5][t], MM[4, 1][t], MM[4, 2][t],
  MM[4, 3][t], MM[4, 4][t], MM[4, 5][t], MM[5, 1][t], MM[5, 2][t], MM[5, 3][t], MM[5, 4][t], MM[5, 5][t],
  MM[6, 1][t], MM[6, 2][t], MM[6, 3][t], MM[6, 4][t], MM[6, 5][t], MM[7, 1][t], MM[7, 2][t], MM[7, 3][t],
  MM[7, 4][t], MM[7, 5][t], MM[8, 1][t], MM[8, 2][t], MM[8, 3][t], MM[8, 4][t], MM[8, 5][t], MM[9, 2][t],
  MM[10, 2][t], Stomach[t], Intest[t], StomachUnAbs[t], IntestUnAbs[t], MBpls[t], FeCar[t], U[1][t],
  U[2][t], U[3][t], U[4][t], U[5][t], CEX[1, 1][t], CEX[1, 2][t], CEX[1, 3][t], CEX[2, 1][t], CEX[2, 2][t],
  CEX[2, 3][t], CEX[3, 1][t], CEX[3, 2][t], CEX[3, 3][t], CEX[4, 1][t], CEX[4, 2][t], CEX[4, 3][t], CEX[5, 1][t],
  CEX[5, 2][t], CEX[5, 3][t], CEX[6, 1][t], CEX[6, 2][t], CEX[6, 3][t], CEX[7, 1][t], CEX[7, 2][t], CEX[7, 3][t],
  CEX[8, 1][t], CEX[8, 2][t], CEX[8, 3][t], CEX[9, 1][t], CEX[9, 2][t], CEX[9, 3][t], CEX[10, 1][t],
  CEX[10, 2][t], CEX[10, 3][t], CE[1, 1][t], CE[1, 2][t], CE[1, 3][t], CE[2, 1][t], CE[2, 2][t], CE[2, 3][t],
  CE[3, 1][t], CE[3, 2][t], CE[3, 3][t], CE[4, 1][t], CE[4, 2][t], CE[4, 3][t], CE[5, 1][t], CE[5, 2][t],
  CE[5, 3][t], CE[6, 1][t], CE[6, 2][t], CE[6, 3][t], CE[7, 1][t], CE[7, 2][t], CE[7, 3][t], CE[8, 1][t],
  CE[8, 2][t], CE[8, 3][t], CE[9, 1][t], CE[9, 2][t], CE[9, 3][t], CE[10, 1][t], CE[10, 2][t], CE[10, 3][t]}, 113}
```

In[5022]:=
```
{varM, Length[varM]}
```

Out[5022]=
```
{{MM[1, 1][t], MM[1, 2][t], MM[1, 3][t], MM[1, 4][t], MM[1, 5][t], MM[2, 1][t], MM[2, 2][t], MM[2, 3][t], MM[2, 4][t],
  MM[2, 5][t], MM[3, 1][t], MM[3, 2][t], MM[3, 3][t], MM[3, 4][t], MM[3, 5][t], MM[4, 1][t], MM[4, 2][t],
  MM[4, 3][t], MM[4, 4][t], MM[4, 5][t], MM[5, 1][t], MM[5, 2][t], MM[5, 3][t], MM[5, 4][t], MM[5, 5][t],
  MM[6, 1][t], MM[6, 2][t], MM[6, 3][t], MM[6, 4][t], MM[6, 5][t], MM[7, 1][t], MM[7, 2][t], MM[7, 3][t],
  MM[7, 4][t], MM[7, 5][t], MM[8, 1][t], MM[8, 2][t], MM[8, 3][t], MM[8, 4][t], MM[8, 5][t], Stomach[t], Intest[t],
  StomachUnAbs[t], IntestUnAbs[t], FeCar[t], U[1][t], U[2][t], U[3][t], U[4][t], U[5][t], AlbX[t], CEX[1, 1][t],
  CEX[1, 2][t], CEX[1, 3][t], CEX[2, 1][t], CEX[2, 2][t], CEX[2, 3][t], CEX[3, 1][t], CEX[3, 2][t], CEX[3, 3][t],
  CEX[4, 1][t], CEX[4, 2][t], CEX[4, 3][t], CEX[5, 1][t], CEX[5, 2][t], CEX[5, 3][t], CEX[6, 1][t], CEX[6, 2][t],
  CEX[6, 3][t], CEX[7, 1][t], CEX[7, 2][t], CEX[7, 3][t], CEX[8, 1][t], CEX[8, 2][t], CEX[8, 3][t]}, 75}
```

In[5016]:= eq0

Out[5016]= $\{$MM[1, 1][0] == 0, MM[1, 2][0] == 0, MM[1, 3][0] == 0, MM[1, 4][0] == 0, MM[1, 5][0] == 0, MM[2, 1][0] == 0, MM[2, 2][0] == 0,
MM[2, 3][0] == 0, MM[2, 4][0] == 0, MM[2, 5][0] == 0, MM[3, 1][0] == 0, MM[3, 2][0] == 0, MM[3, 3][0] == 0, MM[3, 4][0] == 0,
MM[3, 5][0] == 0, MM[4, 1][0] == 0, MM[4, 2][0] == 0, MM[4, 3][0] == 0, MM[4, 4][0] == 0, MM[4, 5][0] == 0, MM[5, 1][0] == 0,
MM[5, 2][0] == 0, MM[5, 3][0] == 0, MM[5, 4][0] == 0, MM[5, 5][0] == 0, MM[6, 1][0] == 0, MM[6, 2][0] == 0, MM[6, 3][0] == 0,
MM[6, 4][0] == 0, MM[6, 5][0] == 0, MM[7, 1][0] == 0, MM[7, 2][0] == 0, MM[7, 3][0] == 0, MM[7, 4][0] == 0, MM[7, 5][0] == 0,
MM[8, 1][0] == 0, MM[8, 2][0] == 0, MM[8, 3][0] == 0, MM[8, 4][0] == 0, MM[8, 5][0] == 0, MM[9, 2][0] == 0,
MM[10, 2][0] == 0, Stomach[0] == 0, Intest[0] == 0, StomachUnAbs[0] == 0, IntestUnAbs[0] == 0, FeCar[0] == 0,
U[1][0] == 0, U[2][0] == 0, U[3][0] == 0, U[4][0] == 0, U[5][0] == 0, AlbX[0] == 0, CEX[1, 1][0] == 0, CEX[1, 2][0] == 0,
CEX[1, 3][0] == 0, CEX[2, 1][0] == 0, CEX[2, 2][0] == 0, CEX[2, 3][0] == 0, CEX[3, 1][0] == 0, CEX[3, 2][0] == 0,
CEX[3, 3][0] == 0, CEX[4, 1][0] == 0, CEX[4, 2][0] == 0, CEX[4, 3][0] == 0, CEX[5, 1][0] == 0, CEX[5, 2][0] == 0,
CEX[5, 3][0] == 0, CEX[6, 1][0] == 0, CEX[6, 2][0] == 0, CEX[6, 3][0] == 0, CEX[7, 1][0] == 0, CEX[7, 2][0] == 0,
CEX[7, 3][0] == 0, CEX[8, 1][0] == 0, CEX[8, 2][0] == 0, CEX[8, 3][0] == 0, CEX[9, 1][0] == 0, CEX[9, 2][0] == 0,
CEX[9, 3][0] == 0, CEX[10, 1][0] == 0, CEX[10, 2][0] == 0, CEX[10, 3][0] == 0, CE[1, 1][0] == 0, CE[1, 2][0] == 0,
CE[1, 3][0] == 0, CE[2, 1][0] == $\frac{17}{2\,437\,500}$, CE[2, 2][0] == $\frac{1}{15\,250}$, CE[2, 3][0] == $\frac{388}{2715}$, CE[3, 1][0] == 0, CE[3, 2][0] == 0,
CE[3, 3][0] == 0, CE[4, 1][0] == 0, CE[4, 2][0] == 0, CE[4, 3][0] == 0, CE[5, 1][0] == $\frac{11}{121\,875}$, CE[5, 2][0] == $\frac{117}{3\,812\,500}$,
CE[5, 3][0] == $\frac{144}{22\,625}$, CE[6, 1][0] == 0, CE[6, 2][0] == 0, CE[6, 3][0] == 0, CE[7, 1][0] == 0, CE[7, 2][0] == 0,
CE[7, 3][0] == 0, CE[8, 1][0] == $\frac{19}{9\,750\,000}$, CE[8, 2][0] == $\frac{9}{381\,250}$, CE[8, 3][0] == $\frac{7}{543}$, CE[9, 1][0] == $\frac{235\,379}{4\,150\,250\,000}$,
CE[9, 2][0] == 0, CE[9, 3][0] == 0, CE[10, 1][0] == $\frac{167\,061}{2\,075\,125\,000}$, CE[10, 2][0] == $\frac{337\,707}{3\,894\,850\,000}$, CE[10, 3][0] == $\frac{180\,684}{5\,778\,425}\}$

```
rr = Range[40];
Transpose[{rr, vars[[rr]]}]
```

```
rr = Range[35, 113];
Transpose[{rr, vars[[rr]]}]
```

In[5018]:=
```
adjNewD = {{Rate, {"Kstom2liv", "Kstom2intes", "Kintes2liv",
      "Kurx[1]", "Kurx[2]", "Kurx[3]", "Kurx[4]",  "Kurx[5]", "FKfecar"},
     {0.04302287018713838`, 6.447287881297196`, 24.892688718635217`,
      0.05, 0.743263161909309`, 0.5, 0.8729947391421071`, 0.48720983462787804`, 0.48720983462787804`}},
    {Met, {{V12, 2}, {V13, 2}, {V24, 2}}, {1, 22.5, 0.19014207349320744`}},
    {PPset, {{1, 4}}, {1.781863130336682`}}, {Inhib, {{AChE, 2}, {AChE, 5}, {AChE, 8}, {AChE, 9}, {AChE, 10}},
     {0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`, 0.8503721520203437`}}};
```

In[5019]:=
```
Clear[vars, varsMassConserving, eq, eq0];
vars = DimethoateModel[BW = 0.2, 3, 0, 0, 78, Scenario → Oral, Adjust → adjNewD, Output → VAR];
{eq, eq0} = ode = DimethoateModel[BW, 3, 0, 0, 78, Scenario → Oral, Output → ODE];
Append[{#[[1, 0, 1]][t] & /@ eq == vars, #[[1, 0]][t] & /@ eq0 == vars, Nvars → Length[vars]},
 bad = Select[Select[Cases[#, _[t], Infinity], Not[MemberQ[vars, #]] &] & /@ Last /@ eq, # =!= {} &];
 If[bad =!= {}, bad, True]]
```

Out[5021]= {True, True, Nvars → 113, True}

DimethoateModel[bwKg, Ingest (dose in mg), Dermal (dose in mg), CAir (air conc in mg/m3), KP_, tmax_, options___Rule]

In[5024]:=
```
DimethoateModel[0.2, 3 * BW, 0, 0, 24, Scenario → Oral, Output → #] & /@ {TIME, ONOFF}
```

Out[5024]= $\left\{\left\{t, 0, \frac{1}{10\,000}, \frac{1}{100}, \frac{1}{60}, \frac{1}{10}, \frac{1}{2}, 1, 4, 24\right\}, 60\ \text{If}\left[t \leq \frac{1}{60}, 1, 0\right]\right\}$

Metabolic Gain & Loss balance, and PD gains & losses:

```
ruleGL = DimethoateModel[0.2, 0.03 * BW, 0, 0, 2, Scenario → Oral, Output → GainLoss];
Plus @@ # & /@ ((GainM - LossM) /. ruleGL)
```

{0, 0, 0, 0, 0, 0, 0, 0, 0, 0}

In[5025]:=
```
{#[[1]], If[MemberQ[{GainM, LossM}, #[[1]]], TBL[#[[2]]], FullSimplify[#[[2]]]]} & /@ ruleGL
```

Out[5025]=
$$\left\{\left\{\text{GainM},\ \begin{matrix}0\\0\\0\\0\\0\\0\\0\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{506\,MM[2,1][t]}{25\left(\frac{107}{25}+MM[2,1][t]\right)}\\0\\0\\0\\\frac{49\,841\,MM[6,1][t]}{25\,000\left(\frac{21\,079}{50\,000}+MM[6,1][t]\right)}\\\frac{759\,MM[7,1][t]}{2500\left(\frac{321}{5000}+MM[7,1][t]\right)}\\\frac{253\,MM[8,1][t]}{100\left(\frac{107}{200}+MM[8,1][t]\right)}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{107\,MM[2,1][t]}{125\left(\frac{31}{25}+MM[2,1][t]\right)}\\0\\0\\0\\\frac{21\,079\,MM[6,1][t]}{250\,000\left(\frac{6107}{50\,000}+MM[6,1][t]\right)}\\\frac{321\,MM[7,1][t]}{25\,000\left(\frac{93}{5000}+MM[7,1][t]\right)}\\\frac{107\,MM[8,1][t]}{1000\left(\frac{31}{200}+MM[8,1][t]\right)}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{8\,MM[2,2][t]}{\frac{31}{25}+MM[2,2][t]}\\0\\0\\0\\\frac{197\,MM[6,2][t]}{250\left(\frac{6107}{50\,000}+MM[6,2][t]\right)}\\\frac{3\,MM[7,2][t]}{25\left(\frac{93}{5000}+MM[7,2][t]\right)}\\\frac{MM[8,2][t]}{\frac{31}{200}+MM[8,2][t]}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{107\,MM[2,3][t]}{1550}+\frac{20}{31}MM[2,4][t]\\0\\0\\0\\\frac{107\,MM[6,3][t]}{1550}+\frac{20}{31}MM[6,4][t]\\\frac{107\,MM[7,3][t]}{1550}+\frac{20}{31}MM[7,4][t]\\\frac{107\,MM[8,3][t]}{1550}+\frac{20}{31}MM[8,4][t]\\0\\0\end{matrix}\right\},$$

$$\left\{\text{LossM},\ \begin{matrix}0\\\frac{107\,MM[2,1][t]}{125\left(\frac{31}{25}+MM[2,1][t]\right)}+\frac{506\,MM[2,1][t]}{25\left(\frac{107}{25}+MM[2,1][t]\right)}\\0\\0\\0\\\frac{21\,079\,MM[6,1][t]}{250\,000\left(\frac{6107}{50\,000}+MM[6,1][t]\right)}+\frac{49\,841\,MM[6,1][t]}{25\,000\left(\frac{21\,079}{50\,000}+MM[6,1][t]\right)}\\\frac{321\,MM[7,1][t]}{25\,000\left(\frac{93}{5000}+MM[7,1][t]\right)}+\frac{759\,MM[7,1][t]}{2500\left(\frac{321}{5000}+MM[7,1][t]\right)}\\\frac{107\,MM[8,1][t]}{1000\left(\frac{31}{200}+MM[8,1][t]\right)}+\frac{253\,MM[8,1][t]}{100\left(\frac{107}{200}+MM[8,1][t]\right)}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{8\,MM[2,2][t]}{\frac{31}{25}+MM[2,2][t]}\\0\\0\\0\\\frac{197\,MM[6,2][t]}{250\left(\frac{6107}{50\,000}+MM[6,2][t]\right)}\\\frac{3\,MM[7,2][t]}{25\left(\frac{93}{5000}+MM[7,2][t]\right)}\\\frac{MM[8,2][t]}{\frac{31}{200}+MM[8,2][t]}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{107\,MM[2,3][t]}{1550}\\0\\0\\0\\\frac{107\,MM[6,3][t]}{1550}\\\frac{107\,MM[7,3][t]}{1550}\\\frac{107\,MM[8,3][t]}{1550}\\0\\0\end{matrix}\ \begin{matrix}0\\\frac{20}{31}MM[2,4][t]\\0\\0\\0\\\frac{20}{31}MM[6,4][t]\\\frac{20}{31}MM[7,4][t]\\\frac{20}{31}MM[8,4][t]\\0\\0\end{matrix}\ \begin{matrix}0\\0\\0\\0\\0\\0\\0\\0\\0\\0\end{matrix}\right\},$$

$$\left\{\text{LossPD},\ \left\{0,\ \frac{1}{40}\left(270\,CE[2,1][t]+24\,CE[2,2][t]+25\,CE[2,3][t]\right)MM[2,2][t],\right.\right.$$
$$0,\ 0,\ \frac{1}{12}\left(270\,CE[5,1][t]+24\,CE[5,2][t]+25\,CE[5,3][t]\right)MM[5,2][t],\ 0,\ 0,$$
$$\frac{1}{5}\left(270\,CE[8,1][t]+24\,CE[8,2][t]+25\,CE[8,3][t]\right)MM[8,2][t],\ \frac{11\,493\,CE[9,1][t]\,MM[9,2][t]}{4166},$$
$$\left.\left.\frac{1}{258\,120}1277\left(270\,CE[10,1][t]+24\,CE[10,2][t]+25\,CE[10,3][t]\right)MM[10,2][t]\right\}\right\},$$
$$\left\{\text{LossPDcex},\ \frac{1}{40}CEX[2,1][t]+\frac{1}{20}CEX[2,2][t]+\frac{1}{250\,000}\left(1750\,CEX[2,3][t]+6250\,CEX[5,1][t]+\right.\right.$$
$$\left.\left.12\,500\,CEX[5,2][t]+1627\,CEX[5,3][t]+250\left(25\,CEX[8,1][t]+50\,CEX[8,2][t]+7\,CEX[8,3][t]\right)\right)\right\}\right\}$$

Mass Conservation (demo using unfit default parameters):

In[5035]:=
```
umol = 1000. (dose = 3 * BW / mwD)
```

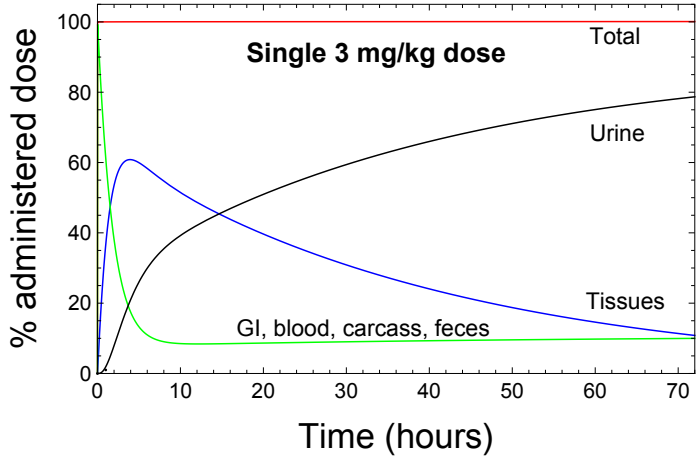
Out[5035]=
```
2.61712
```

```
In[5026]:= SetPars[0.2];
           sol = DimethoateModel[0.2, 3 * BW, 0, 0, 72, Scenario → Oral];

In[5028]:= {MM[2, 2][t], MM[2, 4][t], Blood[#][t] & /@ {1, 2, 3, 4, 5}} /. sol /. t → 10
Out[5028]= {0.00113205, 0.015101, {0.302904, 0.268548, 0.829888, 2.06549, 4.91361}}

In[5041]:= items[T_] := (100 / umol) {
             aa = Plus @@ Flatten[Table[MM[i, j][t], {i, 8}, {j, 5}]],
             bb = Stomach[t] + StomachUnAbs[t] + Intest[t] + IntestUnAbs[t] + FeCar[t] + AlbX[t],
             cc = Plus @@ (U[#][t] & /@ Range[5]),
             dd = Plus @@ Flatten[Table[CEX[i, j][t], {i, 8}, {j, 3}]],
             sum = aa + bb + cc + dd,
             SUM[t]} //. sol /. t → T;

In[5042]:= tt = {0, 1 / 60, 1, 24, 48, 72};
           TBL[tr = Transpose[Prepend[Transpose[items[t] /. t → # & /@ tt], tt]]]
```

Out[5043]//TableForm=

0	0.	0.	0.	0.	0.	0.
$\frac{1}{60}$	0.415502	99.5845	4.49091×10^{-6}	3.88339×10^{-6}	100.	100.
1	36.6847	61.13	1.92212	0.267444	100.004	100.004
24	35.8731	8.80035	54.5992	0.786767	100.059	100.059
48	19.6978	9.51745	70.1724	0.691992	100.08	100.08
72	10.8179	9.9815	78.6941	0.602353	100.096	100.096

```
In[5044]:= PlotData[Plot, FitTo → {items[t][[{5, 1, 2, 3}]], t}, X → {0, 72}, Y → {0, 105},
            Labels → {"Time (hours)", "% administered dose"}, PlotStyle → {Red, Blue, Green, Black}, FontSize → 18]
```



Test 2 (not used)

About *RiskQ*

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Bogen KT. RiskQ 4.2: An interactive approach to probability, uncertainty and statistics for use with Mathematica®. UCRL-MA-110232 Rev. 3. Lawrence Livermore National Laboratory, Livermore, CA,

2002.

Wolfram Research. 2017. Wolfram Language and System Documentation Center. Wolfram Research, Inc., Champaign, IL (www.wolfram.com), http://reference.wolfram.com/language/

RiskQ Functions Used

In[5002]:= `? EV`

EV[x__, options] returns the arithmetic average of (e.g., a vector) x, or the expected value of x if x is a valid cdf, cmf or pmf. If x is a vector, Weights→w may be used (if Sum[w]≠0) to obtain the weighted average value corresponding to the weights−vector w applied to x. If x is a cdf with >2 evenly spaced ordinate values (i.e., evaluated at equal probability intervals) and Empirical→True, then the minimum and maximum abscissa values are ignored. If x is a cdf pertaining to a variate Y, use Function→{fxnY, Y} (or alternatively, EV[fxnY,Y,x]) to return the expected value EfxnY of the specified function fxnY of the (symbolic) variate Y (e.g., if fxnY=Y, then EfxnY=EV[Y]). Use Function→{fxnY, Y, Cdf} (or alternatively, EV[fxnY,Y,x,Cdf], where Cdf denotes any arbitrary 4th or 3rd element in the EV−argument sequence or in the Function−option list, respectively) to return the list {EfxnY, cdfy}, where cdfy lists the sets {yi, [EfxnY|(Y≤yi)]/EfxnY} for ascending values of yi≤Max[Y]−−i.e., cdfy is the relative mean value function for fxnY of a random variate Y that has the specified distribution cdf = x. Note that the range of EfxnY|(Y≤yi) is {0, EfxnY}. Consequently, if Y and fxnY are both ≥0, then cdfy is a valid cdf. See NFx to obtain mean (or weighted mean) of only numeric values (and weights).

In[5010]:= `? Data`

Data[datarows, $expr_1$, ...] returns a list of data rows specified symbolically as a function of the input datarows list, where each $datarows_i = \{x_{i1}, x_{i2},..., x_{in}\}$ has n columns, and $expr_k$ are Data arguments. If datarows is a list but not a list of lists, then it is assumed to specify a single data column. By default, $datarows_1$ must be a list whose jth element ($name_j$) is a unique symbol or string used to name the variate whose values x_{ij} appear in the rest of the jth data column for j=1,...,n; however, if $expr_1$ is a vector containing n symbols and/or strings, then the jth element of $expr_1$ is assumed to be $name_j$. If $expr_1$ is a non−Rule expression (e.g., involving any of the $name_j$), then $expr_1$ is returned (e.g., evaluated with respect to the corresponding specified data column(s)). Alternatively, $expr_k$ may specify one or more of the following options to transform datarows: Append (or Replace), Bin (or Class), Complement, Drop, Fill, Group, Interpolate, Intersection, Merge, Name, Number, Rename, Restructure, Return, Select, Shift, SortBy, Take, Union, and/or UnionAll (or UAll). These options are applied in the order they appear (one or more times) in $expr_k$. Note that these options may not function as desired if any $name_j$) symbol also occurs anywhere else within the matrix of data values. Evaluate Data[option] to get information about any of these Data options. Column names (e.g., $name_1$) appearing in any of these options are assumed to be among those defined for (e.g., as the 1st row of) datarows; any corresponding reassigned name (e.g., X after the assignment X=$name_1$ has been made) used should appear as an argument of HoldForm (e.g., as HoldForm[X]). Data should be nested only if the nested expr is a rule or rule sequence. Data is also an option of ANOCOVAR (see ANOCOVAR).

```
? PlotData
```

PlotData[data,options:] plots an N−by−2 (or (x vs y) data set, or a list of n such sets, with points joined by lines (unless JoinPoints→False is used). Change point style with Style→stylelist which by defualt is {OO, OA, OB, OV, OD, O, A, B, V, D} = {open Point, Triangle, Square, InvTriangle, Diamond,...& their solid counterparts}; use {TO, TA, TB, TV, TD} for transparent open symbols; use {P,X,M,I} for {plus, cross, dash, bar}; & use J to join points from adjacent data sets. E.g, if data = {xyListLo, xyListHi, xyListHat} is a matrix listing corresponding lower−bound, upper−bound, and best−estimate points, use Style→{M,J,M,OO} to plot error bars around open−circle best estimates. Note that Length[stylelist] ≤ (n + nJ) must hold with nJ ≤ 2n−1, where nJ is the number of (non−adjacent) J's, and stylelist cannot end with J. Use Tweak→k to induce a k−fold change in the opaque central disc of points made using an 'OO' Style.

Use Color→color (where color is a list {red,green,blue} of arguments to the Mathematica RGBColor function, or one of the Mathematica 'Named Colors') to color lines joining the specified point set(s); use DotColor to similarly color plotted points. JoinPoints, Color, DotColor or DotSize option (see PlotOptions) values may each also be a list (of length ≤n), to pertain respectively to each point set to be joined. Use FitTo→ {f[x], x} to include a plot of f[x] (which may be a list of functions) vs. any specified symbol x. Use JPL→True (where JPL denotes Join Points by Lines) to set JoinPoints→True, DotSize→0.0001, Style→O.

If the FitTo option is used, or otherwise to a lesser extent (see PlotOptions), Mathematica Plot options (Axes, AxesLabel, AxesStyle, Background, BaseStyle, ColorOutput, Compiled, Epilog, Filling, FillingStyle, FrameStyle, FrameTicks, GridLines, GridLinesStyle, ImageSize, MaxBend, PlotDivision, PlotPoints, PlotStyle [e.g., to color one or more non−DASHed FitTo functions], Prolog, Ticks,FormatType, and TextStyle) may also be used. Use THICK→thick or DASH→dash, where thick and dash may each be a list pertaining to each respective function. Use data=Plot to plot functions only. ONLY IF the FitTo option is used, PlotType→type may also be used, with type=Log (or LinLog or LinearLog) for x vs. Ly, type=LogLin (or LogLinear) for Lx vs. y, or type=LogLog for Lx vs. Ly, where L denotes base−10 logarithm, x the abscissa and y the ordinate. Use Output→ PlotRange to return only the plotrange list {{Xmin, Xmax}, {Ymin, Ymax}} used for plotting. For more details, see PlotOptions.

In[5006]:=
```
? SD
```

SD[x, option] gives the SAMPLE standard deviation (SD) of a vector x of numerical values; the SAMPLE SD of the set Join@@xi inferred by the method of moments if x = {xi,sdi,ni} is a numeric matrix listing sample means xi, sample SDs sdi, and sample sizes ni of a total of Plus@@ni (exhaustive) subsamples; or the POPULATION SD of x if x is a cdf, cmf, or pmf. If x is a cdf with >2 evenly spaced ordinate values (i.e., evaluated at equal probability intervals) and Empirical→True, then the minimum and maximum abscissa values are ignored.

In[5007]:=
```
? TBL
```

TBL[x] = TableForm[x, TableSpacing→1]. TBL[x,r] = TableForm[Take[x,r], TableSpacing→1]. If x is a list such as {m1, a, b, m2, ...} containing at least one or more matrix−like elements x = {m1, m2, ...} where each mi is a list of lists, TBL is applied to each of the mi (padding with null strings if needed to make each mi a true matrix), leaving the other elements {a,b,...} of x unevaluated.

Key *Mathematica* Functions Used

In[5050]:= `? Map`

Map[f, $expr$] or f /@ $expr$ applies f to each element on the first level in $expr$.
Map[f, $expr$, $levelspec$] applies f to parts of $expr$ specified by $levelspec$.
Map[f] represents an operator form of Map that can be applied to an expression. ≫

In[5005]:= `? NonlinearModelFit`

NonlinearModelFit[{y_1, y_2, …}, $form$, {β_1, …}, x] constructs a nonlinear model with structure $form$ that fits the y_i for successive x values 1, 2, … using the parameters β_1, ….
NonlinearModelFit[{{x_{11}, x_{12}, …, y_1}, {x_{21}, x_{22}, …, y_2}, …}, $form$, {β_1, …}, {x_1, …}] constructs a nonlinear model where $form$ depends on the variables x_k.
NonlinearModelFit[$data$, {$form$, $cons$}, {β_1, …}, {x_1, …}] constructs a nonlinear model subject to the parameter constraints $cons$. ≫

In[5008]:= `? Table`

Table[$expr$, n] generates a list of n copies of $expr$.
Table[$expr$, {i, i_{max}}] generates a list of the values of $expr$ when i runs from 1 to i_{max}.
Table[$expr$, {i, i_{min}, i_{max}}] starts with $i = i_{min}$.
Table[$expr$, {i, i_{min}, i_{max}, di}] uses steps di.
Table[$expr$, {i, {i_1, i_2, …}}] uses the successive values i_1, i_2, ….
Table[$expr$, {i, i_{min}, i_{max}}, {j, j_{min}, j_{max}}, …] gives a nested list. The list associated with i is outermost. ≫