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Selection of candidate amphibian dermal exposure models for regulatory use

Leveraging exposure data and Approximate Bayesian computation techniques to model under uncertainty

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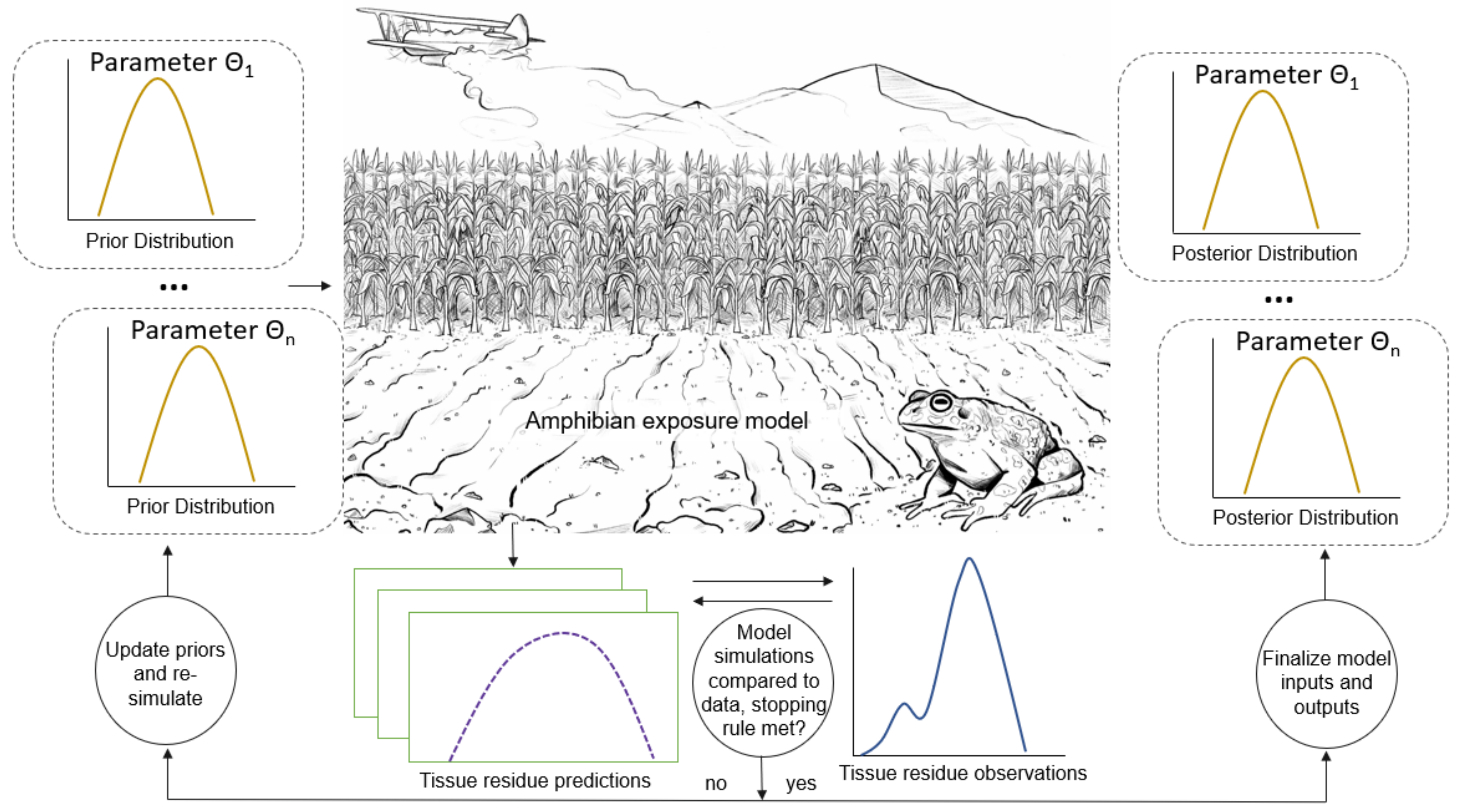

15 September 2020

Office of Research and Development
Center for Computational Toxicology and Exposure

Pesticide Labeling

The label is a binding legal agreement between a regulator, the product registrant and the product user

Pesticides contribute to documented amphibian declines

Amphibian dermal contact has not explicitly assessed, mammals/ birds have been used as proxies for terrestrial dermal exposure

Image: Benny Mazur

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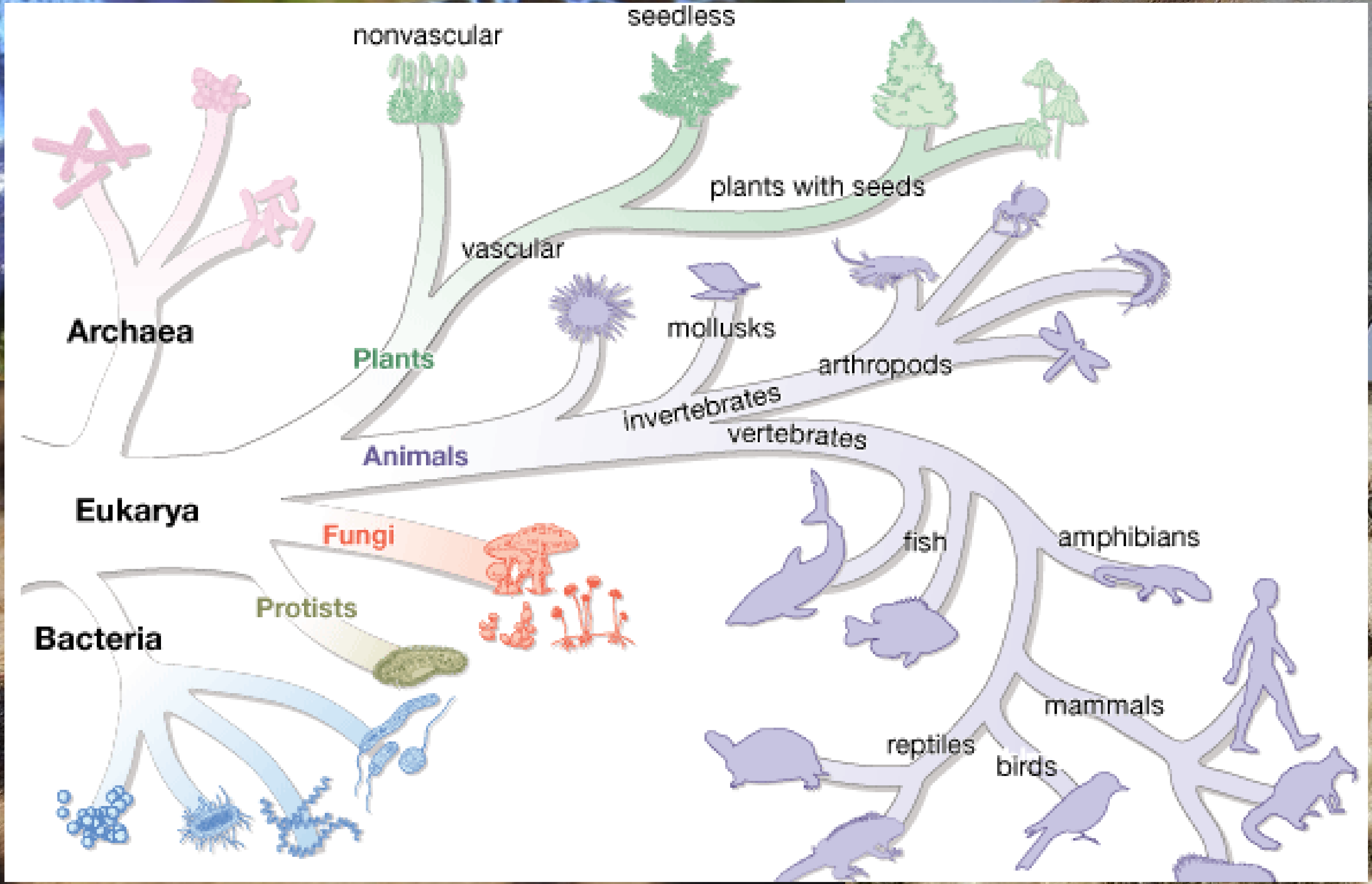

nonvascular
seedless
plants with seeds
vascular
Archaea
Plants
mollusks
arthropods
invertebrates
vertebrates
Animals
Eukarya
Fungi
fish
amphibians
Protists
Bacteria
mammals
reptiles
birds

Amphibian dermal properties

Structural differences:

Relatively thinner

Thin stratum corneum

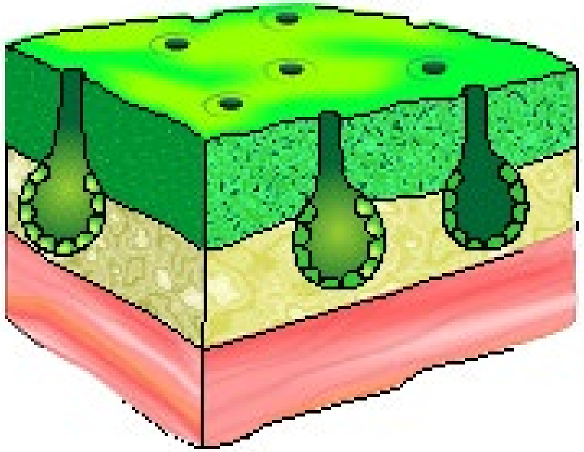
No external hydrophobic barrier

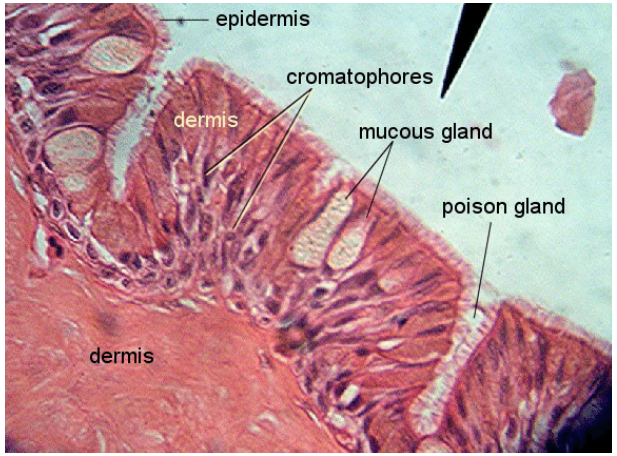
Less keratinized

High rates of gas and water exchange

Seat patch as preferential pathway

Physiological properties change over life history

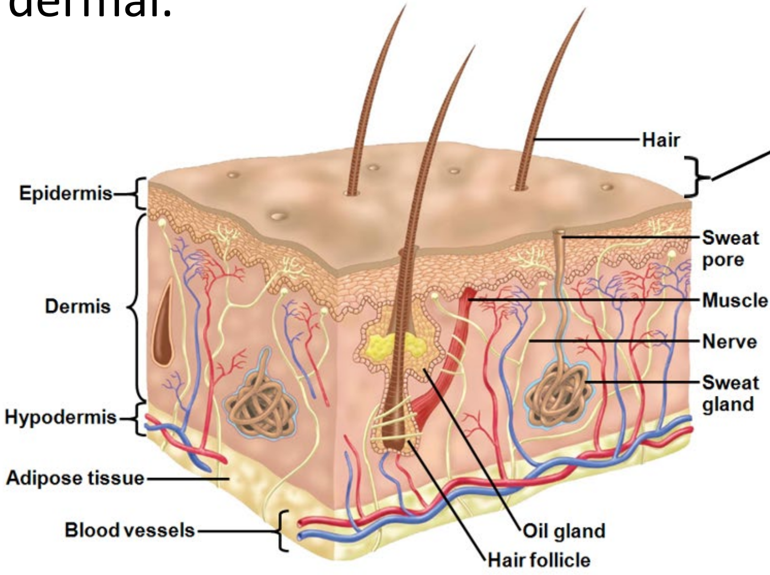


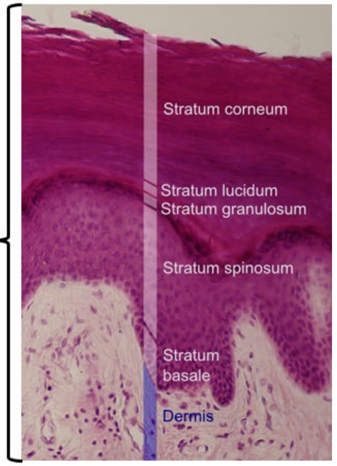


Mammalian dermal properties

Hydrophilic (low K_{ow}) and lipophilic (high K_{ow}) molecules have separate pathways for dermal exposure in humans

Lipophilic molecules get the most attention with a focus on non-ionic (neutral, lipophilic) chemicals for dermal.





Mammalian dermal properties

Hydrophilic (low K_{ow}) and lipophilic (high K_{ow}) molecules have separate pathways for dermal exposure in humans

- High rates of gas and water exchange
- Seat patch as preferential pathway
- Physiological properties change over life history

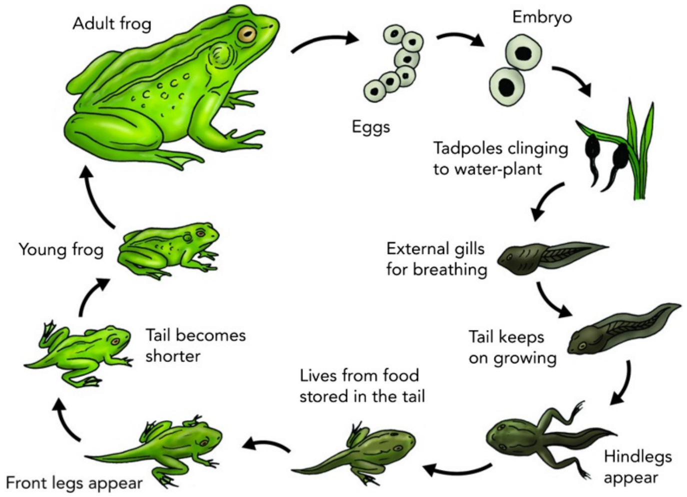
What does this mean for dermal pesticide exposure?

The more terrestrial an amphibian's life cycle is, the more likely it is to use the skin to regulate its water content in order to maintain hydration.

Also more likely to use soil water or puddles as rehydration sources – with higher pesticide concentrations.

Therefore, amphibian dermal contact from enhanced skin permeability can be a key exposure pathway compared to non-amphibian receptors.

First we examine a pathway dose model for terrestrial vertebrates and estimate its contribution to total dose.



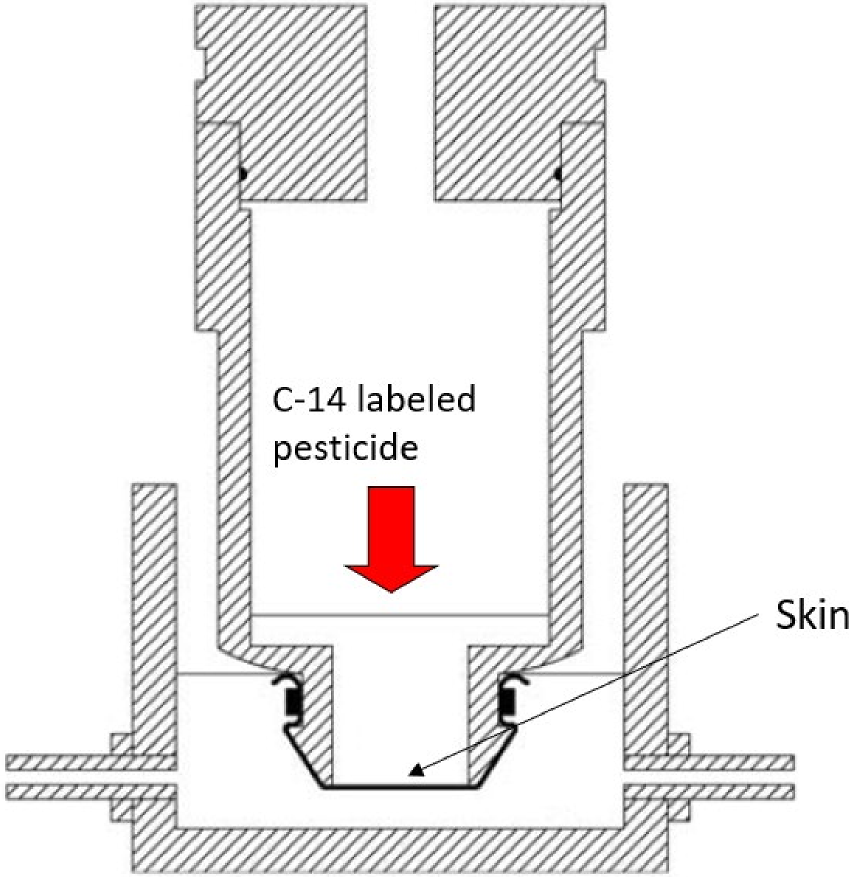
Diffusion-based approaches to dermal exposure

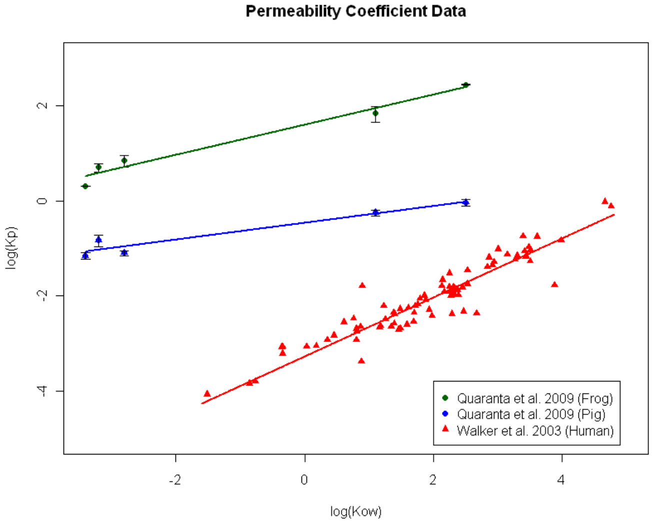
Conductance/Resistance traditionally used to estimate diffusion of a chemical across the dermis

$$K_p = \frac{D}{\Delta x}$$

- Physical differences in skin causes differences in empirical permeability rates – cm/hour
- Number of studies available for mammals, few for non-mammals.
- Permeability coefficient is primarily a function of hydrophobicity - $\log(K_{ow})$ - and molecular volume

$$D_{der} = \frac{C K_p A T B_d F_b}{W}$$





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Monte Carlo Relative Pathway Exposures

Diet-Based Ingestion Exposure Dose (mg/kg BW/d)

$$D_{Diet} = FMR / (BW * (C_{insects} / 1.7))$$

FMR = Field Metabolic Rate (kcal/d)
BW = body weight (g)
$C_{insects}$ = concentration of contaminant on insects
1.7 = insect ingestion rate (kcal/g)

(a) Spray Droplet Inhalation Dose (mg/kg-bw)	(b) Vapor Inhalation Dose (mg/kg)
$SID_a = (C_{air} \times IR_a \times D \times F_I) / (60 \times AW_a)$	$VID_a = (C_s \times IR_a \times D) / (1.0\times10^6 \times AW_a)$
C_{air}= air column concentration (mg a.i. cm^3)*	C_s = saturated air concentration (mg/m^3)*
IR_a = inhalation rate of assessed species (cm^3/hr)*	IR_a = inhalation rate of assessed species (cm^3/hr)*
D = duration of direct spray inhalation	D = duration of exposure, 1 hour
F_I = Fraction of spray inhaled	AW_a = body weight of assessed species (kg)
AW_a = body weight of assessed species (kg)	1.0×10^6 = conversion factor (cm^3/m^3)
60 = conversion factor	

*For description of equations, see STIR Version 1.0 User Guide

$$D_{der} = \frac{C K_p A T B_d F_b}{W}$$

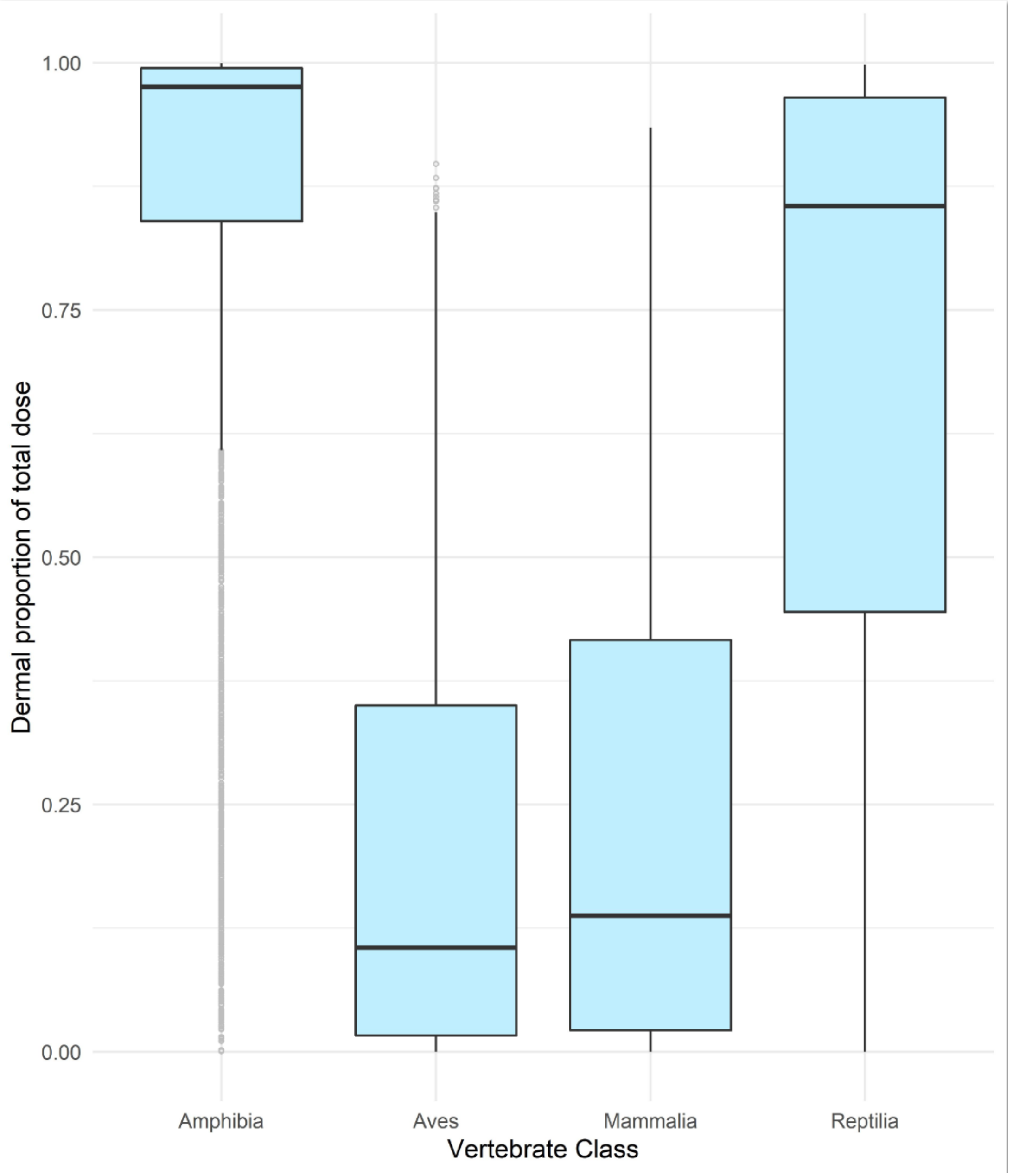
Calculate exposure for diet (Weir et al. 2010) and dermal for amphibians, birds, mammals, reptiles.

Solve for 2000 pesticides and a range of appropriate body weights for insectivores in each class (instead of representative receptor).

Range of K_{ow}.

Compare total dose between classes and relative contribution of dermal.

No tox comparisons, just looking at exposure.



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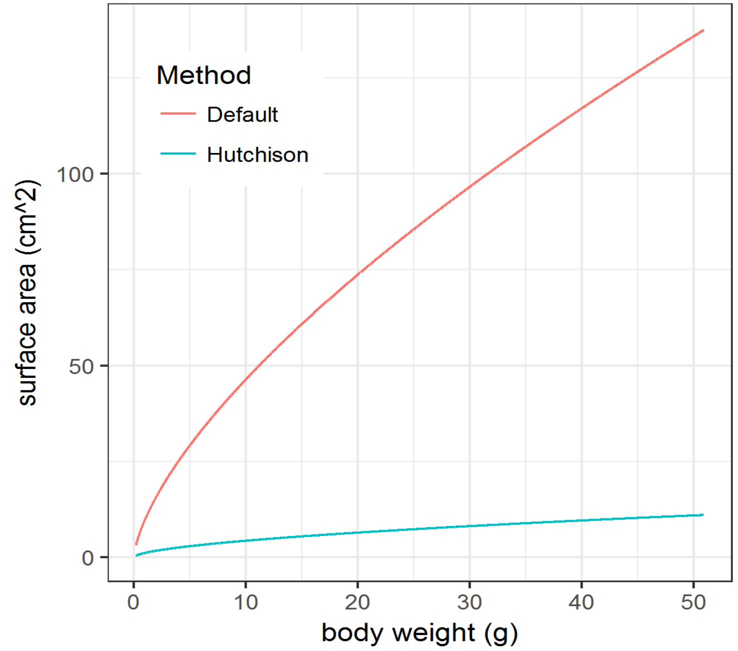
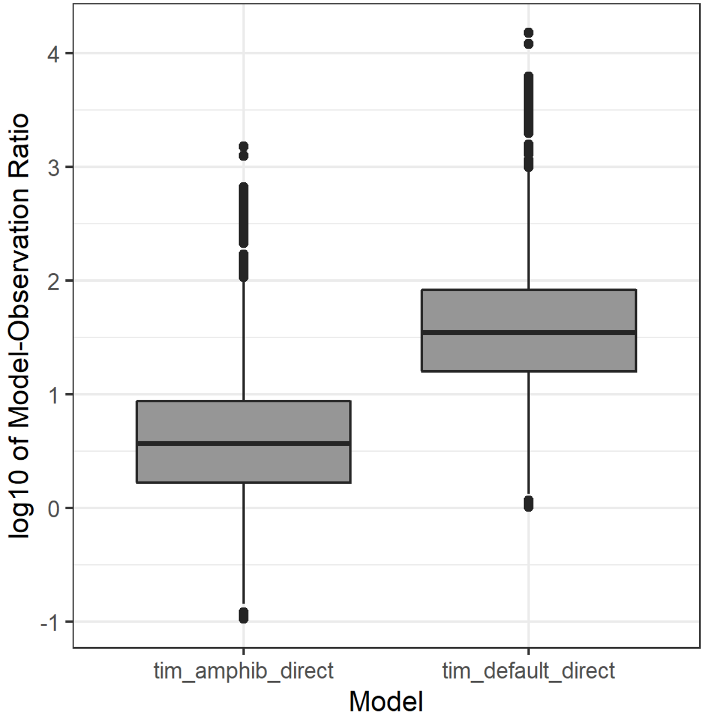
Amphibian Movement Behavior

- Seasonal
- Additive exposures over time
- Spray drift considerations





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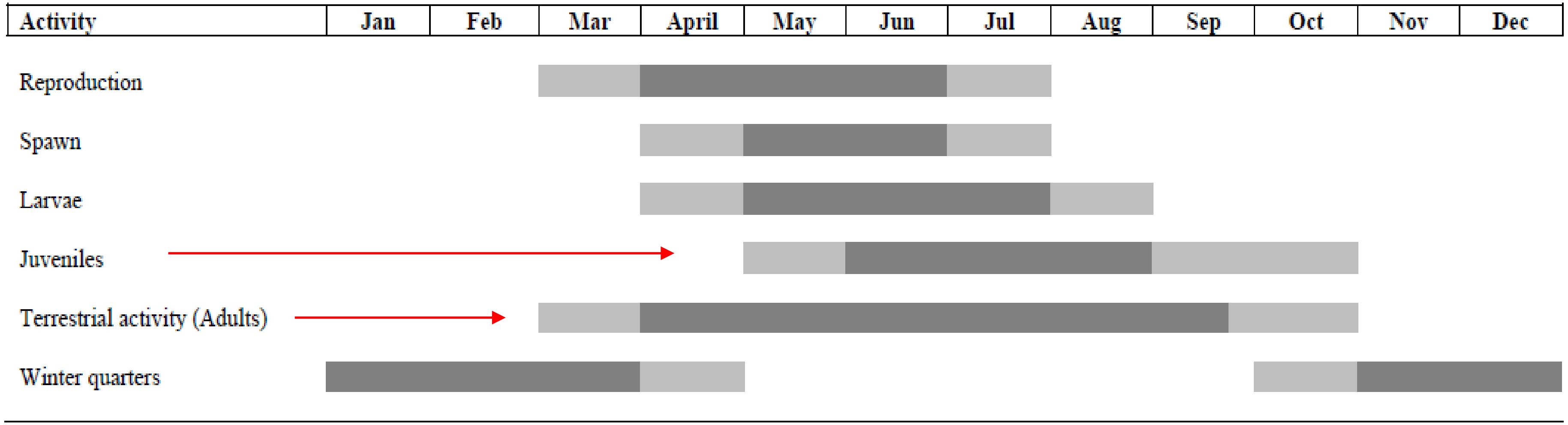
Agriculture Habitat

Adult dispersal to and metamorph dispersal from breeding ponds can coincide with pesticide applications

Seasonal activity of *Hyla arborea* in Germany based on information in Pfeffer et al. (2011). Darker area represents the main period of activity.



Fryday & Thompson 2012

The seat patch

Amphibian seat patch is a preferential path for osmotic water uptake. Water potential dependent.

Amphibian seat patch is crenulated - effective surface area for uptake is much larger than the actual size of the patch.

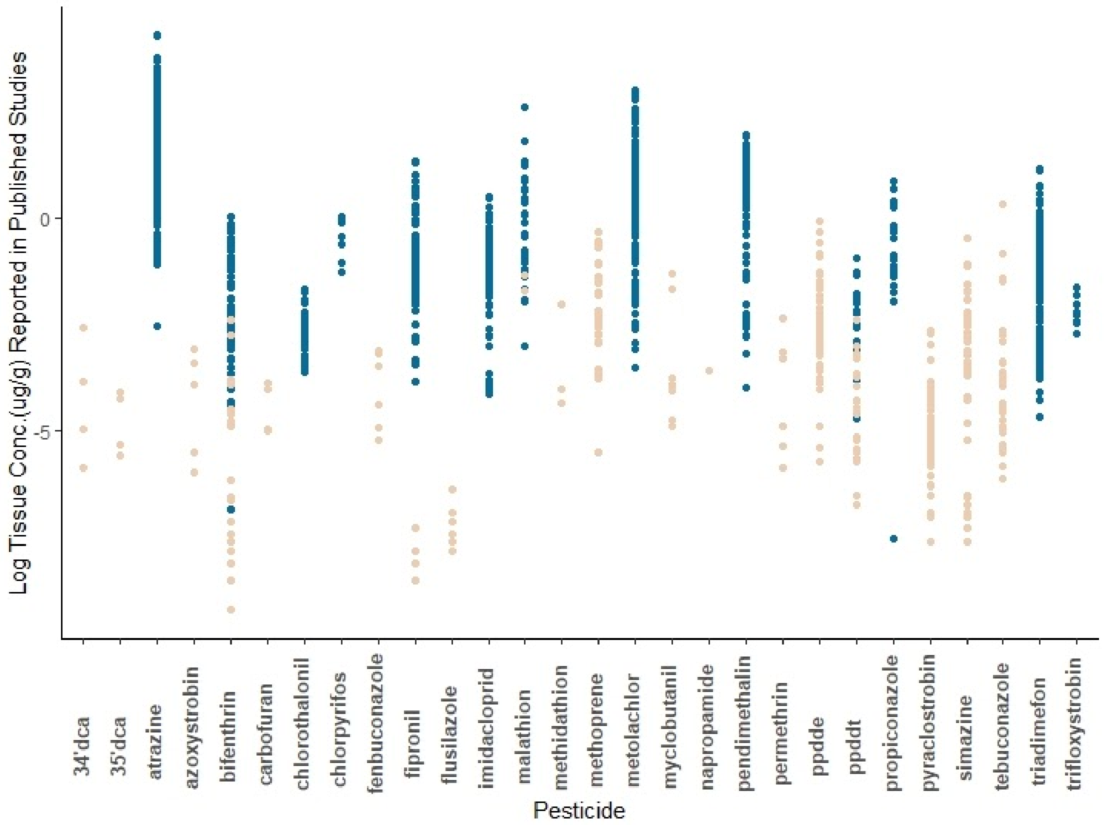
Movement exposes seat patch to pesticides sprayed on bare soil and leaf surfaces.

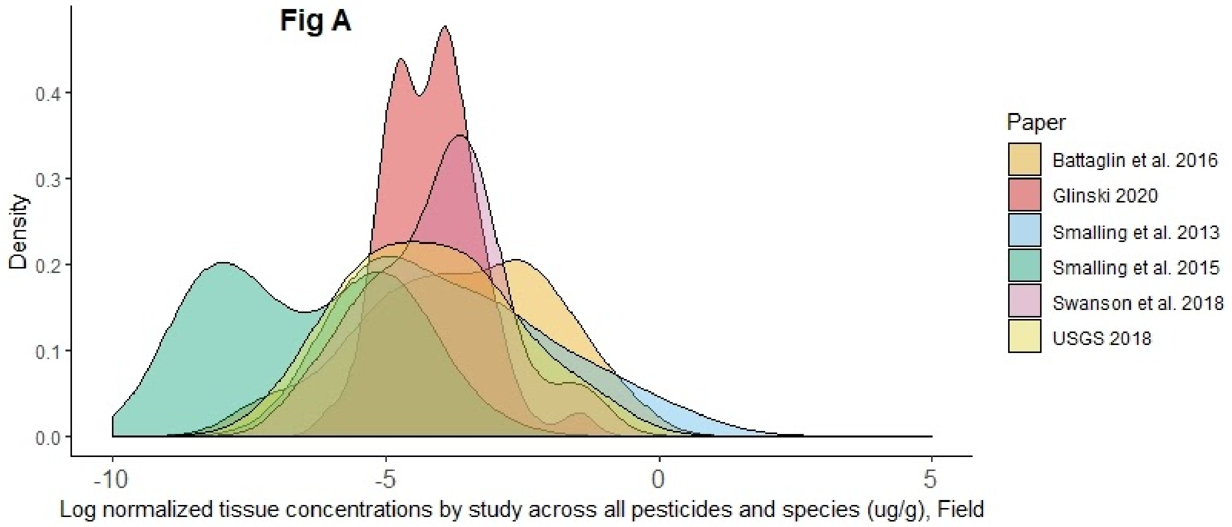
Burrowing behavior

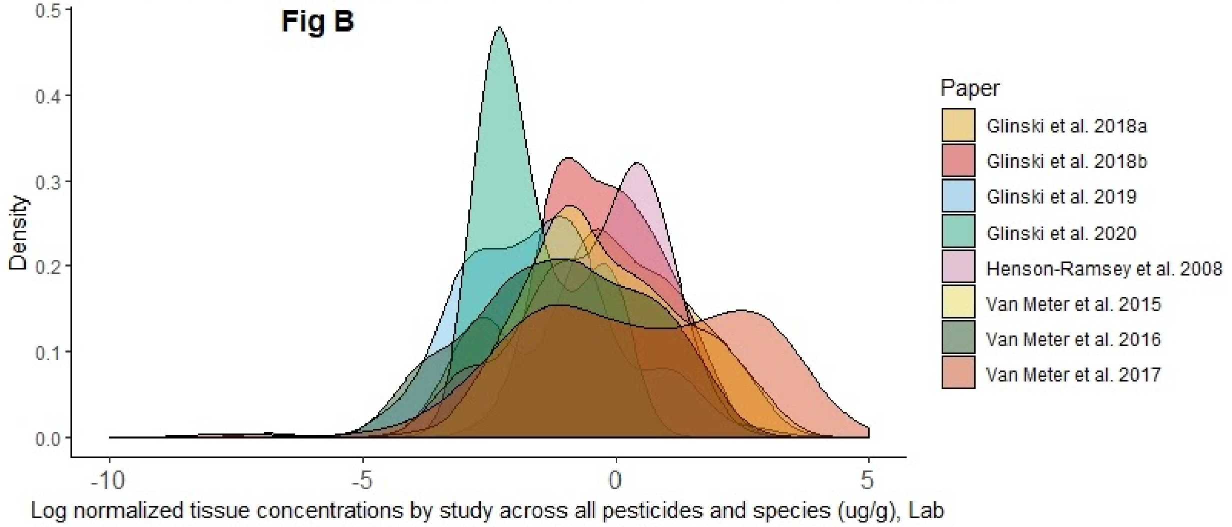
Irrigated farm systems are preferential habitats, terrestrial amphibians prefer soils with high moisture content.

Amphibians (often) burrow, overnight or overwinter, to rehydrate - 100% contact with soil can be a significant portion of exposure.

Collected and compiled amphibian exposure data







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Some parameters are known, some are unknown

- We know the pesticide tissue residue, that is what we are trying to model
- We also know experimental parameters—chemical used, application rate, weight of each amphibian, soil concentration, tissue residue
- We generate predictions for physical + chemical properties using OPERA v2.5 —octanol-water partitioning, molecular weight, biodegradation half-life, etc.

Mansouri *et al. J Cheminform* (2018) 10:10
https://doi.org/10.1186/s13321-018-0263-1

Journal of Cheminformatics

RESEARCH ARTICLE Open Access

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OPERA models for predicting physicochemical properties and environmental fate endpoints

Kamel Mansouri[1,2,3*], Chris M. Grulke[1], Richard S. Judson[1] and Antony J. Williams[1]

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Approximate Bayesian computation (ABC)--Setup

We don’t know other important input parameters; we want inference on these so we can generalize the model to other amphibian spp and pesticides

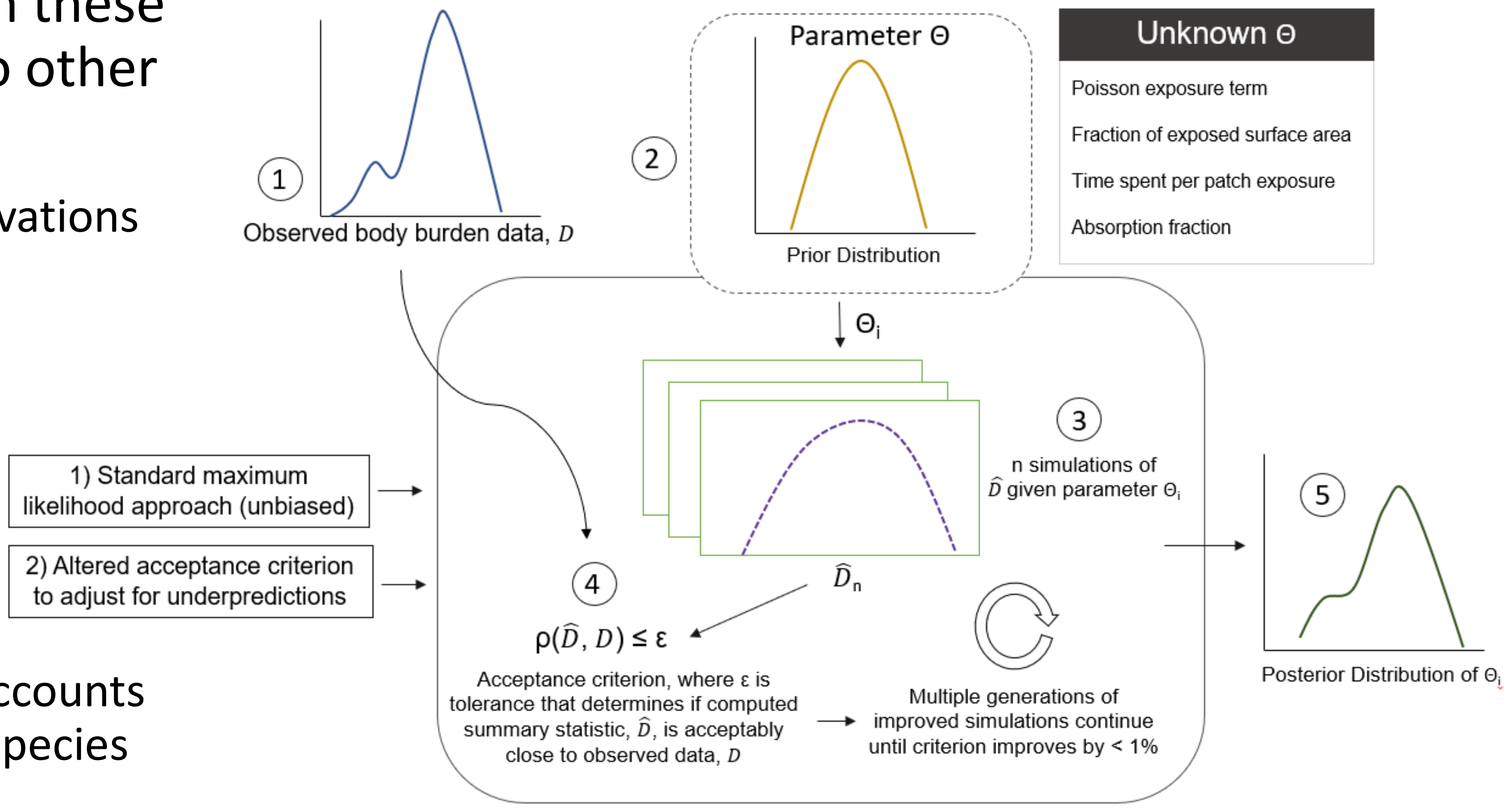
Collated experimental data as our observations $\mathbf{Y} = (y_1,\ldots,y_n)$

Vector of known parameters

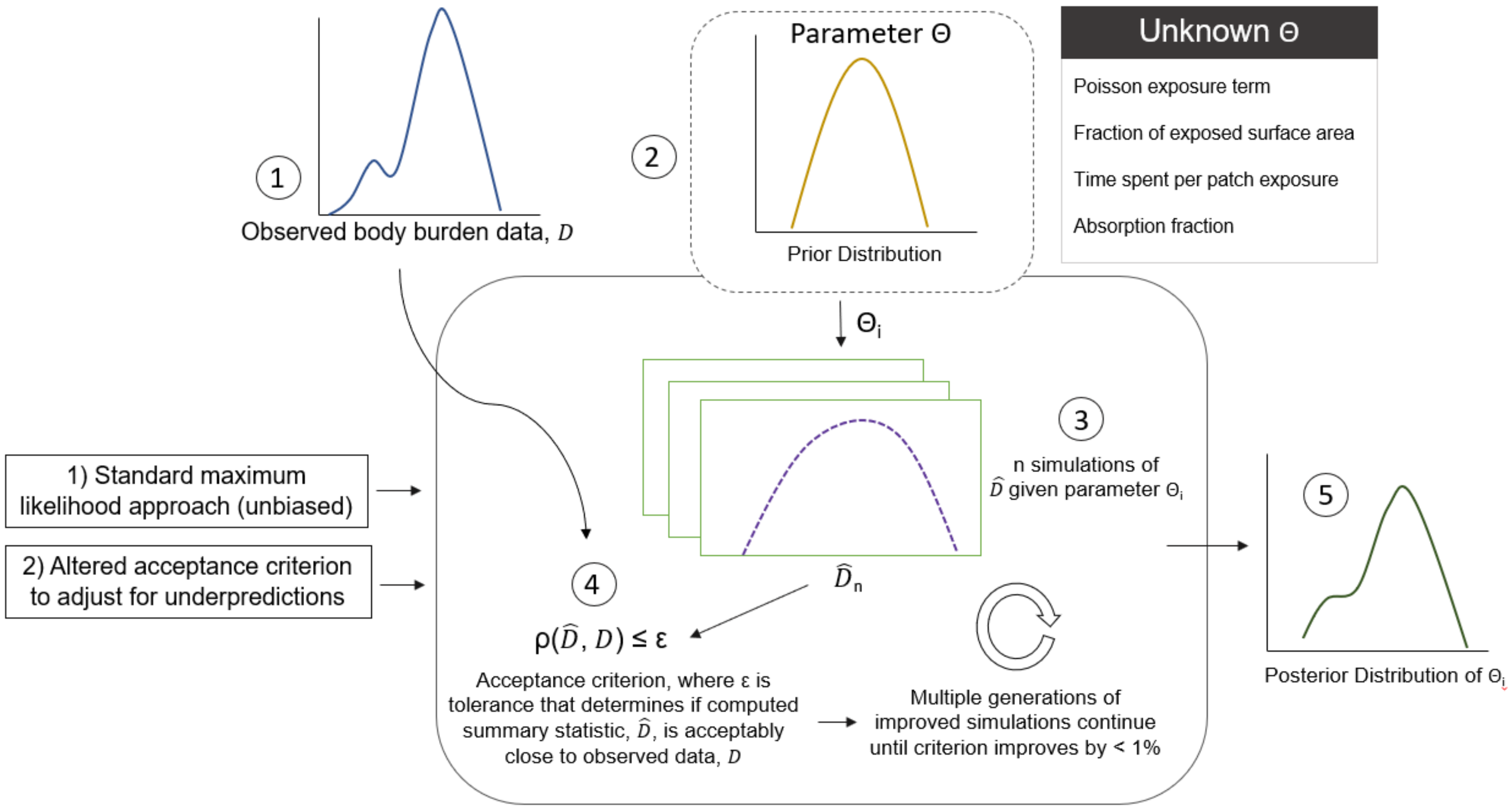
Vector of unknown parameters $(\boldsymbol{\theta}=\boldsymbol{\theta}_1,\ldots\boldsymbol{\theta}_n)$ about these observations

$\boldsymbol{\theta}$ is a random quantity that is sampled from a prior distribution $\boldsymbol{\pi}(\boldsymbol{\theta}|\boldsymbol{\lambda})$

$\boldsymbol{\lambda}$ being a vector of hyperparameters—accounts for variability across study x chemical x species combinations



ABC—Sequential Monte Carlo



We want to find the distributions of our unknown parameters--this will allow us to generalize the model to other amphibian spp x pesticide combinations

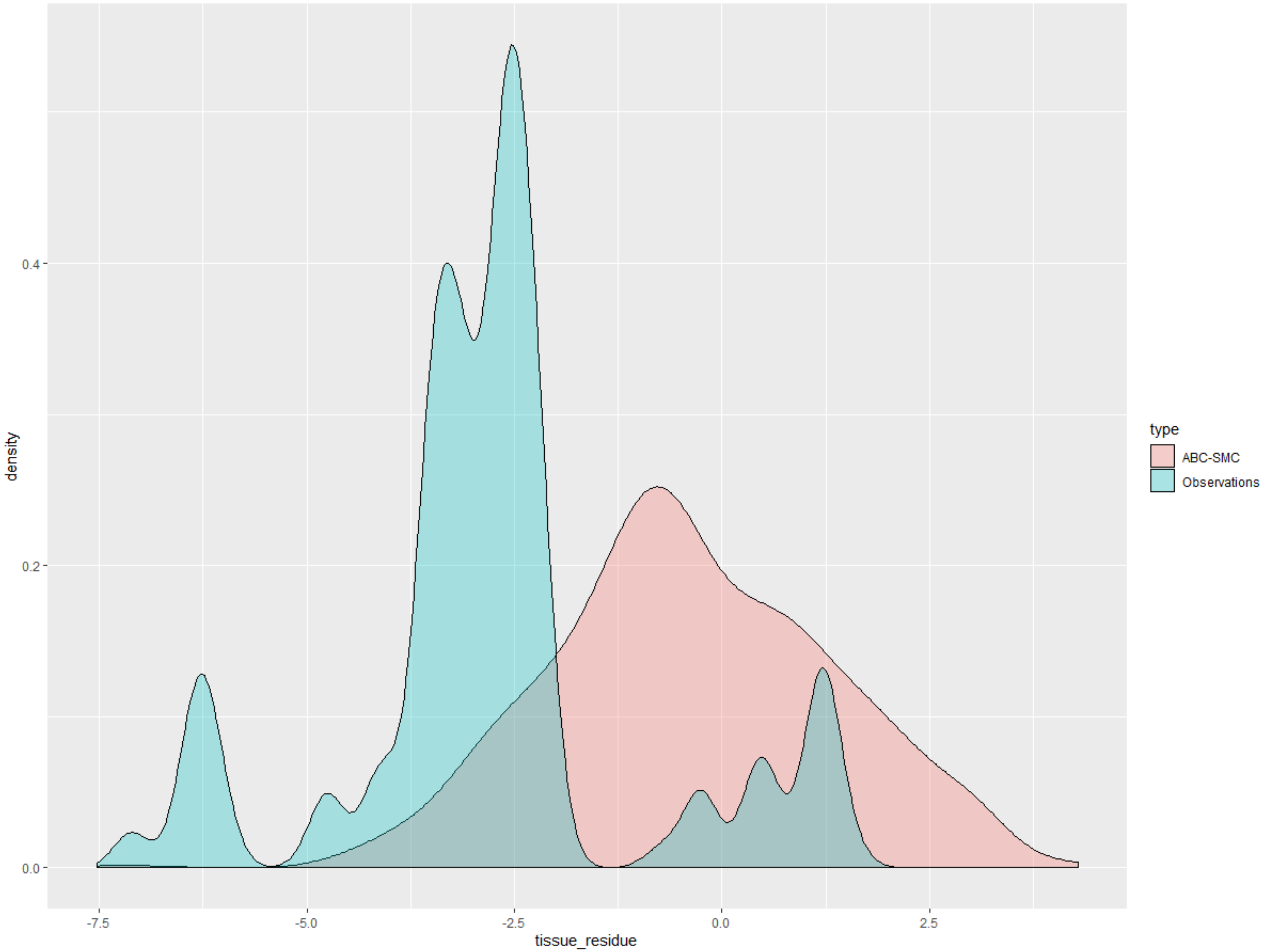
We generate proposal simulations from the prior distributions, calculating predicted body burdens

Compare predictions to the observed body burdens, use particle filtering to accept-reject proposals, based on a fitness criterion

Once we get 5k accepted proposals, we update our priors (MLE) based on the inputs from the accepted simulations

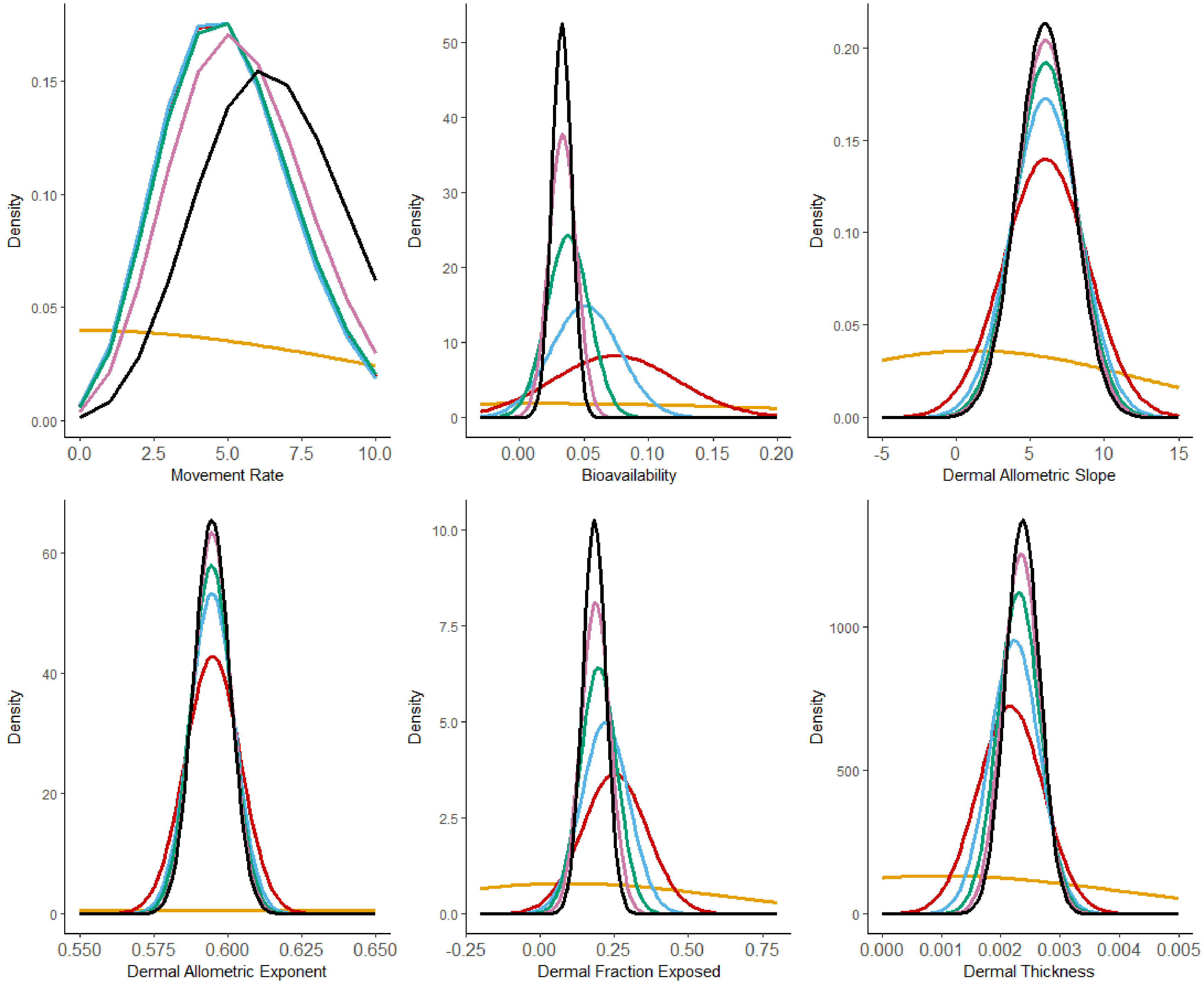
Multiple generations of this iteration approach, until the stopping criterion is met

Simulations vs Observations



Updated priors of important amphibian exposure parameters about which little was known

Candidate model for new pesticide x amphibian combinations



Conclusions

Calculated dietary, inhalation and dermal doses, parameterized for terrestrial vertebrate classes: Amphibians, Birds, Mammals, Reptiles

Amphibians/Reptiles get significant percentage of dose from dermal in simplified model, Birds/Mammals less so

Lots of uncertainty about inputs and form of a more refined amphibian dermal exposure model

ABC-SMC allows for inference on these unknown parameters when we have observations with some known parameters

Resulting probability model can be used for other species x pesticide combinations

Modifications for regulatory use, ensure sufficient degree or protectiveness (issues with MLE)

Implications for eco risk endpoint selection, also assessment of threatened and endangered amphibians

ABC-SMC robust approach for regulatory decision-making under uncertainty, combine the

ABC-SMC is customizable, we can build in a safety factor to the observations or layer other decision rules to the particle filtering approach while maintaining the metanalysis type incorporation of the observations

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Acknowledgments

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