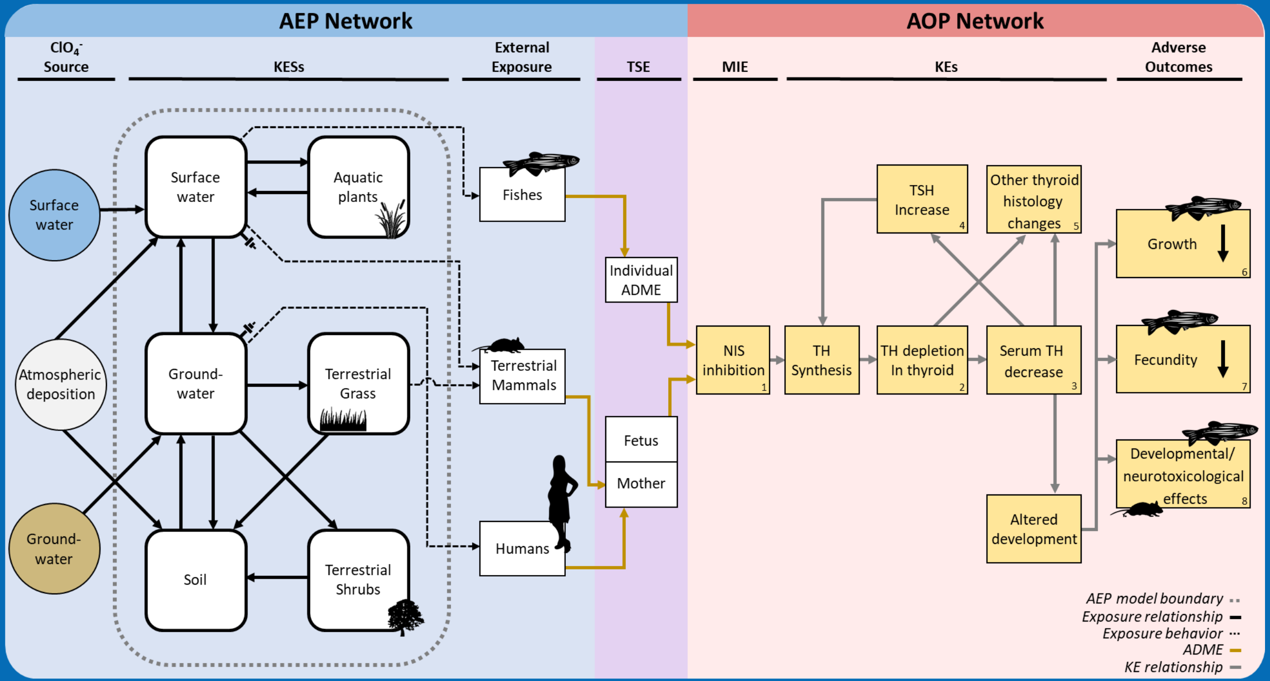
A Quantitative Source-to-Outcome Case Study to Demonstrate the Integration of Human Health and Ecological End Points Using the Aggregate Exposure Pathway and Adverse Outcome Pathway Frameworks



May 3, 2021

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Collaborators: Stephen Edwards, Rory Conolly, Annie Jarabek

Disclaimer

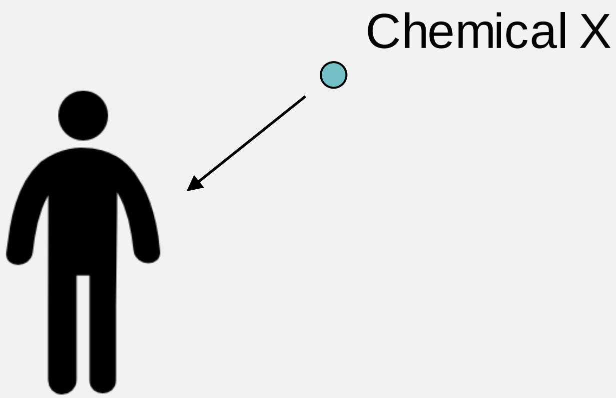
This work was conducted while at US EPA

The views presented in this work are those of the authors and do not necessarily represent the views of US EPA

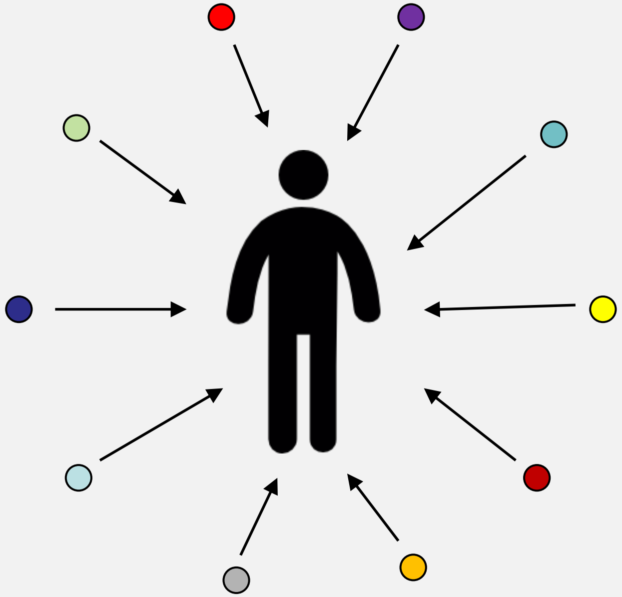
I have no conflicts of interest to declare

Motivation

Risk Assessment:



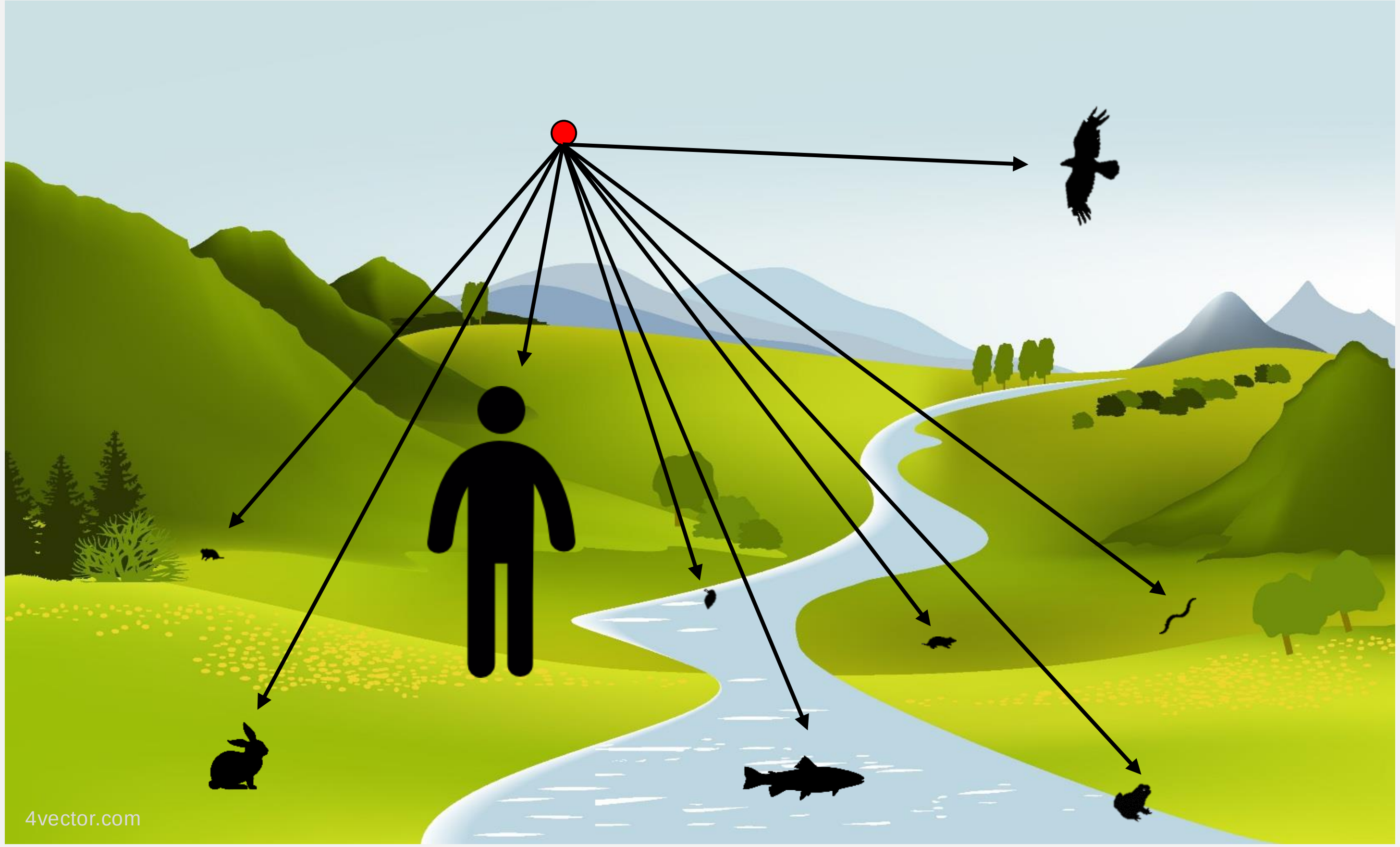
Cumulative Risk Assessment:



Motivation

Cumulative Risk Assessment:

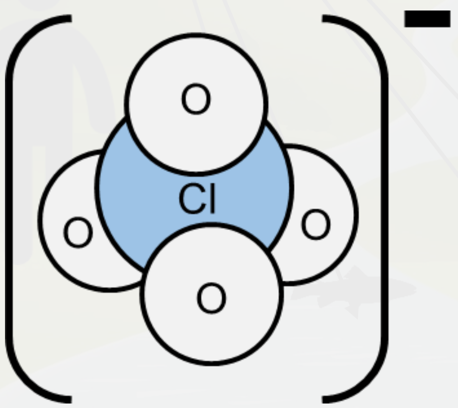
Cumulative Risk Assessment:



Project Goals:

1) **Develop techniques for cross-species data integration to inform risk assessment**

2) **Conduct a case study to demonstrate the application of these techniques**

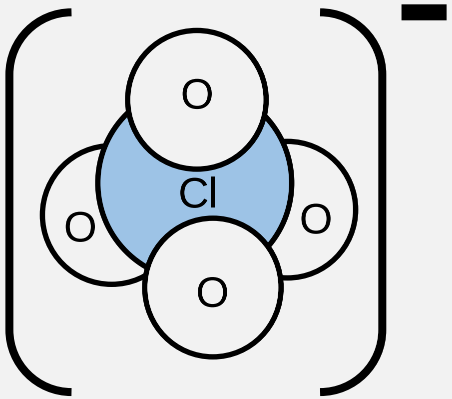


Perchlorate

- Widespread
- Well studied
- Conserved AOP

This work is not a new risk assessment for perchlorate

Perchlorate in the Environment

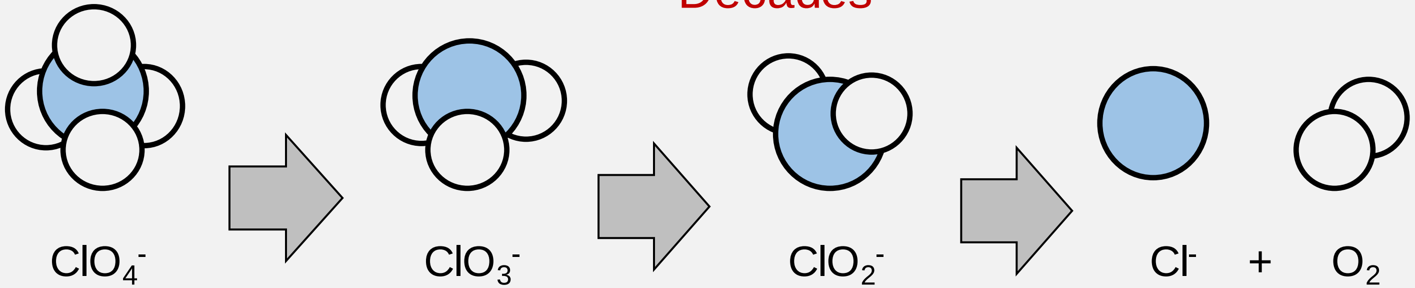


ClO_4^-

Readily forms salts
(Na^+, K^+, Mn^+, NH_4^+)

Highly
Soluble

Decades

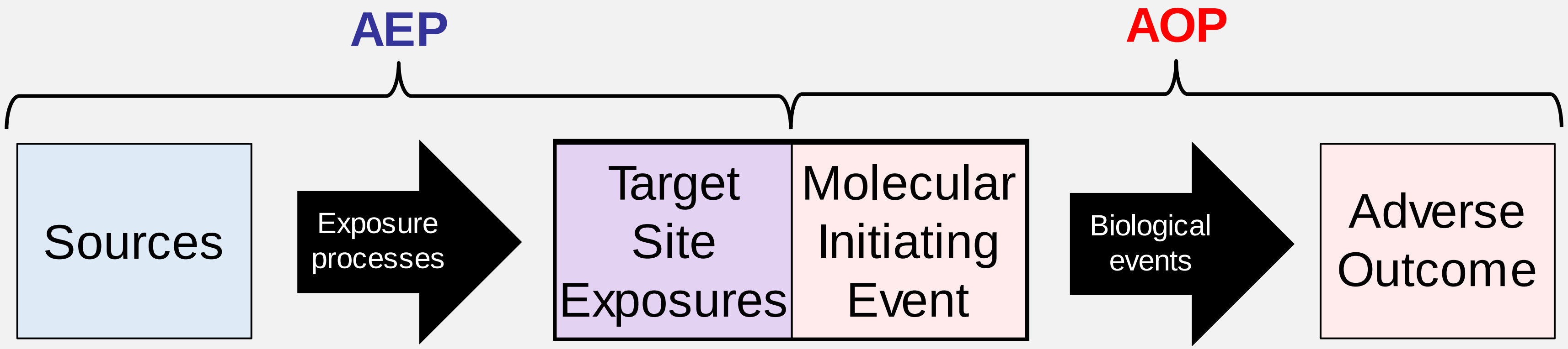


ClO_4^- Perchlorate → ClO_3^- Chlorate → ClO_2^- Chlorite → Cl^- + O_2 Chlorine + Oxygen

Approach

- We used the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to organize and integrate mechanistic data.

Villeneuve et at. (2014), Teeguarden et al. (2016)



• Sources of contamination • Key Exposure States • Key Exposure Relationships • Target Site Exposures	• Molecular Initiating Event • Key Events • Key Event Relationships • Adverse Outcomes

Teeguarden, J.G., Tan, Y., Edwards, S.W, Leonard, J.A., Anderson, K.A., Corley, R.A., Kile, M.L, Simonich, S.M., Stone, D., Tanquay, R.L., Waters, K.M., Harper, S.L., Williams, D.E. (2016). Completing the link between exposure science and toxicology for improved environmental health decision making: The aggregate exposure pathway framework. *Environmental Science & Technology* 50, 4579-4586.
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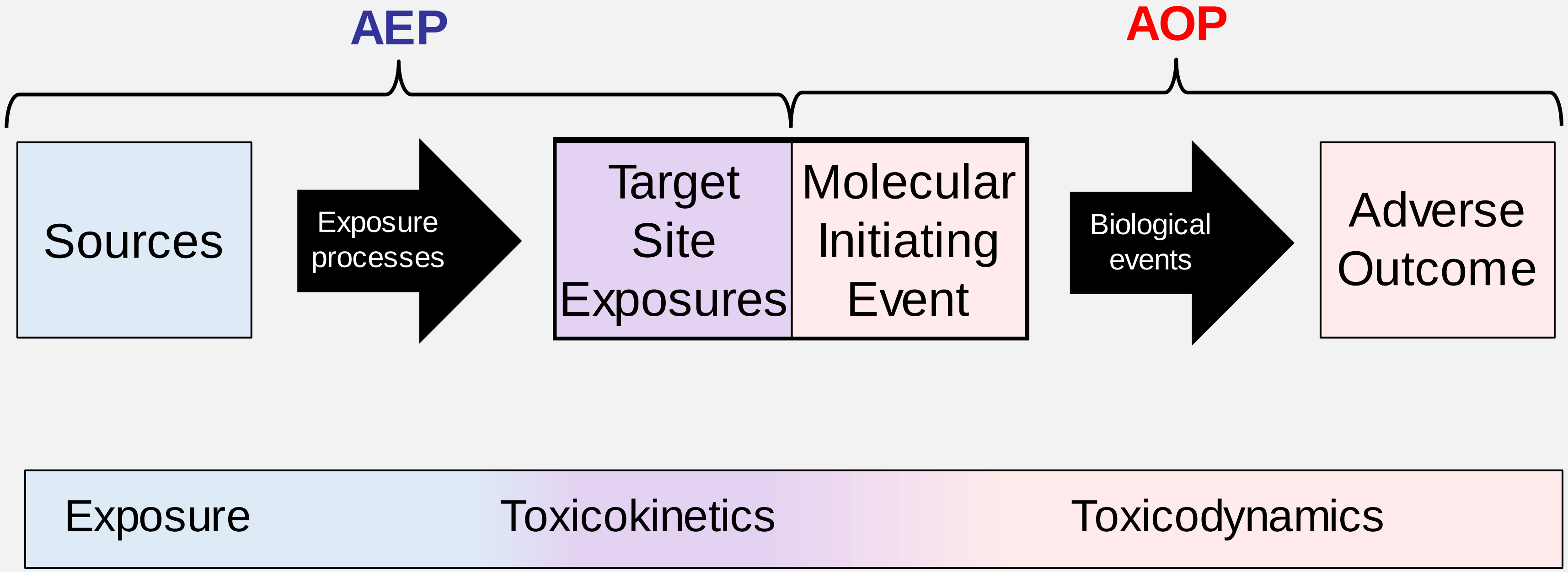

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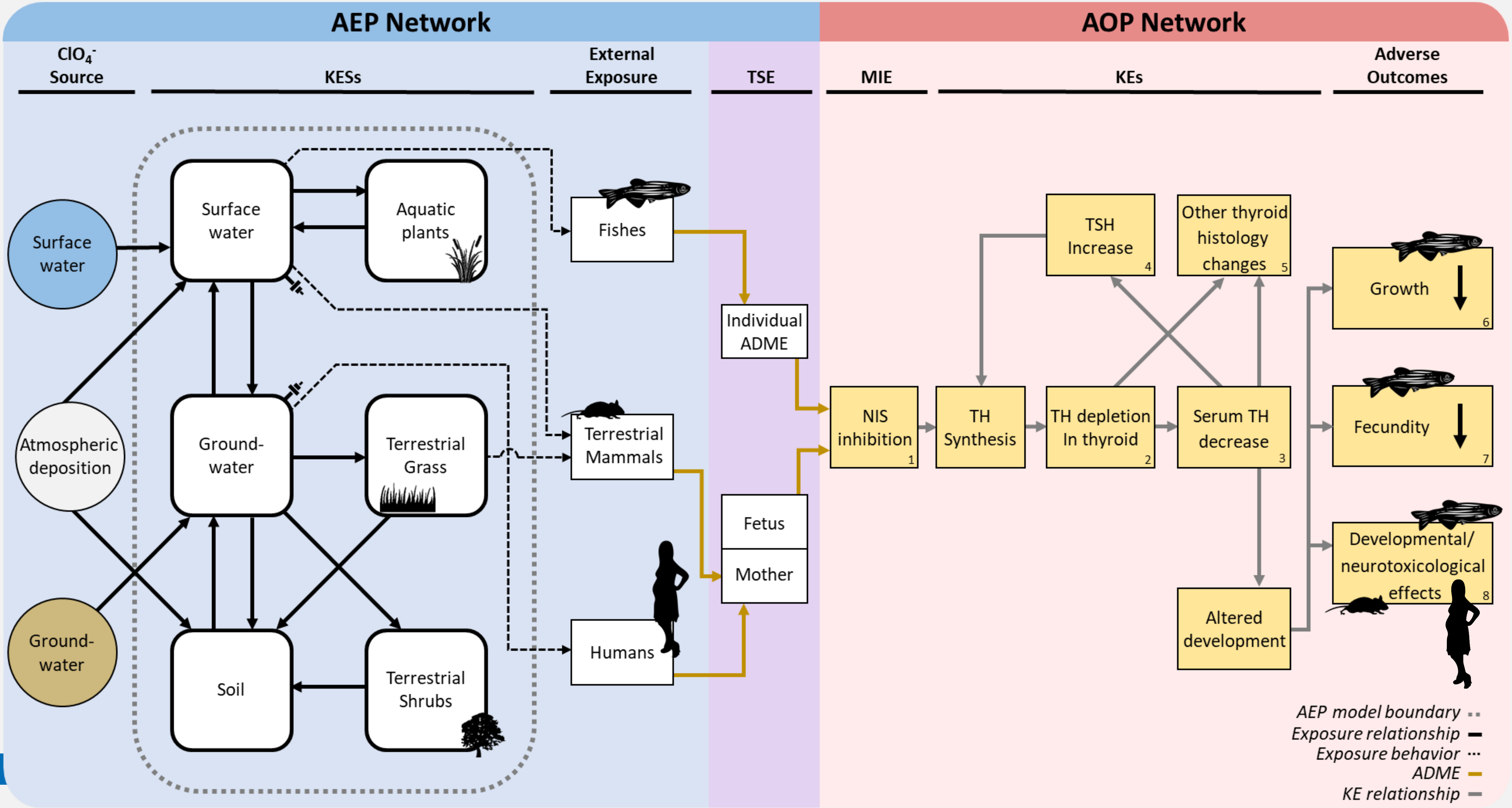
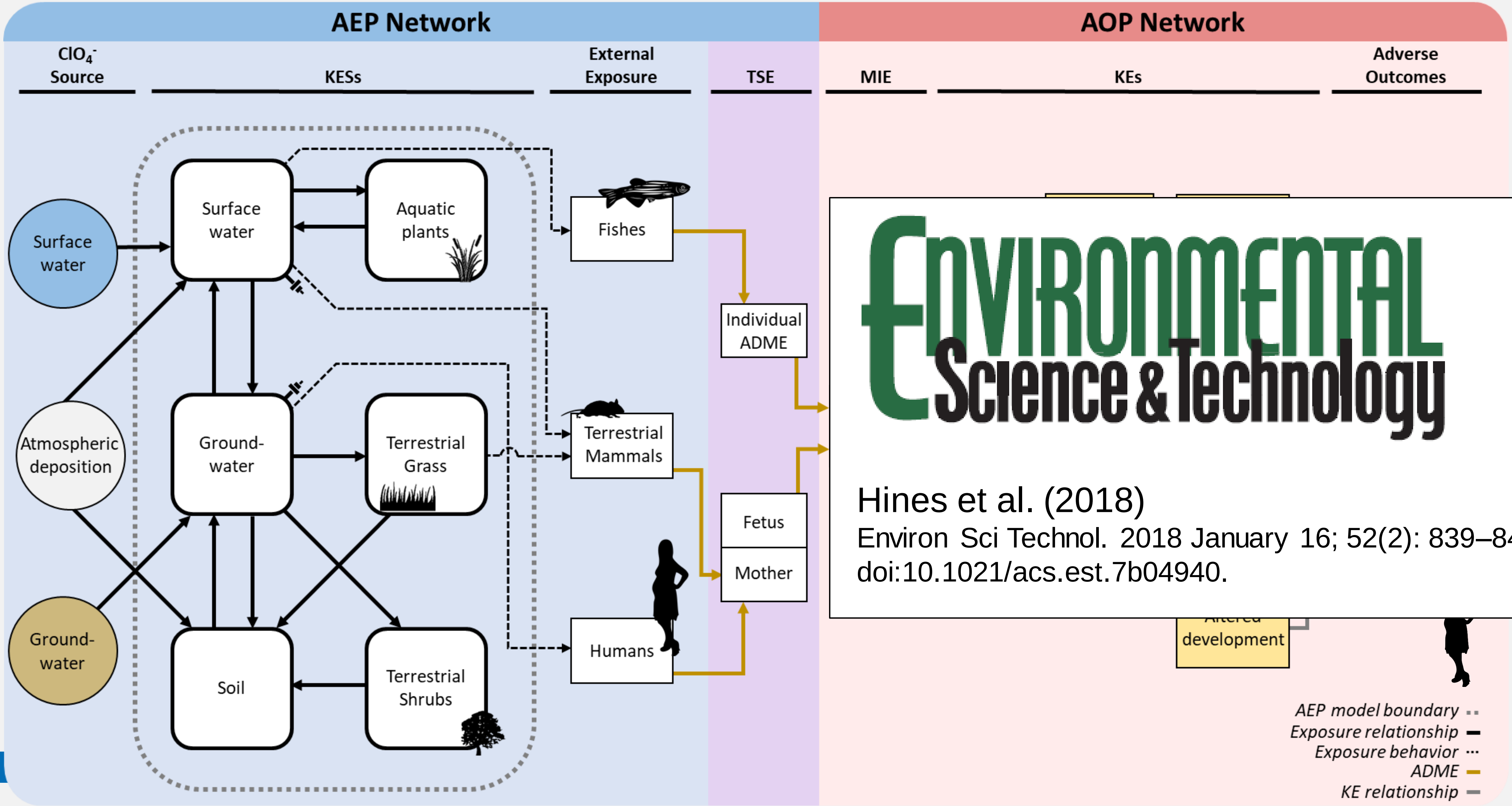

AEP Network
AOP Network
ClO_4^- Source
KESs
External Exposure
TSE
MIE
KEs
Adverse Outcomes
Surface water
Atmospheric deposition
Ground-water
Surface water
Aquatic plants
Ground-water
Terrestrial Grass
Soil
Terrestrial Shrubs
Fishes
Terrestrial Mammals
Humans
Individual ADME
Fetus
Mother
NIS inhibition 1
TH Synthesis
TH depletion In thyroid 2
Serum TH decrease 3
TSH Increase 4
Other thyroid histology changes 5
Altered development
Growth 6
Fecundity 7
Developmental/ neurotoxicological effects 8
AEP model boundary
Exposure relationship
Exposure behavior
ADME
KE relationship

Approach

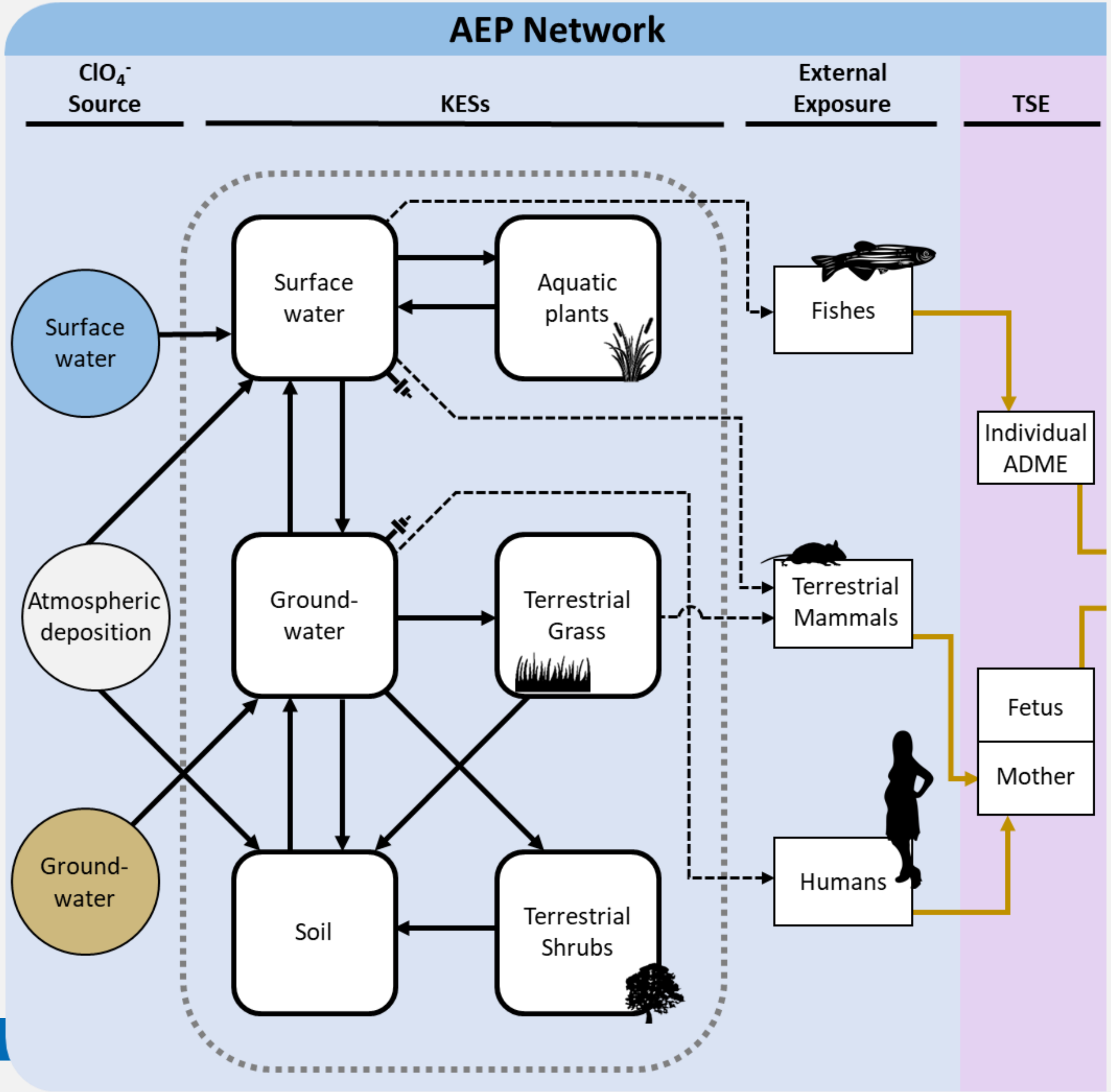


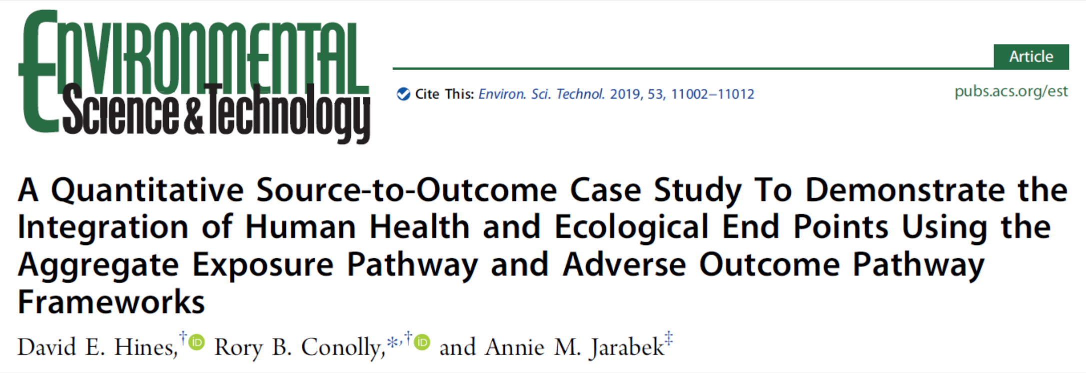
Hines et al. (2018)

Environ Sci Technol. 2018 January 16; 52(2): 839–849.

doi:10.1021/acs.est.7b04940.

Approach





Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2019, 53, 11002−11012

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A Quantitative Source-to-Outcome Case Study To Demonstrate the Integration of Human Health and Ecological End Points Using the Aggregate Exposure Pathway and Adverse Outcome Pathway Frameworks

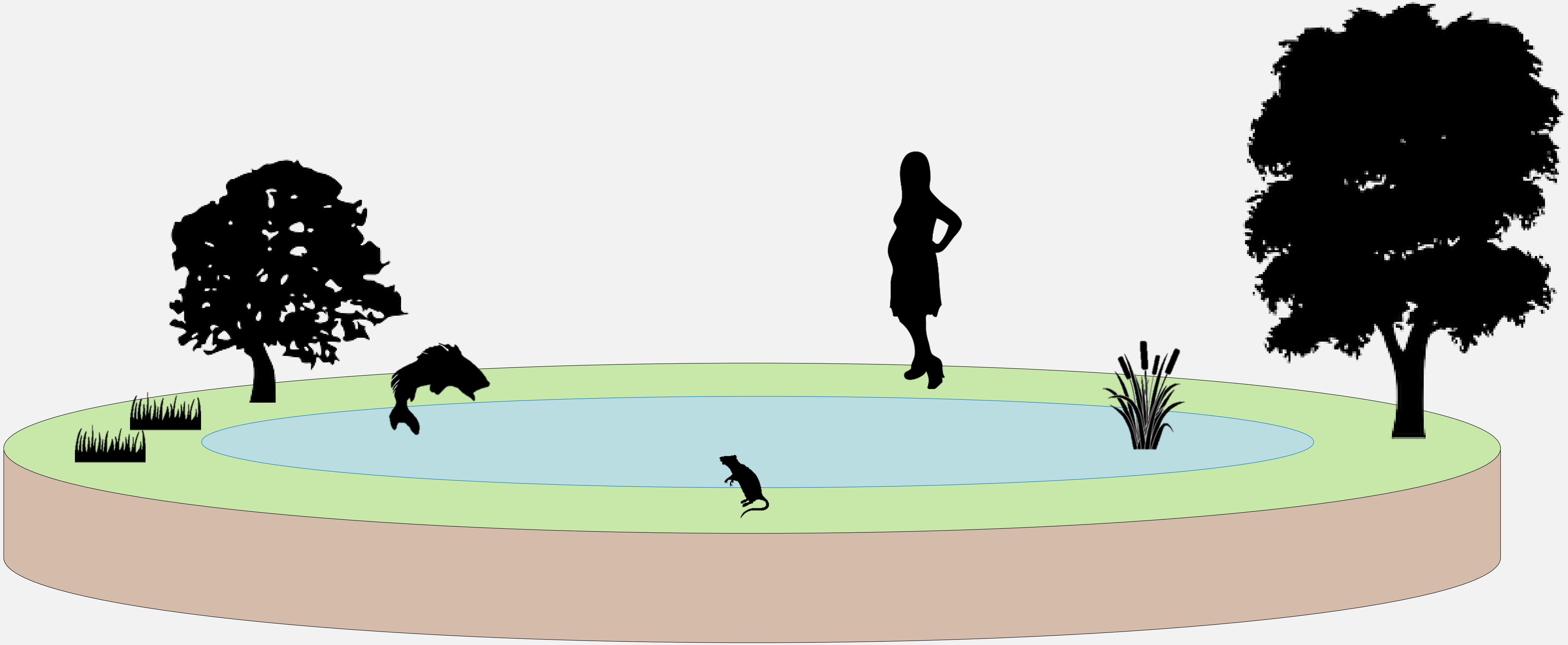
David E. Hines,[†] Rory B. Conolly,[*,†] and Annie M. Jarabek[‡]

External exposure

↓

Internal TSE

Hypothetical constructed wetland



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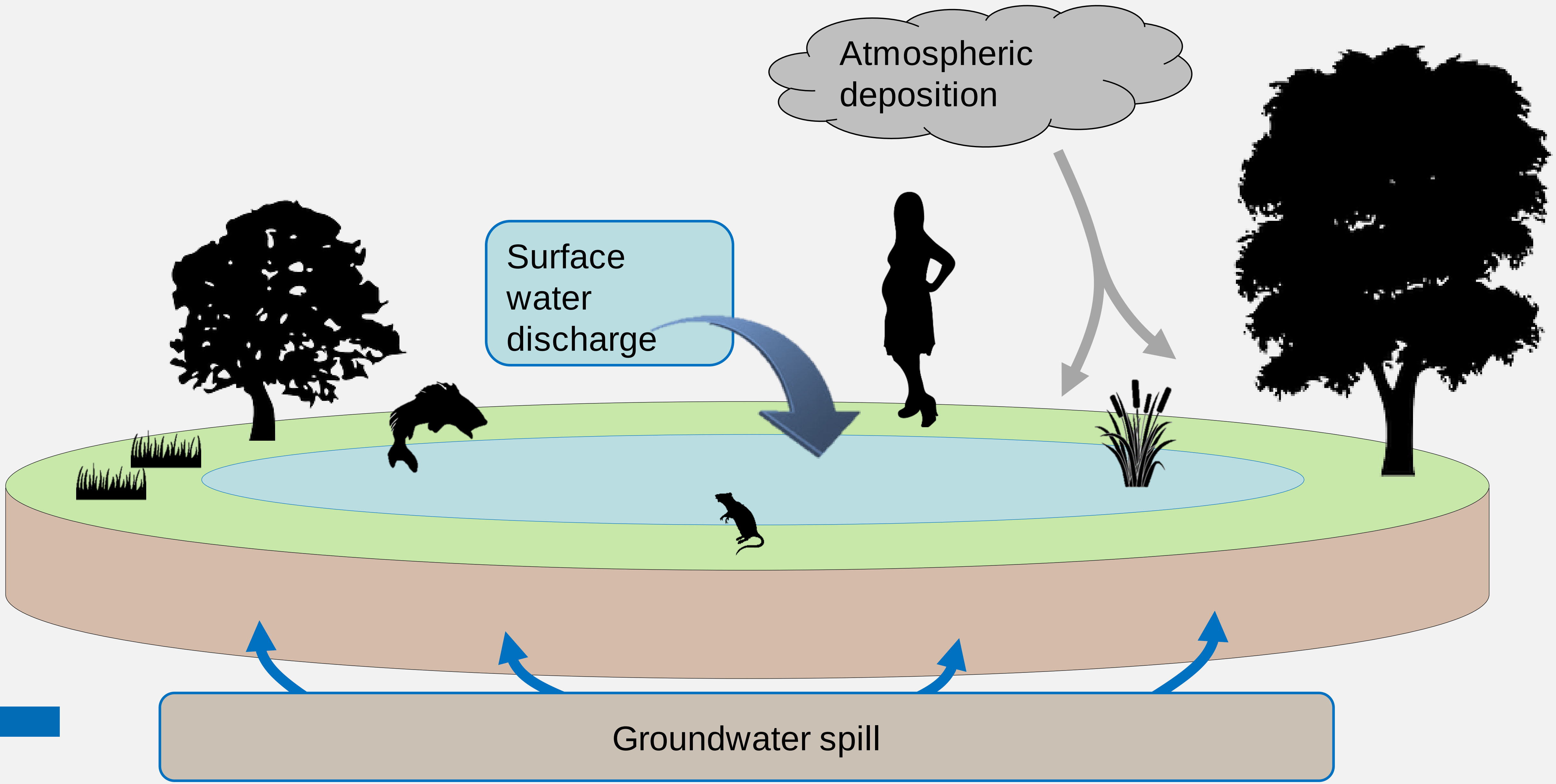
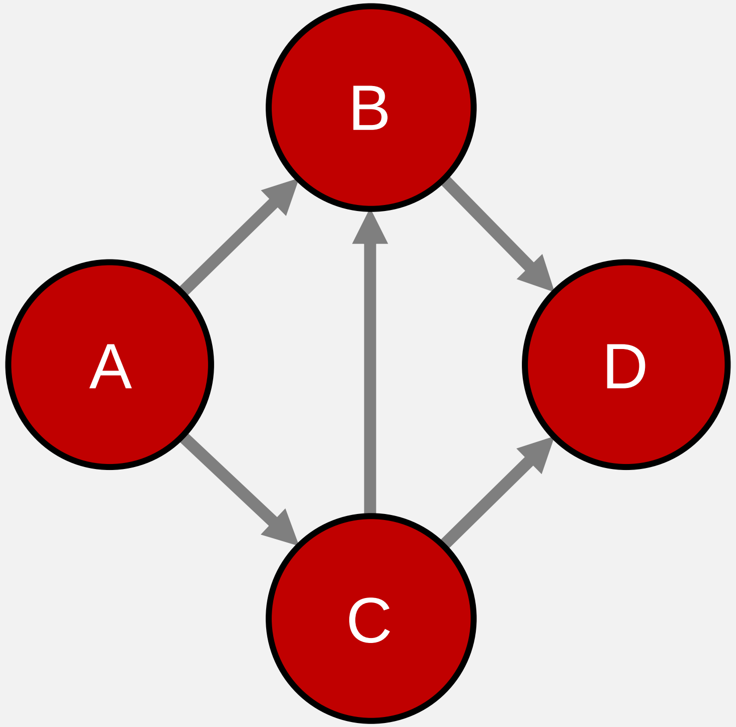


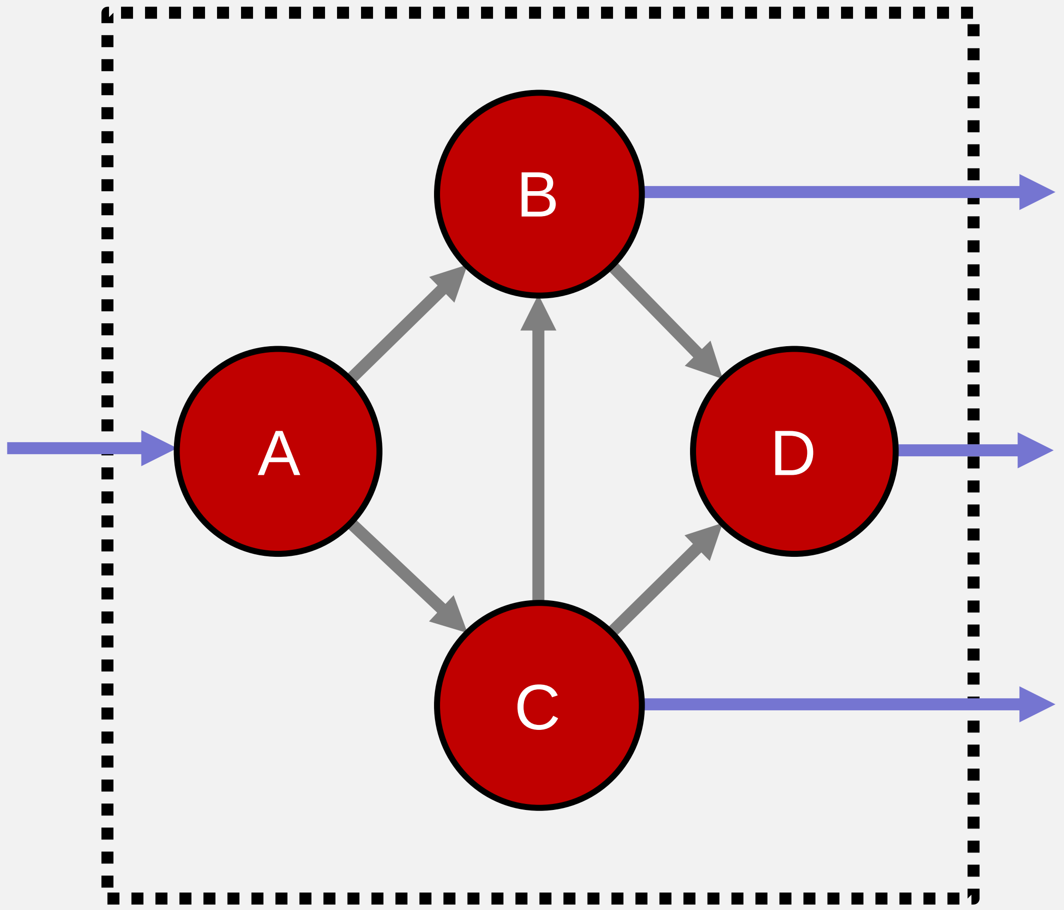
Network Flow Models



Nodes = resource pools (eg. species, biomass, standing stock)

Edges = transport or transformations

Network Flow Models



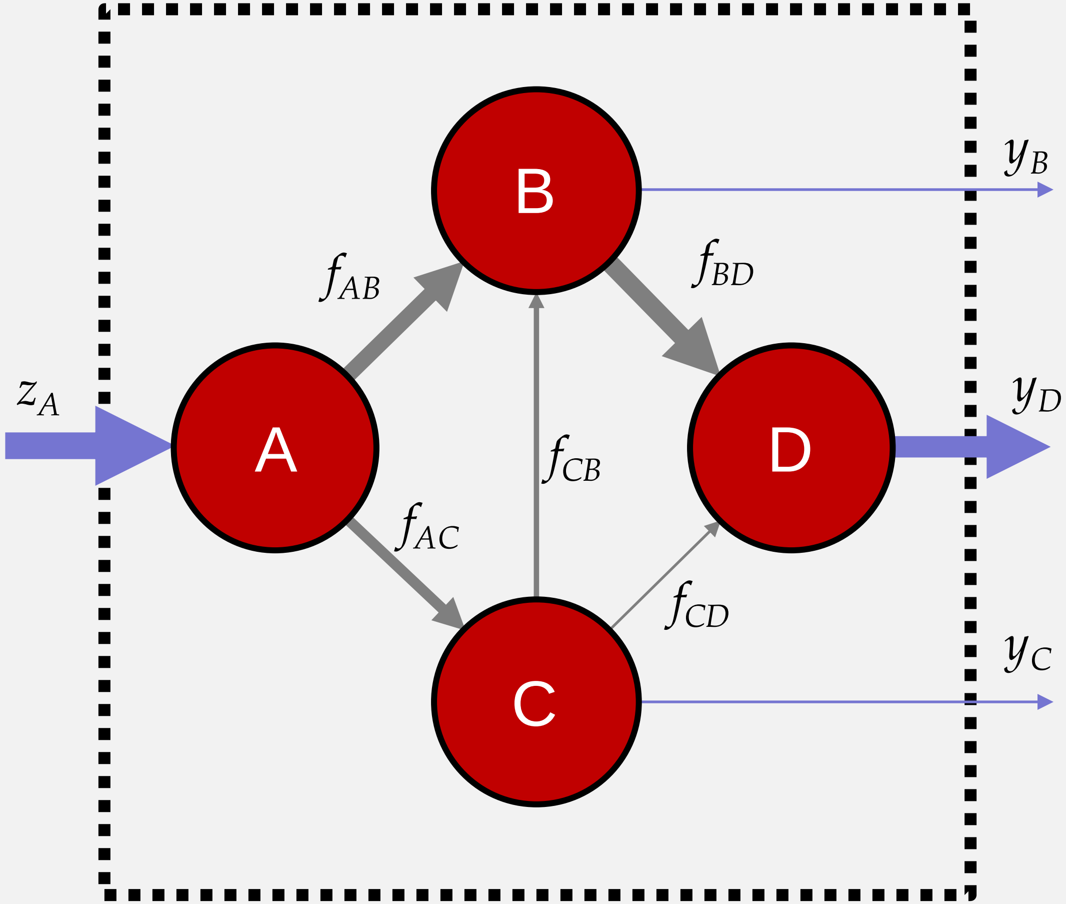
Nodes = resource pools (eg. species, biomass, standing stock)

Edges = transport or transformations

Systems must have a boundary

Systems must be open, has **boundary flows**

Network Flow Models

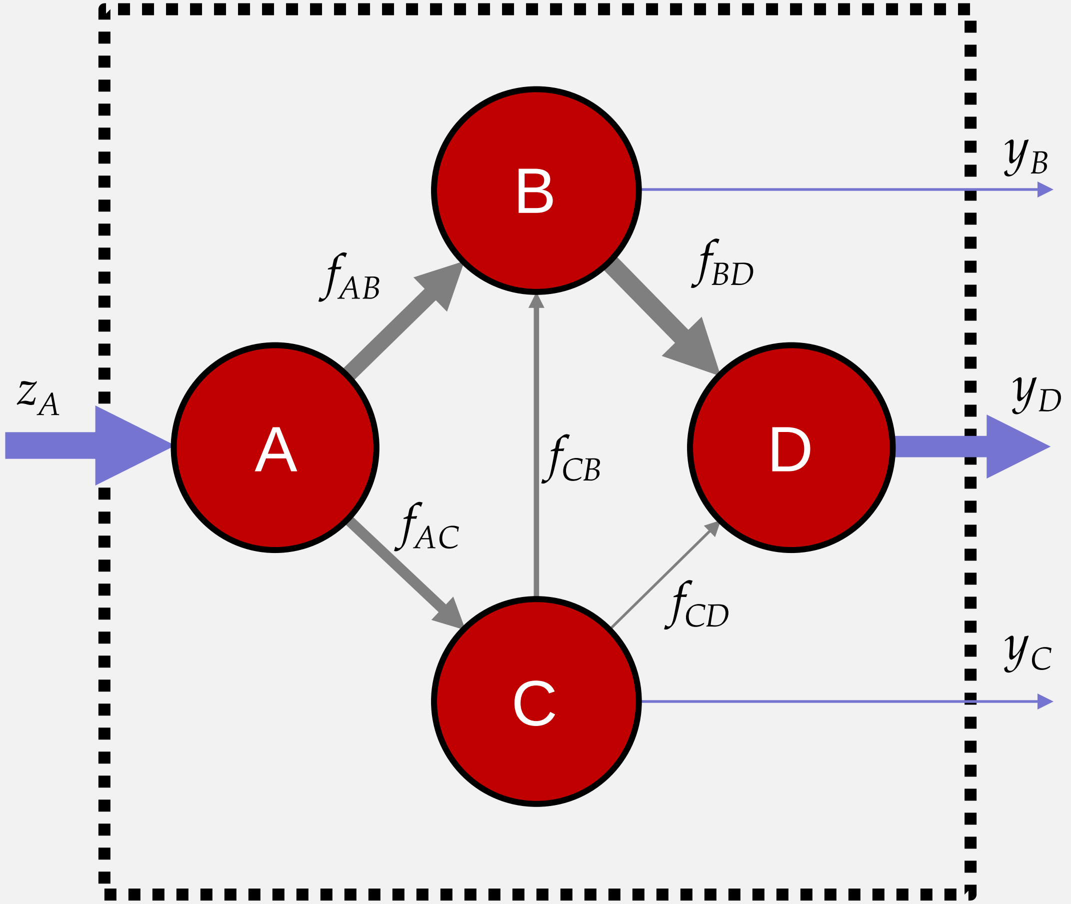


Weighted, directional edges

→ Mass balance

(Thermodynamically conservative)

Network Flow Models



Matrix Representation

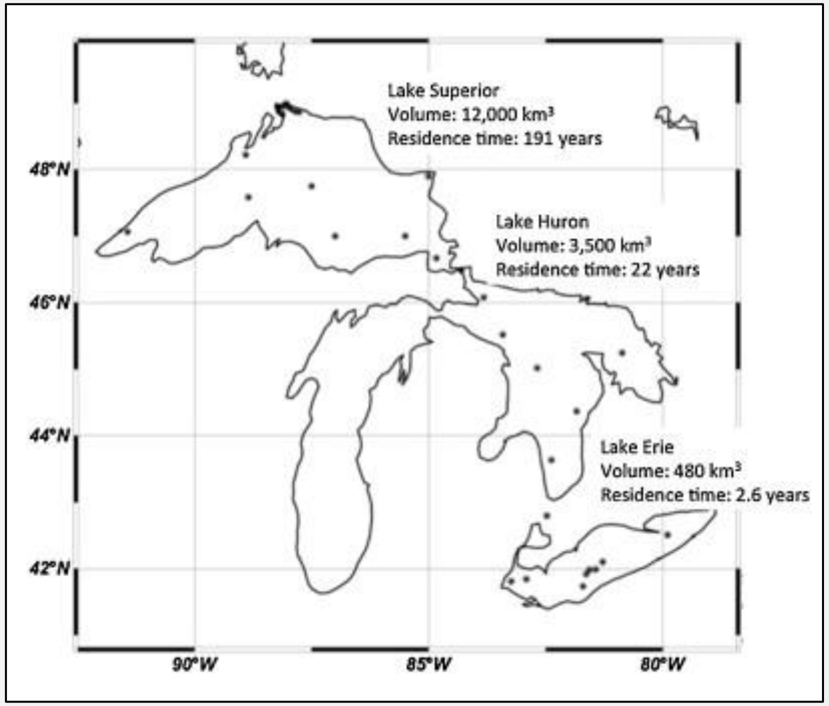
Outputs

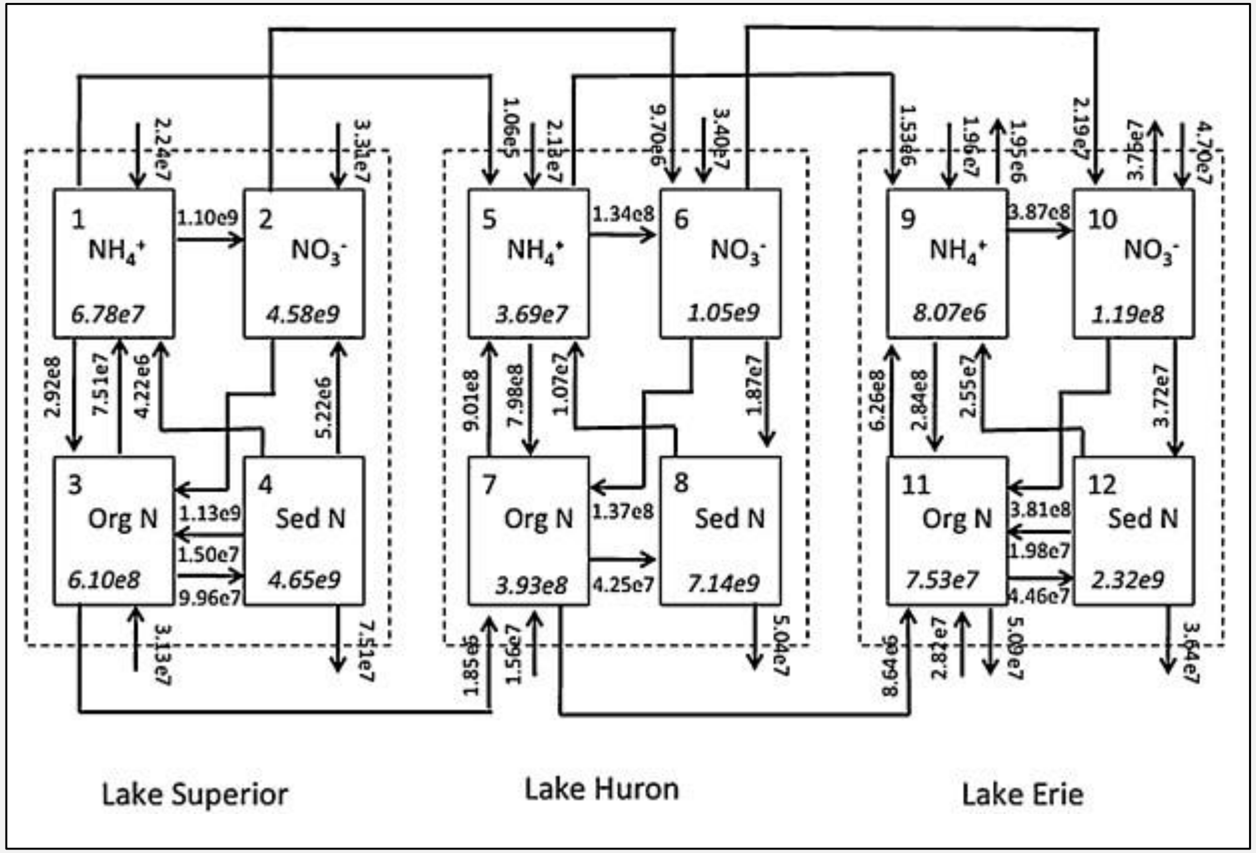
=

$$\text{Flows} = \begin{pmatrix} 0 & f_{AB} & f_{AC} & 0 \\ 0 & 0 & 0 & f_{DB} \\ 0 & f_{CB} & 0 & f_{CD} \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} 0 \\ y_B \\ y_C \\ y_D \end{pmatrix}$$

$$\text{Inputs} = \begin{pmatrix} Z_A & 0 & 0 & 0 \end{pmatrix}$$

Example Network Flow Analysis





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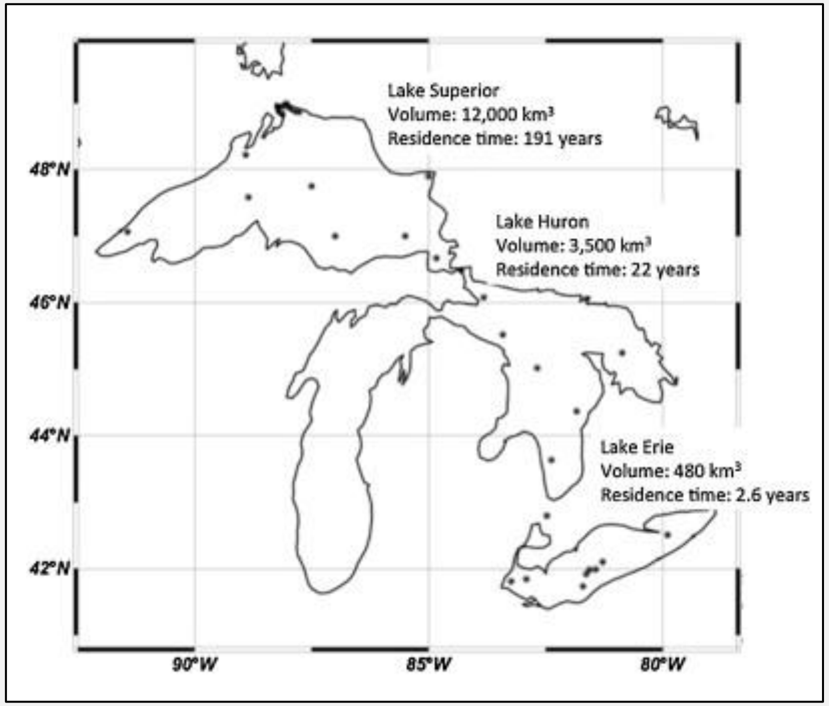
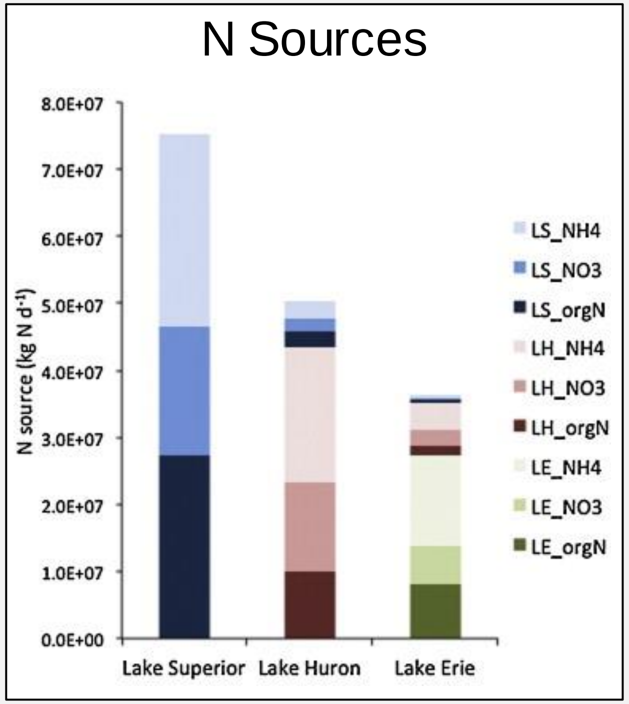
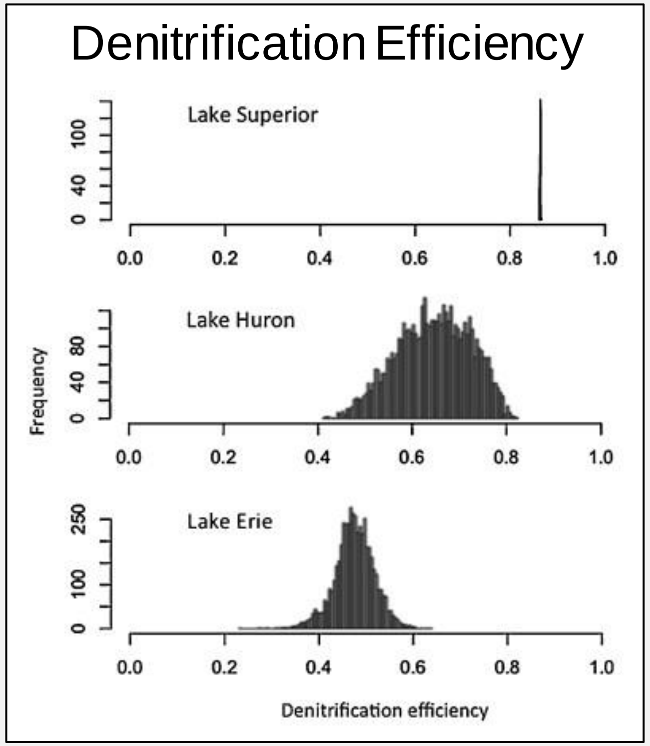
Example Network Flow Analysis







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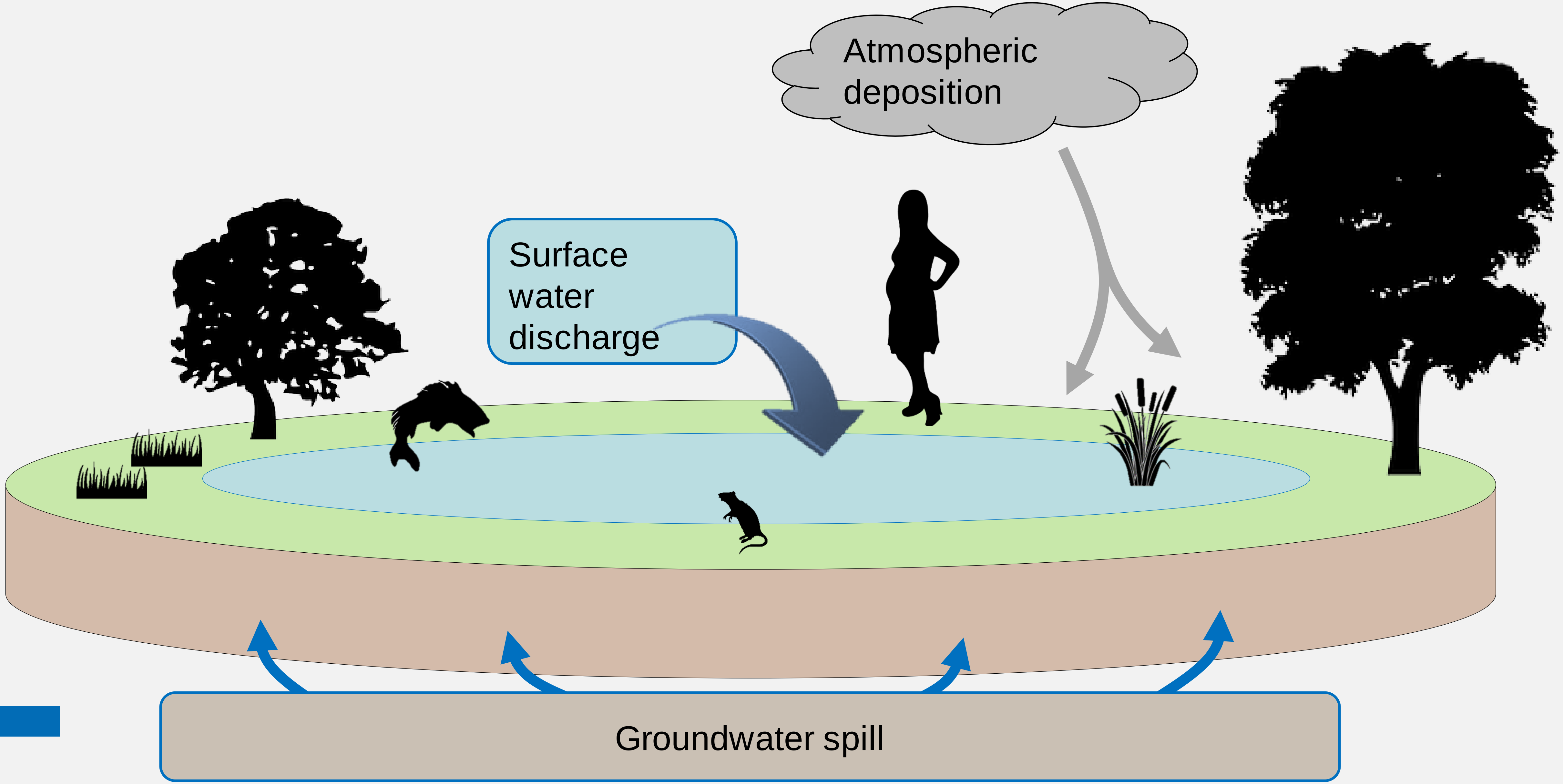
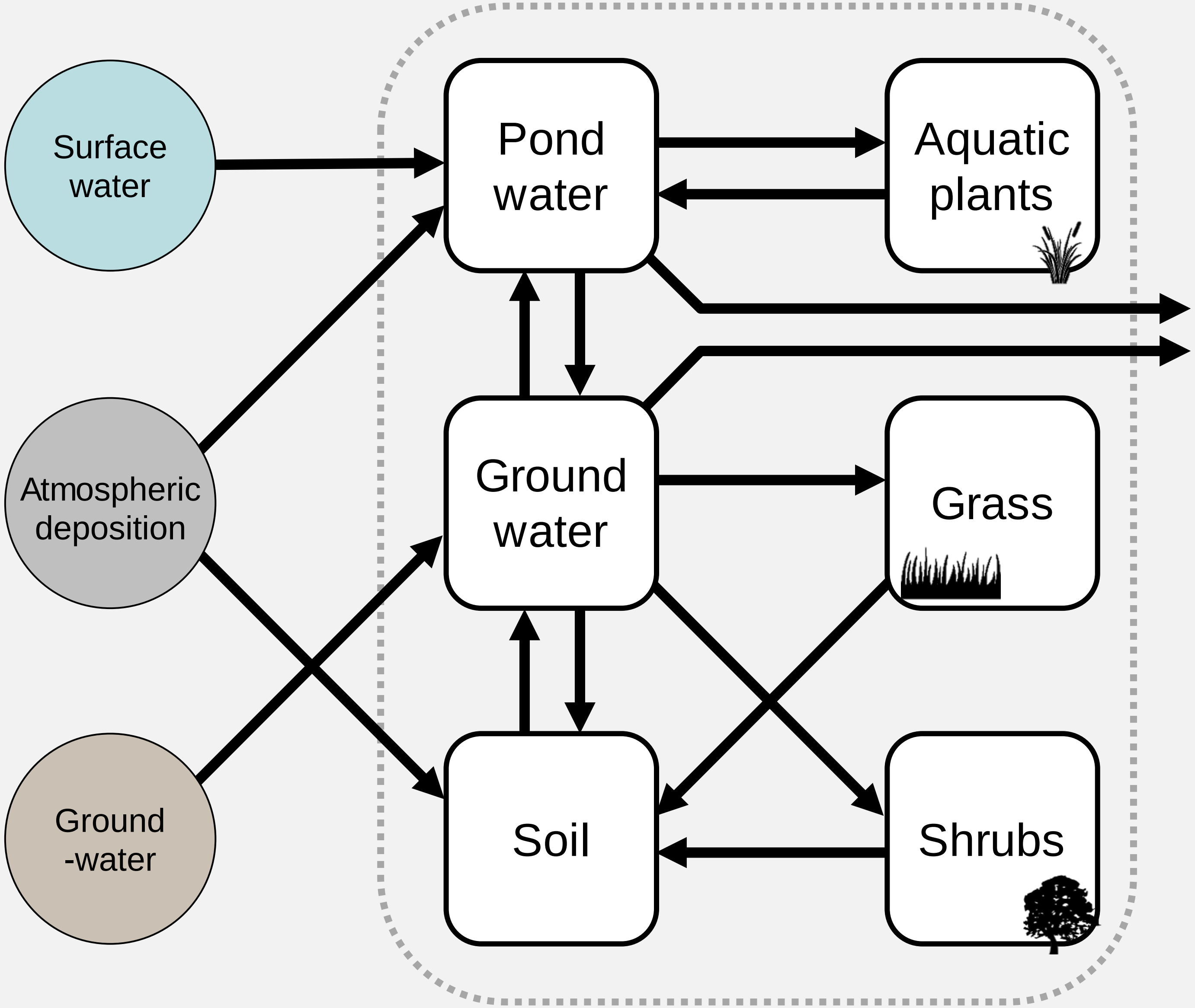


Network representation



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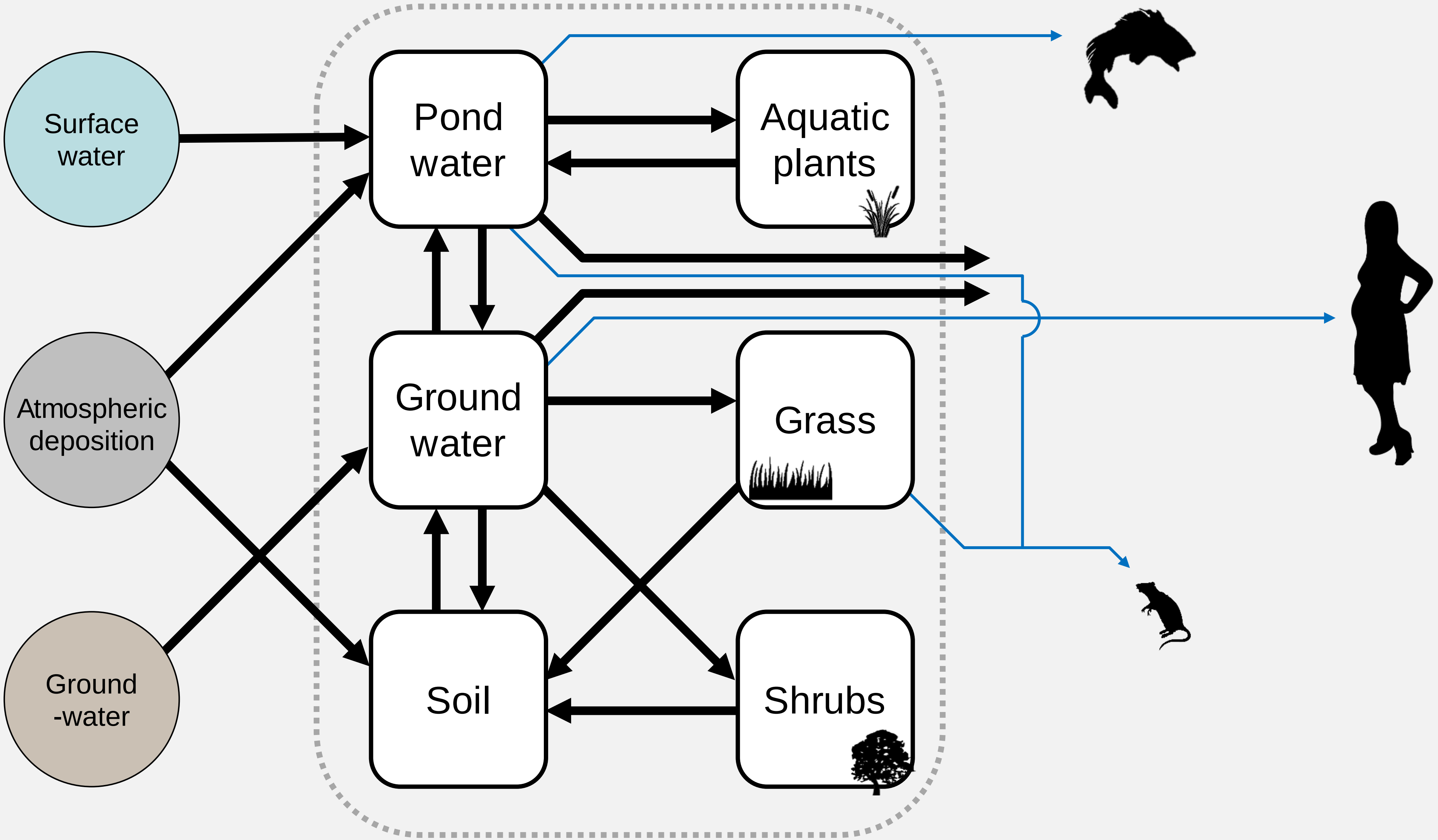

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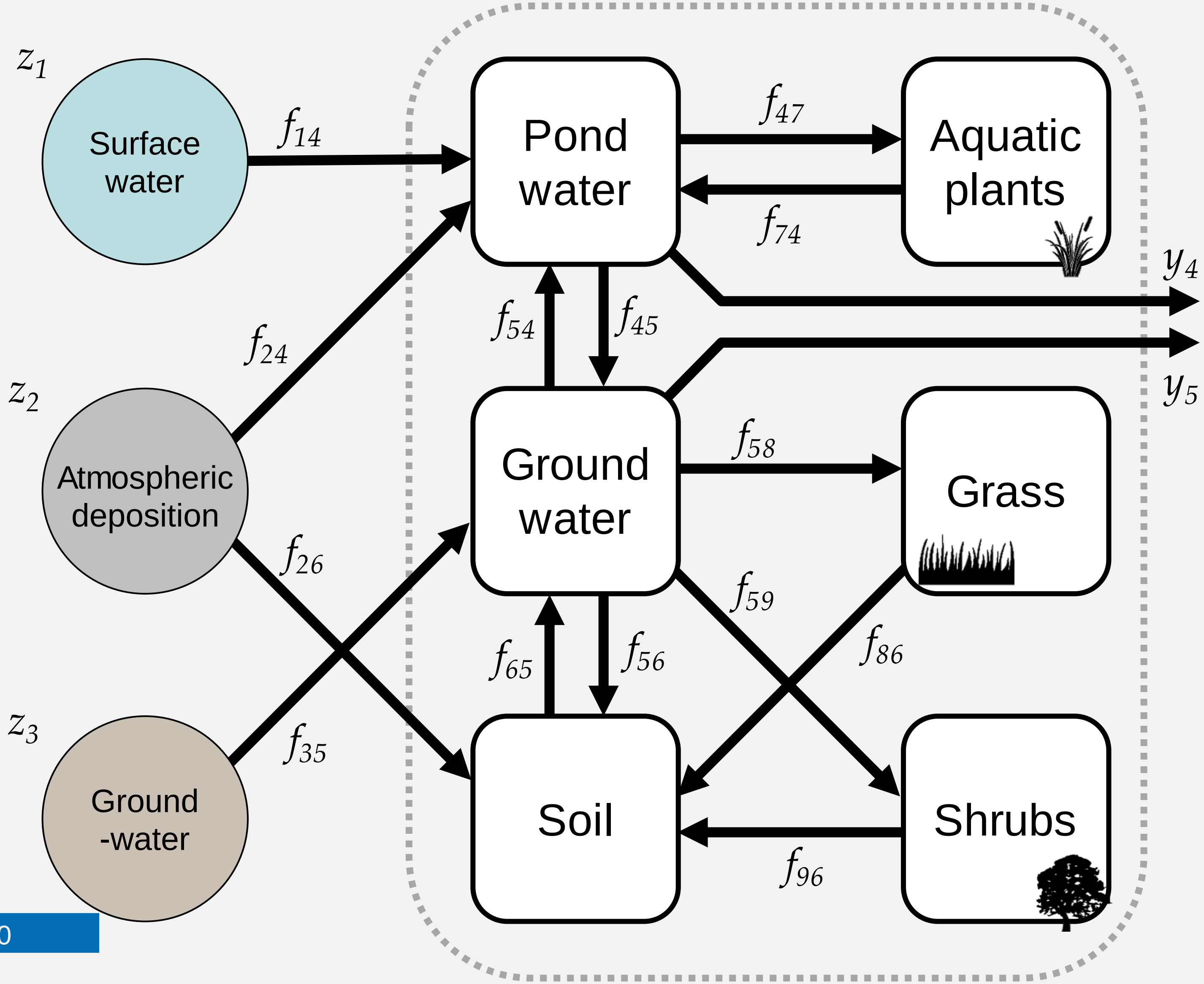


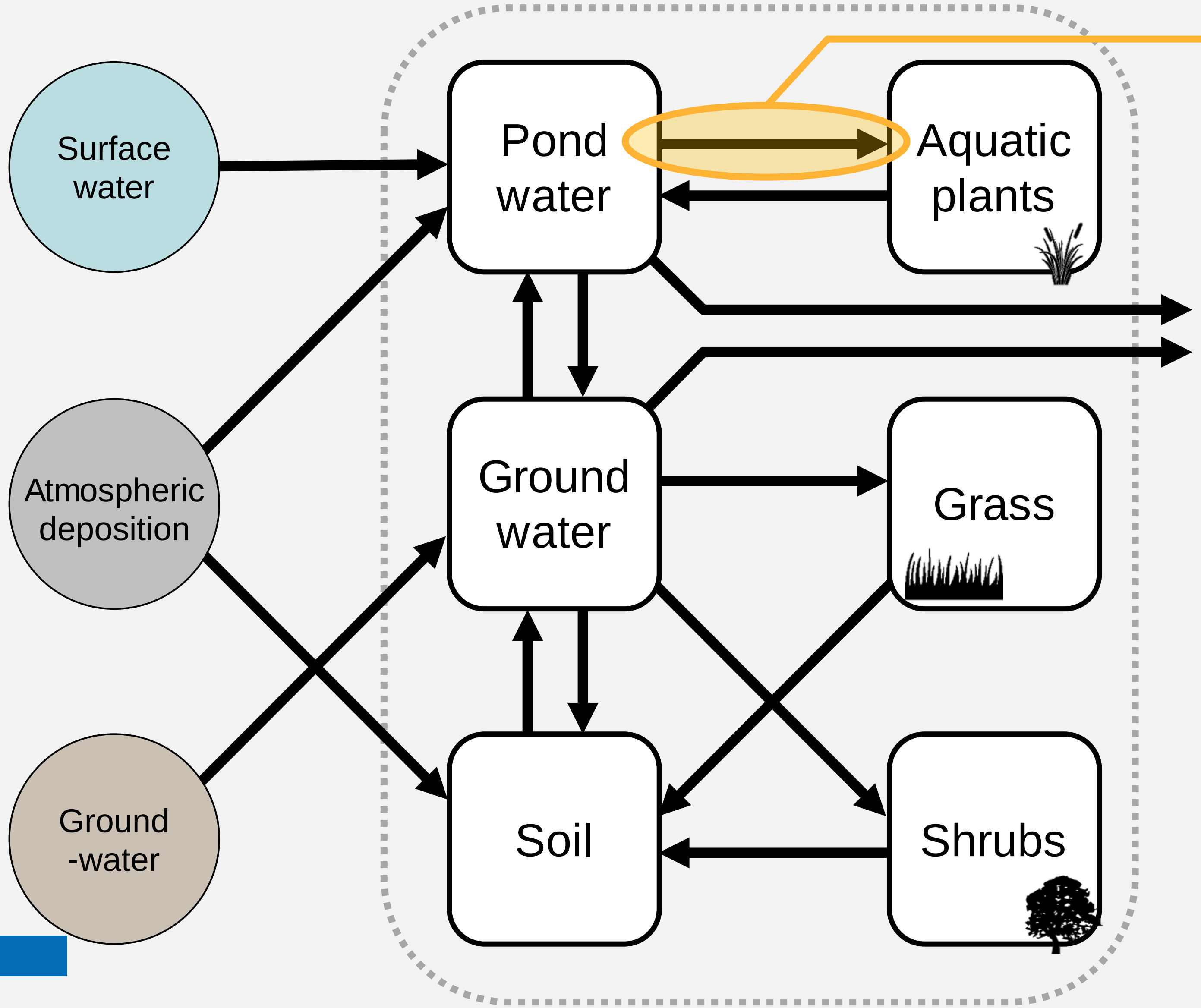
Flows | Outputs

$$
\begin{pmatrix}
0 & 0 & 0 & f_{14} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & f_{24} & 0 & f_{26} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & f_{35} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & f_{45} & 0 & f_{47} & 0 & 0 \\
0 & 0 & 0 & f_{54} & 0 & f_{56} & 0 & f_{58} & f_{59} \\
0 & 0 & 0 & 0 & f_{65} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & f_{74} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & f_{86} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & f_{96} & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
0 \\ 0 \\ 0 \\ y_4 \\ y_5 \\ 0 \\ 0 \\ 0 \\ 0
\end{pmatrix}
$$

$$
\begin{pmatrix}
z_1 & z_2 & z_3 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}
$$

Inputs

Network Parameterization



Completely hypothetical datapoints; not at all real; units = g ClO4(mass)/area/d
Flow IDs correspond to preliminary CSM figure

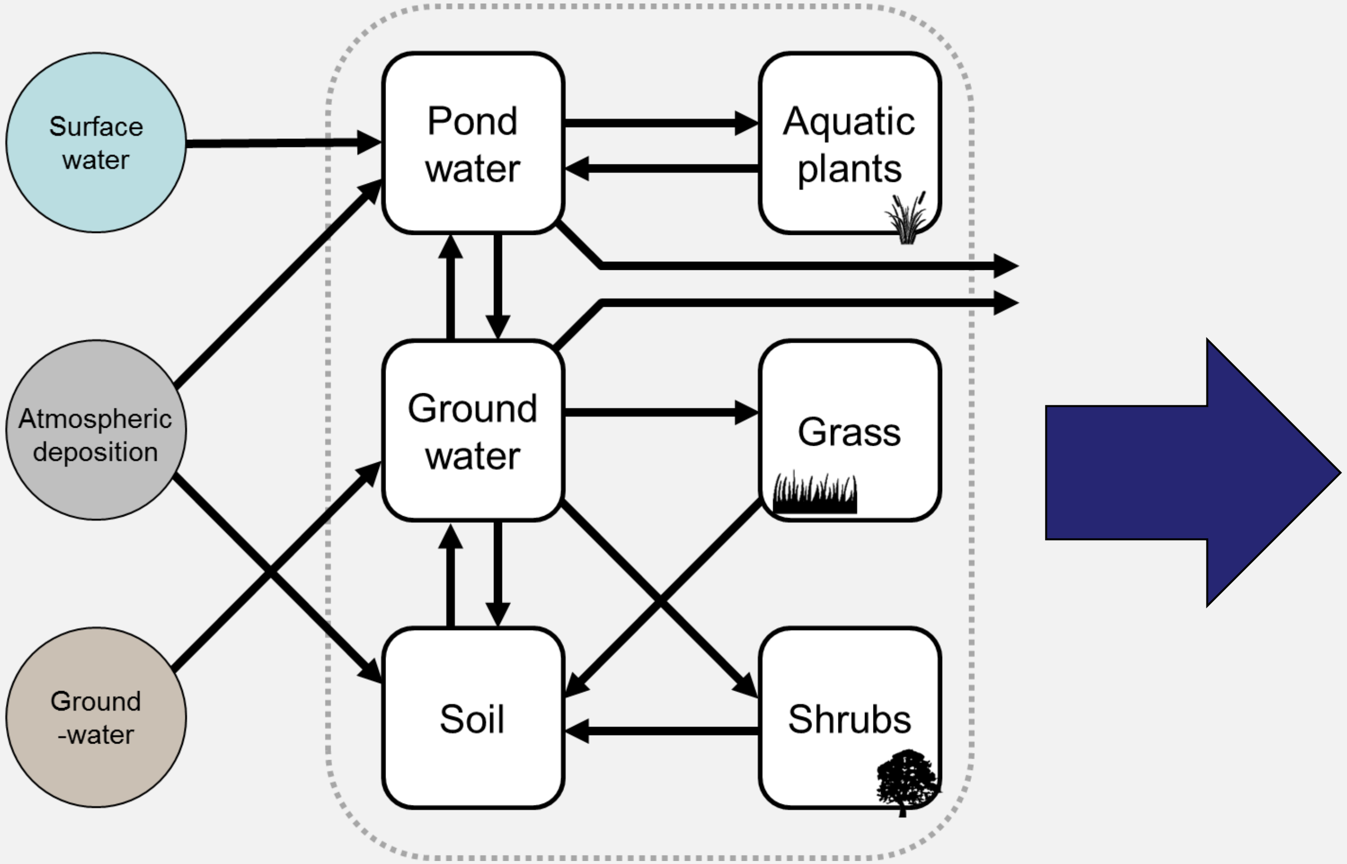
ID	Description	Lower Limit (ug/d)	Data Source	Upper Limit (ug/d)	Data Source	On-Site estimate (ug/d)
1	Atmospheric deposition	0.1	ClO4 in house dust (China)	1	ClO4 in dust after fireworks	0.55
2	Water discharge (upstream input)	50	min reported (similar stream)	1000	max reported (similar stream)	525
3	On-site disposal (if applicable)	10		5000		2505
4	Atmosphere --> surface water	0.1	scale deposition by area	1	scale deposition by area	0.55
5	water loss (downstream output)	25	concentration - outflow	5000	concentration - outflow	2512.5
6	Water discharge --> surface water	50		1000		525
7	disposal remaining as salt	5	estimate based on literature	10	estimate based on literature	7.5
8	disposed ClO4 soil (if applicable)	50		500		275
9	disposed ClO4 water (if applicable)	10		5500		2755
10	on-site runoff (soil --> water)	5	estimate based on ClO4 at site	100	estimate based on ClO4 at site	52.5
11	ClO4 uptake into aquatic plants	5	work backward from plants	100	rate * concentration	52.5
12	groudwater movement to surface	15		30		22.5
13	surface water movement to ground	5		10		7.5
14	groudwater exiting system	10		500		255
15	burial (out of biological reach)	50		100		75
16	soil leaching to ground water	10		500		255
17	ClO4 reaching invertebrates		ClO4 in water at steady state		ClO4 in water at steady state	
18	ClO4 reaching invertebrates		ClO4 in soil at steady state		ClO4 in soil at steady state	
19	Human surface water consumption	5		100		52.5
20	Human well water consumption	5		300		152.5
21	Surface water --> plants	10		200		105
22	groundwater upake by plants	20		200		110
23	ClO4 uptake into terristrial plants	50	work backward from plants	300	rate * concentration	175
24	Human consumption of on-site plants	1		10		5.5
25	human consumption of on-site animals	10		100		55
26	Grazing by terrestrial mamals	30		1000		515
27	Grazing of aquatic plants	75		150		112.5

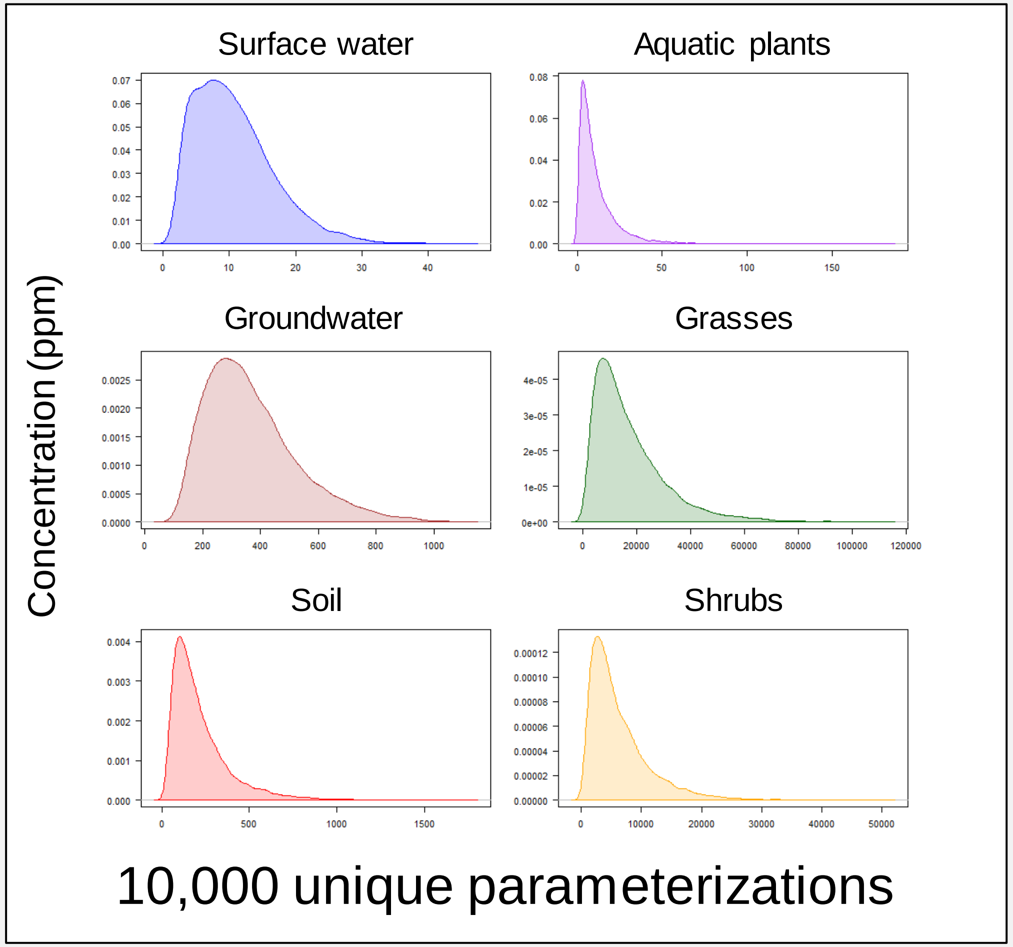
Minimum value Maximum value

- Extract as many rates and standing-stocks as possible from literature
- Missing rate data inferred from standing-stock concentrations and mass-balance
- Monte Carlo sampling; n=10,000

Network set

- Conduct analyses across entire set

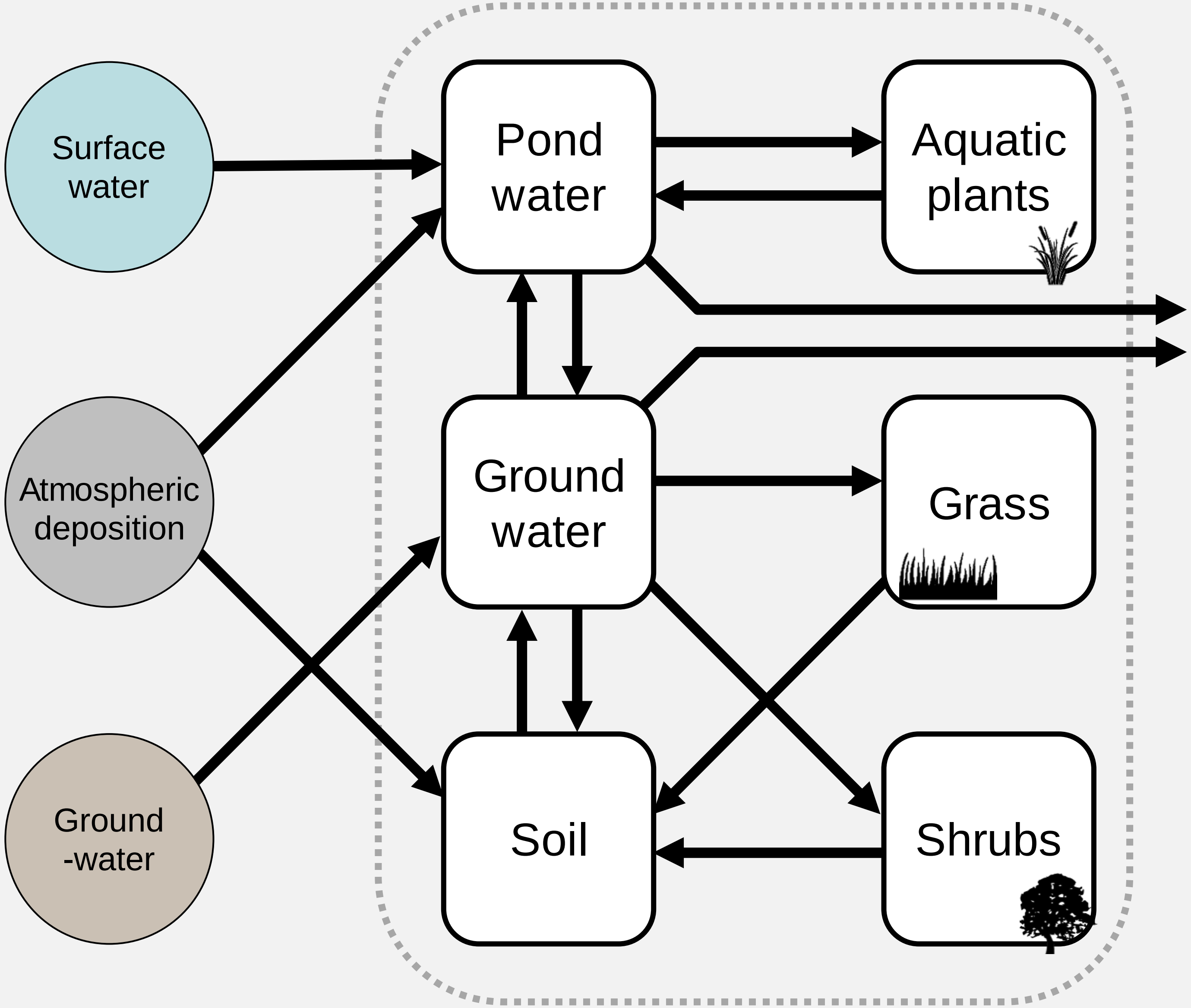




Exposure Scenarios

Mild contamination:

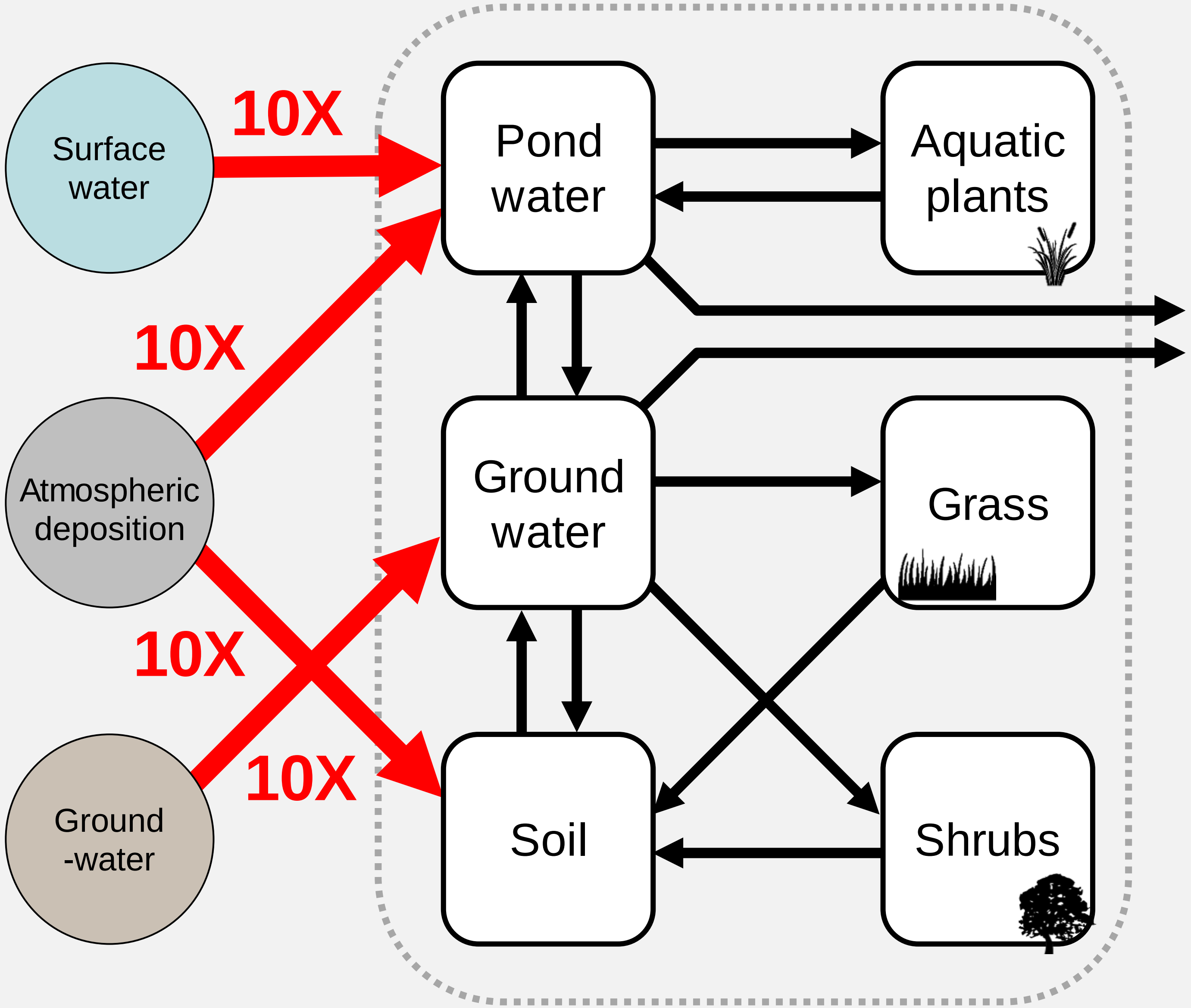
- Perchlorate present throughout ecosystem
- concentrations lower than documented contaminated sites



Exposure Scenarios

Moderate contamination:

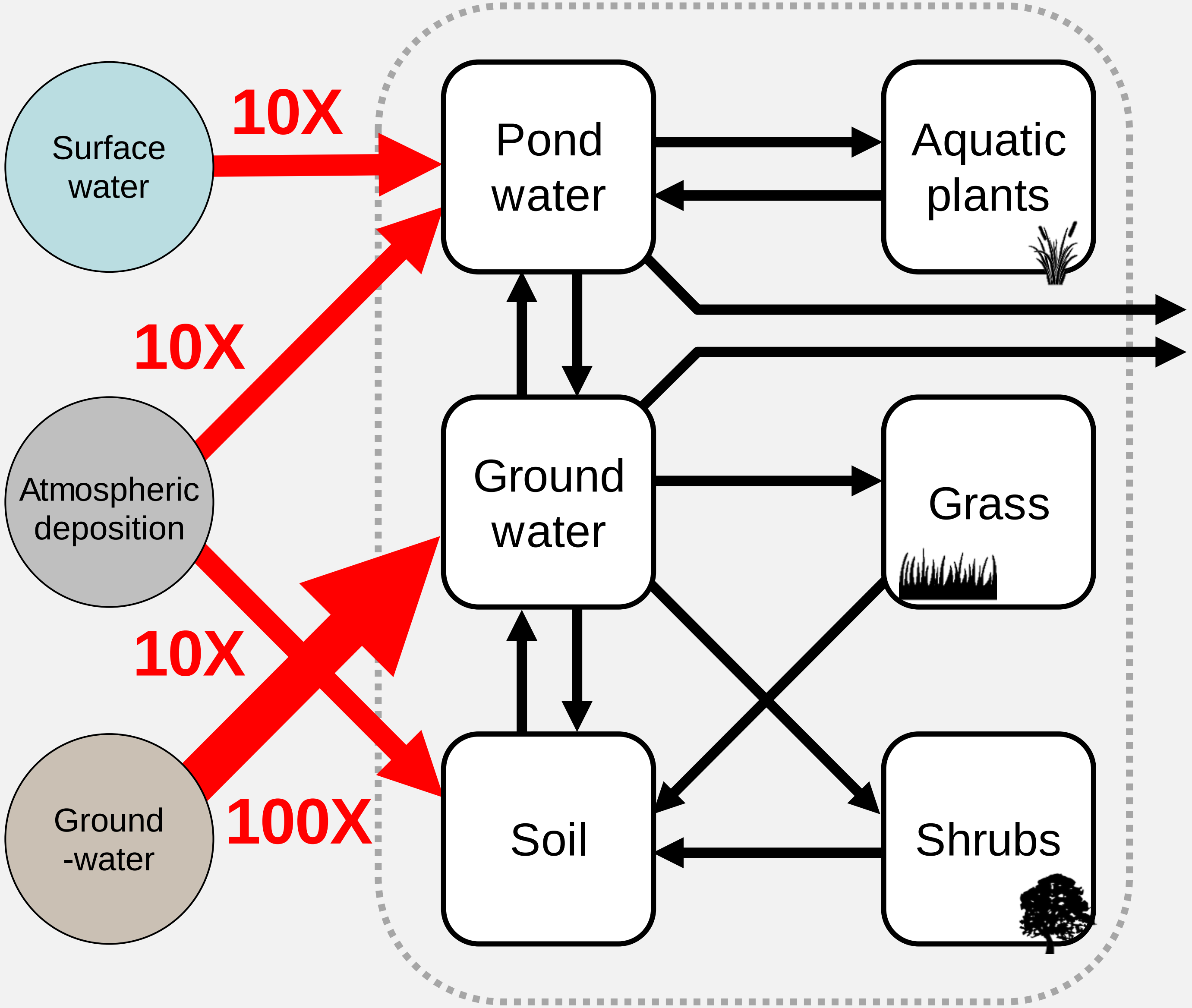
- 10 fold increase to contamination input levels over Mild scenario
- No change in atmospheric deposition



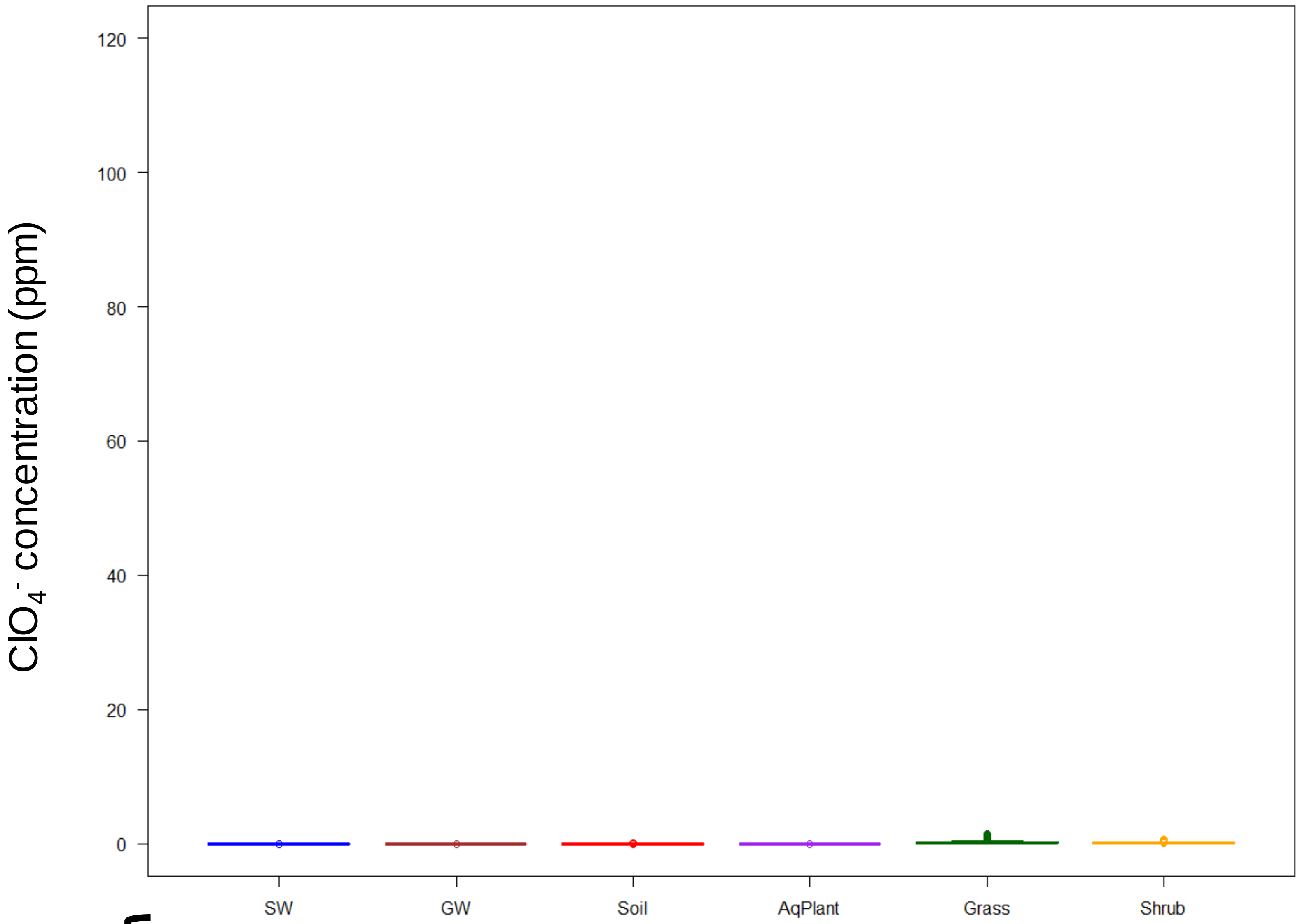
Exposure Scenarios

High contamination:

- 10 fold increase to surface water and atmospheric contamination over Mild scenario
- 100 fold increase to groundwater contamination over Mild scenario
- No change in atmospheric deposition

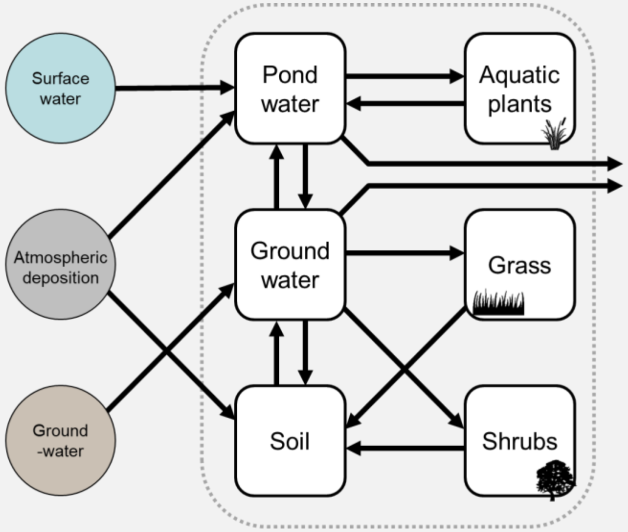


Environmental Concentrations

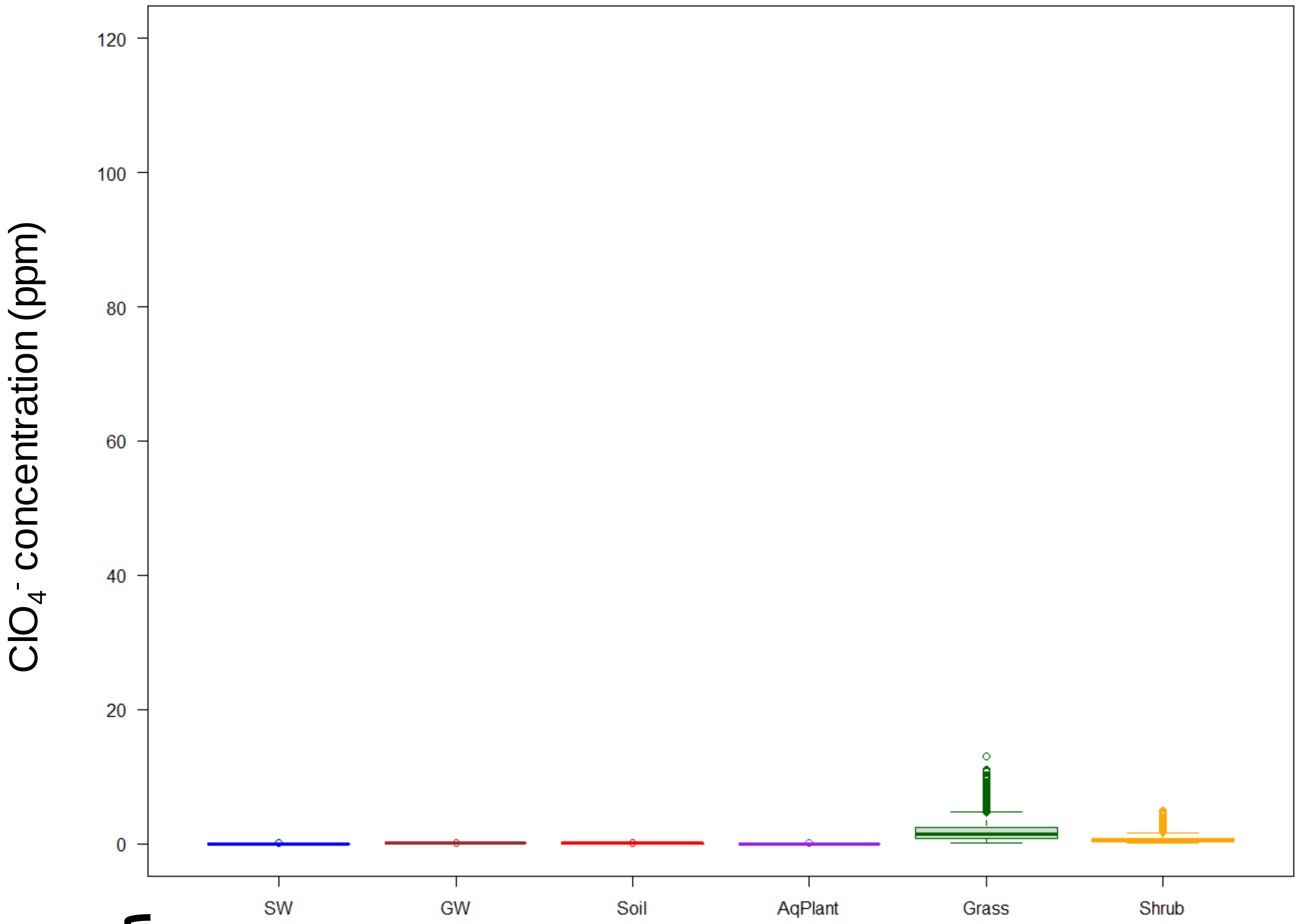


95% range { 0.1 – 1.3 ppb | 1.5 – 7.6 ppb | 0.4 – 7.1 ppb | 0.06 – 7.1 ppb | 24 – 563 ppb | 9.7 – 206 ppb

Mild Contamination

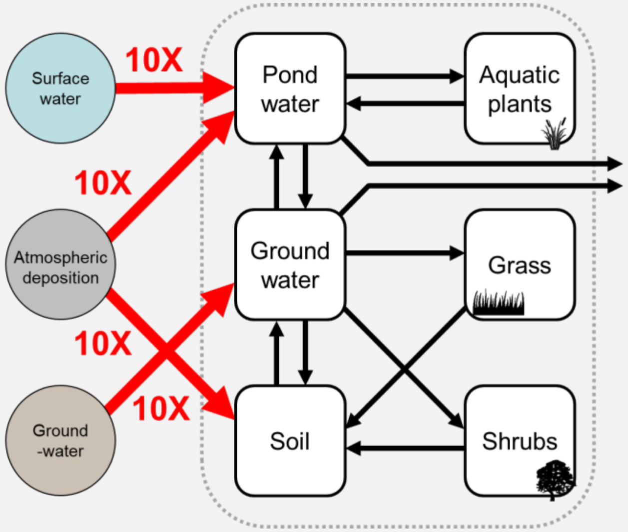


Environmental Concentrations

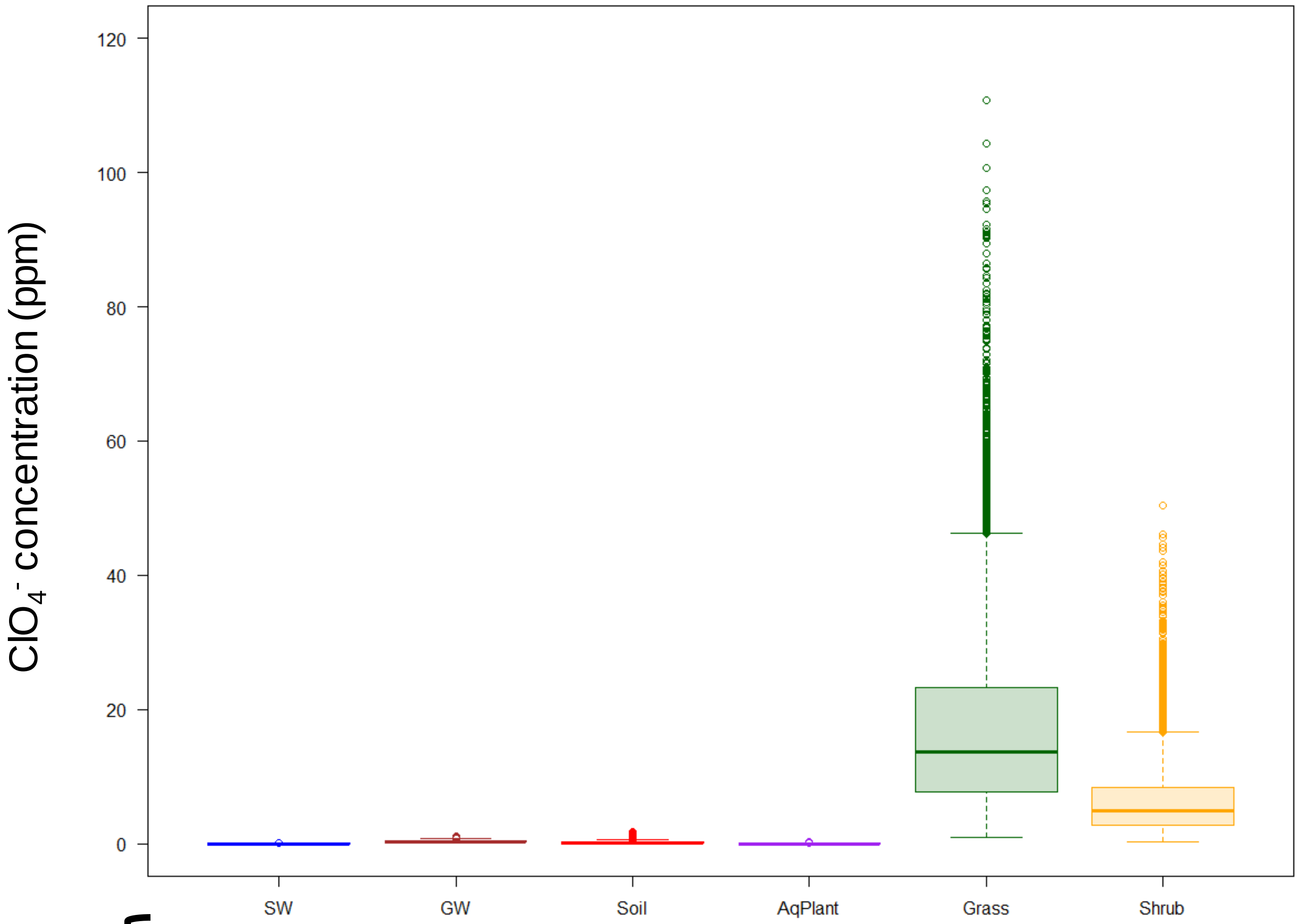


95% range { **1.5 – 13 ppb** | **15 – 77 ppb** | **4.2 – 70.3 ppb** | **0.6 – 25 ppb** | **242 – 5425 ppb** | **98 – 2084 ppb**

Moderate Contamination

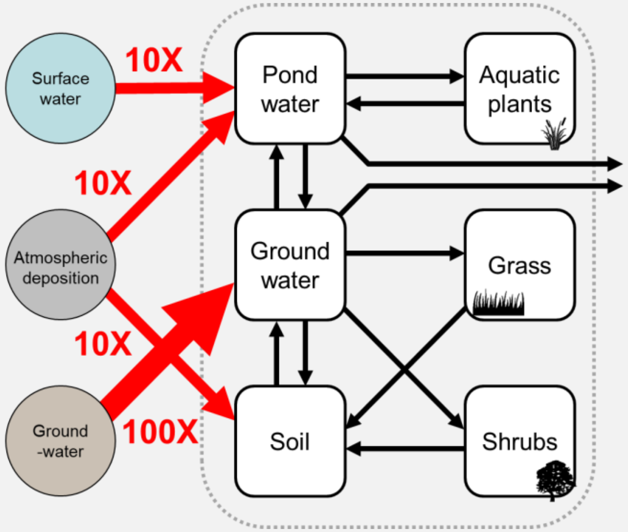


Environmental Concentrations



95% range	SW	GW	Soil	AqPlant	Grass	Shrub
	2.5 – 25 ppb	149 – 761 ppb	43 – 707 ppb	1.1 – 45 ppb	2.5 – 54.4 ppm	1 – 20.3 ppm

High Contamination



Exposure behavior assumptions

Humans:

1) All exposure through drinking of ground water via well
2) Daily water intake of 2L
3) Body mass of 72.3kg

Lumen et al. (2013)

Fishes:

Internal concertation equivalent to water concentration

TSE = [Pond Water]

Small herbivorous mammals:

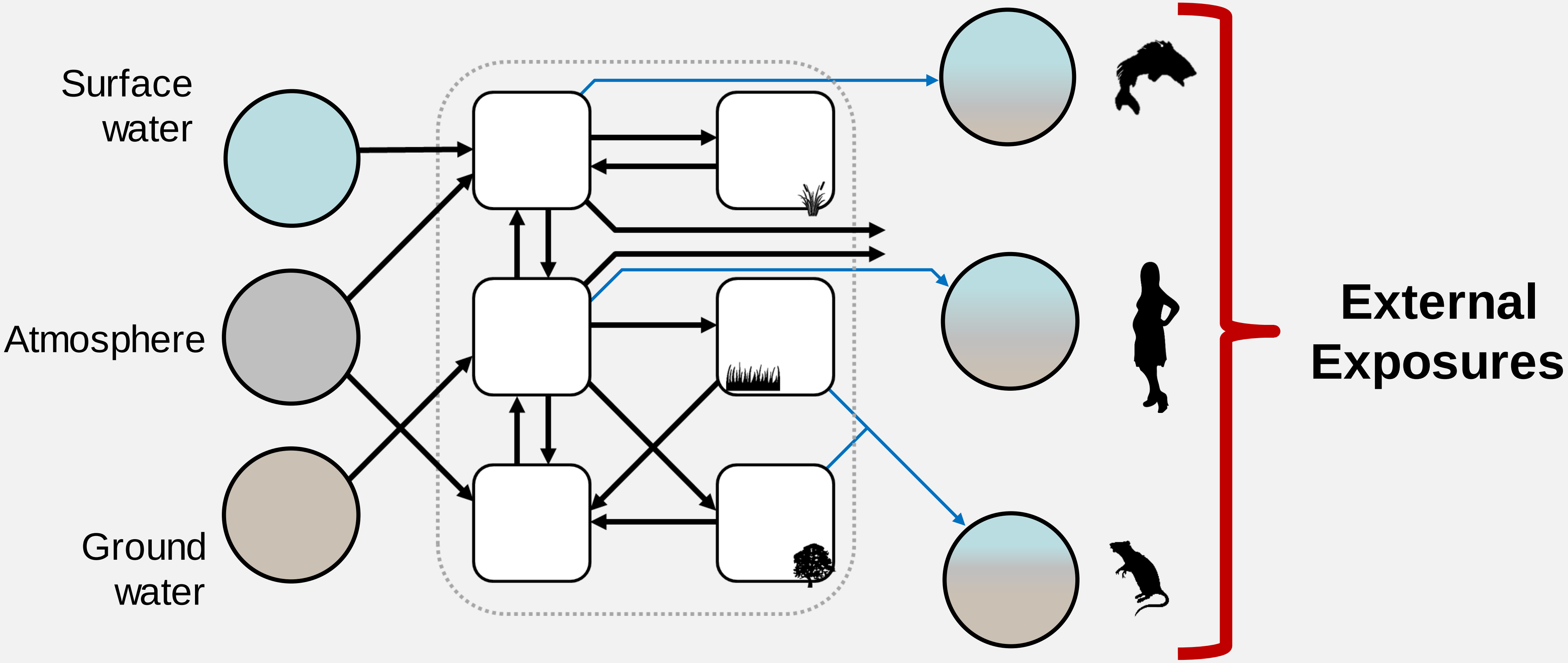
1) Daily intake of 0.005g/kg/d
2) Body weight = 0.044kg
3) Consumes grass (95%)
4) Drinks surface water (5%)

Sample and Suter (1994)
EPA perchlorate (2002)

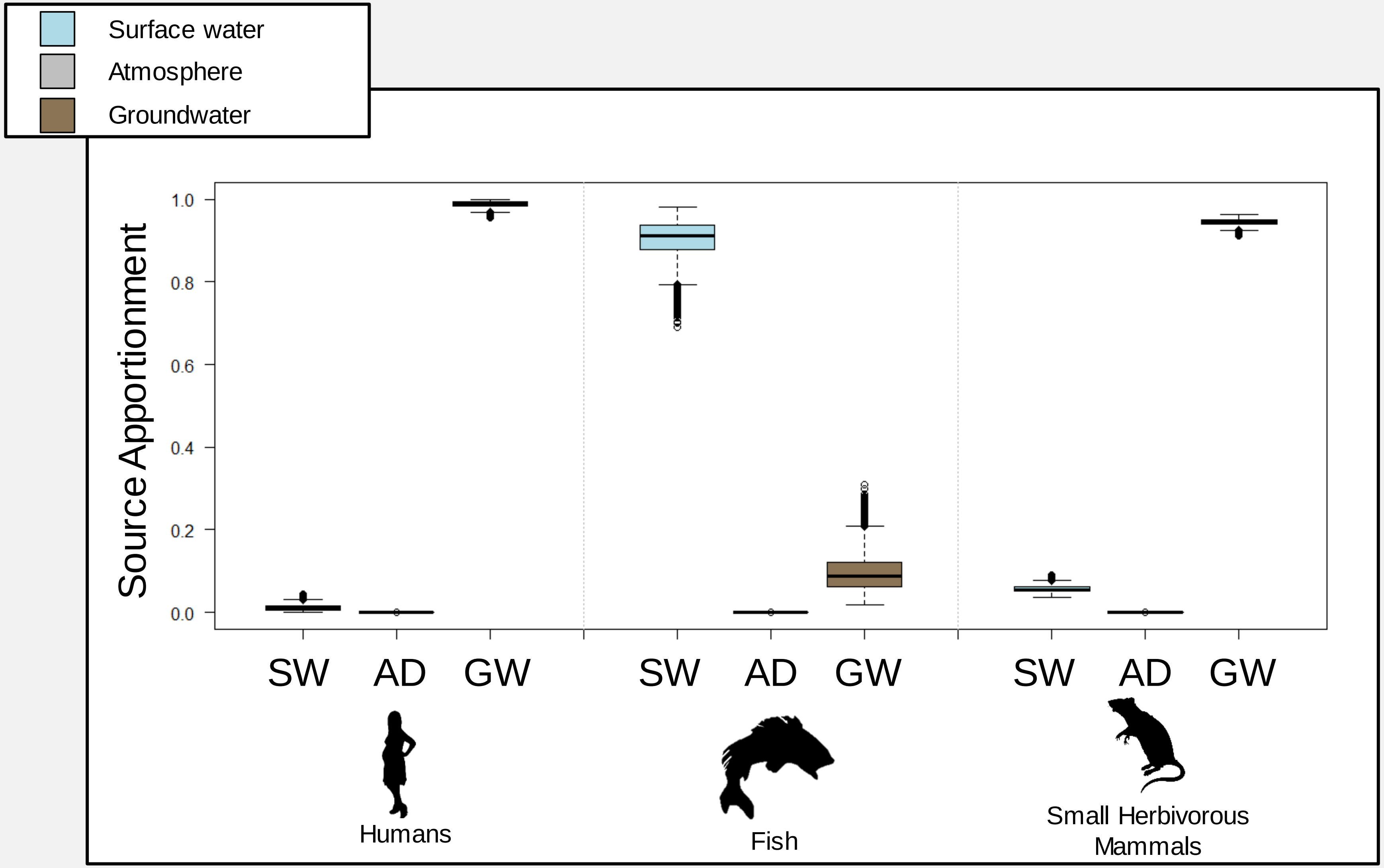
Environ analysis

- Environ analysis is a type of <u>Ecological Network Analysis</u> that can track **where material comes from** in each network compartment

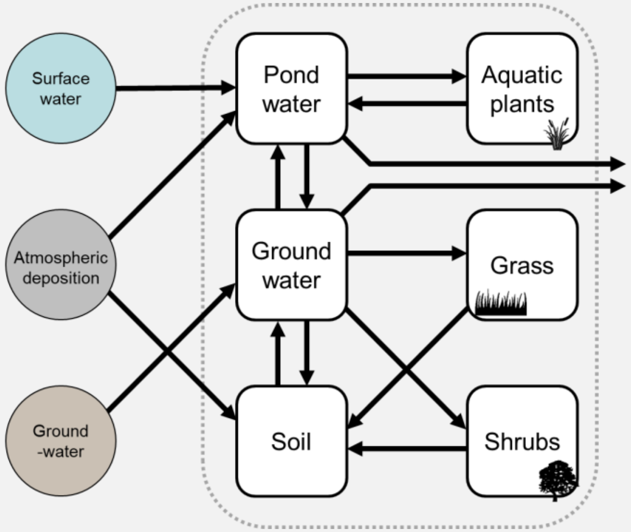
(Patten 1982; Fath and Patten 1999)



Environ Analysis Results



Mild Contamination



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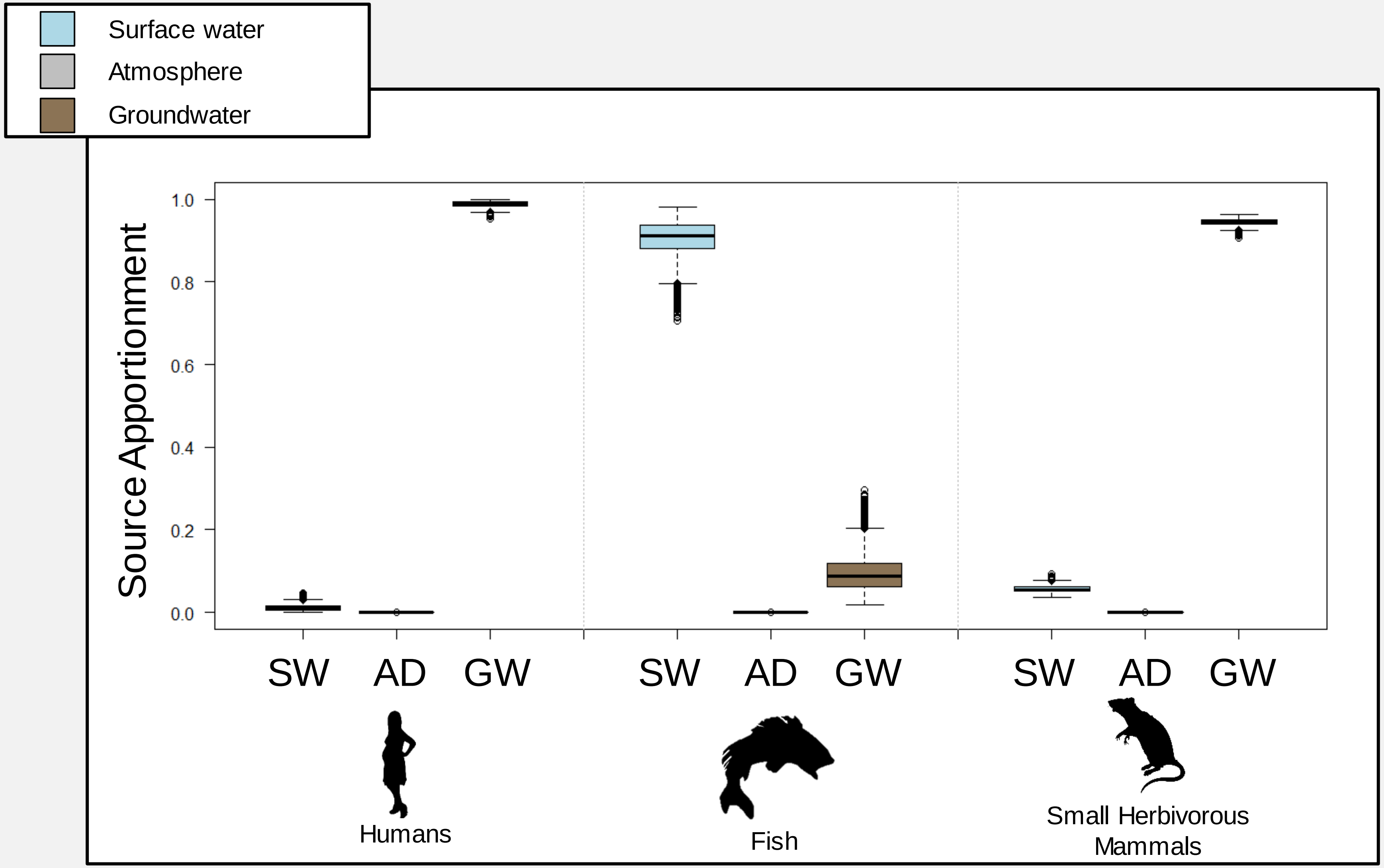
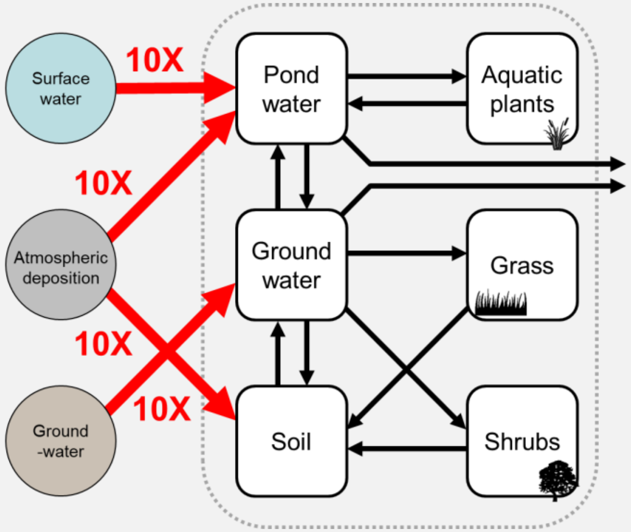
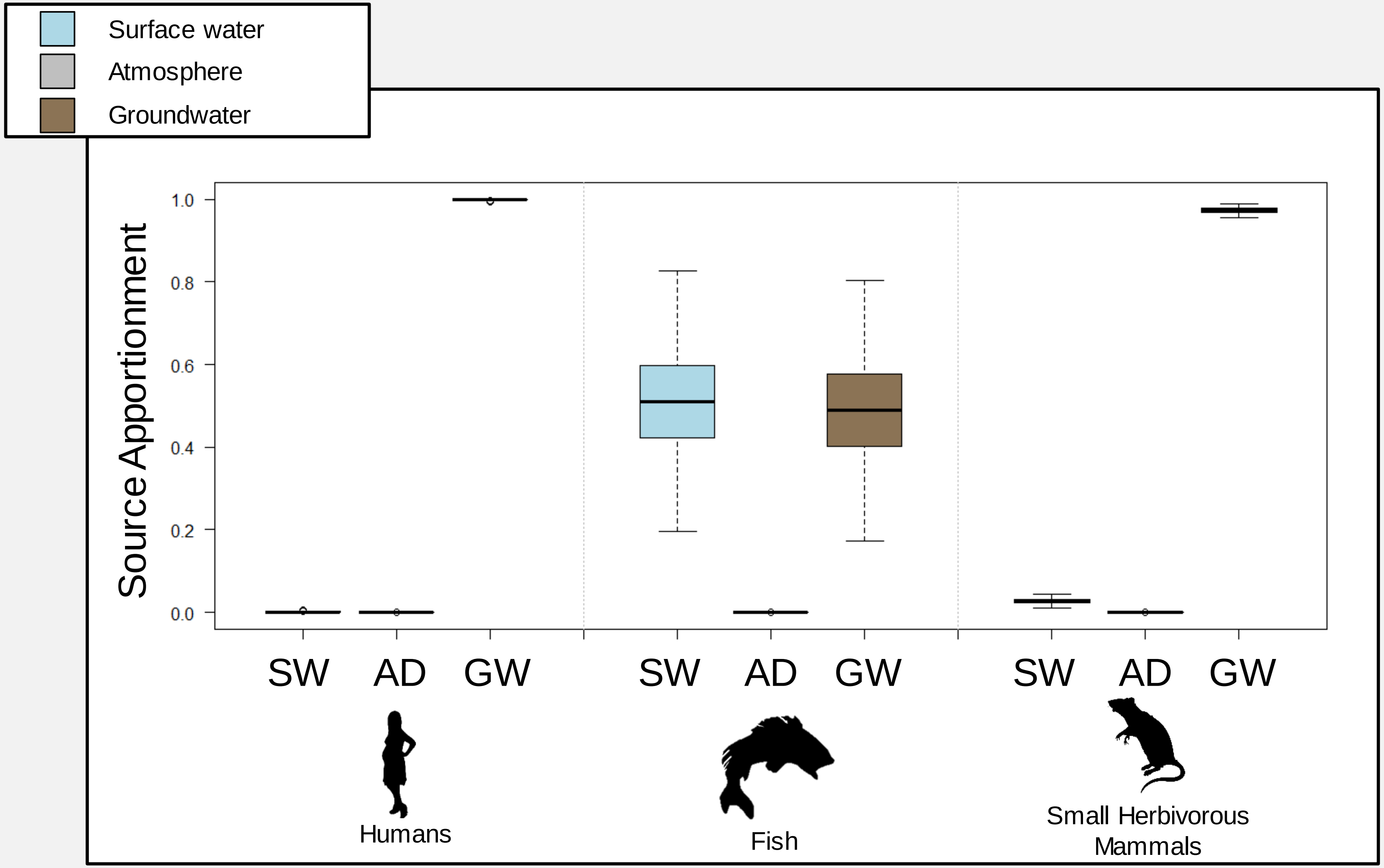


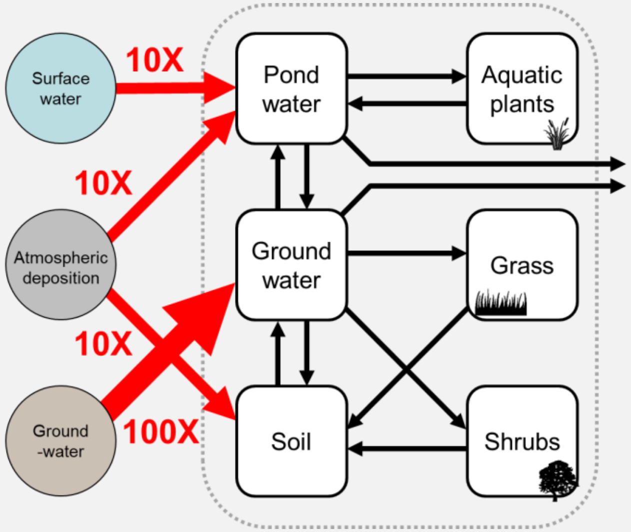
Moderate Contamination



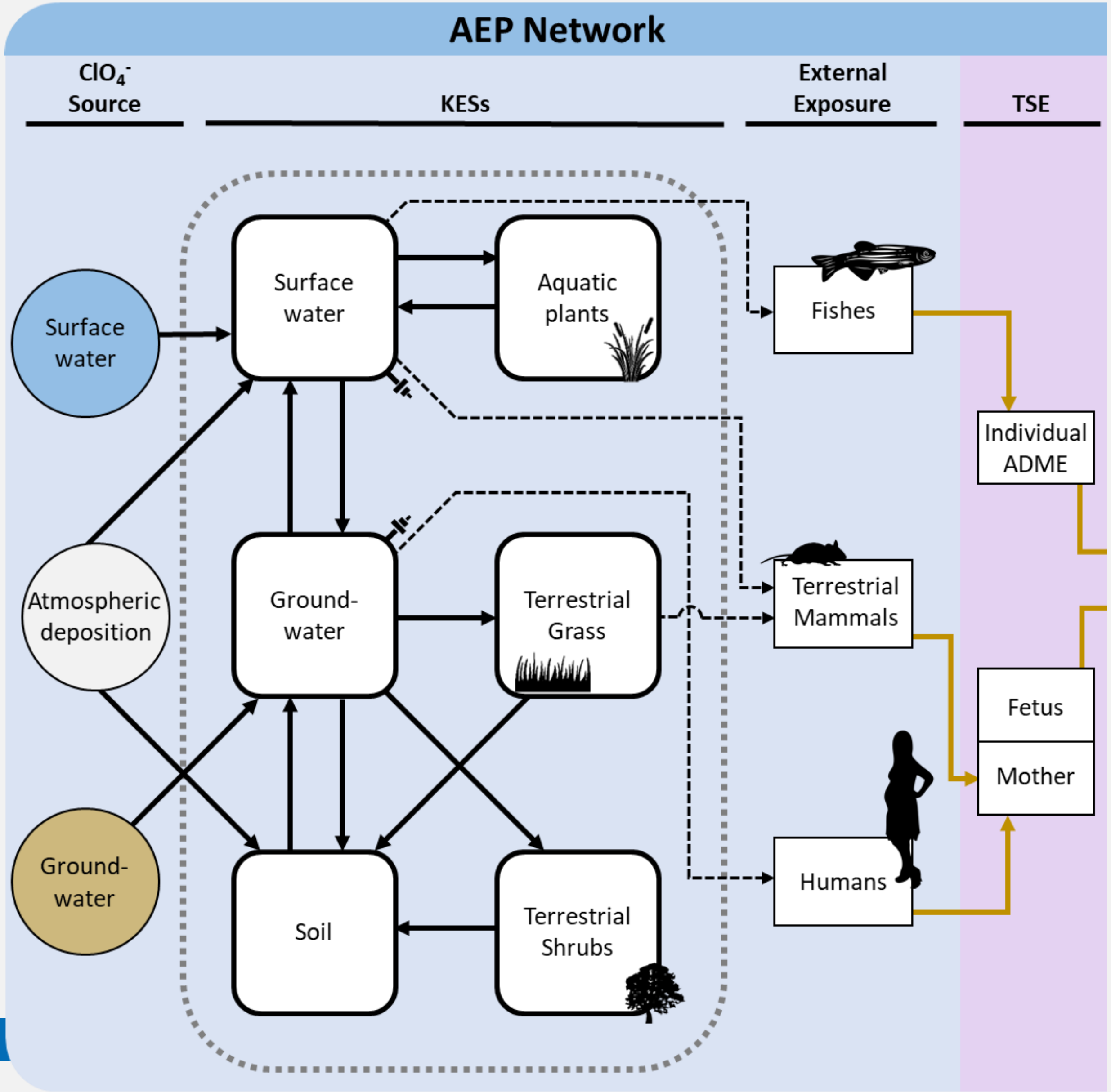
Environ Analysis Results



High Contamination



Approach



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A Quantitative Source-to-Outcome Case Study To Demonstrate the Integration of Human Health and Ecological End Points Using the Aggregate Exposure Pathway and Adverse Outcome Pathway Frameworks

David E. Hines,[†] Rory B. Conolly,[*,†] and Annie M. Jarabek[‡]

External exposure

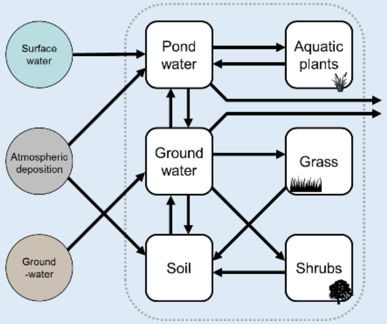
↓

Internal TSE

Linking AEPs to AOPs

AEP	AOP

Exposure network



External exposure

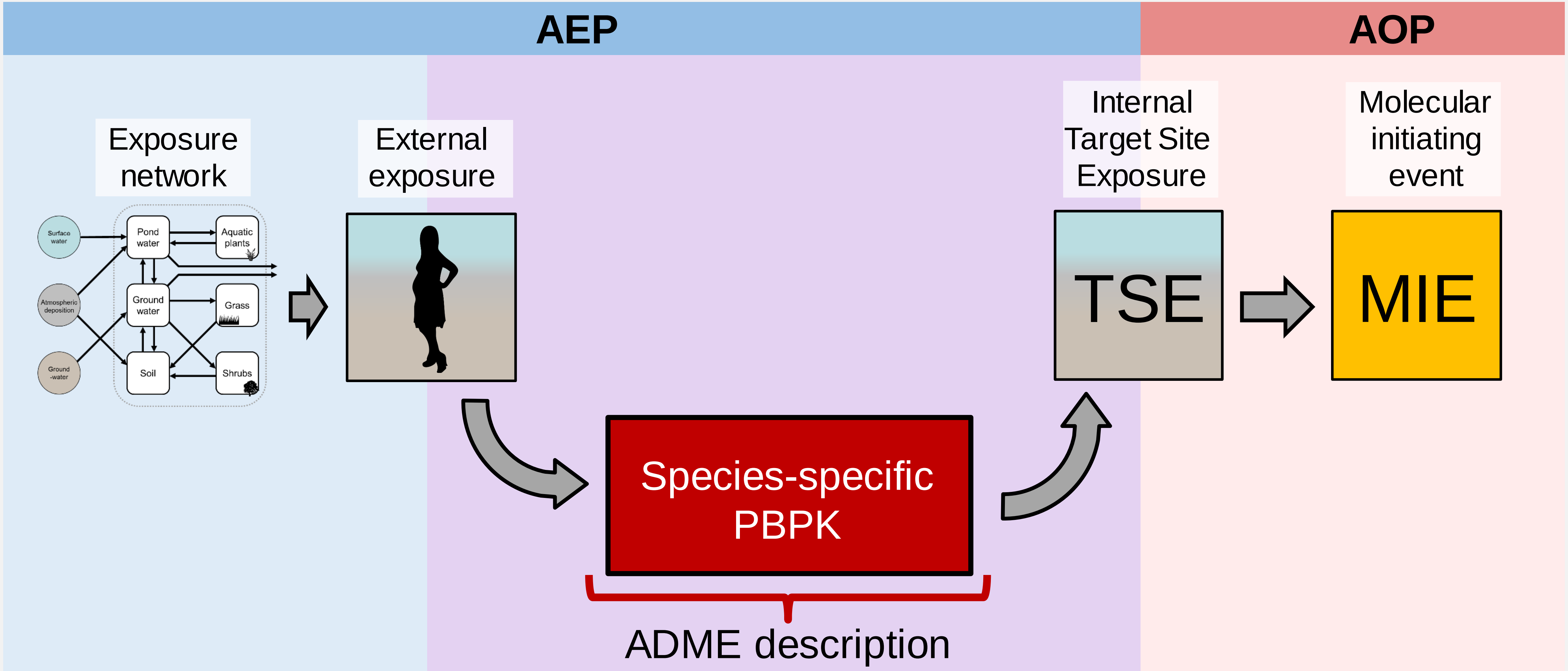
Internal Target Site Exposure

TSE

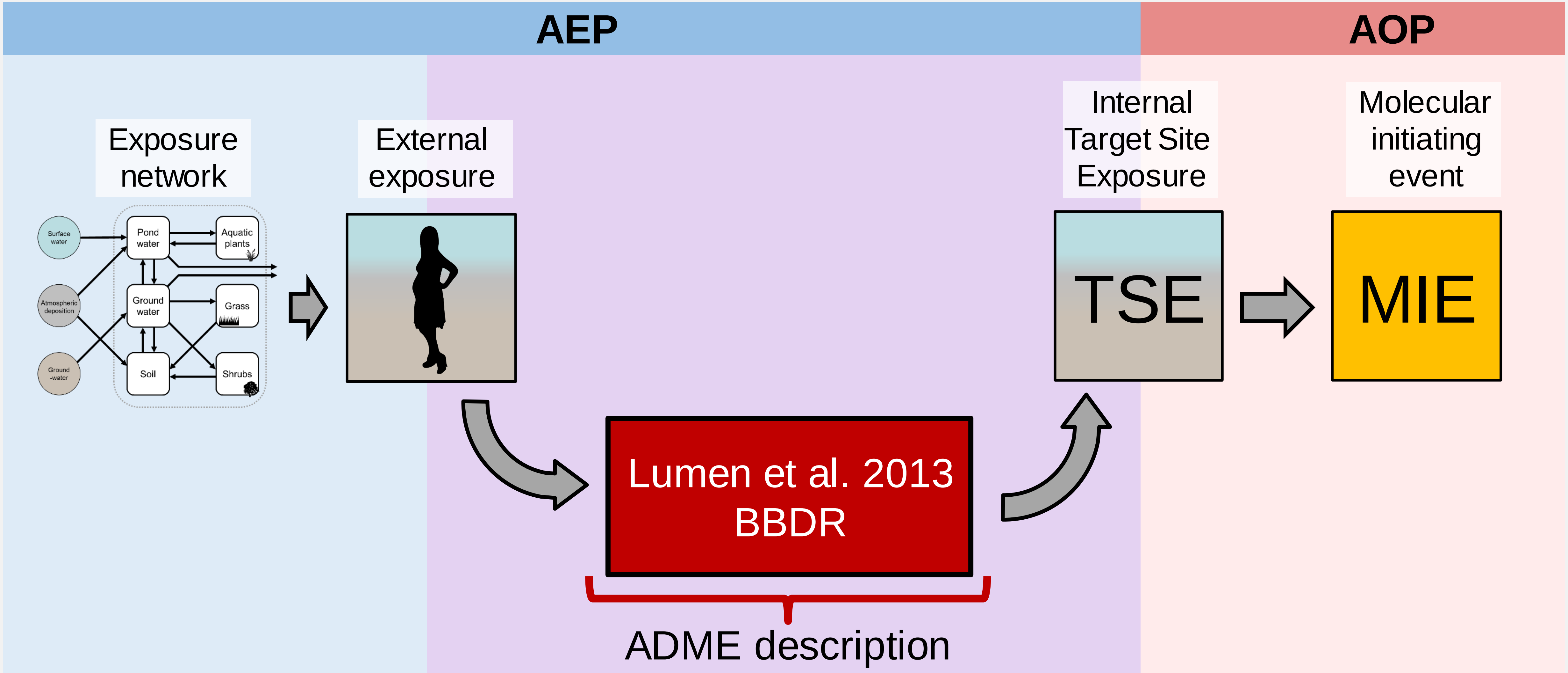
Molecular initiating event

MIE

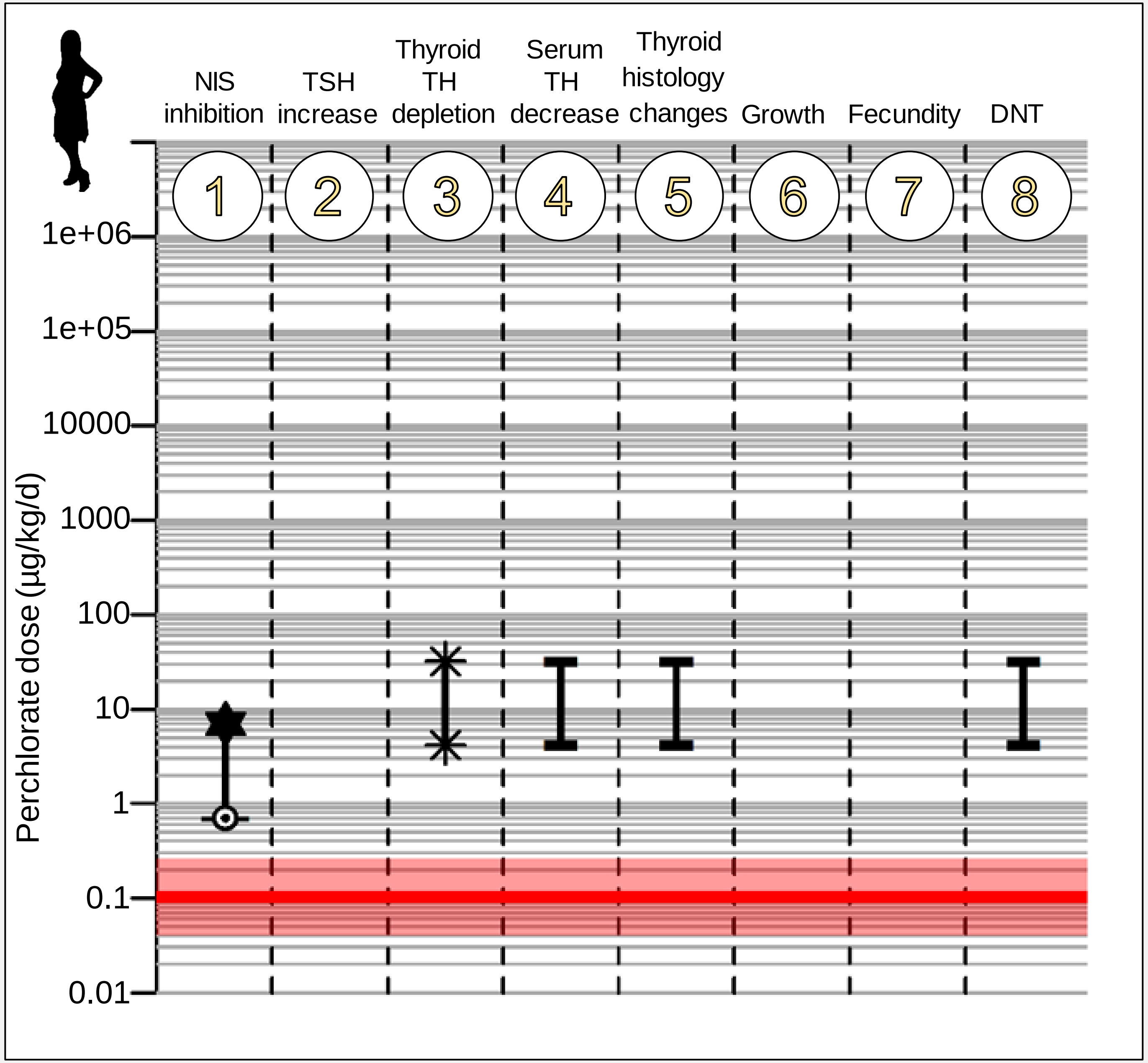
Linking AEPs to AOPs

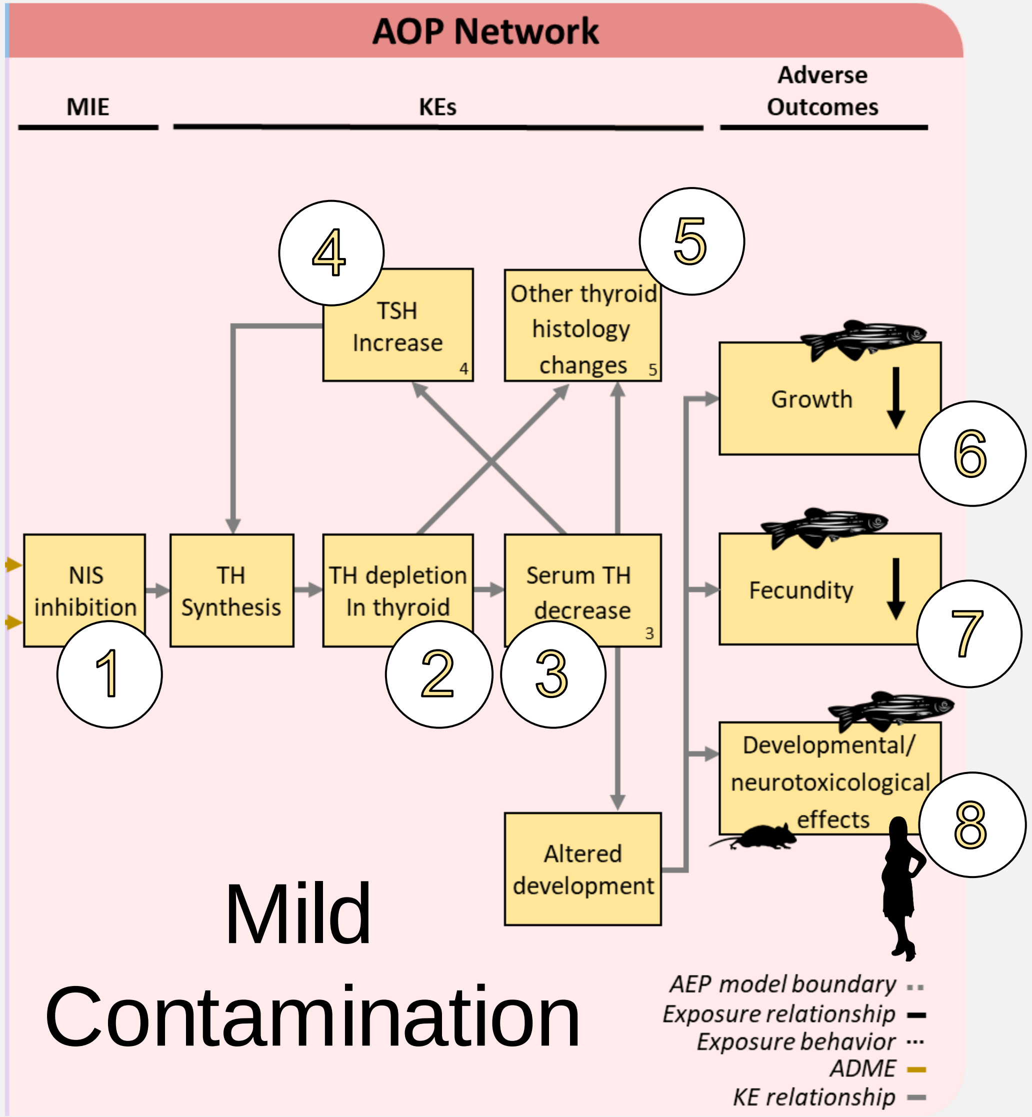


Linking AEPs to AOPs

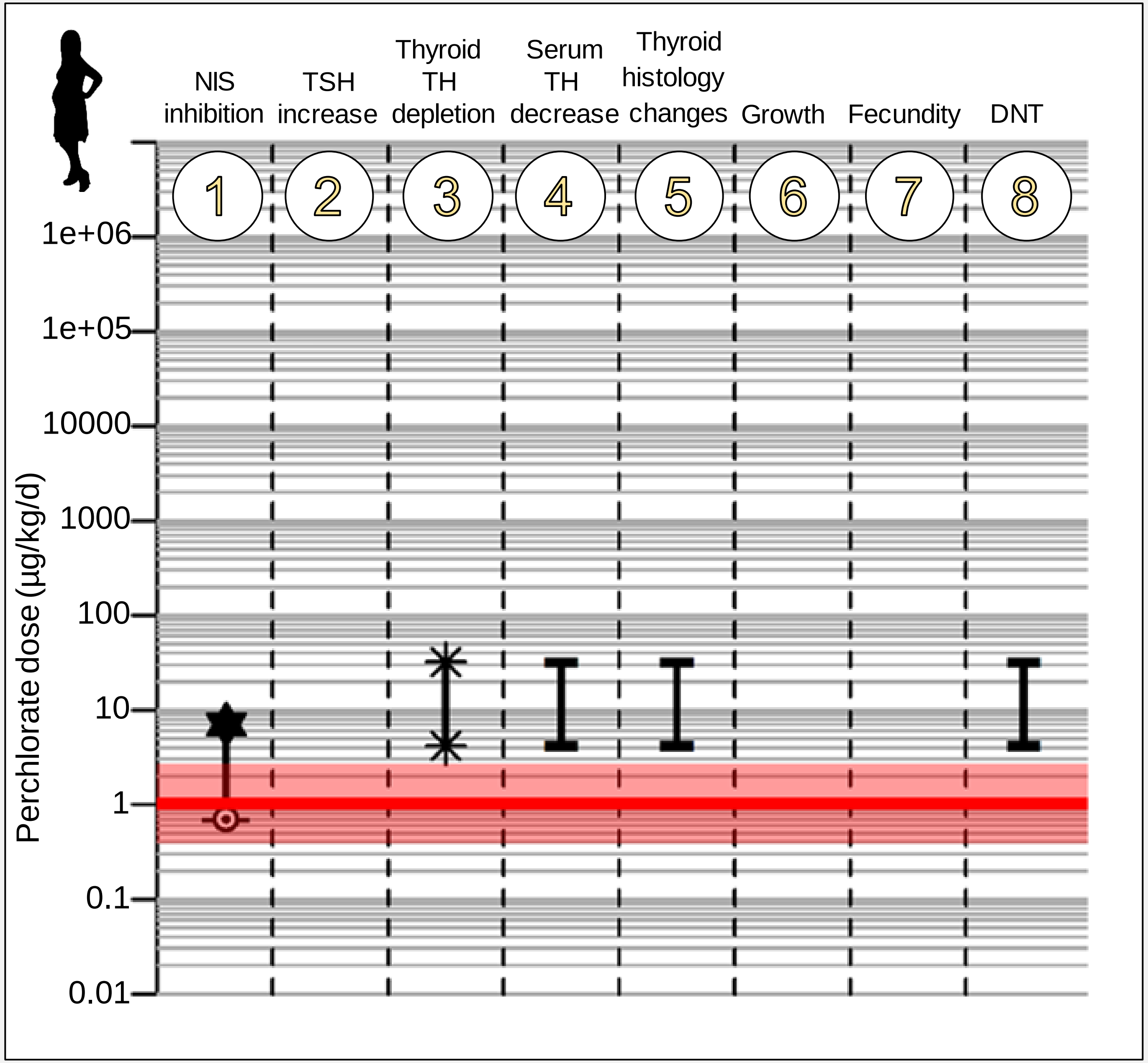


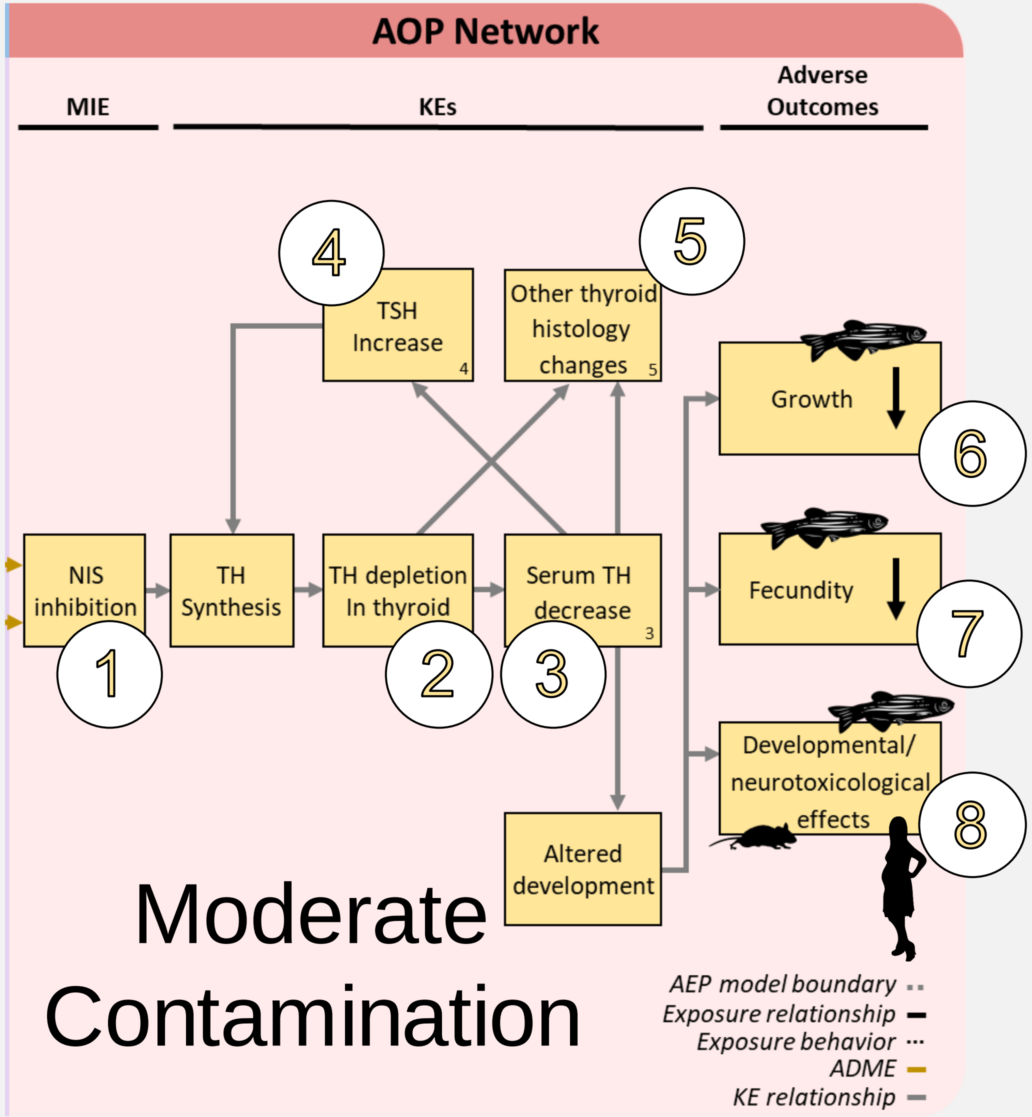
Linking AEPs to AOPs



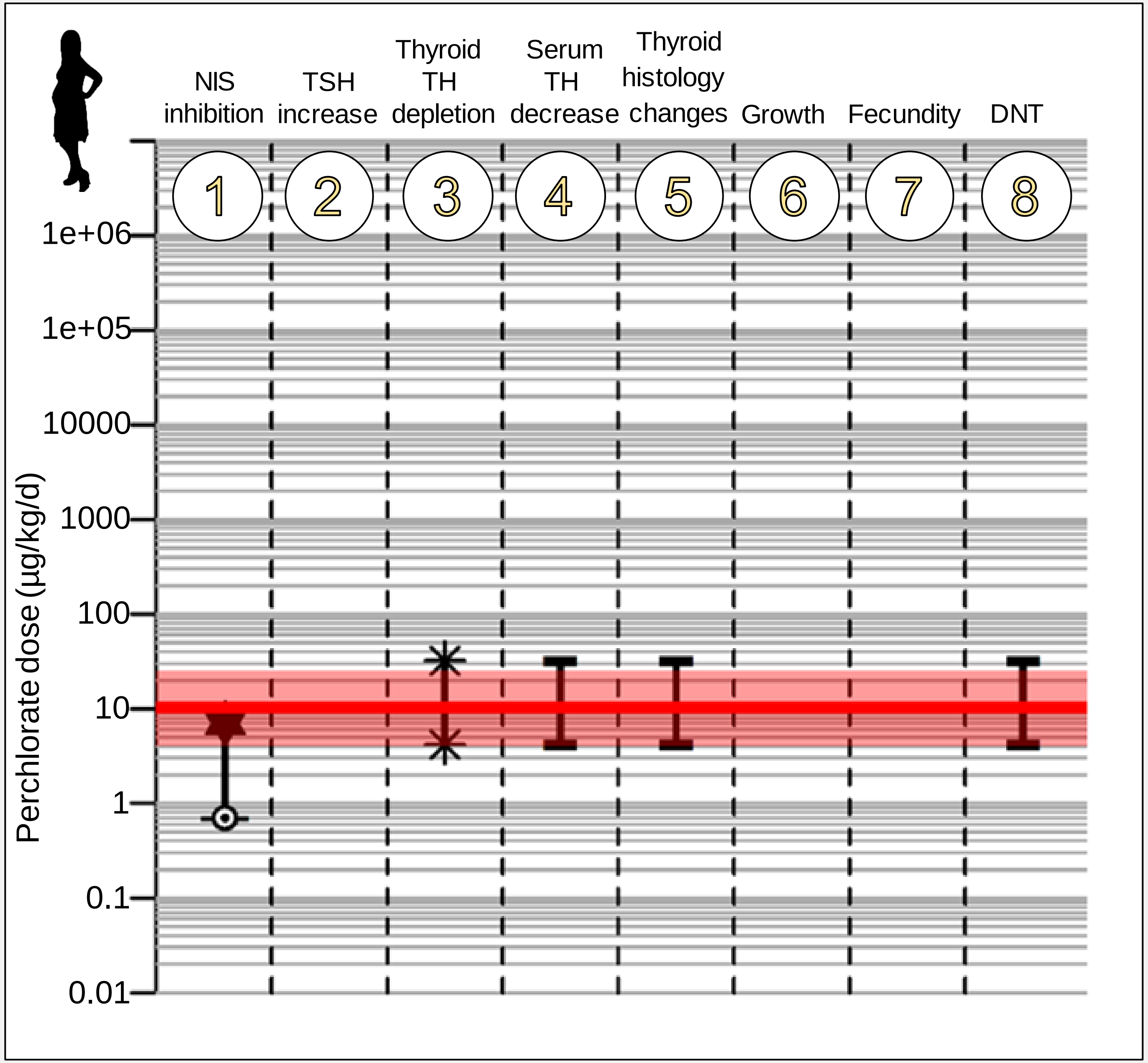


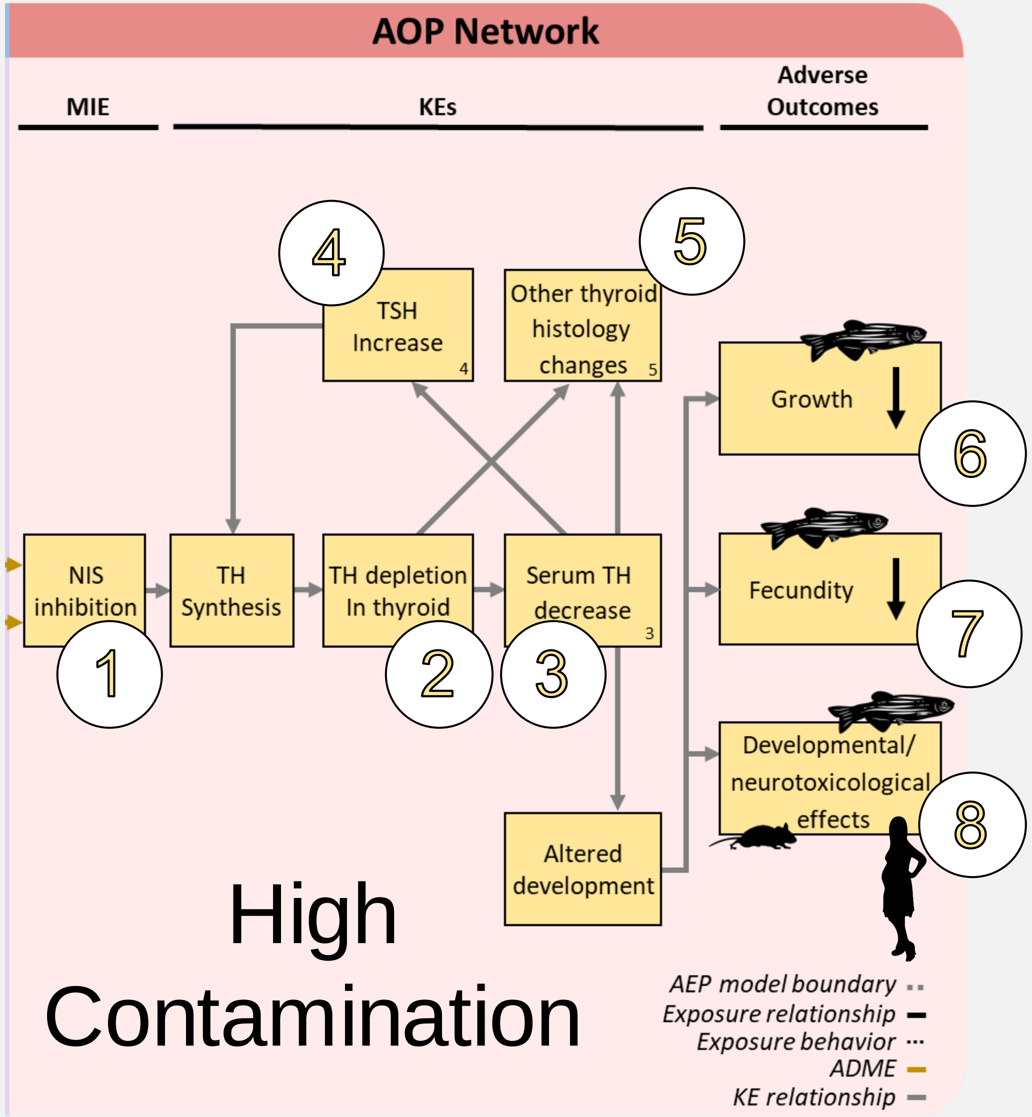
Linking AEPs to AOPs





Linking AEPs to AOPs

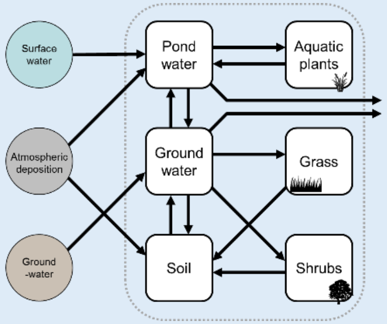




Linking AEPs to AOPs

AEP | **AOP**

Exposure network



External exposure

Internal Target Site Exposure

TSE

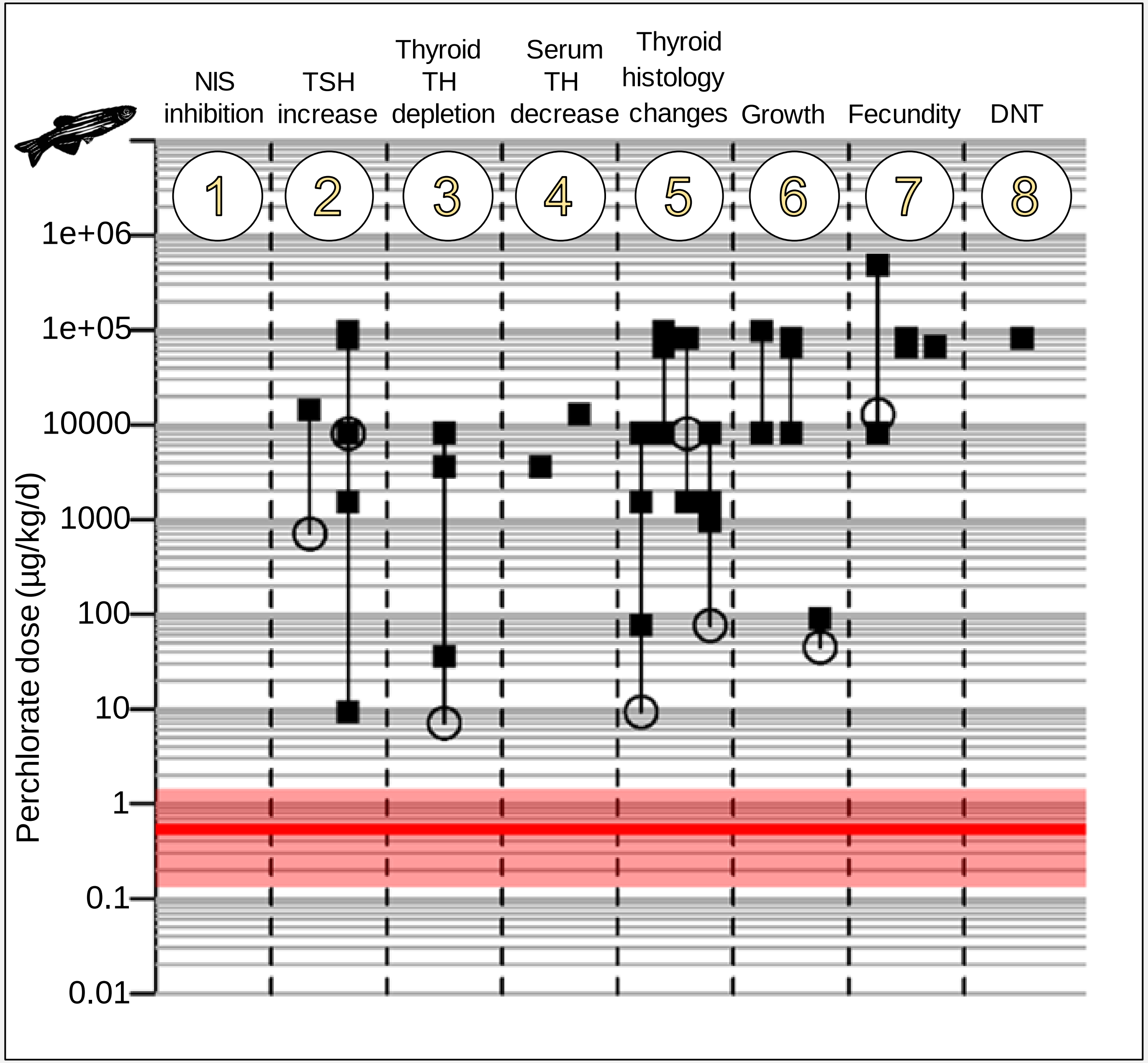
Molecular initiating event

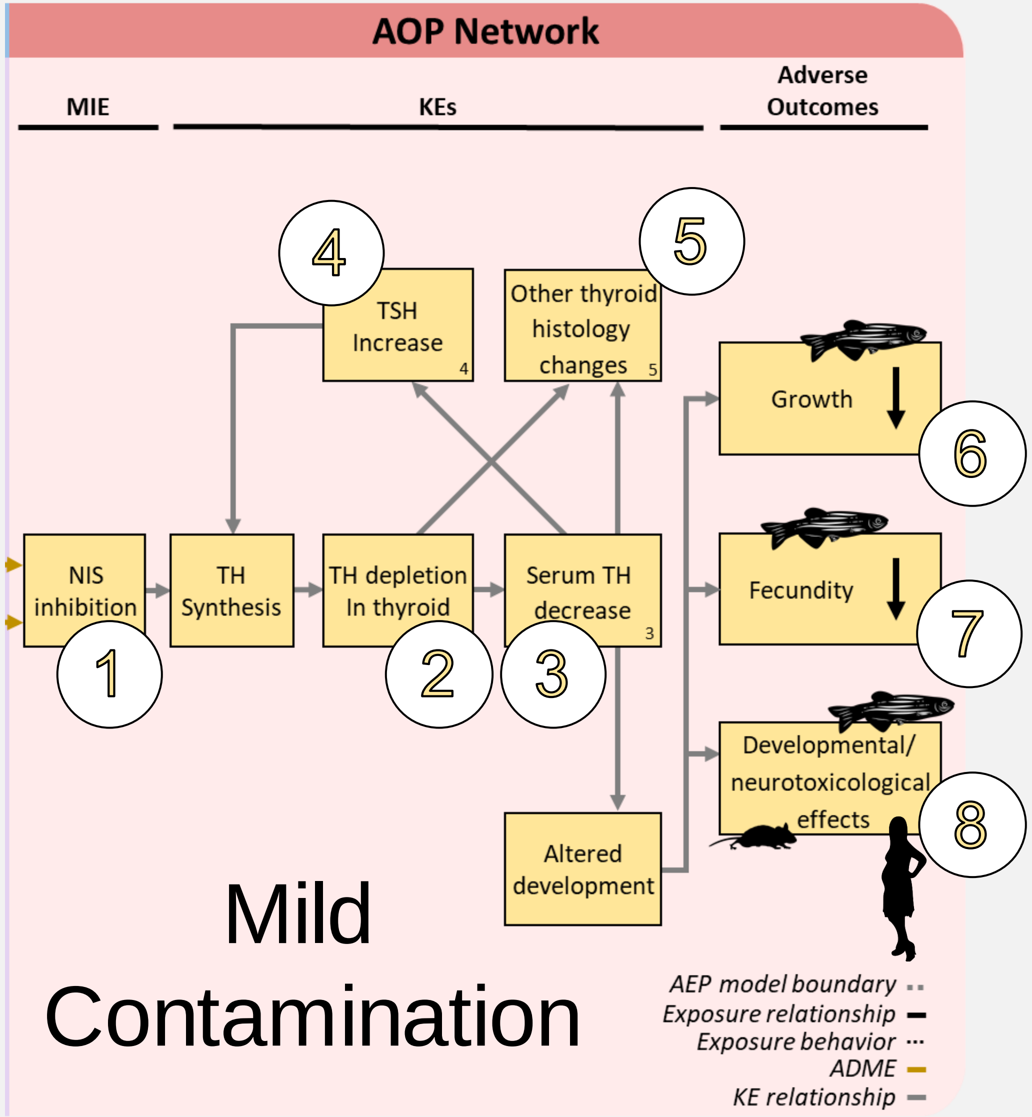
MIE

Assume equivalent to pond water concentrations based on:

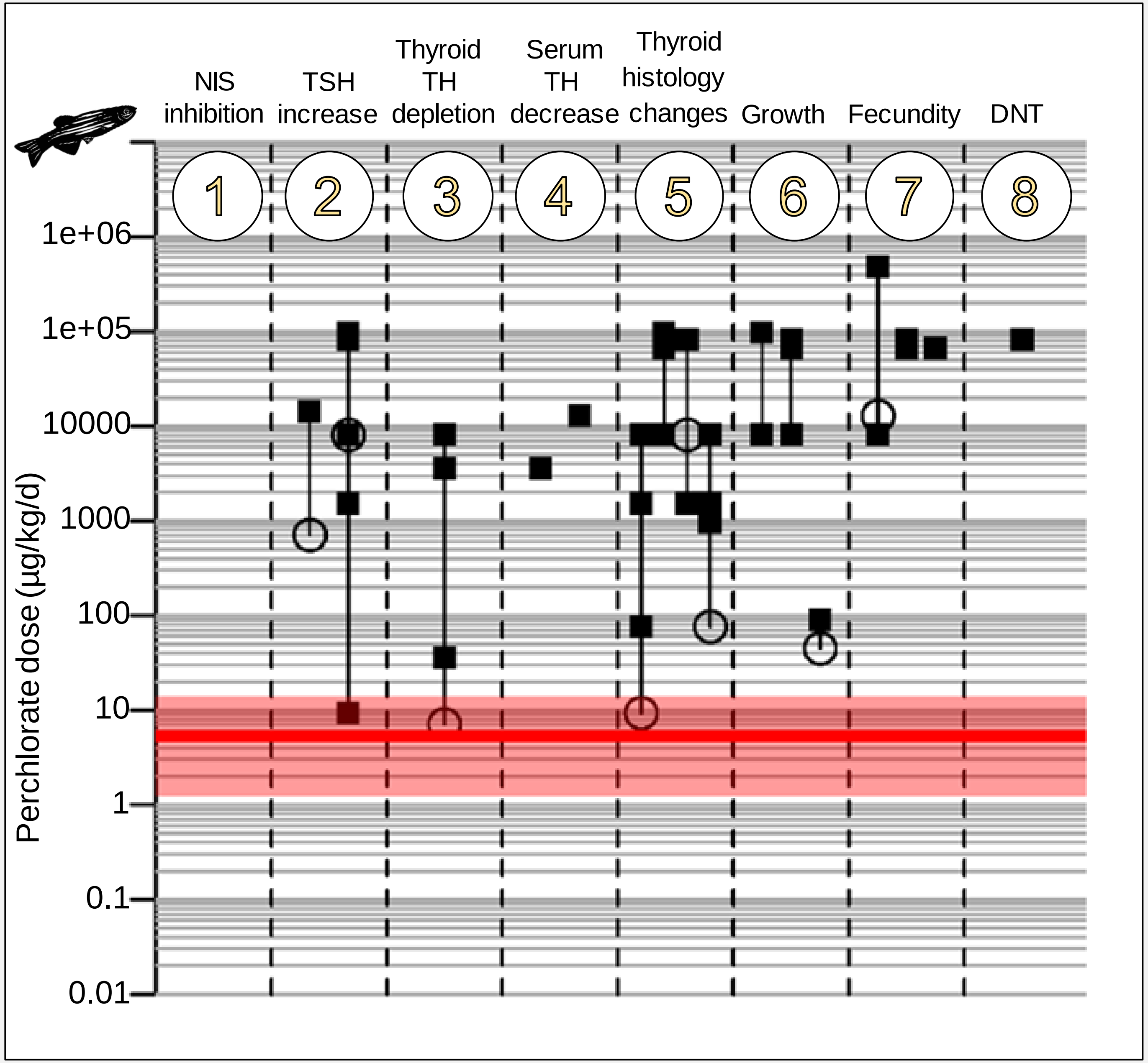
- High mobility of perchlorate
- High efficiency of the gills

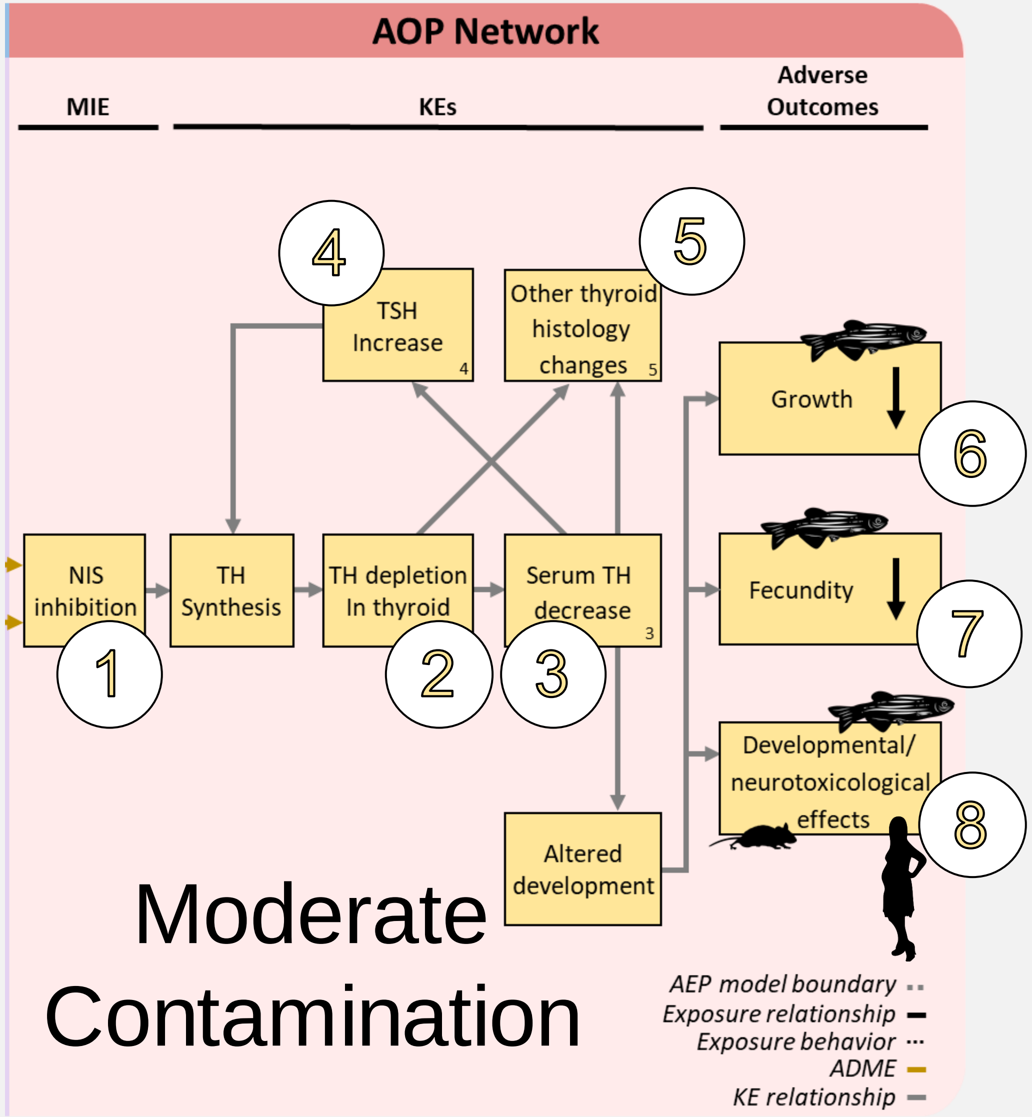
Linking AEPs to AOPs



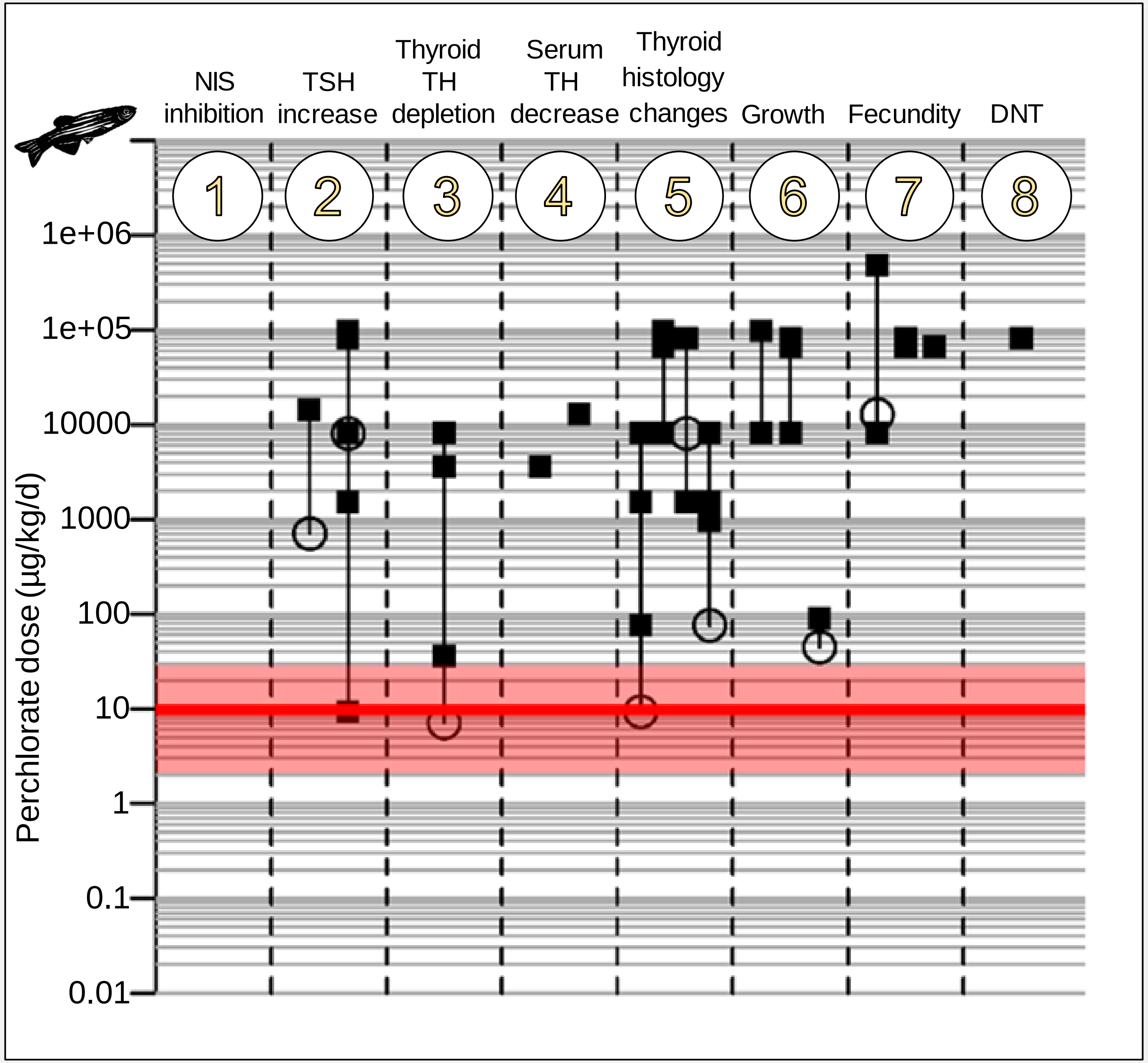


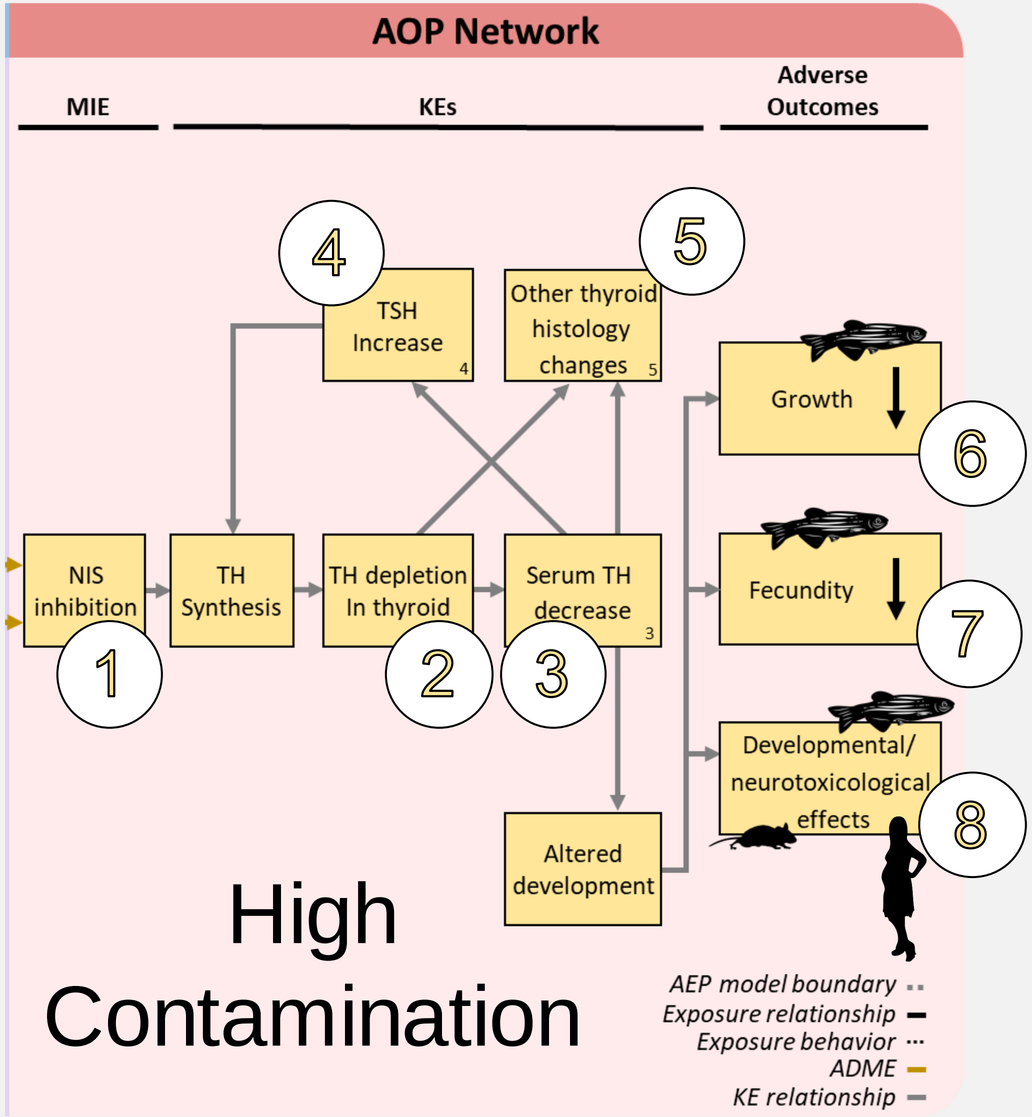
Linking AEPs to AOPs



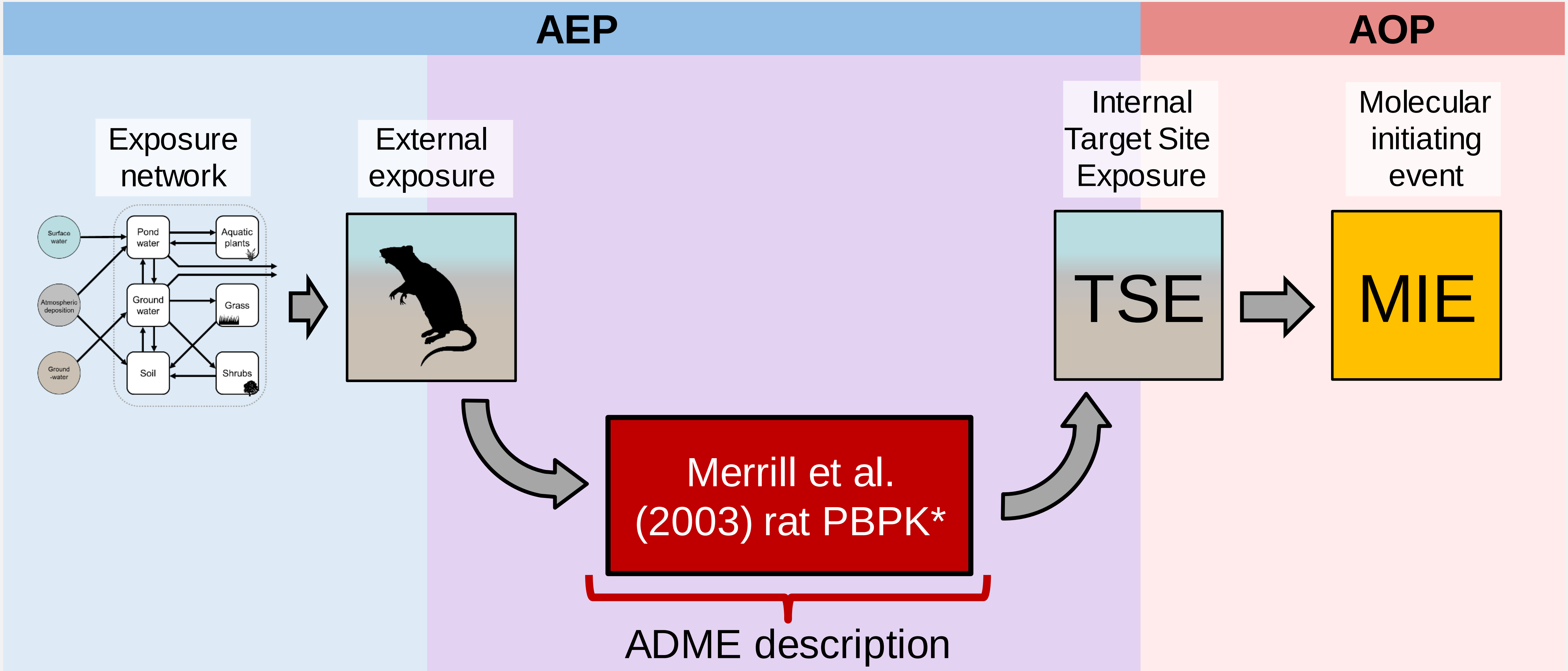


Linking AEPs to AOPs



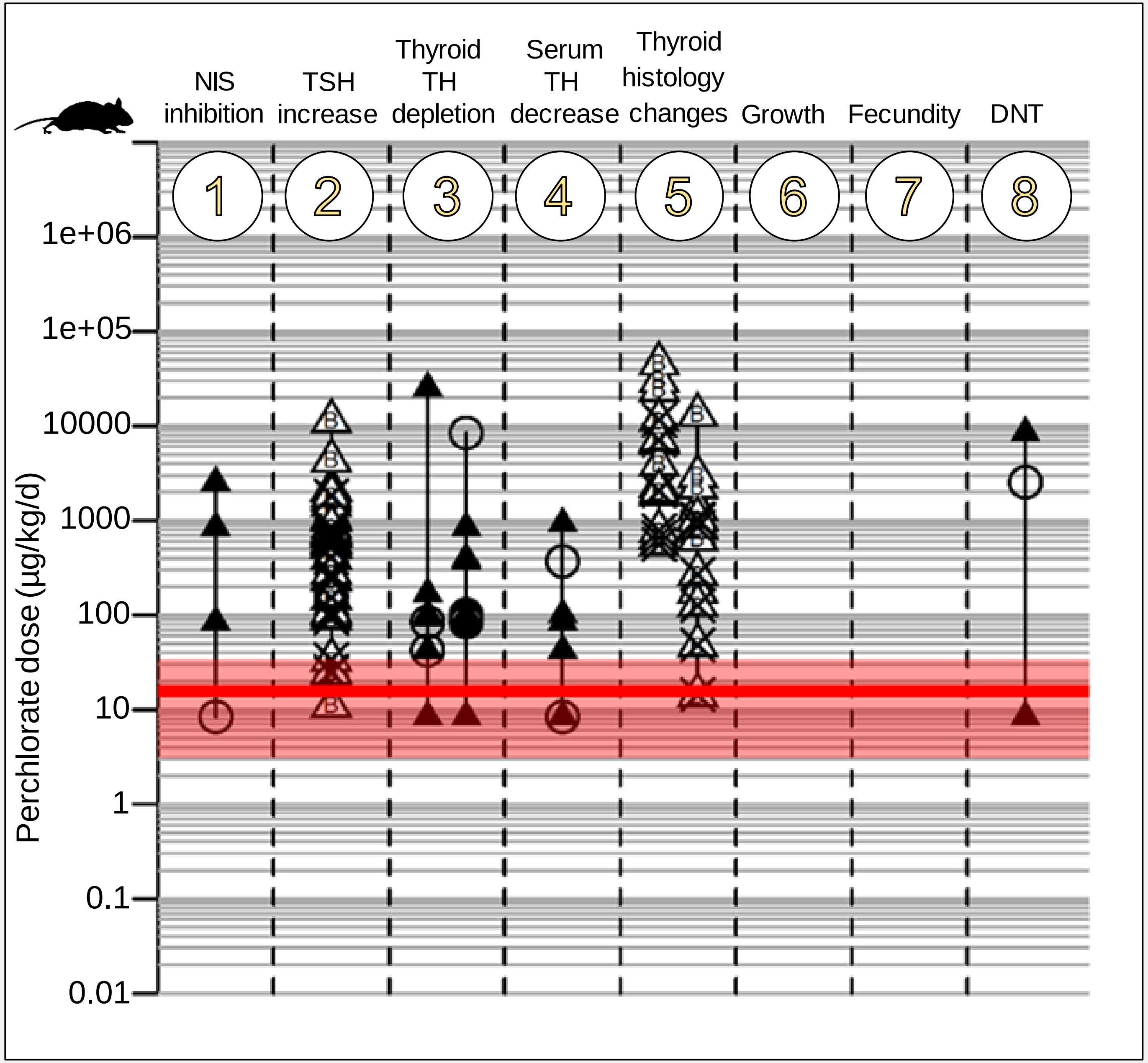


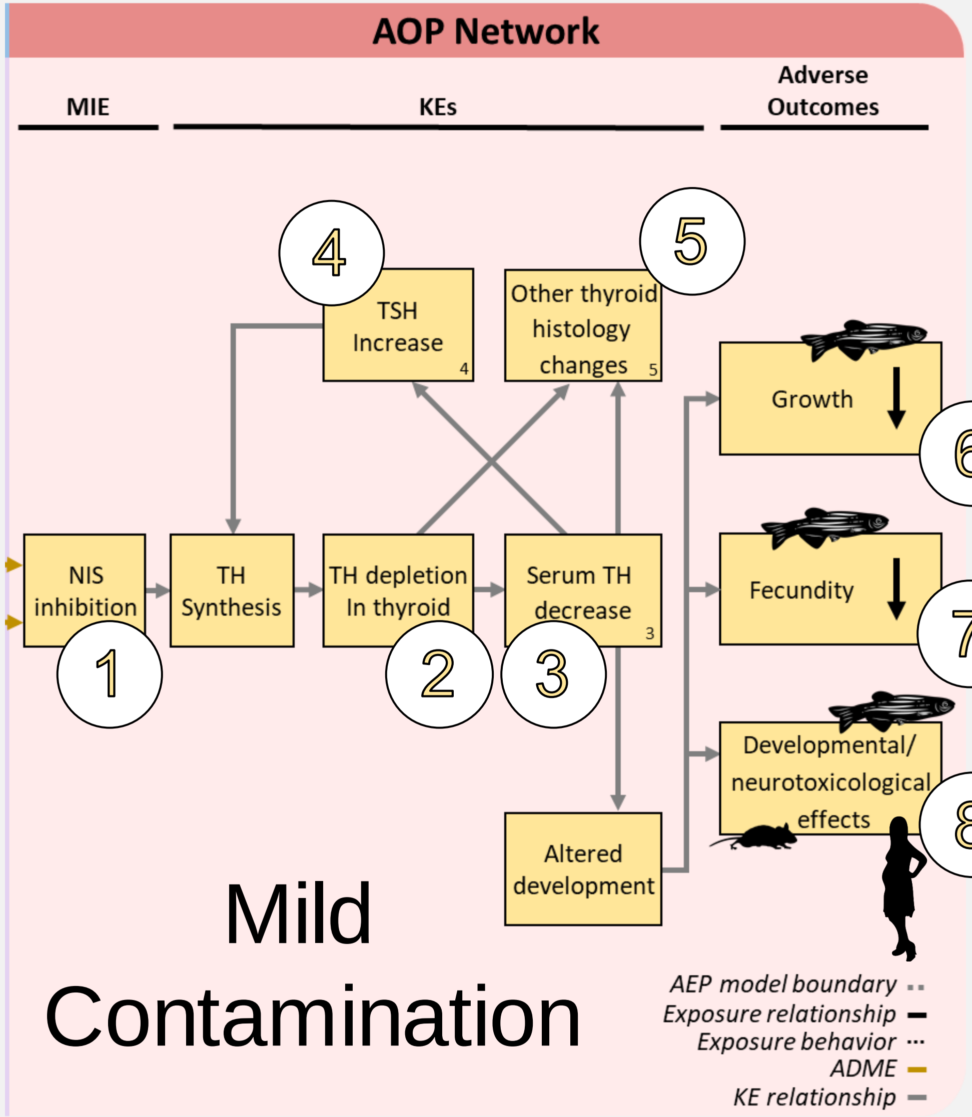
Linking AEPs to AOPs



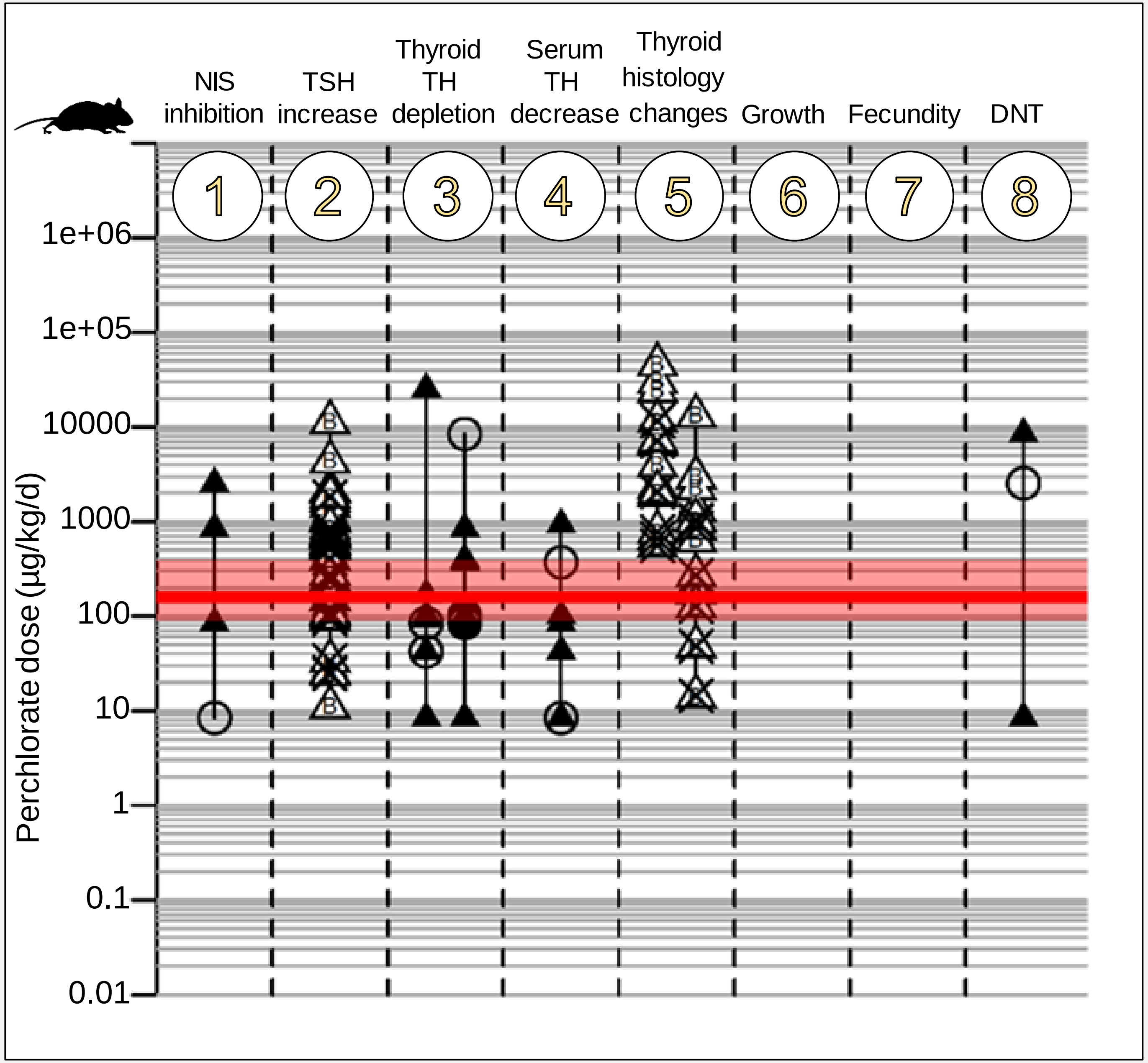
*not yet fully implemented

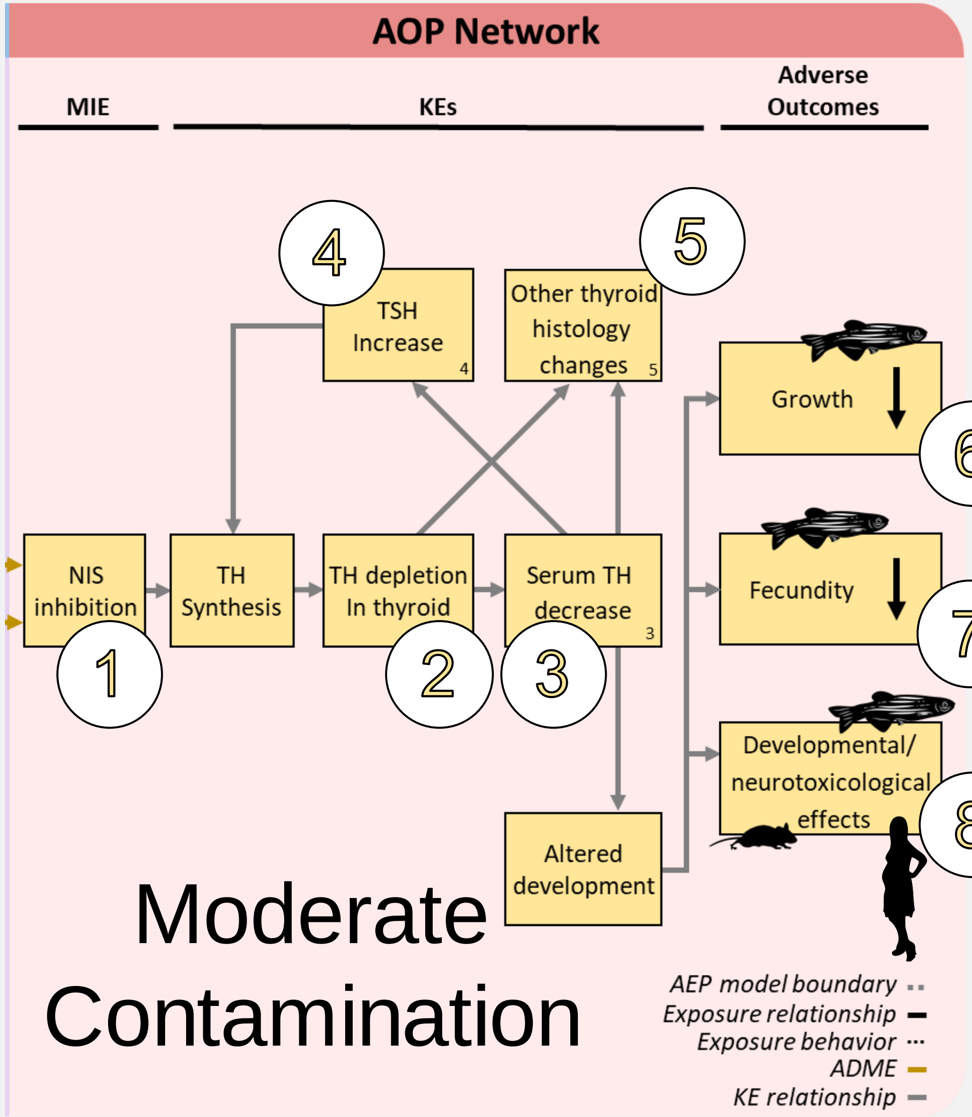
Linking AEPs to AOPs



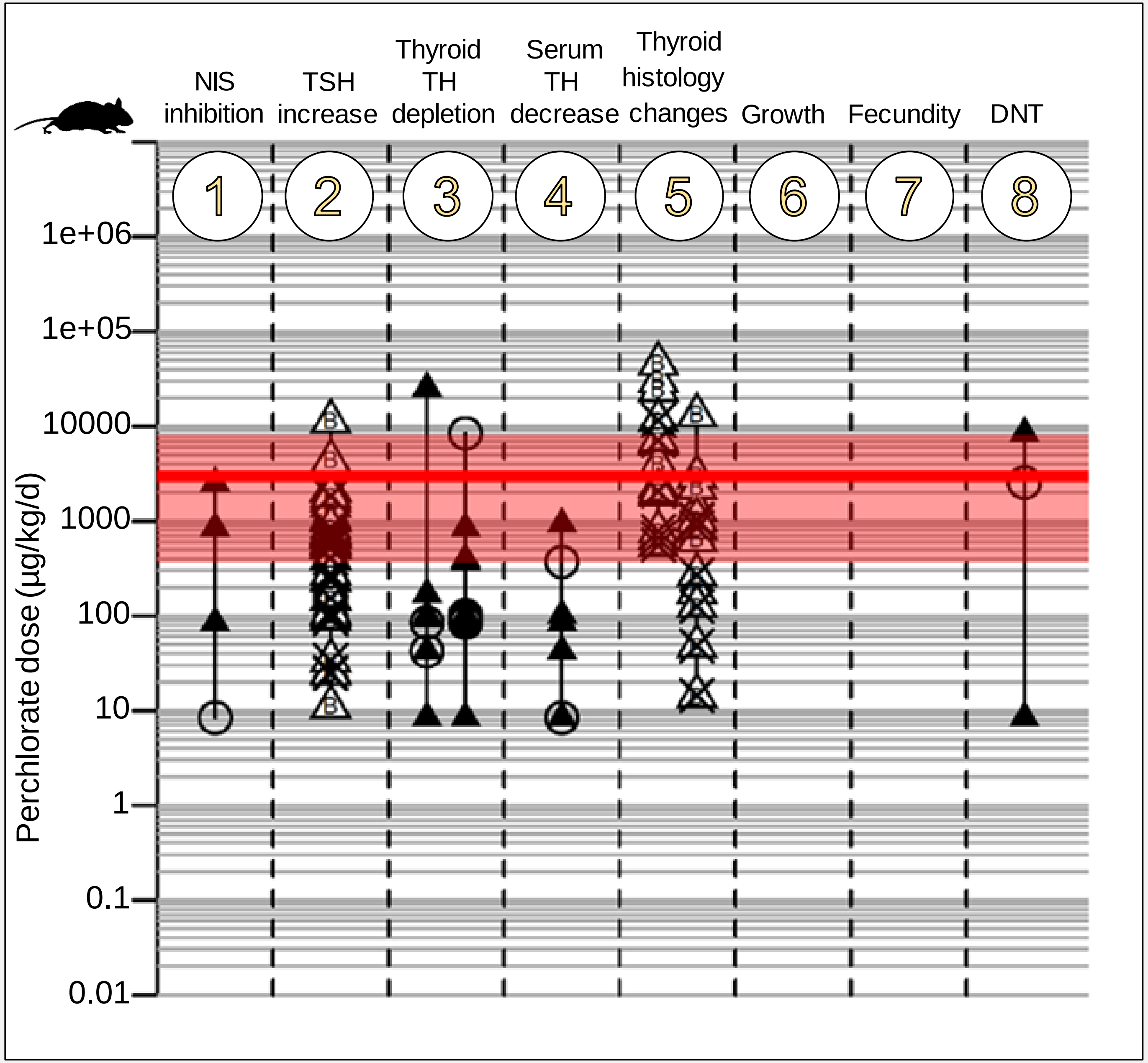


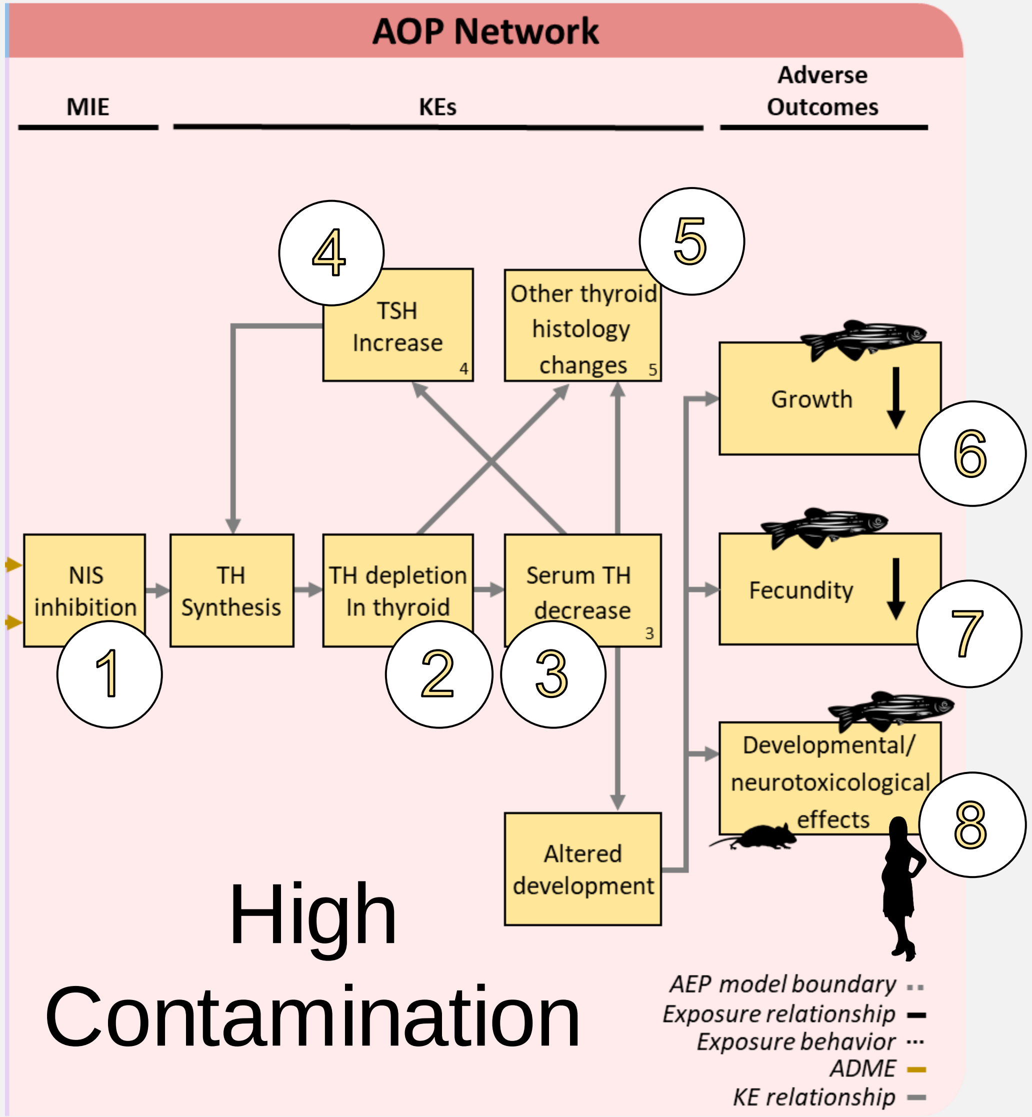
Linking AEPs to AOPs



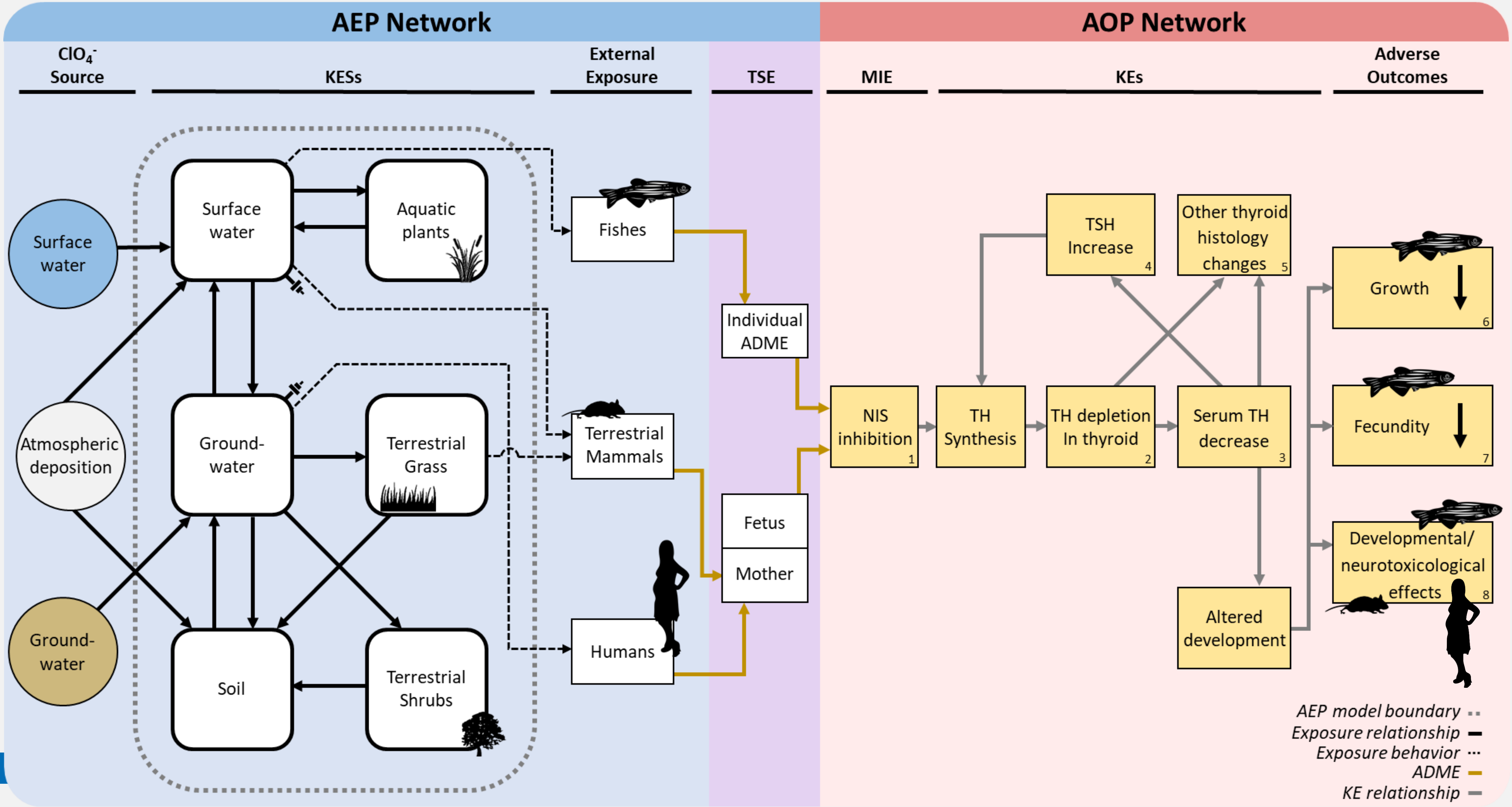


Linking AEPs to AOPs

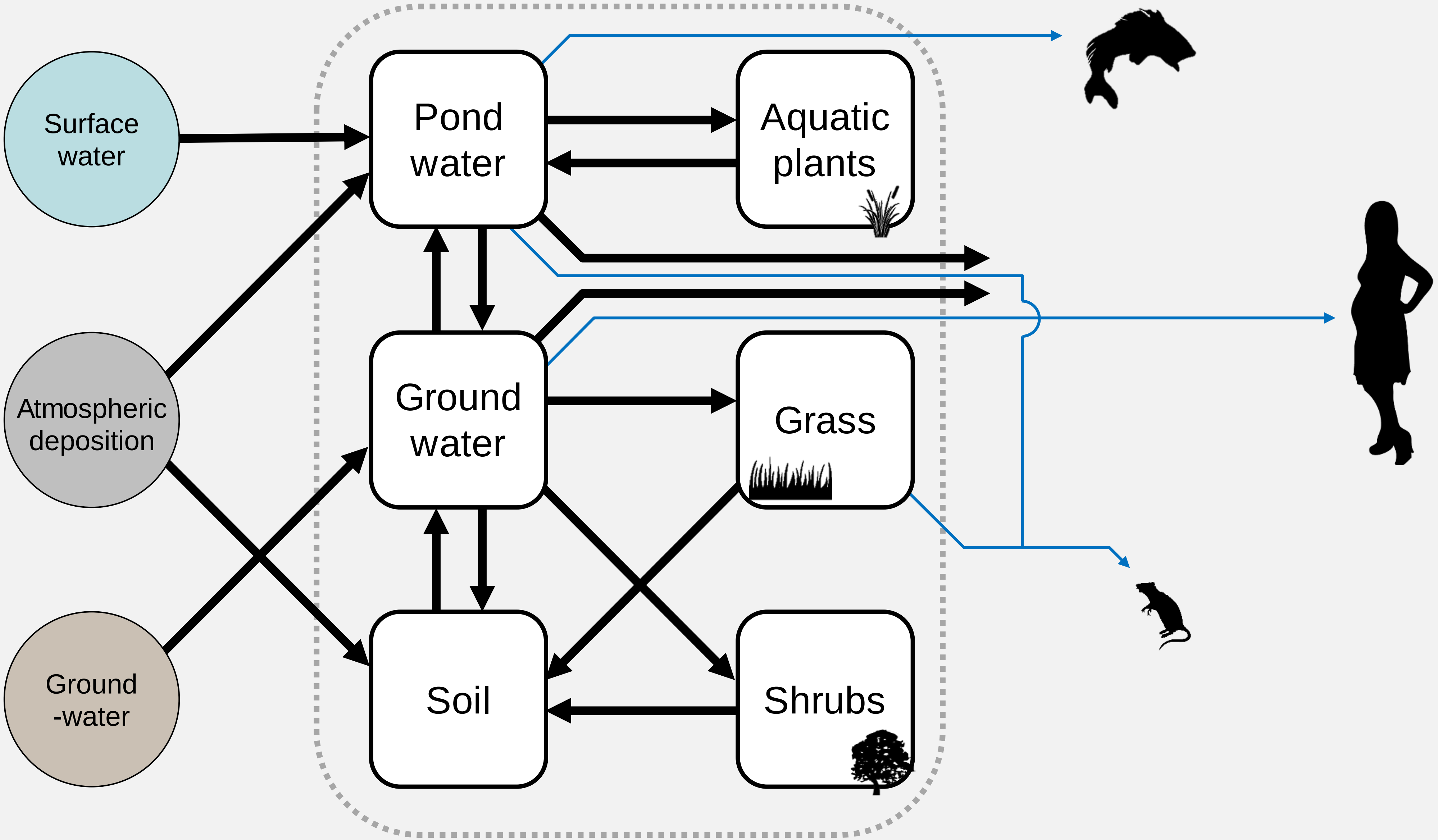




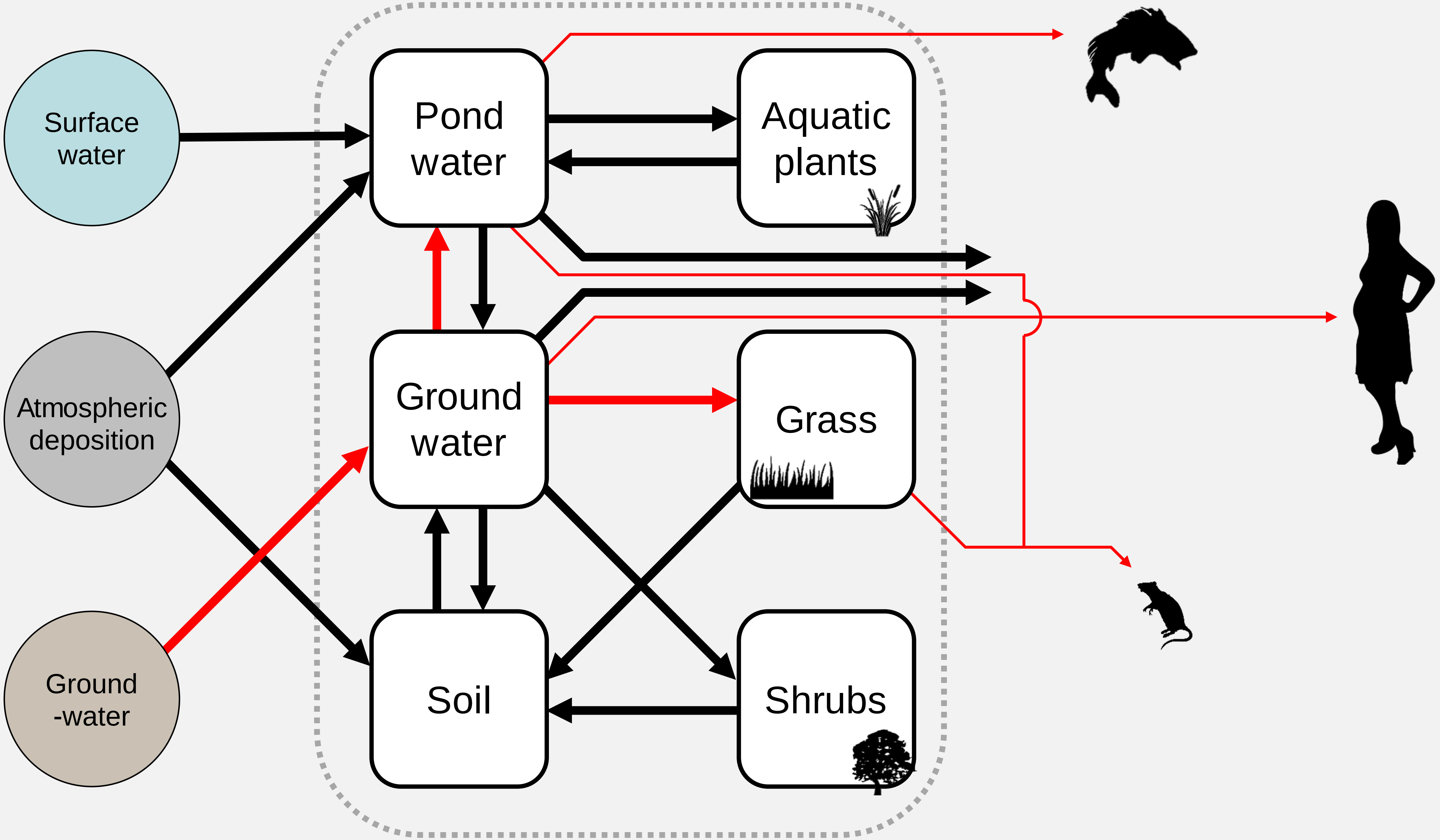
AEP-AOP Construct



Primary exposure pathways



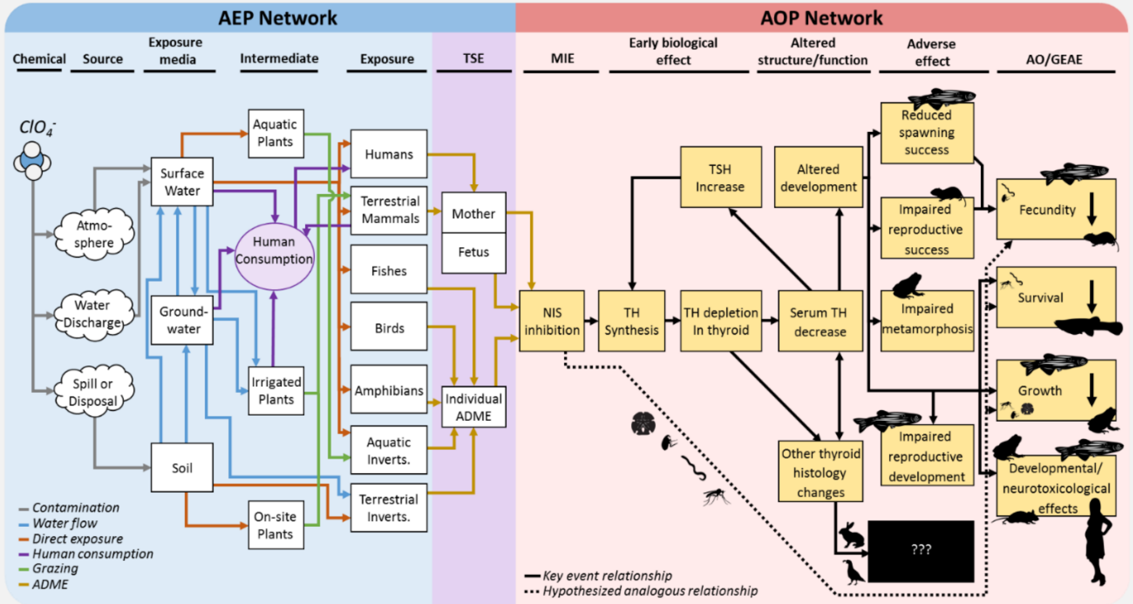
Primary exposure pathways



Conclusions

- AEP and AOP networks can be useful tools to organize data across multiple species.

- Could inform relative source contribution of contaminants in support of risk management decisions.



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