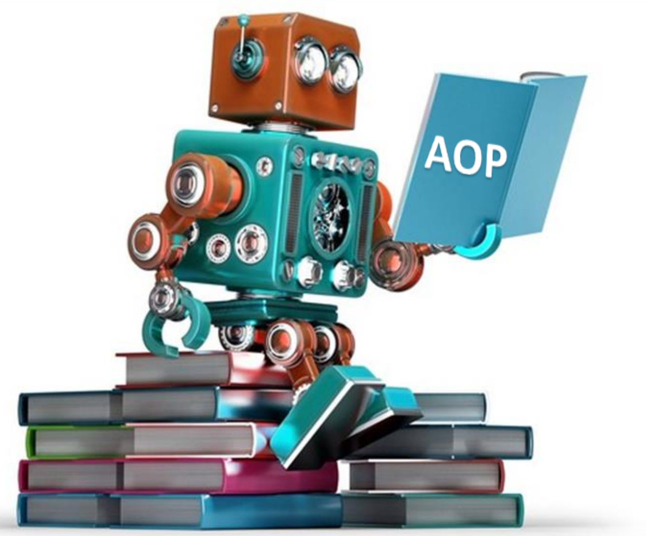
A Machine-Readable AOP Evidence Data Model:

Enhanced data input and retrieval from the AOPwiki



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Environment and Climate Change Canada

Environment and
Climate Change Canada

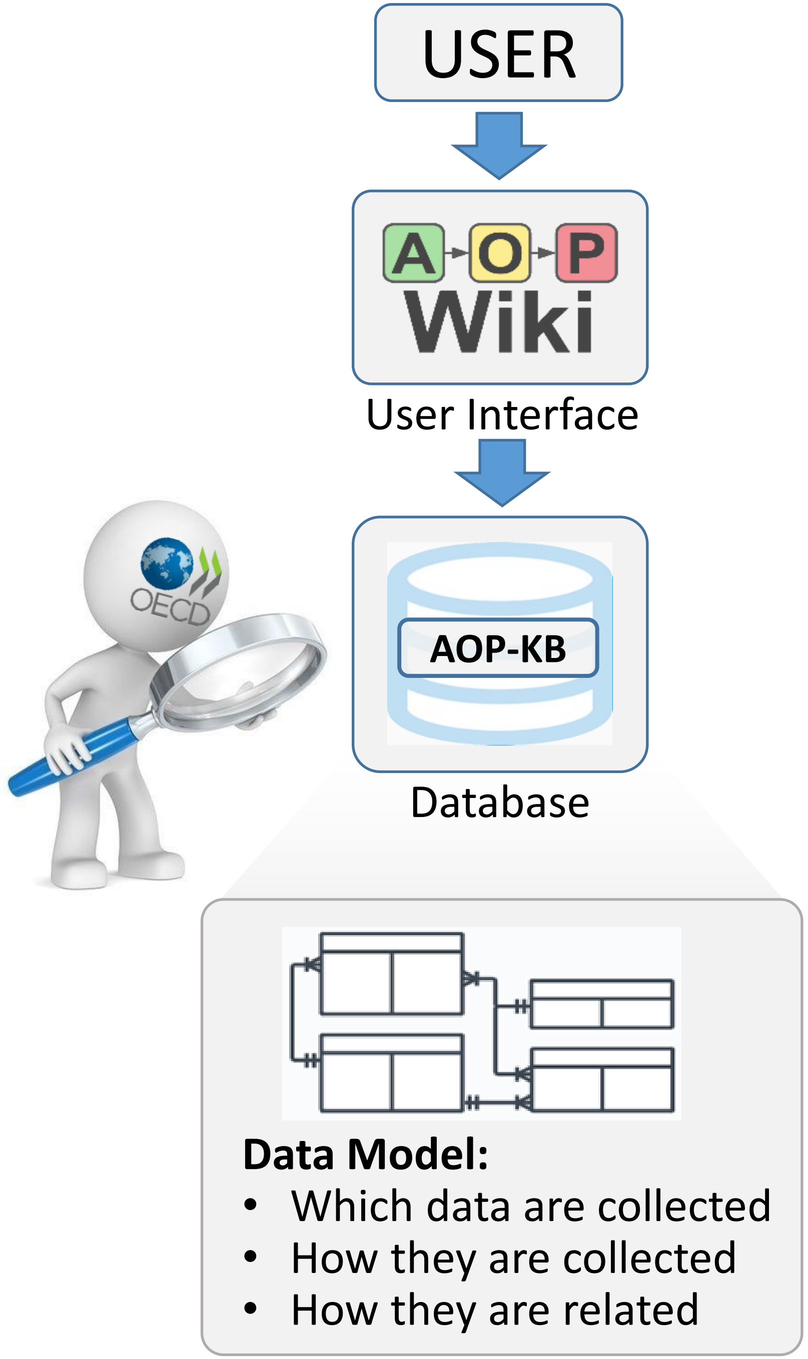
Overview

1) AOP Evidence Data Model
2) User Interface and Workflow (Manual)
3) Data Queries (including cross-database queries)

Update AOP Data Model?

- OECD Subcommittee that oversees the AOP-KB are considering modifications to the current data model

- Based on demand for:
  - Support of “systematic” evidence collection strategies
  - Consistency between author entries
  - Improved tracking and “usability” of data in the AOP-KB
    - Search, aggregate and summarize information
    - Interoperability with other databases



Focus on Key Event Relationship Evidence

- Heaviest Burden of Evidence in the AOP framework
  - KER Evidence = Upstream Effect → Downstream Effect

- Based on Modified Bradford-Hill Criteria
  - Biological Plausibility
  - Empirical Evidence (Dose-, Temporal-, Incidence-concordance)

- Evidence collection is heavily based on **Free Text**
  - Time consuming for Authors
  - Inconsistent formatting/information
  - Hard to QUICKLY find information
  - Not easily interpreted by computers
  - IMPOSSIBLE to automatically aggregate and summarize

AOP-Wiki AOPs Key Events KE Relationships Stressors

Evidence Supporting this KER

Biological Plausibility

Histopathological studies have shown that glial activation is a hallmark of every neurodegenerative disease, including Parkinson's disease (Whitton, 2007 ; Tansey and Goldberg, 2009 ; Niranjan, 2014 ; Verkhratiky et al., 2014). PET studies in PD patients have revealed that microglial activation in the substantia nigra is an early event in the disease process (Iannaccone et al., 2012), and that it is extremely persistent. The role of astrocytes is less clear than the one of microglia, but reactive astrocytes are able to release neurotoxic molecules (Mena and Garcia de Ybenes, 2008 ; Niranjan, 2014). However, astrocytes may also be protective due to their capacity to quench free radicals and secrete neurotrophic factors. The activation of astrocytes reduces neurotrophic support to neurons, and the proportion of astrocytes surrounding dopaminergic neurons in the substantia nigra is the lowest for any brain area suggesting that dopaminergic neurons are more vulnerable in terms of glial support (for review, Mena and Garcia de Ybenes, 2008). In vitro co-culture experiments have demonstrated that reactive glial cells (microglia and astrocytes) can kill neurons (Chao et al., 1995 ; Brown and Bal-Price, 2003 ; Kraft and Harry, 2011 ; Taetzsch and Block, 2013), and that interventions with e.g. i-NOS inhibition can rescue the neurons (Yadav et al., 2012; Brzozowski et al., 2015). Direct activation of glial cells with the inflammogen LPS has also resulted in vivo in the death of DA neurons (Sharma and Nehru, 2015; Zhou et al., 2012; Li et al., 2009).

Circulating monocytes and lymphocytes: Neuroinflammation can disrupt blood-brain barrier integrity (Zhao et al., 2007), facilitating infiltration of circulating monocytes and lymphocytes (Machado et al., 2011; Quian et al., 2010). T cell infiltration has been found in CNS tissue of PD patients (Miklossy et al., 2006 ; Qian et al., 2010), and in animal models, in which depletion or inactivation of lymphocytes has been found to protect striatal DA terminals (for review, Appel et al., 2010).

Empirical Evidence

LPS injections: Lipopolysaccharide (LPS, a known activator of microglia) injected into the substantia nigra successfully replicated the pathogenic features of Parkinson's disease in rats. An increase in the mRNA expression of pro-inflammatory cytokines (TNF-alpha, IL-1 beta) was observed 7 days post-injection; alterations in oxidative stress markers (ROS, lipid peroxidation, NO formation, NADPH oxidase activity, GSH system, SOD and catalase) became significant 14 days post-injection, and this was followed by a significant decline in tyrosine hydroxylase (TH), as marker of dopaminergic neurons (Sharma and Nehru, 2015). LPS-induced downregulation of TH expression seemed to depend on the pro-inflammatory cytokine IL-1 beta, since it was not observed in LPS-injected IL-1 knockout mice (Tanaka et al., 2013). Progressive hypokinesia, selective loss of dopaminergic neurons in substantia nigra and reduction of striatal dopamine content, as well as alpha-synuclein aggregation in substantia nigra was also achieved by unilateral intranasal instilation of LPS every

Relationship: 11

Title

AchE Inhibition leads to ACh Synaptic Accumulation

Authors

CHRISTINE L. RUSSOM (1), DANIEL L. VILLENEUVE* (2), VIRGINIA HENCH (3), CATAIA IVES (3), VIRGINIA C. MOSER (1), CARLIE A. LALONE (2), STEPHEN EDWARDS (3), KRISTIE SULLIVAN (4), and GERALD T. ANKLEY (2)

Empirical Evidence

- At sublethal concentrations (56% of the LD50), researchers found a statistically significant (18%) increase in the amount of acetylcholine in brain tissue of Charles River rats exposed to disulfoton for 3 days, with measured AChE inhibition of 68% as compared to controls (Stavinoha et al., 1969).
- An acute sublethal exposure of chlorpyrifos to Sprague-Dawley rats found significant dose and time related effects including increased inhibition of AChE, increased levels of acetylcholine, and significant impacts to motor activity (nocturnal rearing response) (Karanth et al., 2006).
- Tadpoles (20 d) were exposed to single sublethal concentration of the methyl parathion for 24 h. Analysis of brain tissue found a significant inhibition in AChE activity and a concurrent increase in acetylcholine levels, as compared to controls (Nayeemunnisa and Yasmeen 1986).
- Study of fourth instar Ailanthus silkworm exposed to malathion for 5 days found increased mortality, decreased AChE, and increases in acetylcholine as compared to controls (Pant and Katiyar 1983).
- In a study where female ICR mice were exposed to either the fenobucarb or propoxur, authors reported a significant increase in acetylcholine in brain tissue 10 minutes after injection, with a concurrent significant increase in AChE inhibition (Kobayashi et al., 1985).
- An acute (48h) sublethal exposure to methyl parathion found that AChE levels in brain tissue in fish (Oreochromis mossambicus) were significantly inhibited at all measured durations ranging from 12-48 hrs with inhibition increasing from 36-62% as compared to controls over the time span (Rao and Rao, 1984). The researchers found a significant increase in acetylcholine at all time courses measured (12-48hr) with acetylcholine levels increasing from 33-83% as compared to controls over the same time span (Rao and Rao, 1984).
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- Measurements (in vitro) of AChE inhibition, acetylcholine and electrophysiological responses on the pedal ganglion of the gastropod Aplysia californica, were found to be dose-dependent, with increase in dose resulting in increased AChE inhibition, increased levels of acetylcholine, and a decrease in the electrophysiological response (Oyama et al., 1989).

- Authors report a lot of information
- But it is not being tracked!!

Current Trends in AOP Development

- “systematic” approaches to evidence documentation becoming more common (and strongly encouraged!!!)
- “discrete units” of evidence
- Each unit supports specific Bradford Hill criteria

(i.e. a different “type” of evidence)

UPSTREAM KE

DOWNSTREAM KE

STRESSOR

DOMAIN: SPECIES

EVIDENCE TYPE

PUBLICATION

Relationship: 11

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Empirical Evidence

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- An acute sublet… effects includin… motor activity (…

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DOMAIN: SPECIES

EVIDENCE TYPE

PUBLICATION

Relationship: 11

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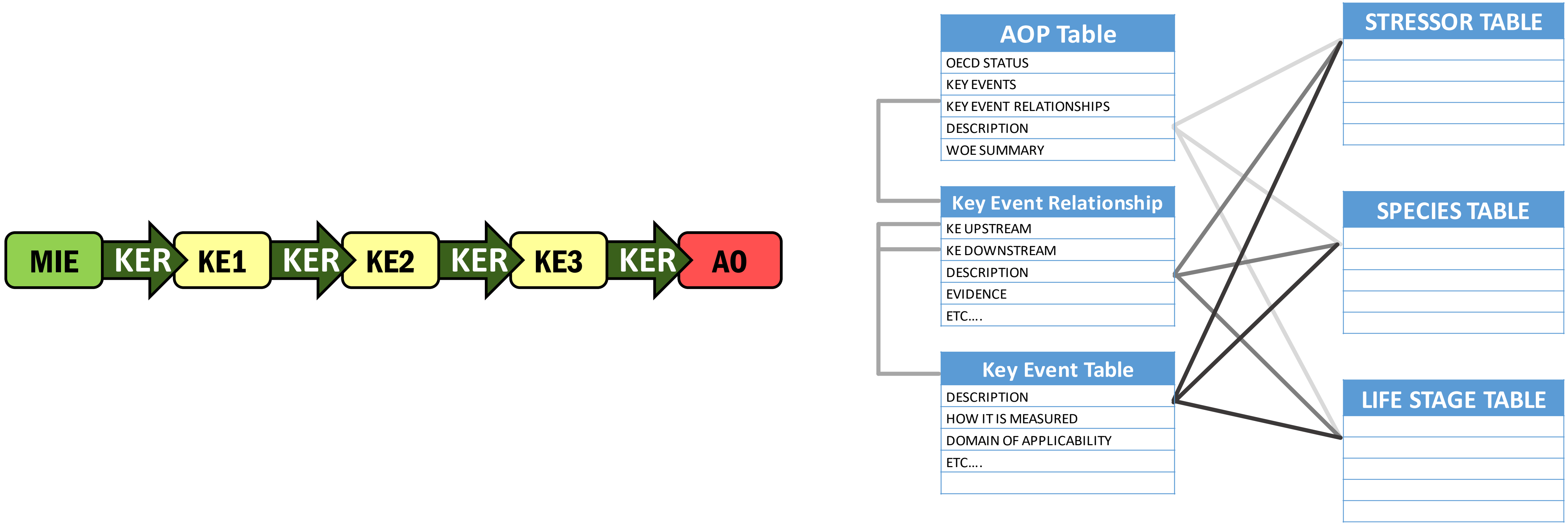
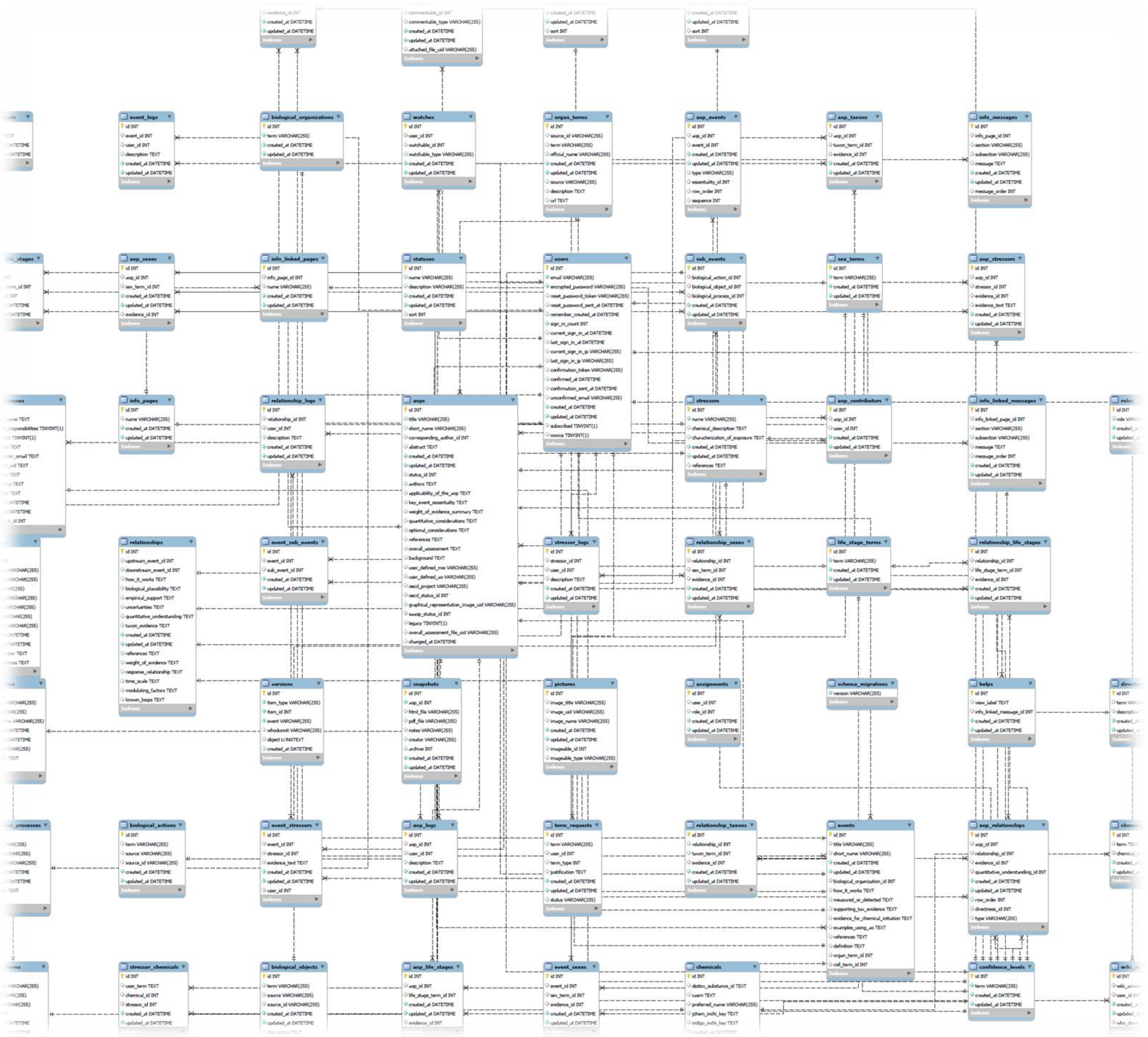
Pilot Study Objectives

1. Develop a more structured data model for KER evidence
2. Develop user interface for data entry
3. Test resulting database with “queries” not currently possible in AOP-KB

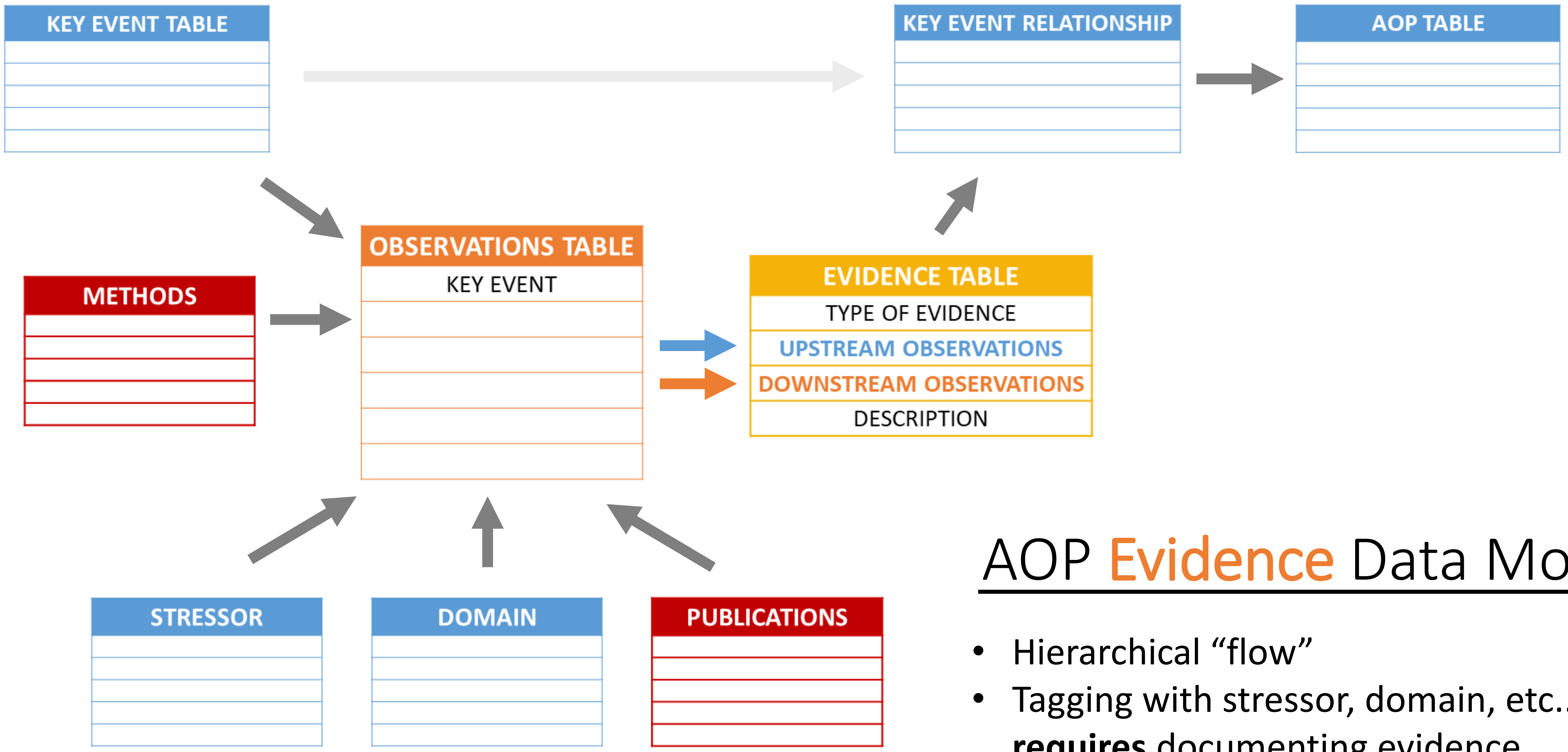
The Current AOP Knowledge Base Data Model



Gets pretty complex….



1) AOP Evidence Data Model



AOP Evidence Data Model

- Hierarchical “flow”
- Tagging with stressor, domain, etc.. **requires** documenting evidence
- Transparent, machine readable annotation and tracking

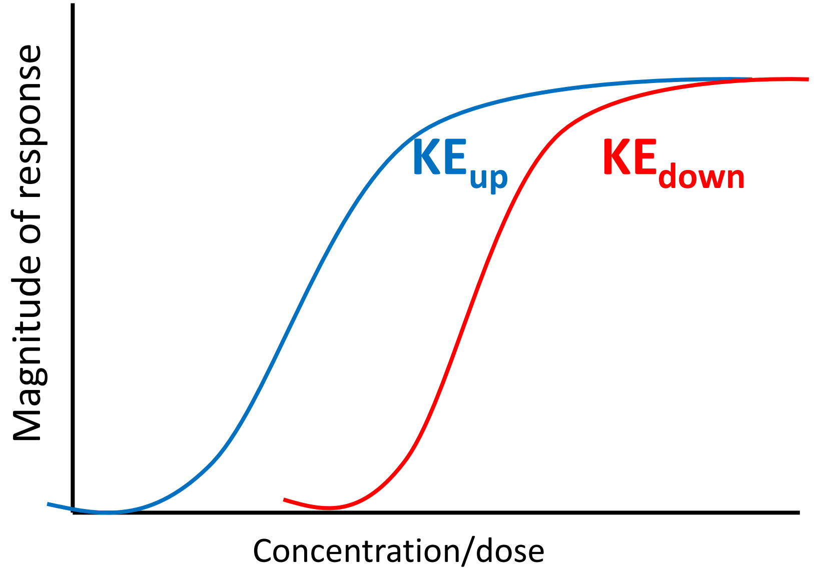
2) Developing Workflows for Data Collection

GOAL:

- A series of “user friendly” forms with **MINIMAL free text**
- Flexible with data requirements to allow results from diverse experiments
- “inspired by” systematic approaches

Developing Workflows for Data Collection

All forms of <u>empirical</u> evidence for KERs (dose, temporal and incidence concordance) require evidence for **BOTH** upstream and downstream KEs



EMPIRICAL EVIDENCE FORM

KER (AOPWIKI ID)	
TYPE OF EVIDENCE	

UPSTREAM OBSERVATION	**DOWNSTREAM OBSERVATION**
ADD NEW	**ADD NEW**

Evidence Summary (free text)

EMPIRICAL EVIDENCE FORM

KER (AOPWIKI ID)	869: Activation Ahr leads to Induction, CYP1A2/CYP1A5
TYPE OF EVIDENCE	Dose Concordance

UPSTREAM OBSERVATION	**DOWNSTREAM OBSERVATION**
ADD NEW	**ADD NEW**

Evidence Summary (free text)

EVIDENCE FORM

eads to Induction, CYP1A2/CYP1A5

DOWNSTREAM OBSERVATION

ADD NEW

mmary (free text)

EMPIRICAL OBSERVATION FORM

Description	Dioxin, in vitro, AhR Ligand Binding, Mouse

Experiment Info	
Stressor	Dioxin
Experiment Type	In vitro
Method	AhR Ligand Binding
Endpoint	AhR Activity
Target Key Event	#18: Activation, AHR
Publication	Smith et al, 2005

Domain of Observation	
Species	Mus musculus
Strain	
Genotype	
Life Stage	
Sex	male
Tissue/Cell Type	Hepatocyte

OBSERVATIONS	
General Effect	Increased with dose

Points of Departure/Summary Data

POD TYPE	POD VALUE	POD UNITS
EC50	2	nM
BMD (1SD)	0.5	nM

ADD NEW

Data Repositories

Repository	Link
EPA EcoToxDB	https://cfpub.epa.gov/ecotox/search.cfm

ADD NEW

EMPIRICAL EV

KER (AOPWIKI ID)	869: Activation Ahr lea
TYPE OF EVIDENCE	Dose Concordance

UPSTREAM OBSERVATION
Dioxin, in vitro, Ahr ligand binding, mouse
ADD NEW

Evidence Sum

EMPIRICAL OBSERVATION FORM

Description	Dioxin, in vitro, EROD, mouse

Experiment Info	
Stressor	Dioxin
Experiment Type	In vitro
Method	EROD Assay
Endpoint	Cytochrome P450 activity
Target Key Event	Activation, Cyp1A2
Publication	Smith et al. 2005

Domain of Observation	
Species	Mus musculus
Strain	
Genotype	
Life Stage	
Sex	male
Tissue/Cell Type	Hepatocyte

OBSERVATIONS

General Effect	Increased with dose

Points of Departure/Summary Data

POD TYPE	POD VALUE	POD UNITS
EC50	5	nM
BMD (1SD)	1	nM

ADD NEW

Data Repositories

Repository	Link
EPA EcoToxDB	https://cfpub.epa.gov/ecotox/search.cfm

ADD NEW

EMPIRICAL EVIDENCE FORM

KER (AOPWIKI ID)	869: Activation Ahr leads to Induction, CYP1A2/CYP1A5
TYPE OF EVIDENCE	Dose Concordance

UPSTREAM EVIDENCE	DOWNSTREAM EVIDENCE
Dioxin, in vitro, Ahr ligand binding, mouse	Dioxin, in vitro, EROD, mouse
ADD NEW	**ADD NEW**

Evidence Summary (free text)

EMPIRICAL EVIDENCE FORM

KER (AOPWIKI ID)	869: Activation Ahr leads to Induction, CYP1A2/CYP1A5
TYPE OF EVIDENCE	Dose Concordance

UPSTREAM EVIDENCE	**DOWNSTREAM EVIDENCE**
Dioxin, in vitro, Ahr ligand binding, mouse	Dioxin, in vitro, EROD, mouse
ADD NEW	**ADD NEW**

Evidence Summary (free text)

In cultured mouse cells, AhR is activated, as demonstrated by in vitro ligand binding reporter assay, at lower doses than EROD induction **(Smith et al., 2005)**

Collaborative KER Evidence Map

Collaborative KER Evidence Map

- A **visual-based** guide to **evidence documentation**
  - Serves as the “main page” for evidence collection

- Inspired by **systematic review approaches**
  - “Literature Review-like” workflow

- **Highly collaborative:** Designed to **encourage crowd contributions**
  - Evidence is divided in to much smaller “units”
  - Single units are easily contributed by individuals, with minimal training
  - Tracking and management of “units”

Collaborative

KER Evidence Map

		Empirical Evidence			Quantitative Understanding		
	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance	Response-response	Time-scale	Modulating factors
Citation	**EVIDENCE MAP**						

✓	Supporting Evidence
✕	Conflicting Evidence
NR	Evidence Not Relevant
	Not yet assessed for support

EMPIRICAL OBSERVATION FORM

Description	Dioxin, in vitro, AhR Ligand Binding, Mouse

Experiment Info	
Stressor	Dioxin
Experiment Type	In vitro
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Endpoint	AhR Activity
Target Key Event	#18: Activation, AHR
Publication	Smith et al, 2005

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Species	Mus musculus
Strain	
Genotype	
Life Stage	
Sex	male
Tissue/Cell Type	Hepatocyte

OBSERVATIONS	
General Effect	Increased with dose

Points of Departure

POD TYPE	POD VALUE	POD UNITS
EC50	2	nM
BMD (1SD)	0.5	nM

ADD NEW

Detailed Data (Optional)

Sample size	Dose	Dose Unit	Effect size	Effect unit
5	0	nM	0	Fold-change
5	1	nM	0.5	Fold-change
5	10	nM	4.3	Fold-change

ADD NEW

CAL EVIDENC

Ahr leads to Ind

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EMPIRICAL OBSERVATION FORM

Description	Dioxin, in vitro, EROD, mouse

Experiment Info	
Stressor	Dioxin
Experiment Type	In vitro
Method	EROD Assay
Endpoint	Cytochrome P450 activity
Target Key Event	Activation, Cyp1A2
Publication	Guy-Man et al, 2049

Domain of Observation	
Species	Mus musculus
Strain	
Genotype	
Life Stage	
Sex	male
Tissue/Cell Type	Hepatocyte

OBSERVATIONS	
General Effect	Increased with dose

Points of Departure

POD TYPE	POD VALUE	POD UNITS
EC50	5	nM
BMD (1SD)	1	nM

ADD NEW

Detailed Data (Optional)

Sample size	Dose	Dose Unit	Effect size	Effect unit
5	0	nM	0	Fold-change
5	1	nM	0.1	Fold-change
5	10	nM	2.3	Fold-change

ADD NEW

rting Evidence
ting Evidence
ce Not Relevant
t assessed for support

Collaborative

KER Evidence Map

		Empirical Evidence			Quantitative Understanding		
	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance	Response-response	Time-scale	Modulating factors
Citation	EVIDENCE MAP						
Sharin T, et al., 2020, Environ Toxicol Chem. 39(9):1693-1701.		✓					

✓	Supporting Evidence
✕	Conflicting Evidence
NR	Evidence Not Relevant
	Not yet assessed for support

Collaborative

KER Evidence Map

		Empirical Evidence			Quantitative Understanding		
Citation	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance	Response-response	Time-scale	Modulating factors
	EVIDENCE MAP						
Sharin T, et al., 2020, Environ Toxicol Chem. 39(9):1693-1701.	✓	✓	NR	NR	NR	NR	NR
Vyhlídalová B, et al., 2019, Toxicol Lett. 313:66-76.	✓	✓	NR	✓			
Vrzal R, et al., 2017, Toxicol Lett.275:77-82.	✓	✓	NR	NR			
Pahlke G, et al., 2016, Toxicol Lett. 240(1):93-104.	✓	✓	✓	NR	✓	NR	NR
Wang K, et al., 2015, Int J Mol Sci. 16(7):16454-68.	✓	✓	NR	NR	NR	NR	✓
Thomas M, et al., 2015, Mol Pharmacol. 87(6):1013-20.	✓	NR	✓	NR		✓	
Vaas S, et al., 2014, Toxicology. 325:31-41.	✓	NR	NR	NR			
Kakutani H, et al., 2014, Toxicology. 324:68-75.	✗	✗	NR	NR			
Vrzal R, et al., 2013, PLoS One. 8(9):e74917.	✓	✓					
Liguori MJ, et al., 2012, Front Genet. 3:213.			✓	✓			
Diani-Moore S, et al., 2011, Chem Biol Interact. 193(2):119-28.		✓					
Braeuning A, et al., 2011, Toxicol Sci. 122(1):16-25.		✓					
Vrba J, et al., 2011, Toxicol Lett. 203(2):135-41.		✓	✓	✓			
Jones SP, et al., 2009, Toxicol Sci. ;109(1):66-74.		✓					
Dvorak Z, et al., 2008, Biochem Pharmacol. 75(2):580-8.				✓	✓		
Gerbal-Chaloin S, et al., 2006, Cell Signal. 18(5):740-50.		✓			✓	✓	
Diani-Moore S, et al., 2006, Toxicol Sci.90(1):96-110.	✓						
Suzuki G, et al., 2006, Toxicol Lett. 161(3):174-87.			✗	✗			
Kanzawa N, et al., 2004, Arch Biochem Biophys. 427(1):58-67.	✓						
Roling JA, et al., 2004, Mar Environ Res. 57(5):377-95.	✓						
Bemanian V, et al., 2004, Comp Hepatol. 3(1):2.	✓						

✓	Supporting Evidence
✗	Conflicting Evidence
NR	Evidence Not Relevant
	Not yet assessed for support

3) Reconstruction of AOPs

AOP #25: Aromatase inhibition leading to reproductive dysfunction

AOP #131: Aryl hydrocarbon receptor activation leading to uroporphyria

Many Challenges:

- Required information not always present or obvious
- Required information in wrong location (e.g. KER evidence on AOP page)
- Information presented in inconsistent formats (tables, bullets, or text)
- etc, etc, etc….

Highlights potential benefits of more structured data input (especially for inexperienced AOP authors!)

Result: Partial Reconstruction of AOP 25 and AOP 131

4) Test resulting database with “queries” that are not currently possible in AOP-KB

Query: What **stressors** were used to for the development of AOP 25 ?

SQL Code (**S**tructured **Q**uery **L**anguage, the most common programming language for interacting with databases)

```
SELECT DISTINCT "Stressor Common Name", "First Author", "Year Published", Journal, Volume, Pages
FROM prototype.empirical_observations AS emp
LEFT JOIN prototype.stressor AS stress ON emp."Stressor" = stress."ID"
LEFT JOIN prototype.key_events AS ke ON emp."Key Event Target" = ke."Key Event Name"
LEFT JOIN prototype.publications AS pub ON emp.Publication = pub.ID
WHERE ke.ID IN (7,8,9,10,11,12,13,14)
ORDER BY "Stressor Common Name"
```

Results:

Stressor Common Name	First Author	Year	Journal	Volume	Pages
Fadrazole	Anthony L. Schroeder	2017	General and Comparative Endocrinology		
Fadrazole	Gerald T. Ankley	2002	Toxicological Sciences	67	121-130
Ketoconazole	Gerald T.Ankley	2012	Aquatic Toxicology	114-115	88-95

Query: What species and tissues were used as evidence for each Key Event in AOP 25, including references?

SQL Code:

```sql
SELECT spec."Common name", tis."Tissue / cell type", ke."Key Event Name", "First Author", "Year Published", Journal, Volume, Pages
FROM prototype.empirical_observations AS emp
LEFT JOIN prototype.key_events AS ke ON emp."Key Event Target" = ke."Key Event Name"
LEFT JOIN prototype.domain_species AS spec ON emp."Domain-Species" = spec.ID
LEFT JOIN prototype.domain_tissue_or_cell_type AS tis ON emp."Domain-Tissue" = tis.ID
LEFT JOIN prototype.publications AS pub ON emp.Publication = pub.ID
WHERE ke.ID IN (7,8,9,10,11,12,13,14)
ORDER BY ke.ID
```

Results:

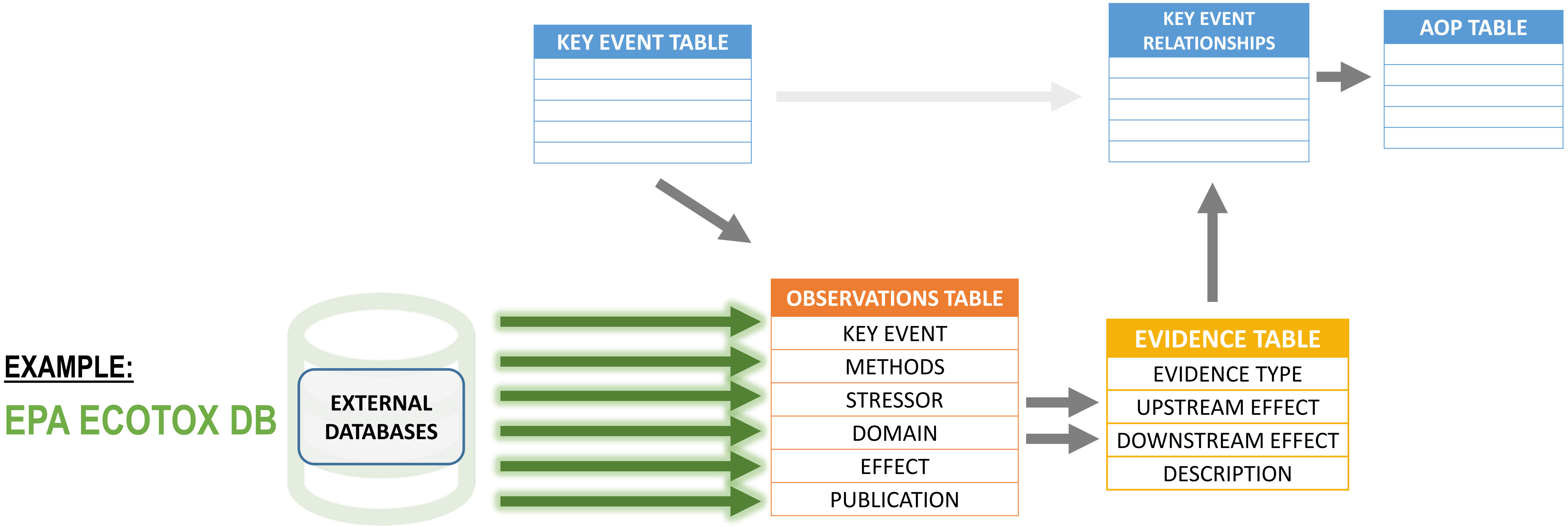
Common name	Tissue	Key Event Name	First Author	Year	Journal
Fathead Minnow	Ovary	Reduction, 17beta-estradiol synthesis by ovarian granulosa cells	Anthony L. Schroeder	2017	General and Comparative Endocrinology
Fathead Minnow	Ovary	Reduction, 17beta-estradiol synthesis by ovarian granulosa cells	Gerald T.Ankley	2012	Aquatic Toxicology
Fathead Minnow	Plasma	Reduction, Plasma 17beta-estradiol concentrations	Anthony L. Schroeder	2017	General and Comparative Endocrinology
Fathead Minnow	Plasma	Reduction, Plasma 17beta-estradiol concentrations	Gerald T.Ankley	2012	Aquatic Toxicology
Fathead Minnow	Plasma	Reduction, Plasma 17beta-estradiol concentrations	Gerald T. Ankley	2002	Toxicological Sciences
Fathead Minnow	Plasma	Reduction, plasma vitellogenin concentrations	Gerald T.Ankley	2012	Aquatic Toxicology
Fathead Minnow	brain	Aromatase inhibition	Gerald T. Ankley	2002	Toxicological Sciences

Query: What Point of Departure Values are reported for each species and tissue for Dose-Response evidence for AOP 131?

```sql
SELECT emp."Key Event Target", pod_types."POD Type", "POD value", "POD units", spec."Common name", tis."Tissue / cell type" AS Tissue
FROM prototype.point_of_departure_table AS pod
LEFT JOIN prototype.empirical_observations AS emp ON pod.Observation_ID = emp.ID
LEFT JOIN prototype.key_events AS ke ON emp."Key Event Target" = ke."Key Event Name"
LEFT JOIN prototype.pod_types ON pod."POD Type" = pod_types.ID
LEFT JOIN prototype.domain_species AS spec ON emp."Domain-Species" = spec.ID
LEFT JOIN prototype.domain_tissue_or_cell_type AS tis ON emp."Domain-Tissue" = tis.ID
LEFT JOIN prototype.publications AS pub ON emp.Publication = pub.ID
WHERE ke.ID IN (1,2,3,4,5,6)
AND "POD value" <> ""
ORDER BY ke.ID
```

Key Event Target	POD Type	POD value	POD units	Common name	Tissue
Activation, AHR	NOEC	1	nM	mouse	Plasma
Activation, AHR	LOEC	2	nM	mouse	Plasma
Activation, AHR	EC50	15	nM	mouse	Plasma
Activation, AHR	EC50	200	pM	mouse	Plasma
Activation, AHR	EC50	2	nM	ring-necked pheasant	hepatocyte
Induction, CYP1A2/CYP1A5	NOEC	5	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	LOEC	10	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	EC50	50	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	NOEC	5	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	LOEC	10	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	EC50	50	nM	mouse	hepatocyte
Induction, CYP1A2/CYP1A5	EC50	1	nM	chicken	hepatocyte
Induction, CYP1A2/CYP1A5	EC50	0	nM	chicken	hepatocyte
Induction, CYP1A2/CYP1A5	EC50	3	nM	chicken	hepatocyte

Enhanced Interoperability



Query: What studies in EcoToxDB provide measurements for any of the Key Events in AOP 131 (Ahr activation leads to uroporphyria)?

```sql
SELECT mes.description, spec.common_name AS species, chem.chemical_name, ref.author, ref.source, ref.publication_year
FROM ecotox.results AS res
LEFT JOIN ecotox.tests ON res.test_id = tests.test_id
LEFT JOIN ecotox."references" AS ref ON tests.reference_number = ref.reference_number
LEFT JOIN ecotox.measurement_codes AS mes ON res.measurement = mes.code
LEFT JOIN ecotox.species AS spec ON tests.species_number = spec.species_number
LEFT JOIN ecotox.chemicals AS chem ON tests.test_cas = chem.cas_number
WHERE mes.code IN ("AHMR","AHRC","1A5M","C1A2","CA2M","UPRP","UPDC","PORP")
```

OVER 200 HITS!!!

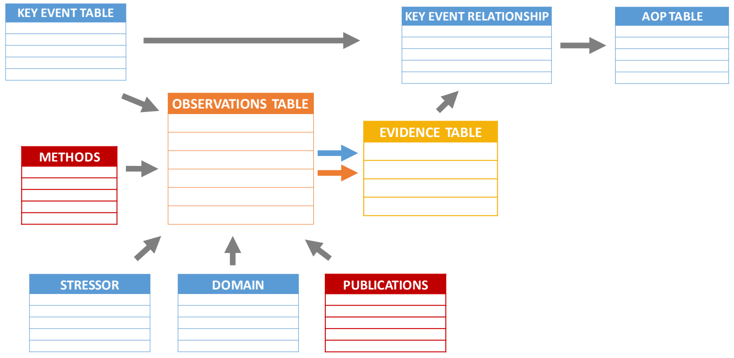
Description	Species	Chemical_name	Author	Publication	Year
Porphyrin	House Mouse	5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid, Sodium salt (1:1)	Krijt,J., O. Psenak, M. Vokurka, A. Chlumska, and F. Fakan	Toxicol. Appl. Pharmacol.189(1): 28-38	2003
Porphyrin	House Mouse	Arsenous acid, sodium salt (1:3)	Garcia-Vargas,G., M.E. Cebrian, A. Albores, C.K. Lim, and F. De Matteis	Hum. Exp. Toxicol.14:475-483	1995
Porphyrin	House Mouse	Arsenic acid (H3AsO4), Sodium salt (1:?)	Garcia-Vargas,G., M.E. Cebrian, A. Albores, C.K. Lim, and F. De Matteis	Hum. Exp. Toxicol.14:475-483	1995
Cytochrome P-450 1A2 mRNA	House Mouse	N'-(3,4-Dichlorophenyl)-N,N-dimethylurea	Takeuchi,S., M. Iida, H. Yabushita, T. Matsuda, and H. Kojima	Chemosphere74(1): 155-165	2008
Porphyrin	House Mouse	5-[2-Chloro-4-(trifluoromethyl)phenoxy]-N-(methylsulfonyl)-2-nitrobenzamide	Krijt,J., O. Psenak, M. Vokurka, A. Chlumska, and F. Fakan	Toxicol. Appl. Pharmacol.189(1): 28-38	2003
Aryl Hydrocarbon Receptor protein mRNA	Quail	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	Xia,J., L. Qin, Z.H. Du, J. Lin, X.N. Li, and J.L. Li	Chemosphere171:259-264	2017
Cytochrome P-450 1A2 mRNA	House Mouse	N'-(3,4-Dichlorophenyl)-N-methoxy-N-methylurea	Takeuchi,S., M. Iida, H. Yabushita, T. Matsuda, and H. Kojima	Chemosphere74(1): 155-165	2008
Cytochrome P-450 1A2	House Mouse	2-Methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide	Dai,D., Y. Cao, G. Falls, P.E. Levi, E. Hodgson, and R.L. Rose	Pestic. Biochem. Physiol.70(3): 127-141	2001
Aryl Hydrocarbon Receptor	Rainbow Trout	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	De La Casa-Resino,I., J.M. Navas, and M.L. Fernandez-Cruz	Alt. Lab. Anim. (ATLA)42:25-30	2014
Aryl Hydrocarbon Receptor protein mRNA	Chinese Rare Minnow	2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctanoic acid	Liu,Y., J. Wang, Y. Wei, H. Zhang, Y. Liu, and J. Dai	Aquat. Toxicol.88(3): 183-190	2008

Query: What studies in EcoToxDB provide **evidence** for **BOTH** Key Events in the **first KER** of **AOP131** (AHR activation leads to CYP Induction)?

```
-- EcoToxDB studies that have evidence for BOTH KEs of KER 869 (AHR --> Cyp1A2/5)
SELECT mes.description, spec.common_name AS species, chem.chemical_name, ref.author, ref.source, ref.publication_year
FROM ecotox.results AS res
LEFT JOIN ecotox.tests ON res.test_id = tests.test_id
LEFT JOIN ecotox."references" AS ref ON tests.reference_number = ref.reference_number
LEFT JOIN ecotox.measurement_codes AS mes ON res.measurement = mes.code
LEFT JOIN ecotox.species AS spec ON tests.species_number = spec.species_number
LEFT JOIN ecotox.chemicals AS chem ON tests.test_cas = chem.cas_number
WHERE res.test_id IN(
    SELECT test_id
    FROM ecotox.results
    WHERE measurement IN ("AHMR", "AHRC")
    INTERSECT
    SELECT test_id
```

Measurement	Species	Chemical_name	Author	Publication	Year
Aryl Hydrocarbon Receptor protein	Quail	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	Xia,J., L. Qin, Z.H. Du, J. Lin, X.N. Li, and J.L. Li	Chemosphere171:259-264	2017
Cytochrome P450 1A5 mRNA	Quail	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	Xia,J., L. Qin, Z.H. Du, J. Lin, X.N. Li, and J.L. Li	Chemosphere171:259-264	2017
Cytochrome P450 1A5 mRNA	Quail	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	Xia,J., L. Qin, Z.H. Du, J. Lin, X.N. Li, and J.L. Li	Chemosphere171:259-264	2017

Summary:



- Developed a structured data model for KER evidence
  - More Explicit Annotation of Evidence
  - Enhanced tracking, transparency, consistency, machine readability

		Empirical Evidence			Quantitative Understanding		
	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance	Response-response	Time-scale	Modulating factors
Citation	EVIDENCE MAP						
Sharin T, et al., 2020, Environ Toxicol Chem. 39(9):1693-1701.	✓	✓	NR	NR	NR	NR	NR
Vyhlídalová B, et al., 2019, Toxicol Lett. 313:66-76.	✓	✓	NR	✓			
Vrzal R, et al., 2017, Toxicol Lett.275:77-82.	✓	✓	NR	NR			
Pahlke G, et al., 2016, Toxicol Lett. 240(1):93-104.	✓	✓	✓	NR	✓	NR	NR
Wang K, et al., 2015, Int J Mol Sci. 16(7):16454-68.	✓	✓	NR	NR	NR	NR	✓
Thomas M, et al., 2015, Mol Pharmacol. 87(6):1013-20.	✓	NR	✓	NR		✓	
Vaas S, et al., 2014, Toxicology. 325:31-41.	✓	NR	NR	NR			
Kakutani H, et al., 2014, Toxicology. 324:68-75.	×	×	NR	NR			
Vrzal R, et al., 2013, PLoS One. 8(9):e74917.	✓	✓					
Liguori MJ, et al., 2012, Front Genet. 3:213.			✓	✓			
Diani-Moore S, et al., 2011, Chem Biol Interact. 193(2):119-28.		✓					
Braeuning A, et al., 2011, Toxicol Sci. 122(1):16-25.		✓					
Vrba J, et al., 2011, Toxicol Lett. 203(2):135-41.		✓	✓	✓			
Jones SP, et al., 2009, Toxicol Sci. ;109(1):66-74.		✓					
Dvorak Z, et al., 2008, Biochem Pharmacol. 75(2):580-8.				✓	✓		
Gerbal-Chaloin S, et al., 2006, Cell Signal. 18(5):740-50.		✓			✓	✓	
Diani-Moore S, et al., 2006, Toxicol Sci.90(1):96-110.	✓						
Suzuki G, et al., 2006, Toxicol Lett. 161(3):174-87.			×	×			
Kanzawa N, et al., 2004, Arch Biochem Biophys. 427(1):58-67.	✓						
Roling JA, et al., 2004, Mar Environ Res. 57(5):377-95.	✓						
Bemanian V, et al., 2004, Comp Hepatol. 3(1):2.	✓						

- Developed a user interface
  - Machine Readable, Controlled vocabs, Minimal free text
  - Discreet “units” of evidence
  - Highly collaborative

Able to conduct useful queries that are not possible in current AOP-KB, including cross-database queries

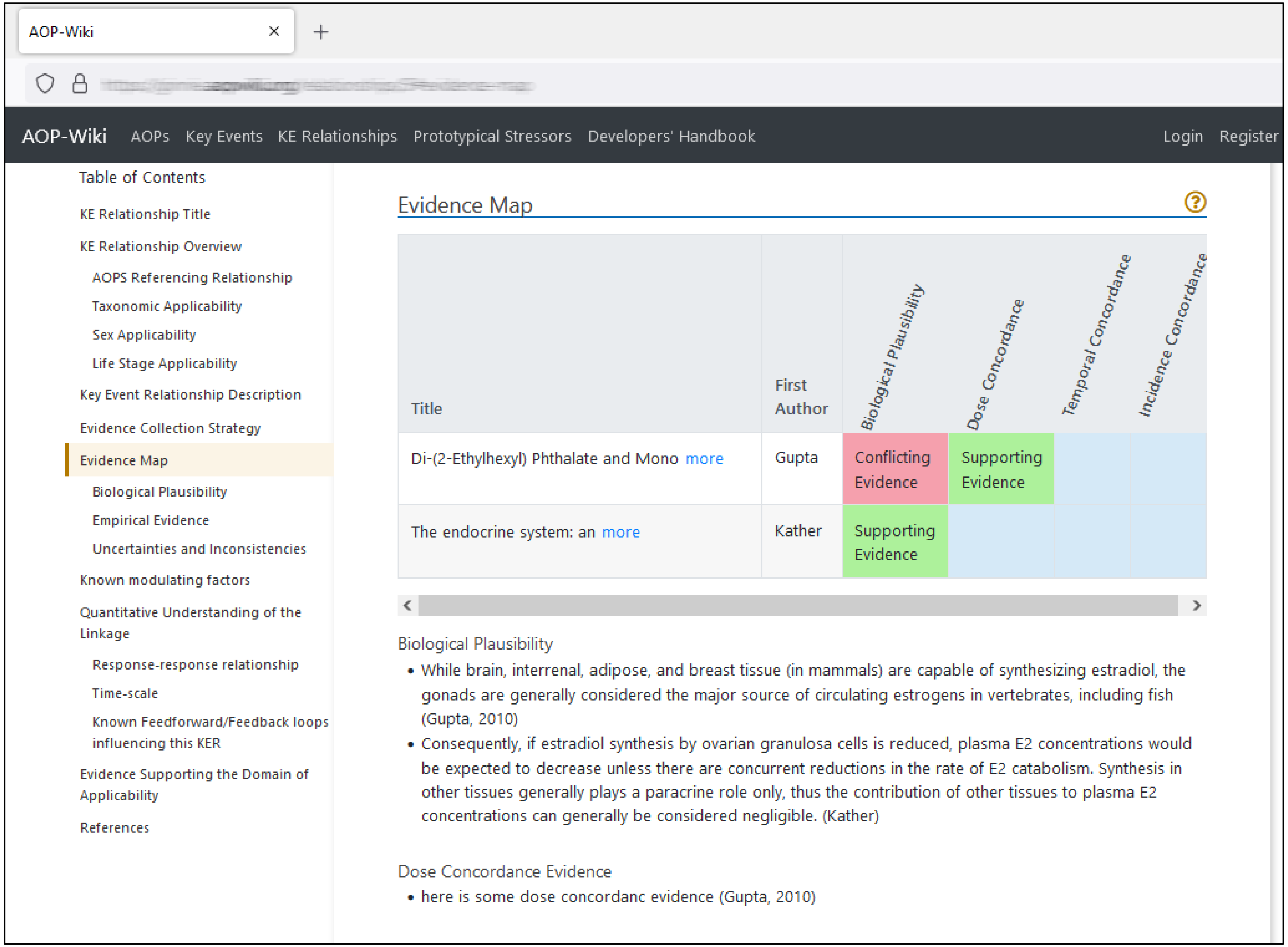
NEXT STEPS

- Current Pilot Study
  - Contract with RTI (developers of AOPwiki)
  - Pilot Data model and user interface complete in Fall 2022

- Expand upon "pilot study #1 (2021)"
  - Develop KER Data Model on same platform as AOPWiki
    - RubyOnRails (web app framework) on an Amazon Server
  - Fully compatible with current AOP-Wiki data model
  - Built on a "test clone" of AOPwiki
  - Assess potential for "permanent" integration

- CONSULT, TEST, CONSULT, and TEST!!!!

Prototype built on AOP-Wiki “clone”



AOP-Wiki

AOP-Wiki | AOPs | Key Events | KE Relationships | Prototypical Stressors | Developers' Handbook | Login | Register

Table of Contents

Evidence Map

Title	First Author	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance
Di-(2-Ethylhexyl) Phthalate and Mono more	Gupta	Conflicting Evidence	Supporting Evidence		
The endocrine system: an more	Kather	Supporting Evidence			

Biological Plausibility

- While brain, interrenal, adipose, and breast tissue (in mammals) are capable of synthesizing estradiol, the gonads are generally considered the major source of circulating estrogens in vertebrates, including fish (Gupta, 2010)
- Consequently, if estradiol synthesis by ovarian granulosa cells is reduced, plasma E2 concentrations would be expected to decrease unless there are concurrent reductions in the rate of E2 catabolism. Synthesis in other tissues generally plays a paracrine role only, thus the contribution of other tissues to plasma E2 concentrations can generally be considered negligible. (Kather)

Dose Concordance Evidence

- here is some dose concordanc evidence (Gupta, 2010)

YOUR FEEDBACK REQUIRED!!!

AOPWiki FORUM https://aopwiki.org/forums/showthread.php?tid=171

Environment and Climate Change Canada

RTI INTERNATIONAL

Ginnie Hench
Steven Edwards

CCAAM Canadian Centre For Alternatives to Animals Methods

EPA

OECD

Thank You!!

Extra slides