



Using the AOP framework to aid in gene set identification

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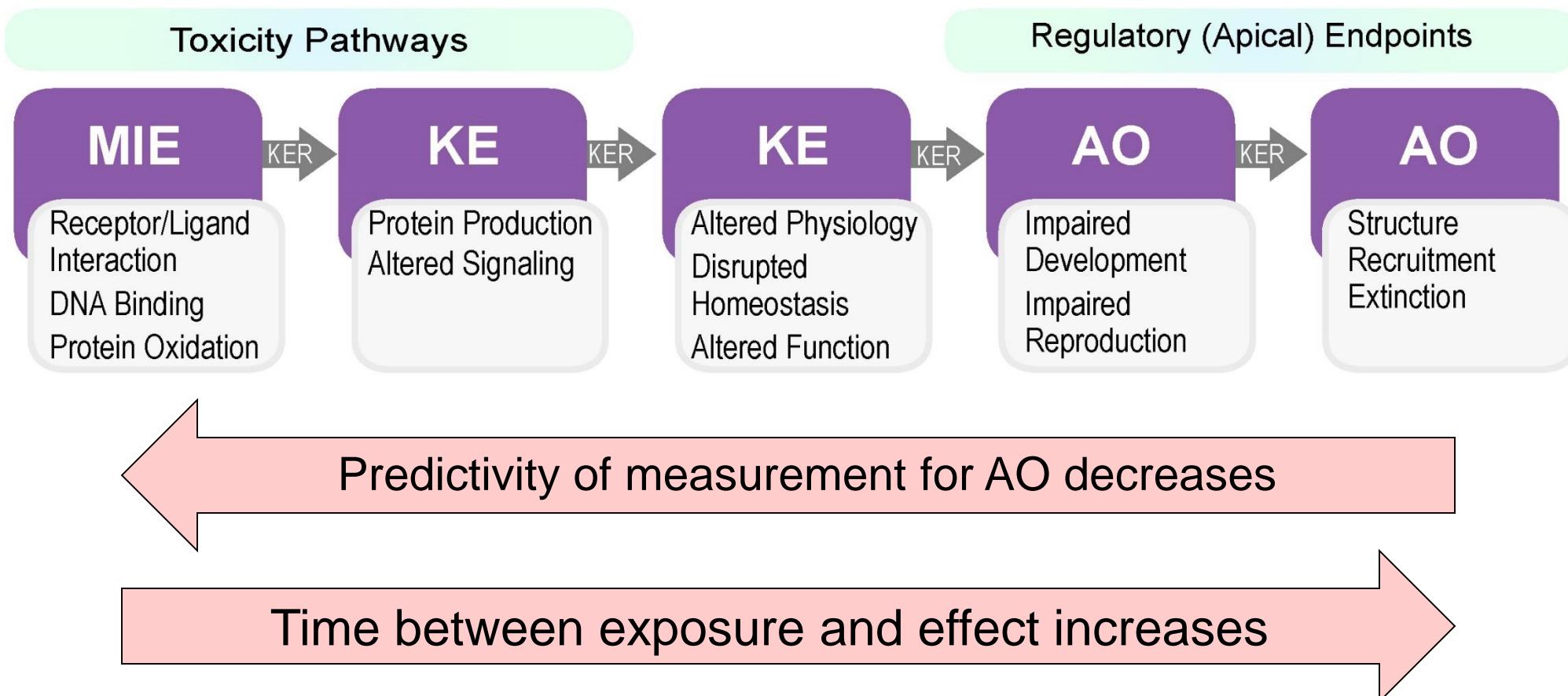
U.S. Environmental Protection Agency

The views expressed in this presentation are those of the presenter, and do not necessarily reflect the views and policies of the Agency.

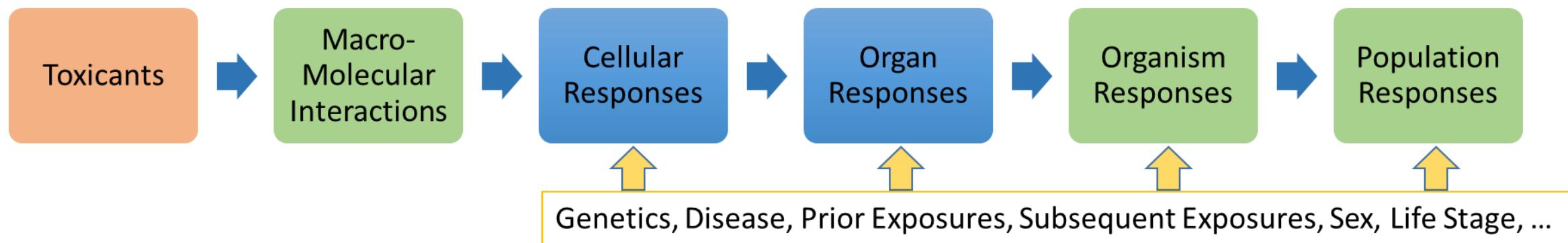
Conflict of Interest

- The presenter has no conflict of interest.
- The views expressed in this presentation are those of the presenter and do not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AOPs Connect Toxicity Pathways to Regulatory Endpoints



Factors Determining Predictivity of Early Key Events

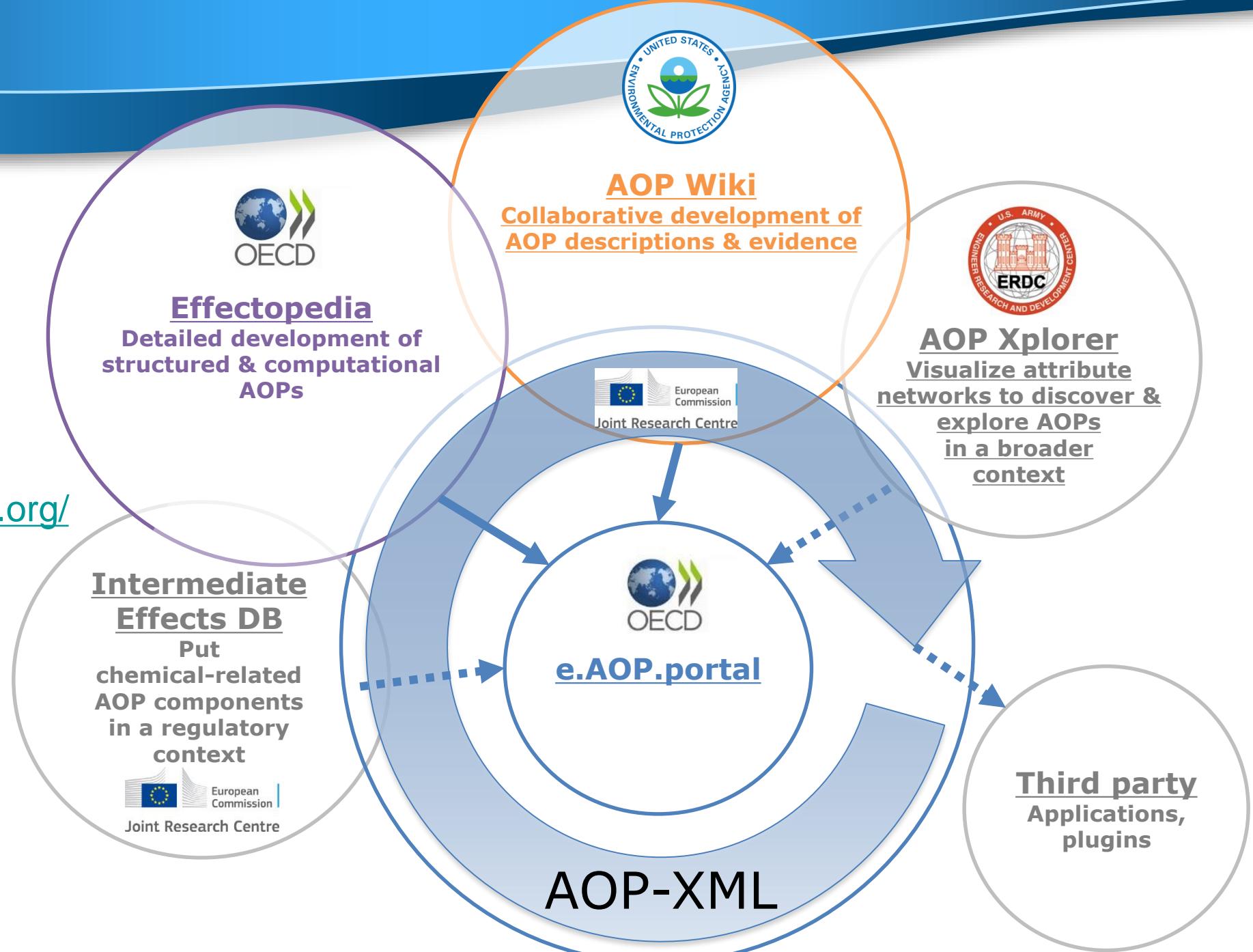


- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs

<http://aopkb.org/>

<https://aopwiki.org/>

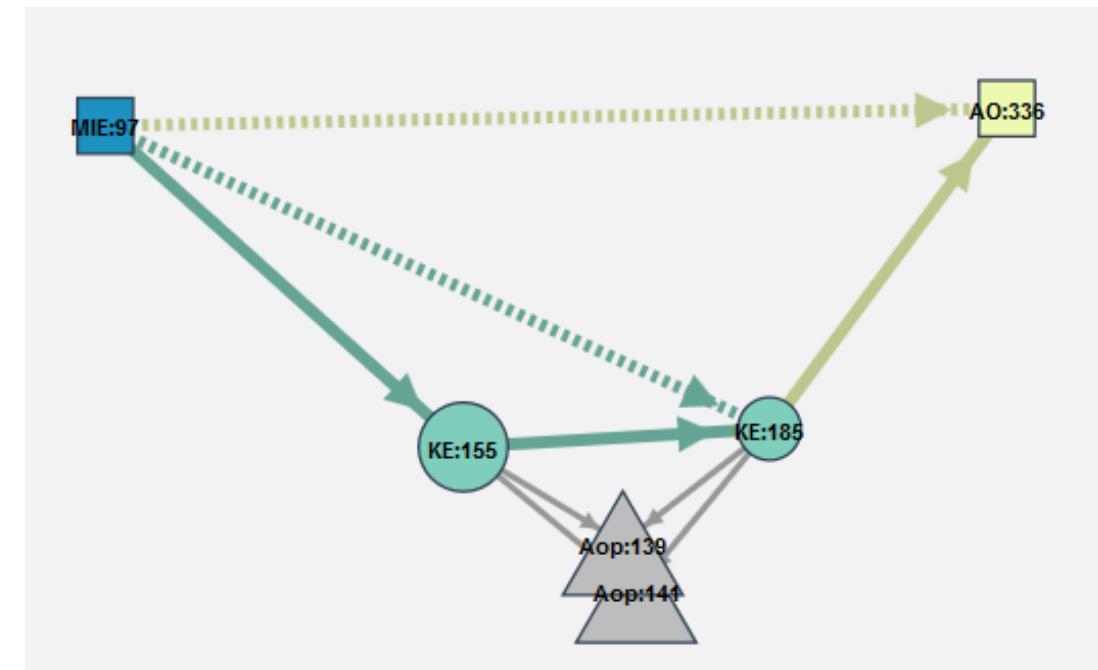
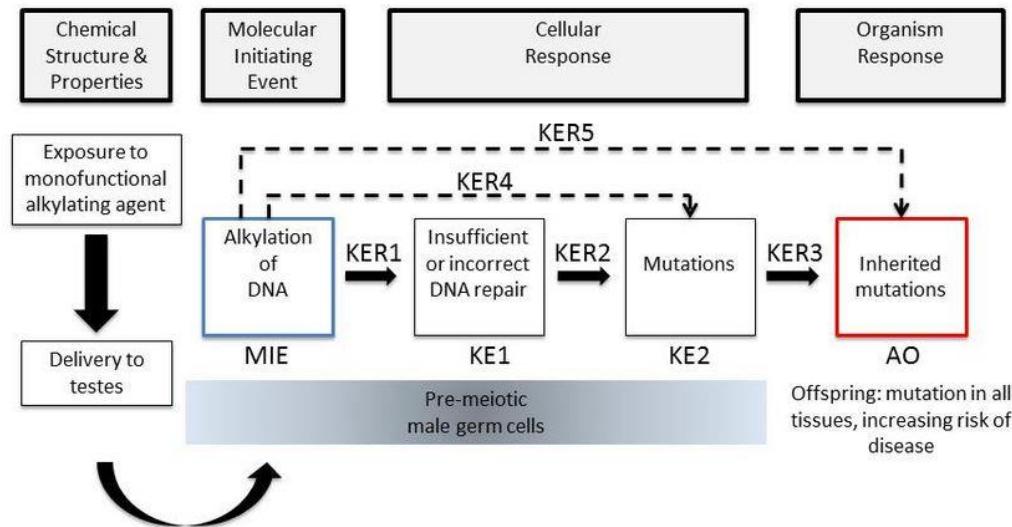
<https://www.effectopedia.org/>



AOP Title

Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations

Short name: Alkylation of DNA leading to heritable mutations

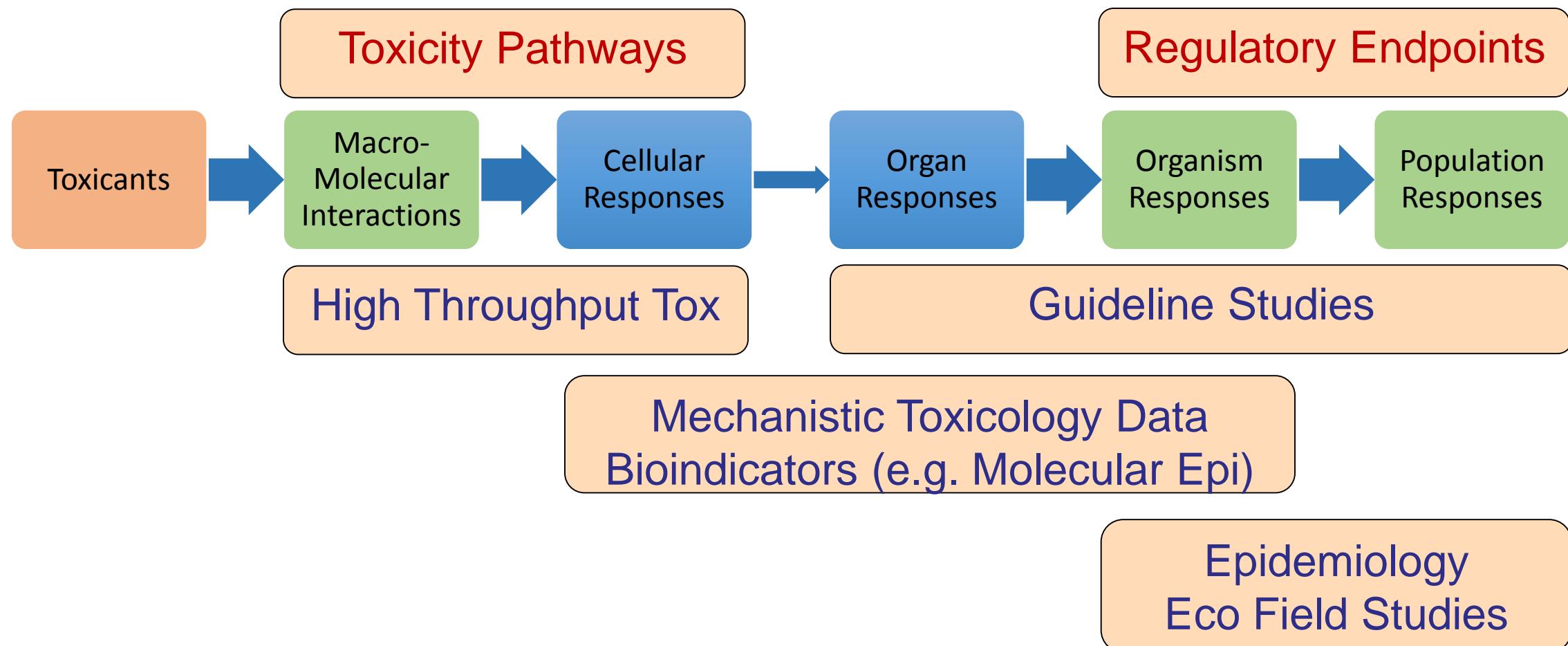


Relationships Among Key Events and the Adverse Outcome

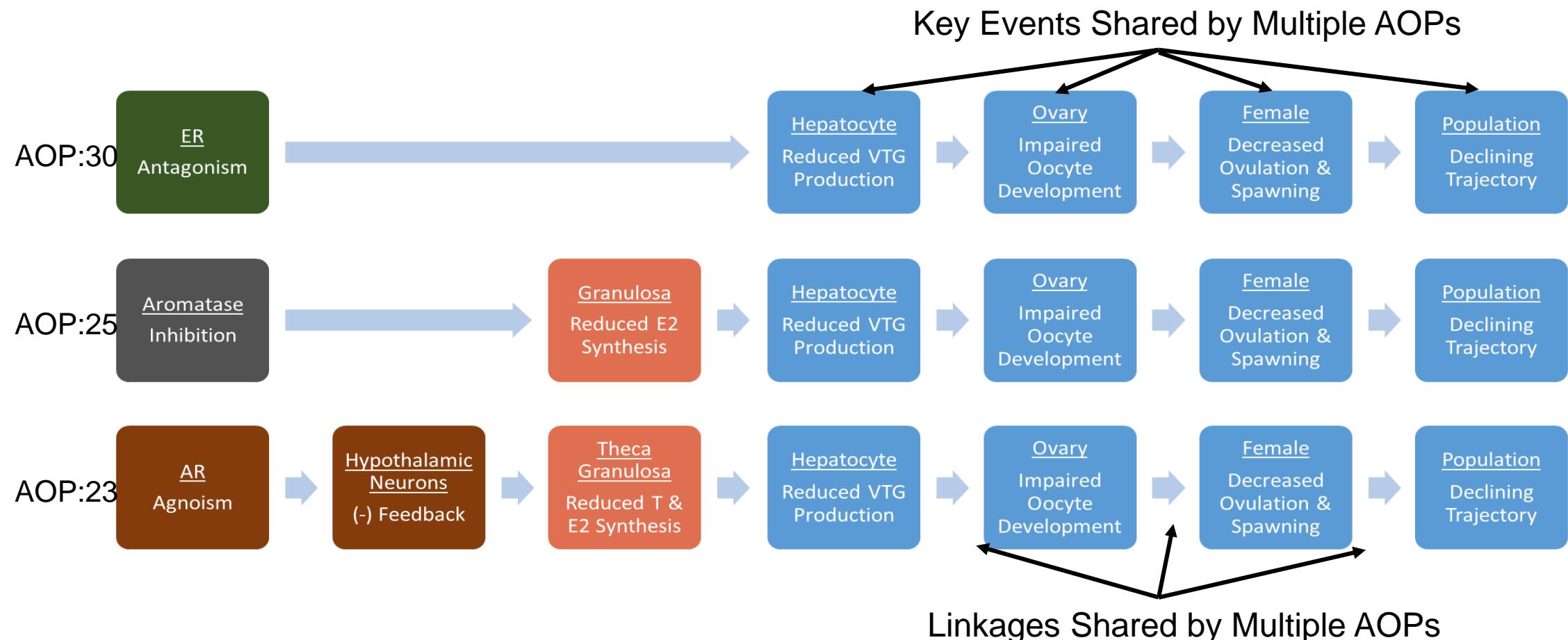
| Event | Description | Triggers | Weight of Evidence | Quantitative Understanding |
|---|---------------------|--|--------------------|----------------------------|
| DNA, Alkylation | Directly Leads to | Insufficient or incorrect DNA repair, N/A | Strong | Moderate |
| Insufficient or incorrect DNA repair, N/A | Directly Leads to | Mutations, Increase | Strong | Moderate |
| DNA, Alkylation | Indirectly Leads to | Mutations, Increase | Strong | Moderate |
| DNA, Alkylation | Indirectly Leads to | Heritable mutations in offspring, Increase | Strong | Moderate |
| Mutations, Increase | Directly Leads to | Heritable mutations in offspring, Increase | Strong | Moderate |

Carole Yauk –
<https://aopwiki.org/aops/15>

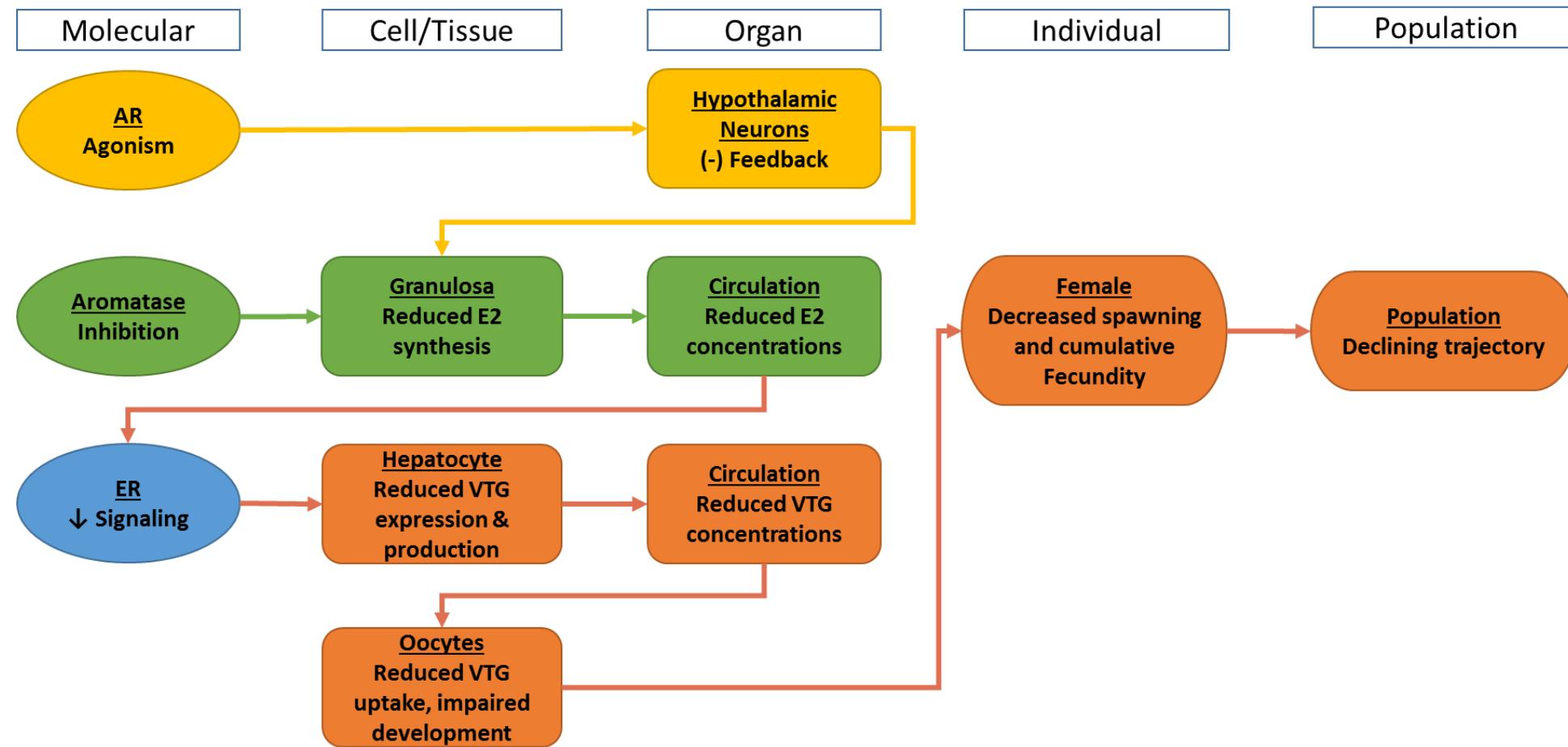
AOP Provides Understanding & Scaffold for Data



AOP networks emerge as AOPs are entered into the AOP-Wiki

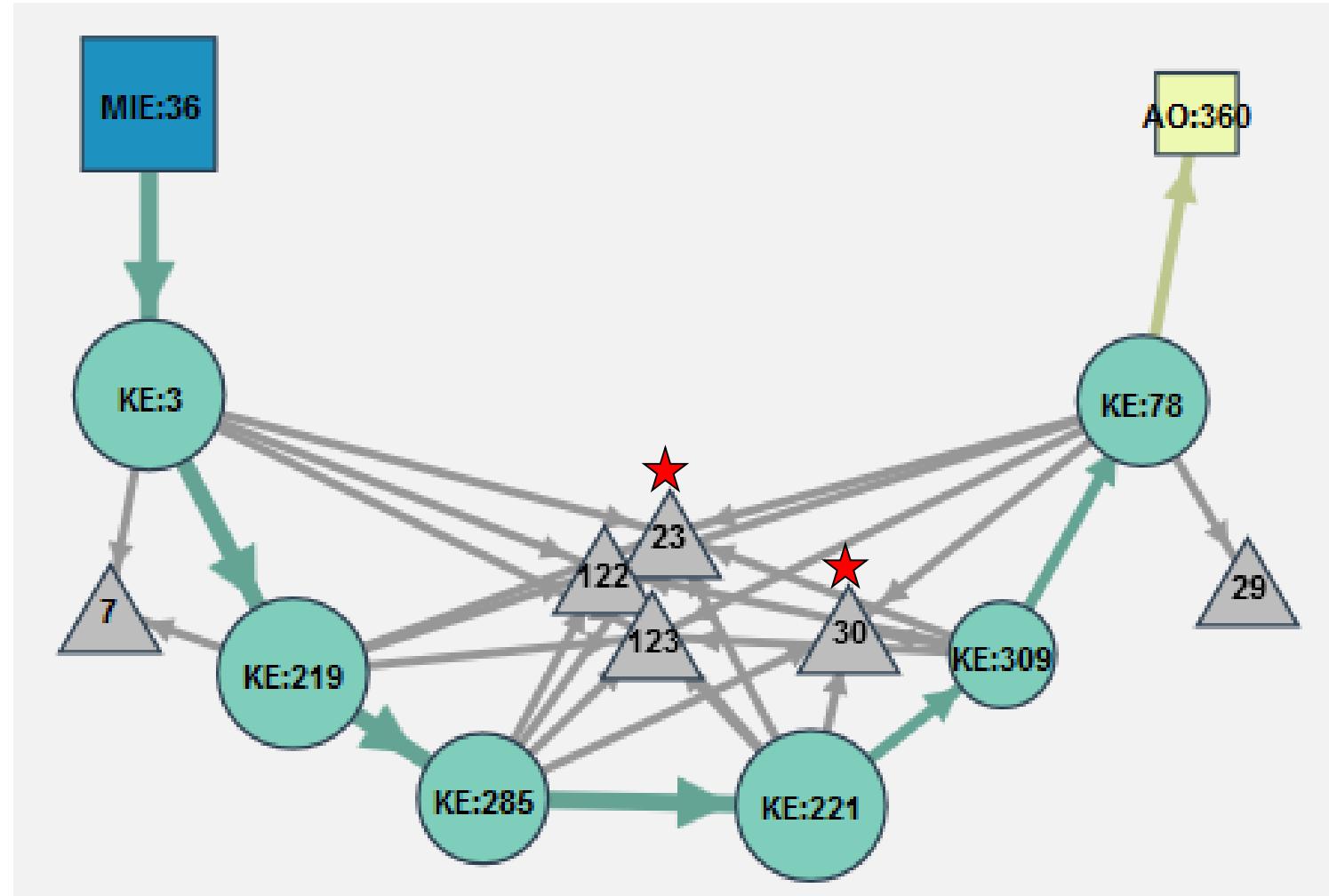


AOP Network as Stored in the AOP-Wiki

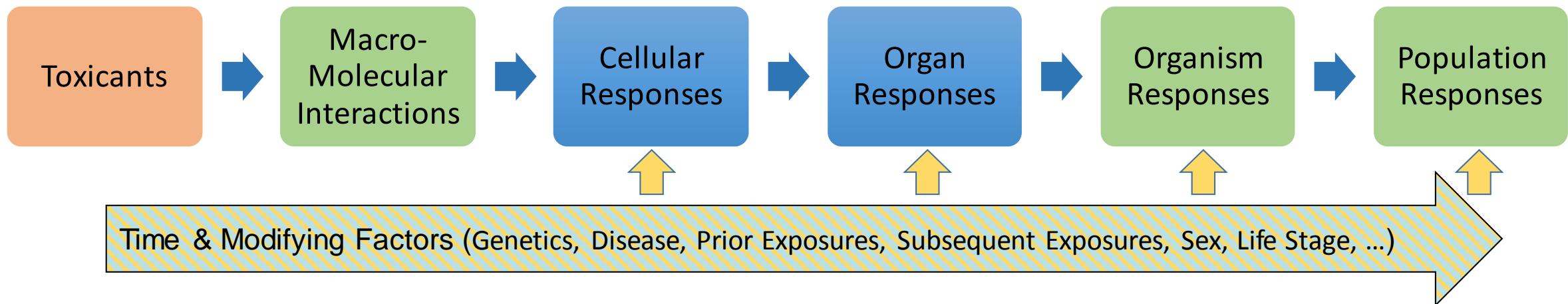


Aromatase inhibition leading to reproductive dysfunction (in fish)

Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)

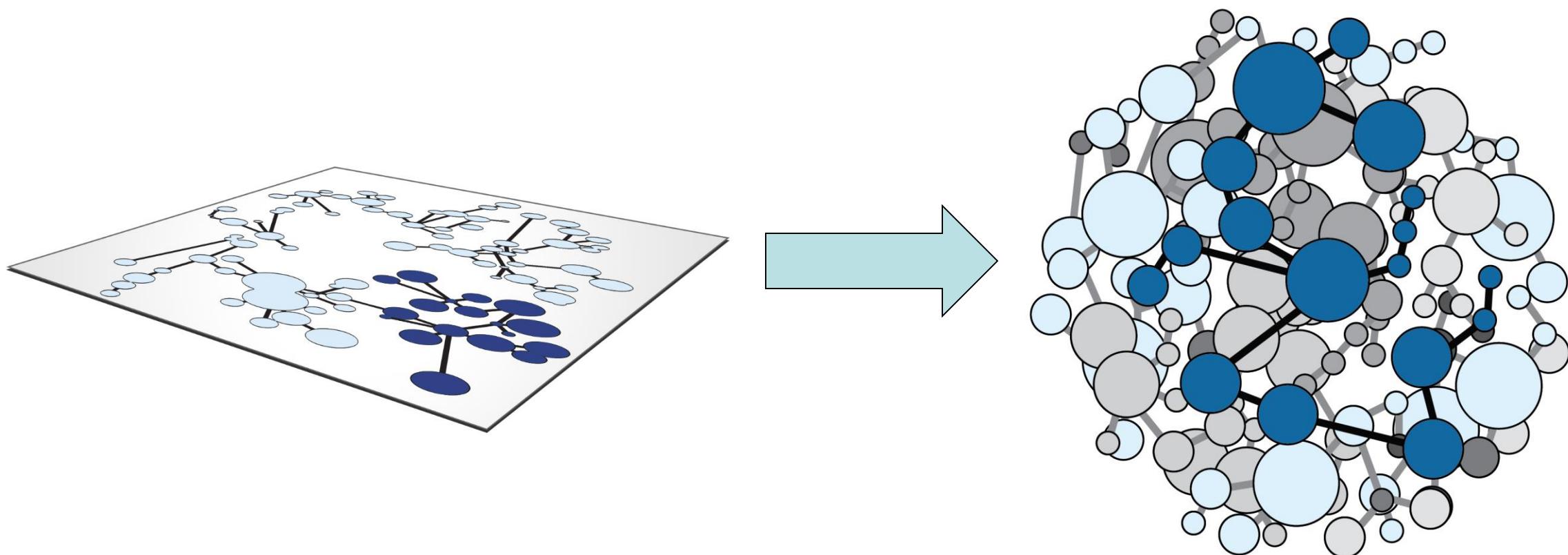


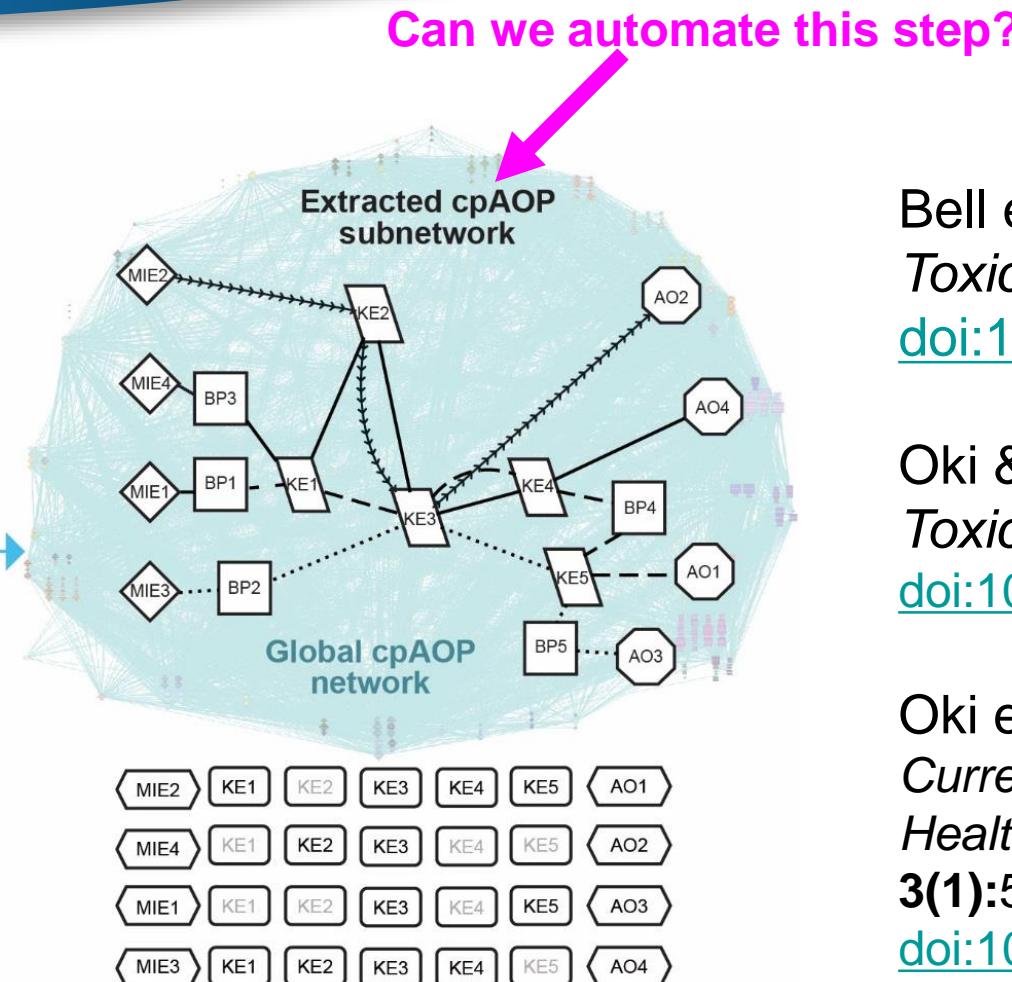
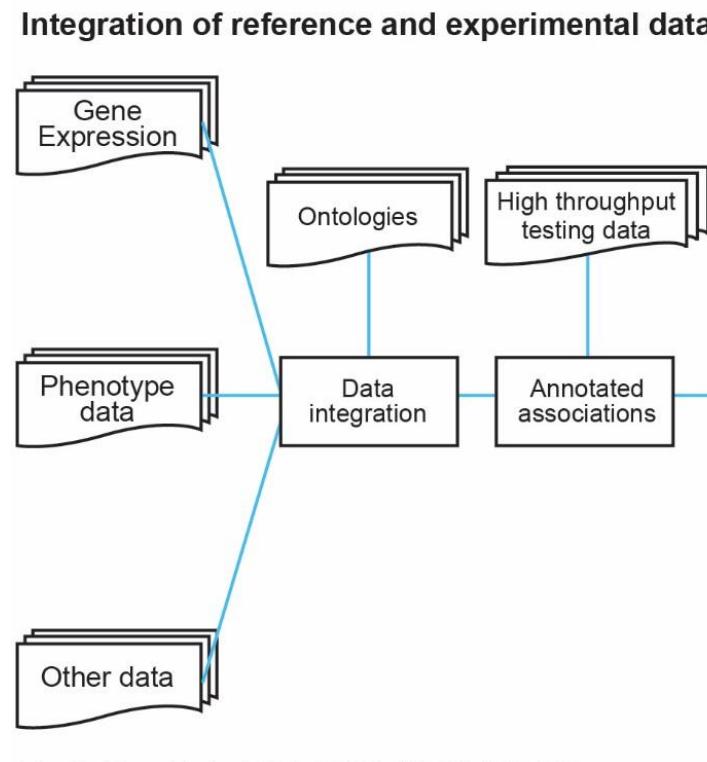
Factors Determining Predictivity of Early Key Events



- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs

Too many AOPs, too little time...





Bell et al. (2016)
Toxicol. Sci., 150:510-520
[doi:10.1093/toxsci/kfw017](https://doi.org/10.1093/toxsci/kfw017)

Oki & Edwards (2016)
Toxicology, 350–352:49–61
[doi:10.1016/j.tox.2016.04.004](https://doi.org/10.1016/j.tox.2016.04.004)

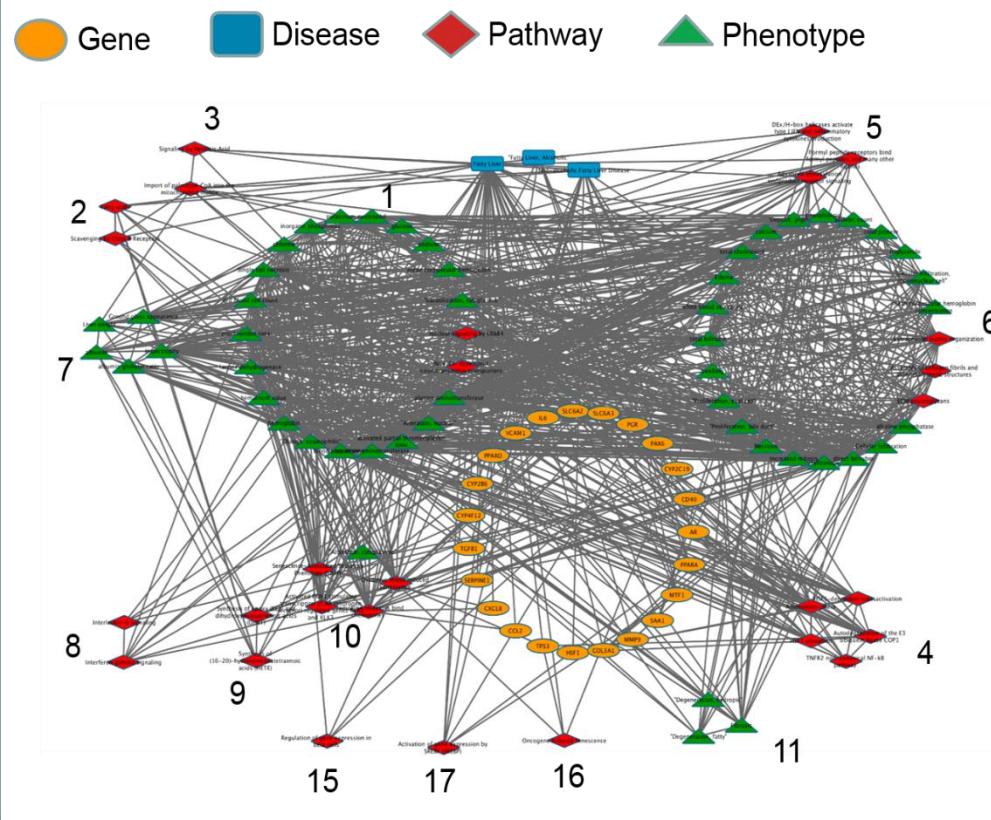
Oki et al. (2016)
Current Environmental Health Reports,
3(1):53-63
[doi:10.1007/s40572-016-0079-y](https://doi.org/10.1007/s40572-016-0079-y)

Automating Extraction of Subnetworks

- Standardize lift values across datasets
- Community detection to approximate key events
 - Currently using random walk to identify densely connected subgraphs
- Build out from an adverse outcome or molecular initiating event of interest

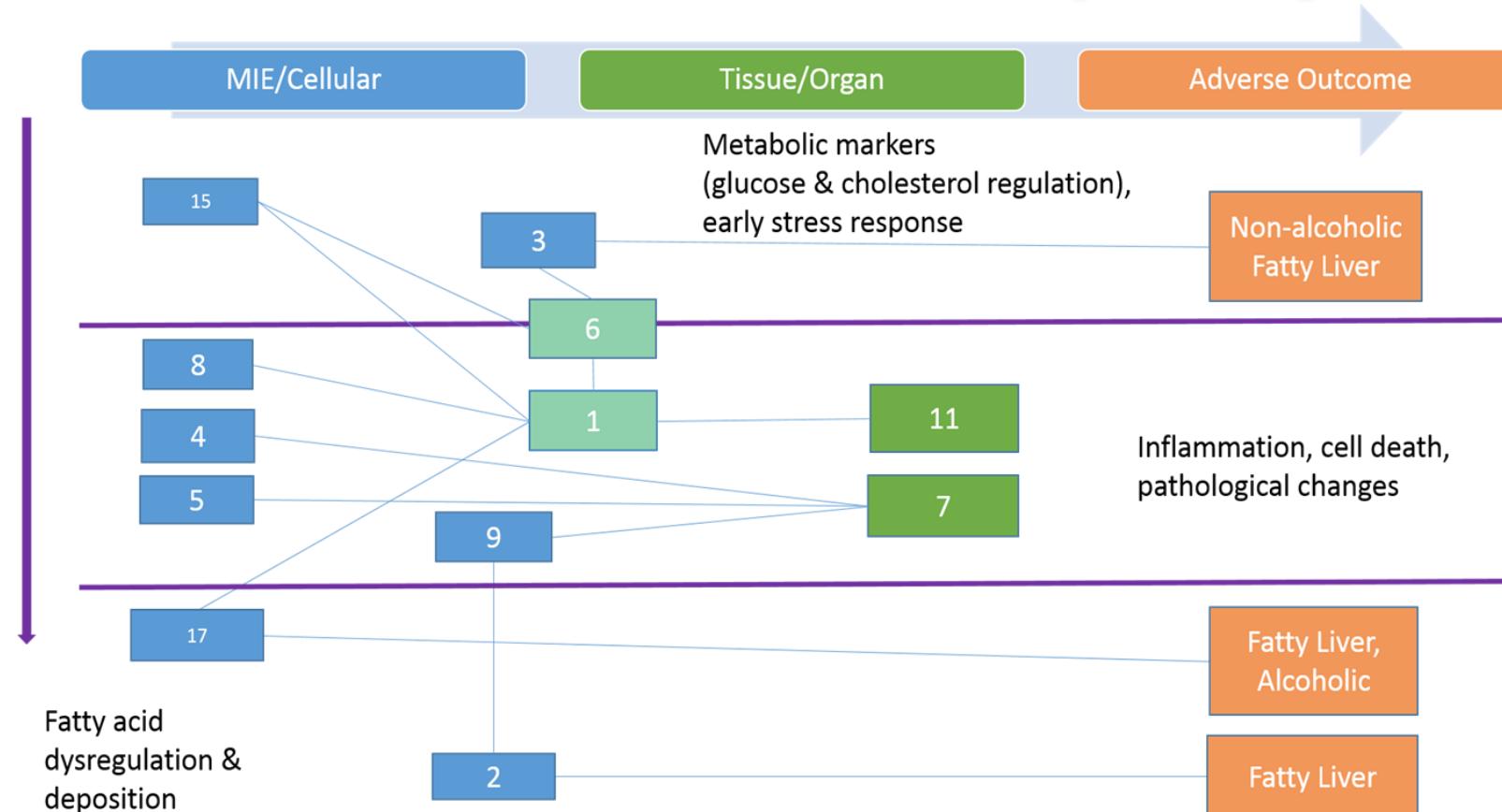
cpAOP network for Fatty Liver disease from ToxCast, CTD and TG-Gates data

| | |
|---|-------------|
| alanine aminotransferase | 1 phenotype |
| activated partial thromboplastin time | 1 phenotype |
| aspartate aminotransferase | 1 phenotype |
| chlorine | 1 phenotype |
| hemoglobin | 1 phenotype |
| hematocrit value | 1 phenotype |
| inorganic phosphorus | 1 phenotype |
| potassium | 1 phenotype |
| lactate dehydrogenase | 1 phenotype |
| neutrophil | 1 phenotype |
| prothrombin time | 1 phenotype |
| red blood cell count | 1 phenotype |
| Singl cell necrosis | 1 phenotype |
| Nuclear signalling by ERBB4 | 1 Pathway |
| Na+/Cl- dependent neurotransmitter transporters | 1 Pathway |
| Alteration, nuclear | 1 phenotype |
| blood urea nitrogen | 1 phenotype |
| Change, eosinophilic | 1 phenotype |
| mean corpuscular hemoglobin | 1 phenotype |
| Vacuolization, cytoplasmic | 1 phenotype |
| glucose | 1 phenotype |
| sodium | 1 phenotype |
| Scavenging by Class B Receptors | 2 Pathway |
| Fatty acids | 2 Pathway |
| Import of palmitoyl-CoA into the mitochondrial matrix | 3 Pathway |
| Signaling by Retinoic Acid | 3 Pathway |
| HSF1 activation | 4 Pathway |
| Attenuation phase | 4 Pathway |
| HSF1-dependent transactivation | 4 Pathway |
| Autodegradation of the E3 ubiquitin ligase COP1 | 4 Pathway |
| TNFR2 non-canonical NF- κ B pathway | 4 Pathway |
| Formyl peptide receptors bind formyl peptides and many other ligands | 5 Pathway |
| Advanced glycosylation endproduct receptor signaling | 5 Pathway |
| DEx/H-box helicases activate type I IFN and inflammatory cytokines production | 5 Pathway |
| calcium | 6 phenotype |
| total protein | 6 phenotype |

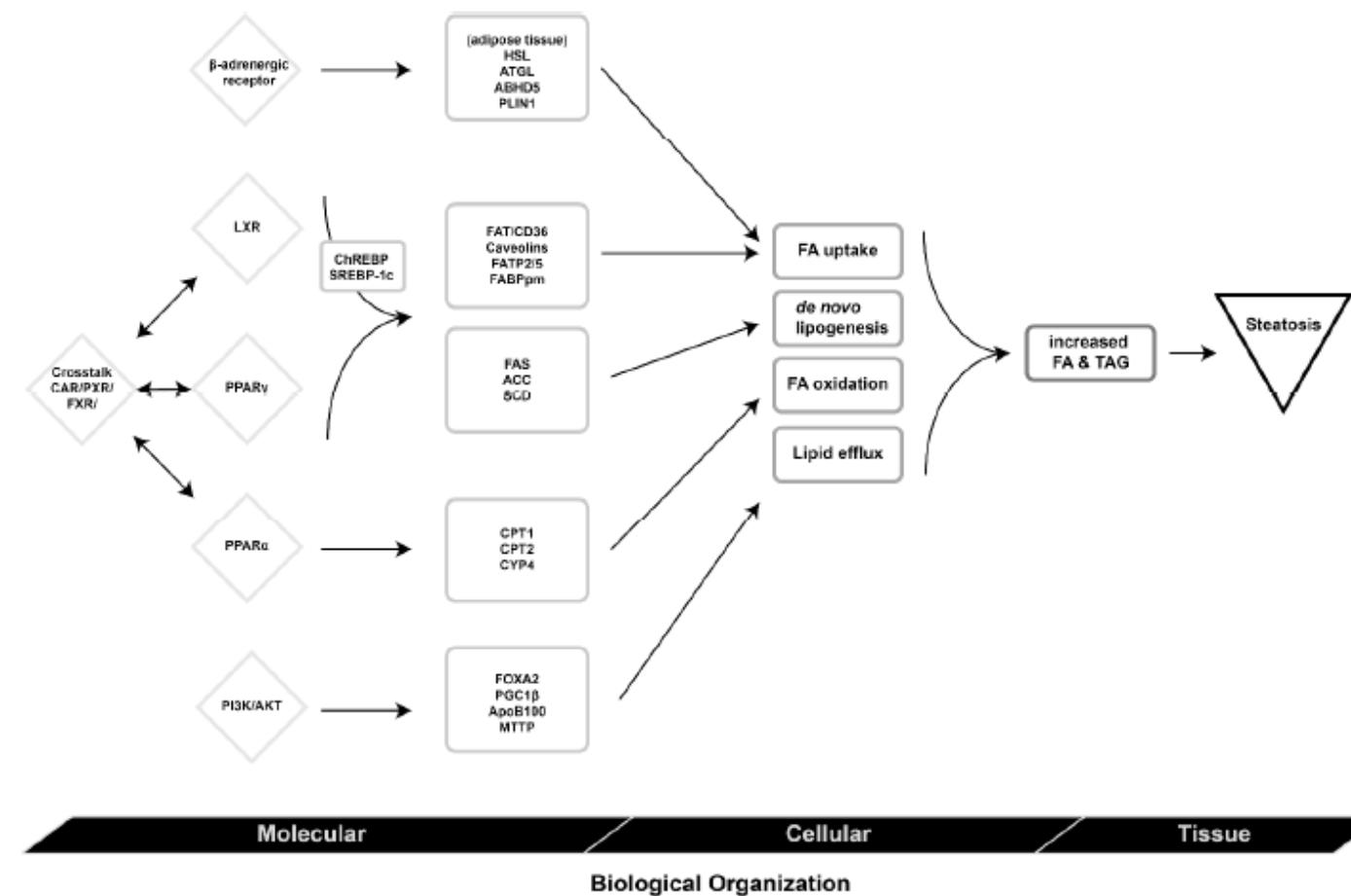


| | |
|---|--------------|
| phospholipid | 6 phenotype |
| total cholesterol | 6 phenotype |
| triglyceride | 6 phenotype |
| Extracellular matrix organization | 6 Pathway |
| Assembly of collagen fibrils and other multimeric structures | 6 Pathway |
| alkaline phosphatase | 6 phenotype |
| Cellular infiltration | 6 phenotype |
| Cellular infiltration, mononuclear cell | 6 phenotype |
| direct bilirubin | 6 phenotype |
| Deposit, pigment | 6 phenotype |
| Edema | 6 phenotype |
| g-glutamyltranspeptidase | 6 phenotype |
| Increased mitosis | 6 phenotype |
| mean corpuscular hemoglobin concentration | 6 phenotype |
| Necrosis | 6 phenotype |
| platelet count | 6 phenotype |
| Proliferation, bile duct | 6 phenotype |
| Proliferation, oval cell | 6 phenotype |
| Swelling | 6 phenotype |
| total bilirubin | 6 phenotype |
| white blood cell count | 6 Pathway |
| ECM proteoglycans | 7 phenotype |
| albumin globulin ratio | 7 phenotype |
| Ground glass appearance | 7 phenotype |
| Hypertrophy | 7 phenotype |
| Liver weight | 7 phenotype |
| albumin | 8 Pathway |
| Interferon gamma signaling | 8 Pathway |
| Interleukin-6 signaling | 8 Pathway |
| Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) | 9 Pathway |
| Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) | 9 Pathway |
| Degeneration, fatty | 11 phenotype |
| Degeneration, hydropic | 11 phenotype |
| Fibrosis | 11 phenotype |
| Regulation of gene expression in beta cells | 11 phenotype |
| Activation of gene expression by SREBF (SREBP) | 15 Pathway |
| | 17 Pathway |

cpAOP generated for Fatty Liver disease by random walk community analysis



Expert-derived Putative AOPs for Liver Steatosis



[Aop:36](#)
[Aop:57](#)
[Aop:58](#)
[Aop:59](#)
[Aop:60](#)
[Aop:61](#)
[Aop:62](#)
[Aop:72](#)

Michelle Angrish et al.
Toxicol. Sci. (2016)
150 (2): 261-268
doi:10.1093/toxsci/kfw018

Accelerating AOP Development

Associations
derived from public
data sources

OECD AOP-KB Working Group

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- **Robert Kavlock**
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- **Cataia Ives**
- **Rose Combs**
- **Landon Grindheim**
- **Max Felsher**
- **Brendan Ferreri-Hanberry**
- **David Lyons**



- **Clemens Wittwehr**
- **Brigitte Landesmann**
- **Ivana Campia**
- **Sharon Munn**
- **Ahmed Sayed**
- **Maurice Whelan**
- **Hristo Aladjov**
- **Magda Sachana**
- **Joop DeKnecht**



- **Ed Perkins**
- **Lyle Burgoon**
- **Natalia Garcia Reyero**

- Collaborative Partners
 - OECD External Advisory Group on Molecular Screening & Toxicogenomics
 - IPCS/WHO Mode of Action Steering Committee

Chemical Safety for Sustainability cpAOP Team

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- Holly Mortensen
- Rong-Lin Wang
- Maureen Pittman
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 - Benjamin King
 - Allan Peter Davis
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 - Scott Auerbach
- Mixtures Collaborator
 - Jane Ellen Simmons
- cpAOP Collaborators
 - Michelle Angrish
 - Charles Wood
 - Brian Chorley
 - Dan Villeneuve
 - Sean Watford
 - Keith Houck
- ADME/AEP Collaborators
 - Cecilia Tan
 - Jeremy Leonard

Questions?

