Potential Biomonitoring of Quaternary Ammonium Compounds (QACs)

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Agenda

- Are QACs good candidates for biomonitoring?
- Known or suspected health effects
  - Consideration of available data
  - Weight of evidence considerations
- Conclusions

Should QACs be Considered for Biomonitoring?

- What characteristics of a chemical/chemical class are best suited for biomonitoring?

Are QACs Good Candidates for Biomonitoring?

Property	QACs	Organophosphorus Pesticides
Exposure Routes	Primarily dermal – minimal percutaneous penetration	Dermal, inhalation, oral
Known or Suspected Human Health Effects	Various irritation-related point of contact effects	Well documented systemic
Prop 65 - Cancer	No	Yes
Prop 65 - Reproductive	No	Yes
Systemic Biomarker Relevant to Health Effects	No	Yes
Good Candidate for Biomonitoring?	No	Yes

Known or Suspected Health Effects

- Consideration of Available Data
  - Regulatory Toxicology studies relative to Academic/investigative studies
  - Adverse Outcome Pathways
  - Weight of Evidence considerations
- Especially relevant for:
  - Reproductive and Developmental Effects
  - Altered Cellular Function and Effects on Metabolism
  - Respiratory Effects

Consideration of Available Data
Laboratory Studies vs. Academic/Investigative Studies

Attribute	Regulatory Safety Assessment	Academic/Investigative
Purpose	Designed to Meet Regulatory Needs – Risk Assessment and Possible Risk Management	Often - Hypothesis Generating or probing specific endpoints (e.g., part of an Adverse Outcome Pathway)
Dose Selection Criteria	Maximum Tolerated Dose, Mindful of confounding toxicity No Observable Adverse Effect Level (NOAEL)	Dependent upon endpoint of focus – generally selected to perturb system being studied
Study Plan and Protocols	Regulatory Guidelines – well established – significant historical database	Often more flexible – less constrained by guidelines, but more difficult to put into context of safety assessment
Other	Careful attention to control potential confounding factors (food consumption, stress, diet, etc.)	Careful attention to assay conduct and refinement

Consideration of Available Data
The Adverse Outcome Pathway (AOP)

- AOP – “A conceptual framework that links a molecular-level initiating event with adverse effects relevant for risk assessment”
- Molecular-level key event followed by key events leading to toxicity
- Especially useful to design screening assays to predict toxicity *in absence* of in vivo toxicology studies measuring apical endpoints*

*Apical Endpoint – “An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant”

Consideration of Available Data
Weight of Evidence

- This approach is beneficial when:
  - “The information from a single piece of evidence alone is not sufficient to fulfil an information requirement. This could be, for example, due to clear deficiencies in one of the existing studies or when Individual studies provide different or conflicting conclusions.” ECHA
- Weighting of evidence depends upon:
  - Data quality
  - Consistency of results
  - Nature and severity of effects
  - Relevance of information

Known or Suspected Health Effects
Developmental and Reproductive Toxicity

Regulatory Toxicology Studies

10 studies =-GLP and Guideline compliant (all negative)

- 2 rabbit and 1 rat prenatal developmental studies: developmental NOAEL > highest dose tested, 3 to 20x > maternal NOAEL
- 2 two-gen reproductive studies: reproductive effects do NOT occur in the absence of parental toxicity

Academic/Investigative Studies

Melin et al. 2014, 2016; Hrubec et al. 2017

- Doses clearly caused overt toxicities to the dams and exceeded the MTD – e.g., 40% maternal mortality at high dose, clinical signs including reduced appetite, reduced activity, cyanosis → developmental effects due to maternal tox
- Unquantified doses claimed from ‘ambient exposure’

Developmental and Reproductive Toxicity

- Weight of Evidence – QACs do not pose a hazard to human health

Known or Suspected Health Effects
Altered Cellular Function & Effects on Metabolism

Regulatory Toxicology Studies

- No evidence of endocrine-related Including high-dose, short term studies as well as subacute, sub-chronic and chronic toxicity studies in mice, rats, rabbits (all routes of exposure, inhalation, oral and dermal)
- Intestinal toxicity and decreased serum cholesterol in sub-chronic dog toxicology study (highest dose tested)
- Developmental and Reproduction Studies (ADBAC and DDAC separately)
  - 2 rabbit and 1 rat prenatal developmental studies: developmental NOAEL > highest dose tested, 3 to 20x > maternal NOAEL
  - 2 two-gen reproductive studies: reproductive effects do NOT occur in the absence of parental toxicity

Academic/Investigative Studies

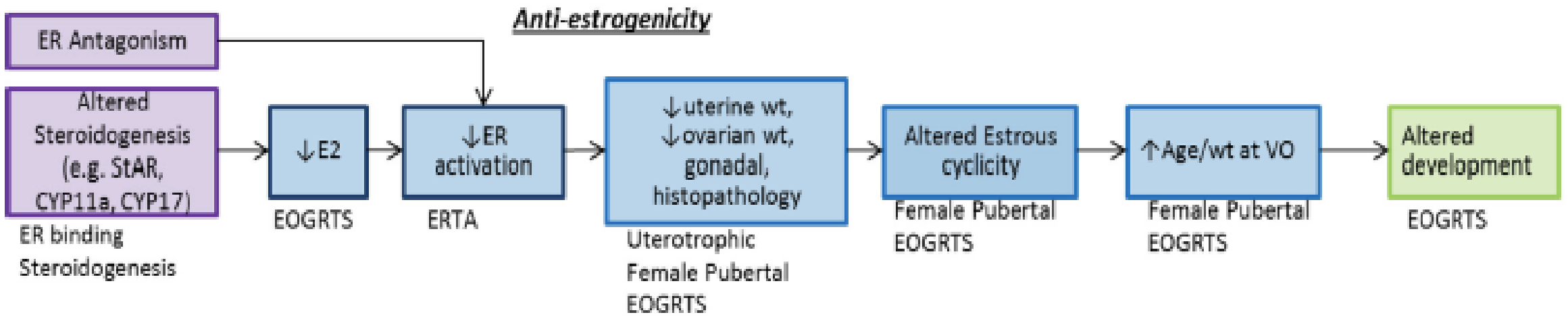
- Datta et al, 2017) Inhibition of mitochondrial respiration *in vitro*
- Levine et al., 2007 - Mitochondrial disruption & inhibition of steroidogenesis in Leydig cells
- Herron et al. (2016) - Inhibition of cholesterol biosynthesis *in vitro*
- Herron et al. (2019) – QAC cross the blood-placental barrier and embryonic blood-brain barrier and alter sterol and lipid homeostasis in mice

Known or Suspected Health Effects
Altered Cellular Function & Effects on Metabolism

- Assays are measuring events on the Adverse Outcome Pathway (AOP) for anti-estrogenicity
  - Point-of-Contact cytotoxicity - membrane disruption and mitochondrial toxicity to epithelial cells
  - Lipophilic cations (like QACs) selectively accumulate in mitochondria – dose-dependent disruption in ATP production
- Consider the role of these pathways in AOP for anti-estrogenicity

Altered Cellular Function & Effects on Metabolism

Adverse Outcome Pathway - Anti-estrogenicity



Browne et al. 2017

Altered Cellular Function & Effects on Metabolism

- Most important – Studies measuring effects on apical endpoints (guideline developmental and reproductive toxicity studies) show no toxicity – high value in WOE assessment
- Weight of Evidence – QACs do not pose hazard to human health

Known or Suspected Health Effects
Respiratory

- Hazard - Mode of Action – point of contact effects
  - Asthma
    - May exacerbate existing condition at high exposure levels (like all irritants)
  - Pulmonary sensitization (immunologically mediated)
  - Human experience and case reports, epidemiology
    - Unlikely - Mode of Action, lack of dermal sensitization properties
- Exposure - Non-volatile
  - Only Inhalable (<100 µm) or respirable (~<10 µm) aerosol droplets relevant
- Weight of Evidence – QACs do not pose hazard to human health

Conclusions – QACs (ADBAC & DDAC)

- QACs control and prevent the spread of serious illness in hospitals, homes, schools, and food processing and preparation establishments
- Safety widely studied and evaluated globally
- Lack of significant human health effects and point-of-contact mode of action means that biomonitoring of QACs is of minimal value in protecting public health