Computational Toxicology of Pesticide Exposure in Cannabis Products

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Common pests in cannabis (and other crops)

- Spider mites
- Caterpillars
- Snails
- Powdery mildew
- Leaf miners
- Rodents

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Risk = Hazard $\times$ Exposure
Human health is a key consideration in establishing action levels
Example: Organophosphate pesticides

NPR, 2016
Organophosphates affect neural signaling at synapses

(Leung et al., in revision)
Cannabinoids also affects neural signaling at synapses

(Leung et al., in revision)
What do we know about hazard of pesticide use in cannabis?

- Pesticides, including organophosphates, are found in some cannabis samples in various states.
- Organophosphates affect the central nervous system, cardiovascular and respiratory systems.
- Clinical signs of acute exposure in humans are numbness, dizziness, tremor, abdominal cramps, sweating, lacrimation, salivation, and blurred vision.
- Chronic symptoms include impaired memory, disorientation, speech difficulties, nausea and weakness.
- Toxicology data are mostly based on animal ingestion studies.
What do we not know about the hazard?

- Interaction between cannabinoids and pesticides at different levels of biological organization
- Unknown toxicity of the combustion by-products in cannabis smoke
Adverse Outcome Pathways Framework: Connect Adverse Outcomes to Structural Properties

Chemical → Macro-Molecular Interaction → Cellular Responses → Organ Responses → Organism Responses

Toxicity Pathway

modified from Ankley et al. 2010; Environ. Toxicol. Chem. 29: 730-741
Adverse outcome pathways of developmental neurotoxicity

**Molecular initiating event (MIE) and key events (KEs)**

- **MIE**
  - Disruption of the endocannabinoid system by inhibiting serine hydrolases

- **KE1**
  - Alteration of post-synaptic retrograde signaling

- **KE2**
  - Disruption of crosstalk between cannabinoid receptors and receptor tyrosine kinases

- **KE3**
  - Alterations in redox potential and mitochondrial respiration in differentiated neurons

- **KE4**
  - Reduction in proliferation, differentiation, and migration in neuroprogenitor cells

- **KE5**
  - Disruption of axogenesis and synaptogenesis in differentiated neurons

- **KE6**
  - Reduced connectivity and functionality of neural networks

(Leung et al., in revision)
Adverse outcome pathways is a novel tool for cumulative assessment of chemical mixtures that produce the same type of effects through different toxicity pathways.

- Slide 13 -
Looking into the future of \textit{in vitro} to \textit{in vivo} extrapolation

\textbf{Source node:} Pesticide

\textbf{Target node:} Molecular target

\textbf{Node size:} Connectivity

\textbf{Edge thickness:} Affinity score

\textbf{Target classification:}
- G-protein coupled receptor
- Nuclear receptor
- Cytochrome P450
- Cholinesterase
- Translocator protein 18 kDa

(Leung and Meyer, in preparation)
Risk = Hazard × Exposure
Exposure = Residue level $\times$ Consumption rate
What do we know about residue levels and consumption rates of cannabis?

Currently:
- No surveillance of pesticide residues in cannabis
- Limited data on consumption from other states, but not California

Action levels can be established based on:
- Limit of detection
- Federal tolerance (for fresh fruit and vegetables)
- Reported human pesticide exposures

Our approach: based on assumptions on toxicology and consumption
Monte Carlo analysis provides a more realistic model with physiological parameters

Use actual consumption data from CDC NHANES database to model cannabis consumption rates

Sample parameters:
- Age
- Sex
- Race/ethnicity
- Body weight

These data are publicly available
(http://www.cdc.gov/nchs/nhanes.htm)
Summary

- Human health is a key consideration in establishing action levels.
- Adverse outcome pathway is a useful tool for hazard analysis and to fill the data gap for pesticide exposure from cannabis products.
- Further studies will integrate population-level exposure simulation and high throughput screening data for use in predictive risk analysis.
For further information

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Poster #38
“Cannabis Use Rates for Deriving Health Protective Pesticide Thresholds”
- by Amanda Palumbo, Ph.D.