Case Study on the Use of New Approach Methodologies and Adverse Outcome Pathways for Chemical Hazard Evaluation

**Learning objectives:**

* Gain familiarity with publicly accessible EPA sources of computational toxicology data and associated translational knowledge frameworks.
* Apply data from “new approach methods” to address a toxicological question.

**Instructions:**

1. Read through the scenario and charge.
2. Work through the series of questions sequentially, using the public resource provided in the links.
3. Feel free to work with others if you’d like.

**Scenarioa:**

Non-targeted analysis of South Carolina drinking water samples identified several unknown peaks in the water supply from a particular community. Follow up investigation via suspect screening identified one of the compounds to be **4-methylaniline** and subsequently reported detection of up to 0.6 µg/L in drinking water and 27 µg/L in upstream source water. The mayor has asked state public health officials to advise as to potential health risks and local environmental advocates have raised concerns about effects to resident fish and wildlife. The governor has requested a report from state heath and environmental officials by the end of the business week.

Charge: Use information from [US EPA’s CompTox Chemicals Dashboard](https://comptox.epa.gov/dashboard/), and the [AOP-Wiki](https://aopwiki.org/) to address the following questions (Parts 1 and 2):

a The scenario described is fictional and intended for training purposes. Any resemblance to real events is unintentional.

**Part 1 – Information in the CompTox Chemicals Dashboard**

1. [CompTox Chemicals Dashboard](https://comptox.epa.gov/dashboard/)
   1. What are some of the synonyms for 4-methylaniline that should be considered when searching for literature related to health or environmental hazards? [Hint – under “Chemical Details” drop-down, click on synonyms]
   2. Based on available hazard data, are the detected concentrations of potential concern for human health or ecological effects? [Hint – use the “Hazard Data” tab]
      1. Selecting the “human” radio button, select “screening level” from the drop down menu in the upper left.
      2. Selecting the “eco” radio button, select “point of departure” from the drop-down menu in the upper left.
   3. Does the chemical elicit specific bioactivity at concentrations more than 10 times lower than cytotoxic concentrations?
      1. Select the – “Bioactivity tab” – check out the plot on the ToxCast summary page; X-axis = concentration (µM); Y-axis = magnitude of response in assay; vertical dashed line = lower bound for cytotoxicity).
      2. You may also want to scroll down to the “Bioactivity Summary Grid” and sort the table lowest to highest by AC50 or logAC50.
      3. What is the most sensitive bioactivity? (assay endpoint name and gene symbol)
   4. Are there any “OECD Endorsed AOPs” associated with this bioactivity.
      1. Hint – Scroll down to the “Bioactivity Summary Grid”, sort the table lowest to highest by AC50 or log AC50, examine the AOP and Event columns.
      2. What AOPs does this bioactivity link to (click the links to access the corresponding AOPs in the AOP-Wiki.
      3. What key event(s) does this bioactivity link to (click on the link in the event column to access the corresponding key event description in the AOP-Wiki.

**Proceed to Part 2**

**Part 2: Adverse Outcome Pathways**

1. [AOP-Wiki](https://aopwiki.org/)
   1. What endorsed AOPs were already linked to the bioactivity you identified?
   2. Based on those AOPs, what are some potential hazards to humans exposed to 4-methylaniline? What are some potential hazards to aquatic wildlife?
   3. Are there other other non-endorsed AOPs (i.e., those still under development and/or review) that are relevant for methylaniline’s bioactivity?
      1. Hint – click the link to the “Event” page associated with the most sensitive ToxCast Bioactivity
      2. On the “Event page” scroll down to the “Key Event Overview, AOPs including this Key Event” table.
      3. What other apical hazards may be associated with the key event and which are most relevant to humans versus wildlife (Hint: clicking the links in the “AOP Name” column will take you to the AOP page for each AOP in the table).
   4. Based on one of the AOPs you identified, what are one or more measurements you might consider making in the exposed human population to determine if there is evidence of potential for an adverse effect? (Hint: key events are measurable biological changes)
   5. Based on one of the AOPs you identified, what are one or more measurements you could make in fish exposed to 4-methylaniline in the laboratory to evaluate whether the exposure concentrations measured in surface water might elicit the hazard associated with the AOP?

For future reference:

1. If no endorsed AOPs are annotated in the “Bioactivity Summary Grid”, you may still be able to find AOPs by searching the AOP-Wiki on the AOP search page.
   * 1. Within the AOP-Wiki, click “AOPs” on the black upper menu ribbon.
     2. In the “Search AOPs Box”, you can type in key words, like an enzyme name into the box and hit search.
     3. You can also type key words, like an enzyme name” into the “Title” field of the AOP-listing table to filter the results for AOPs that contain your key word in the title.

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Based on what you found using the CompTox Chemicals Dashboard and AOP-Wiki, what are some of the conclusions and/or recommendations you might include in your preliminary report to the governor?