



# Breakout Group A: Practical Applications

- What are the challenges that need to be addressed to facilitate use of these models? In what contexts?
- Identify specific opportunities (now and in the future) to use these models in:
  - Regulatory decision-making
  - Prioritization/Lead Screening/Industry applications
  - Others
- At what point is a computational approach suitable (or sufficient) for an actual risk assessment?
- What would render models unacceptable for regulatory use, and are there conditions that could be met to increase acceptability? For example, increase the transparency of the algorithm, validate it for certain groups of substances, use it in combination with other non-animal methods?
- Do regulatory agencies need to use open source and freely available software (as in no cost) when making a screening, regulatory or policy decision? Is a proprietary algorithm/code a show stopper for regulatory decisions for these endpoints?
- How would we go about building software tools for a combined approach (e.g. QSAR + read-across + structural alerts)?



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- What are the challenges that need to be addressed to facilitate use of these models? In what contexts?
- Transparency
- Protection of CBI (e.g., information and network security)
- Model updates based on new data, but consideration of impact of these updates on current decisions
- Full transparency for regulatory use – can do so without sharing with everyone
- Multiplicity of models – how to choose
- Communication of usefulness and limitations
- Characterizing the applicability domain (e.g., unique chemistries)
- Defining how they fit into an integrated approach
- Including a mechanistic component adds confidence building



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- Identify specific opportunities (now and in the future) to use these models in:
  - Regulatory decision-making
  - CPSC currently writing guidance on how they will accept alternative methods (foundation is ICCVAM guidance)
  - Period of exploration to establish utility of these approaches; need to see how much coverage there is – new chemicals still have lots of questions, but others (e.g., degradants) could have promise
  - Start with them as research tools and then eventually more formal decision making
    - Prediction accuracy for specific domains/mechanisms of action would help with establishing relevance
  - Prioritization/Lead Screening/Industry applications
    - “some information” is better than no information as a starting point – but need model performance assessment as well
    - Could be used to screen out very toxic
    - Use these data to drive additional data requests/requirements – can then feedback into process downstream
    - How do estimates from consensus model compare to models that have been built internally
    - Obvious screening decisions (yes/no) or move on to additional testing requests
  - Others
    - At what point are manufacturers/others required to make information available to the agency? (e.g., new information requirements for a chemical)
    - Need a method that would be used specifically to evaluate models – e.g., hold back a hidden evaluation set that is routinely used



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- At what point is a computational approach suitable (or sufficient) for an actual risk assessment?
- Policies must be in line with a rapidly evolving field
- If generalized performance is consistent with local performance (e.g., specific domains)
- Using the criteria contained in the OPPT-TSCA strategy
- Need to be able to see analogs and performance
- Statistical strength
- Domain of applicability



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- What would render models unacceptable for regulatory use, and are there conditions that could be met to increase acceptability? For example, increase the transparency of the algorithm, validate it for certain groups of substances, use it in combination with other non-animal methods?
- “Black box” issue is a big issue; ultimately, need to be able to defend results, so transparency is critical
- Version control issues that confound results such that different results for same substance
  - Risk assessment policy changes may be needed to account for this issue (e.g., RA based on version X.X)
- Poor applicability domain (if chemistry not represented in the training set)



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- Do regulatory agencies need to use open source and freely available software (as in no cost) when making a screening, regulatory or policy decision? Is a proprietary algorithm/code a show stopper for regulatory decisions for these endpoints?
- Must be transparent, but not necessarily to the public because of CBI
- Safeguards for IP are already in place (e.g., Feds can request open access to model without releasing outside)
- “Open source” doesn’t have to mean everyone has access to everything
- Ultimately, need to be able to make decisions that are defensible in court – this requires transparency
- Maintenance and access to data



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- How would we go about building software tools for a combined approach (e.g. QSAR + read-across + structural alerts)?
- Build a standard server for each model (create a regulatory protocol for providing this endpoint used for submission)
- JRC QSAR reporting format provides guidance – available for several existing models (e.g., OPERA)
  - Intend to do the same for the consensus model to provide transparency
  - NOTE: also needs to be delivered via an API to developers
- Run full set through Dow profilers and circulate mechanistic results to the model participants to use in building regional models



# Next Steps

- Publication and distribution of results
- Characterization of model set by stakeholders
- Comparison of consensus model to internal/existing models
- Ongoing dialog among stakeholders to facilitate even better predictions