U.S. AIR FORCE

USSF

AFRL

Development of a Rapid Risk Assessment Process and Software Tools to Support Air Force Operational Decision-making and Technology Acquisitions

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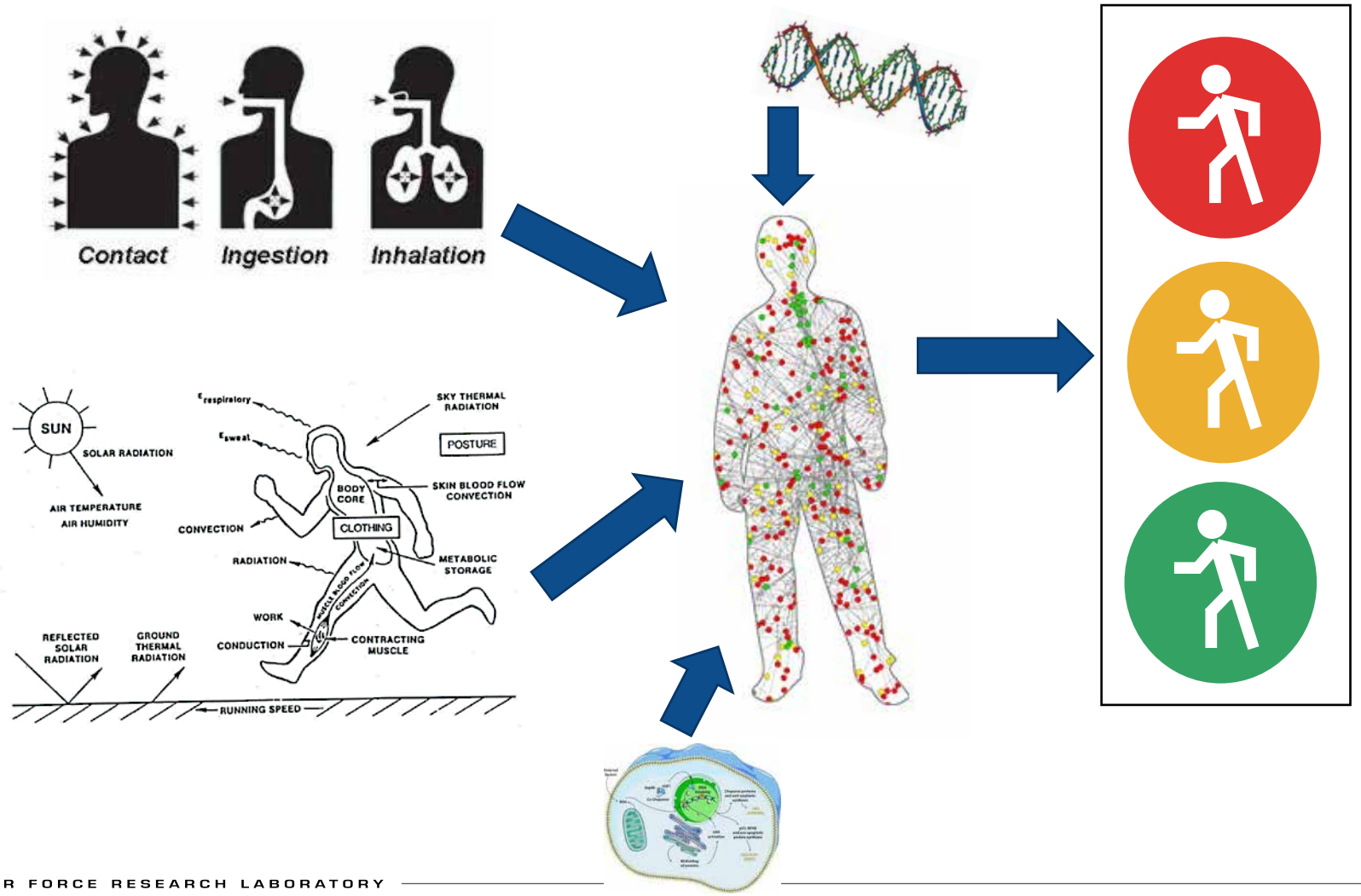
AFRL/711 HPW/RHBAF

Presentation to SACATM

September 22, 2022

Rapid assessment of chemical risk

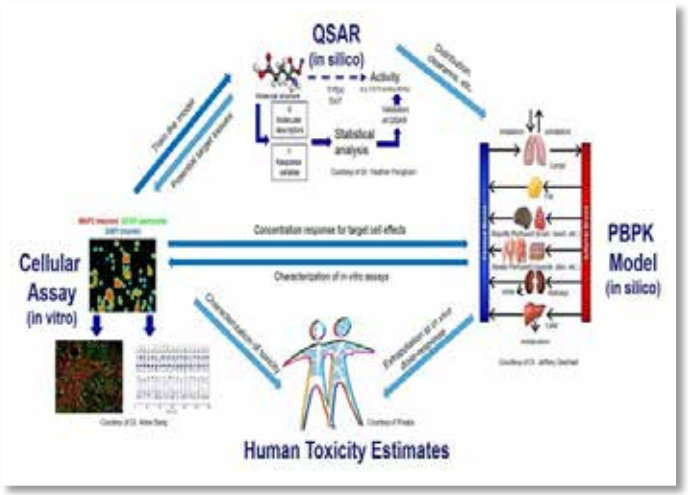
-6.2 effort to develop comprehensive model to predict individual susceptibility to chemical risk



Main Goal: Rapid assessment of human health risk due to operational chemical and physical stressors

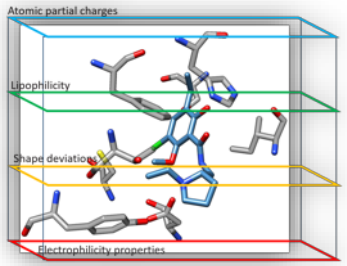
Key Deliverable(s)/Product(s):

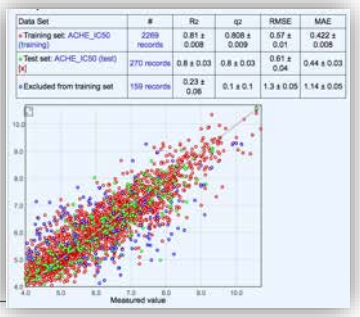
- ***In silico* models:** Curated collection of prediction models for human toxicity
  - Focused on rapid assessment of new or novel chemistries, incorporating knowledge of AF relevant exposure scenarios and physiological stressors



- ***In vitro* data:** Collect necessary data to improve prediction of AF chemical risk
  - Expand chemical domain of current models to improve in silico predictions for AF-specific exposures

- **Risk assessment workflows:** Curated workflow to streamline assessments
- Initial focus is on neurotoxicity and inhaled hazards



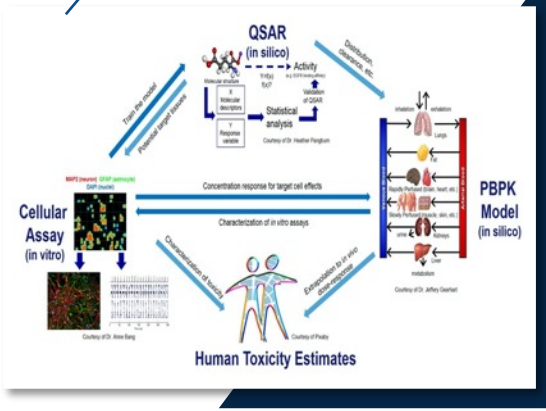


Predictive risk products

-6.3 products to support rapid risk assessment & chemical decisions

ToxAdvisor-lite
(Mobile app)
- Exposure guidelines
- Risk predictions
- Recommend next steps

ToxAdvisor
(Desktop application)
- Exposure guidelines
- Curated risk predictions and models
- Risk calculations, workflows



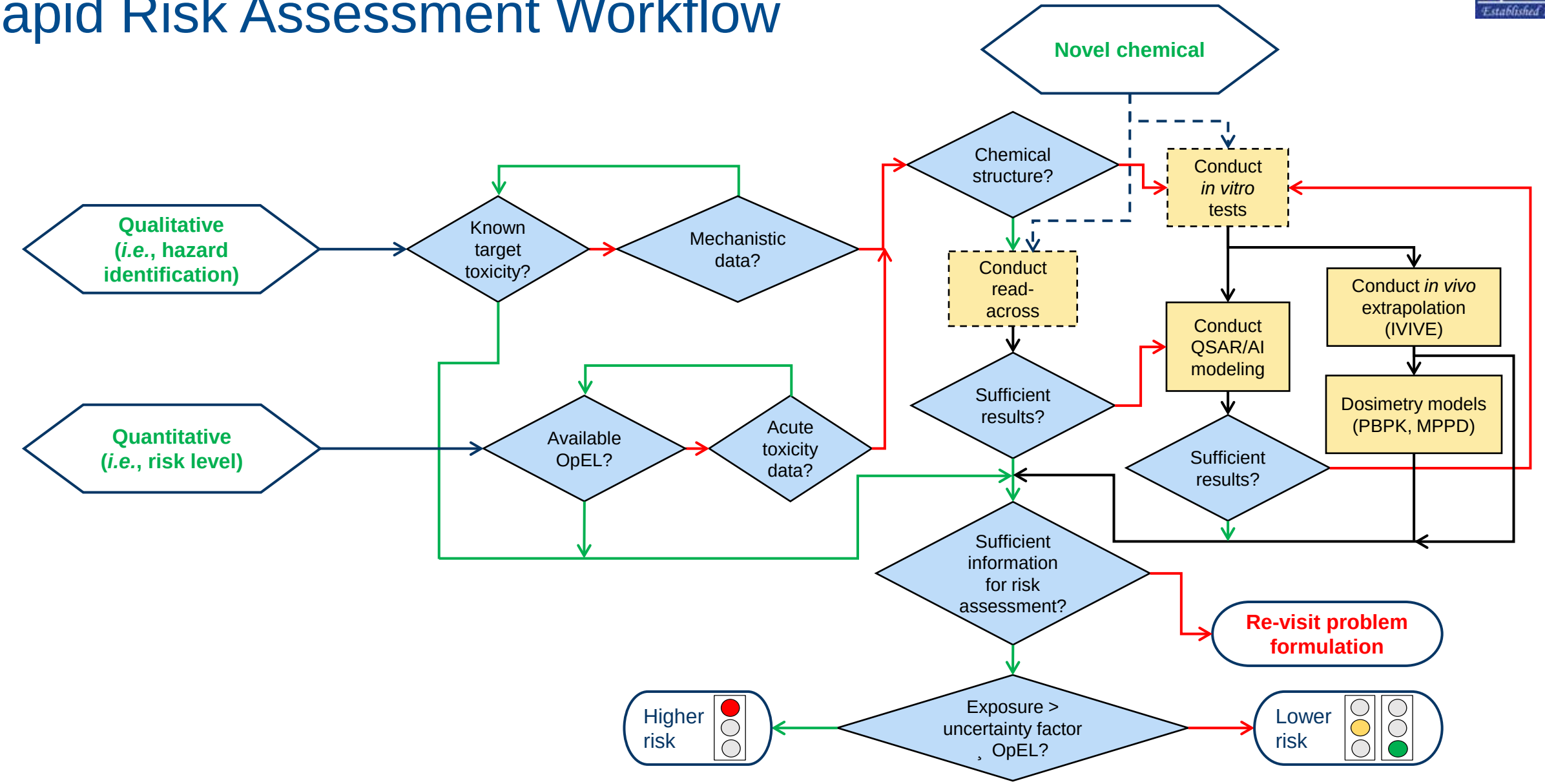
Predictive Risk Capability Build
- Exposure guideline database
- Risk prediction models
- Toxicity data database
- Dosimetry models
- Exposure scenario catalog
- Risk assessment workflows

App content process

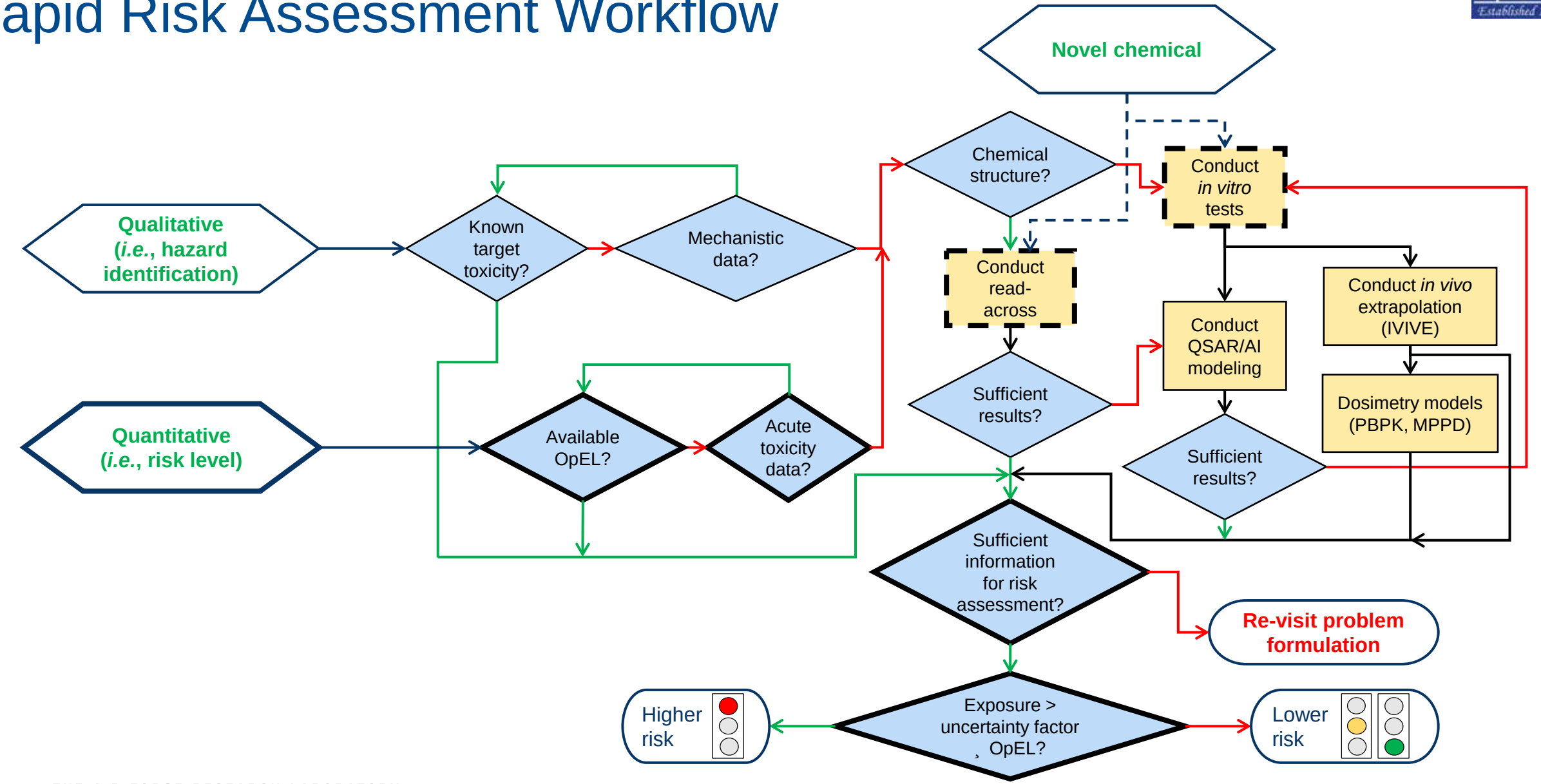
User POV - assessment process

Customer-facing

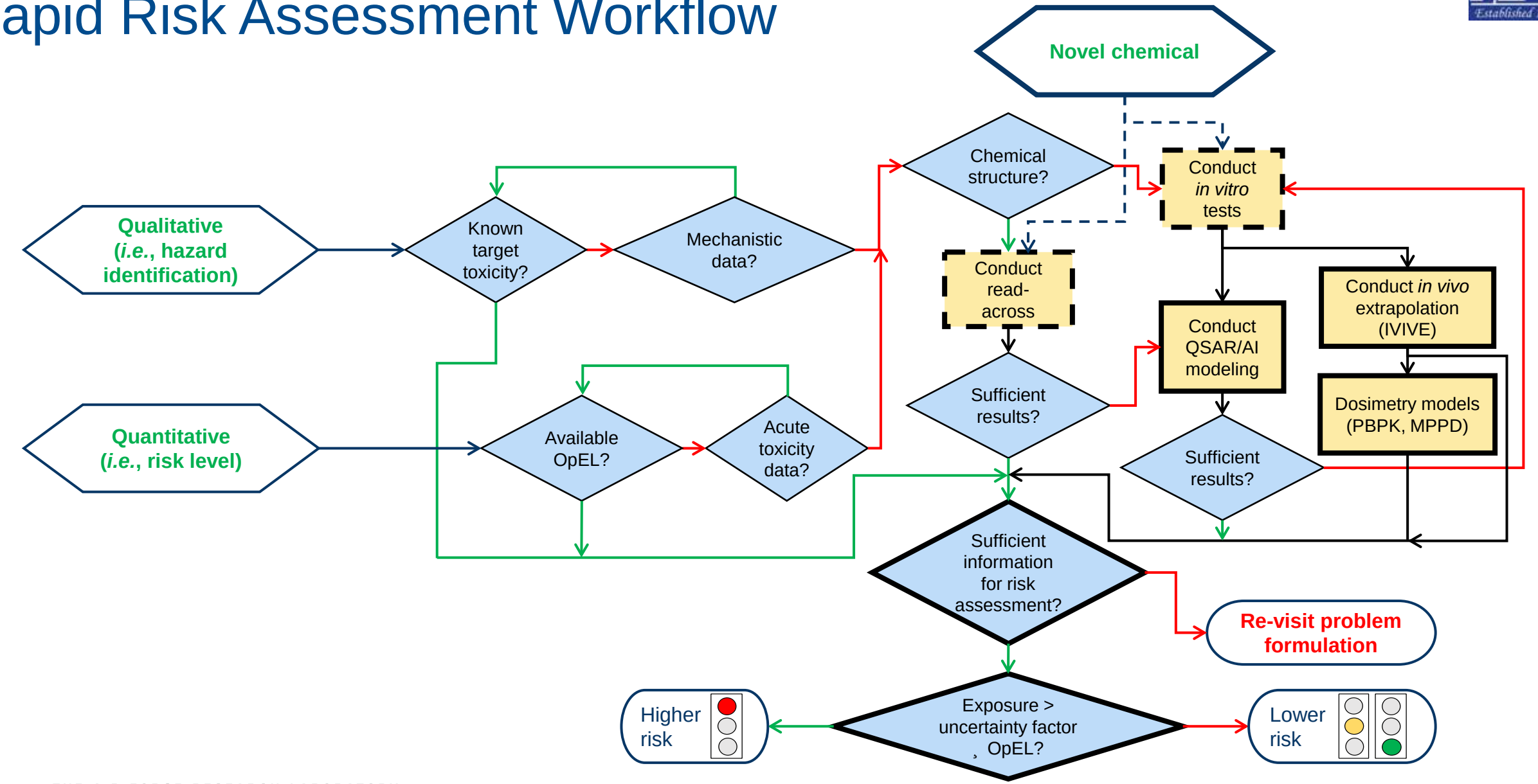
Rapid Risk Assessment Workflow



Rapid Risk Assessment Workflow

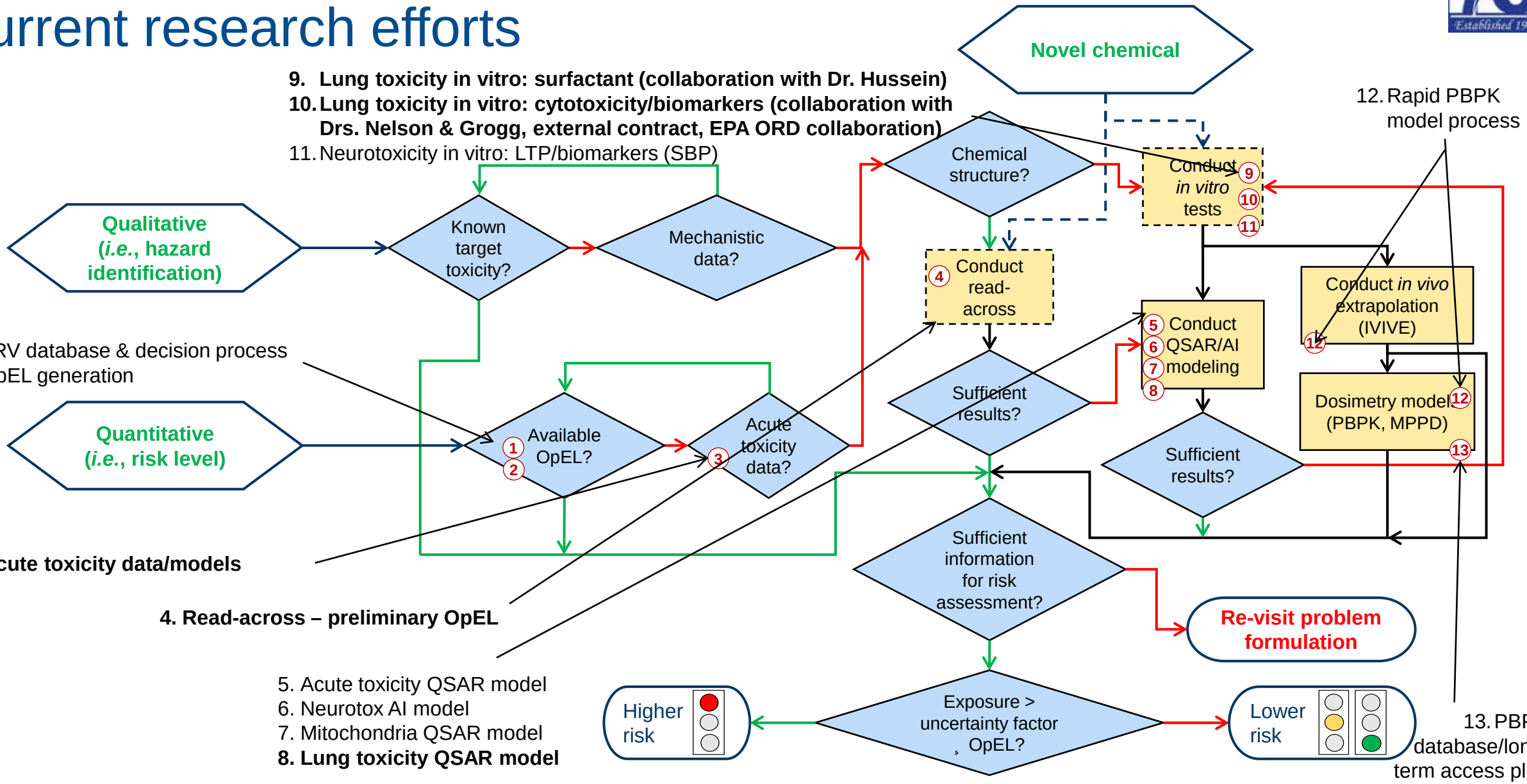


Rapid Risk Assessment Workflow



Current research efforts

9. Lung toxicity in vitro: surfactant (collaboration with Dr. Hussein)
10. Lung toxicity in vitro: cytotoxicity/biomarkers (collaboration with Drs. Nelson & Grogg, external contract, EPA ORD collaboration)
11. Neurotoxicity in vitro: LTP/biomarkers (SBP)

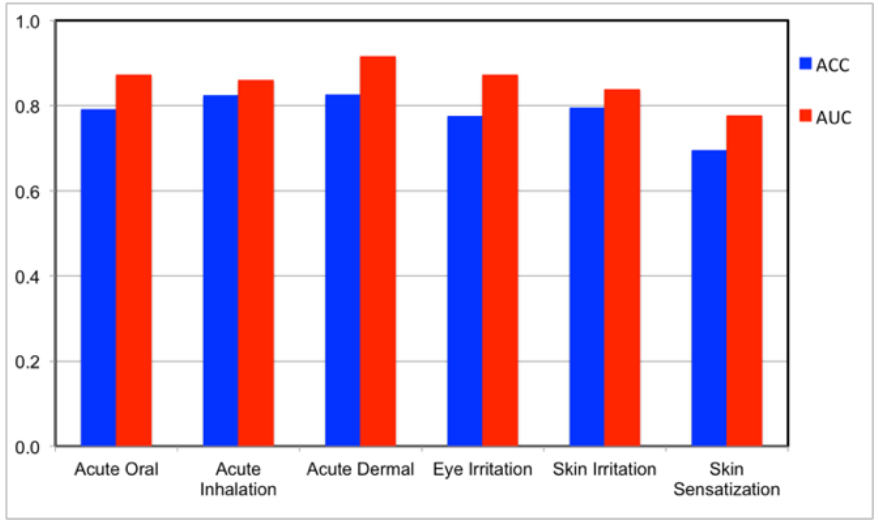


QSAR models: Predicting Acute Toxicity of Poorly Characterized Chemicals

- Novel AI model
- Predicts toxic/nontoxic based on GHS classification, chemical structure

Message passing neural network (MPNN) model

Model validation



Built on >40,000 chemical database

Used to predict toxicity of > 250,000 chemicals

ACC = (TP+TN)/Nchem – accuracy

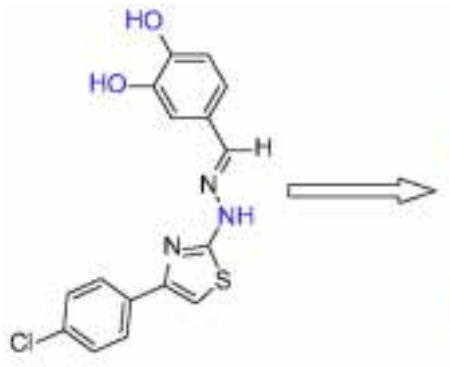
AUC – area under ROC curve

Artificial Intelligence models: Neurotoxicity Target Prediction

- Novel AI model
- Predicts ligand binding to neurotransmitter receptors

Neuro targets

- Acetylcholine
- AChE
- AMPA
- CHAT
- GABA
- Glutamate
- Glycine
- DRD2,3&4
- Kinate
- PX2
- Serotonin



Rahim et al. Bioorg Chem. 2015. 62:106-16.

McCarthy et al. 2022.

Rapid risk assessment products: creating databases, workflows and prediction tools for toxicity reference values

Hazard quotient (HQ) = Measured air concentration / toxicity reference value
Hazard index (HI) = sum of HQs for all chemicals

Tier I:
Occupational Authorities

OSHA
NIOSH
ACGIH
WEEL (AIHA or OARS)

Tier II:
MEGs

TEEL
AEGL
CEGL
PPRTV
ERPG
MRL
HEAST
IRIS
ACGIH

Tier III:
Other

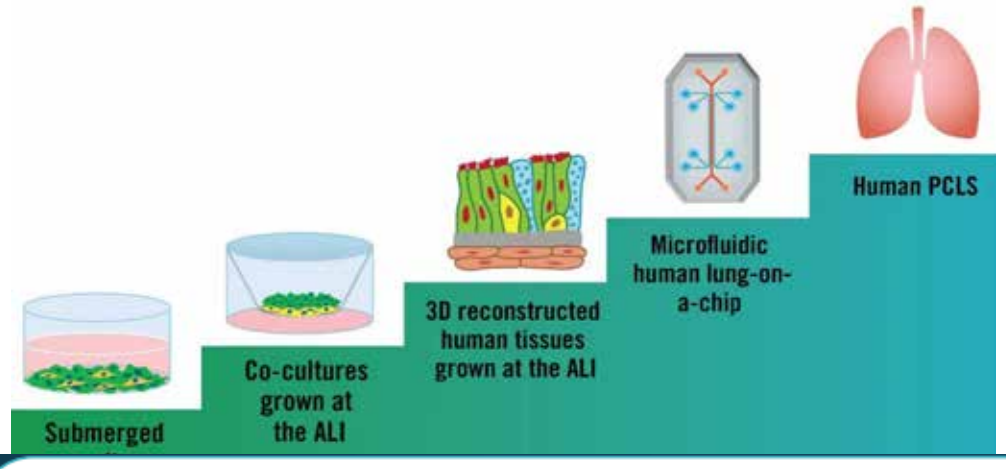
California OSHA SDSs
GESTIS
Hanford Site Screening Values

	Overall Minimum TRV (ppm)	Tier 1 Minimum OEL (8-hr TWA) (ppm)	Tier 1 Minimum Ceiling equiv. TRV (C, IDLH, STEL) (ppm)	Tier 2 Minimum OEL (8-hr TWA) (ppm)	Tier 2 Minimum Acute TRV (10-min to 1 hr) (ppm)	Tier 2 Minimum C equiv. TRV (CRIT, up to 1 hr) (ppm)	Tier 2 Minimum TRV (14-dy to 1 yr) (ppm)	Tier 3 Minimum OEL (8-hr TWA) (ppm)	Tier 3 Minimum C equiv. TRV (C, IDLH, STEL) (ppm)	Calculated Ceiling Equiv. (lowest occup TWA*3)	Best Ceiling Equivalent (Tier 1 > 3 > 2 > calc.)
1											
1											
✓	1.30E+00	5.00E+01	3.85E+02	6.45E+00	5.02E+01	1.08E+03	2.61E-01	1.30E+00	2.25E+02	3.90E+00	3.90E+00
1	1.70E+00							1.70E+00		5.10E+00	5.10E+00
1	1.40E+00				5.02E+01	1.08E+03		1.40E+00		4.20E+00	1.08E+03
1	6.67E+01				6.67E+01	1.43E+03					1.43E+03
1	7.49E+01				7.49E+01	1.61E+03					1.61E+03
1	1.30E+00							1.30E+00		3.90E+00	3.90E+00

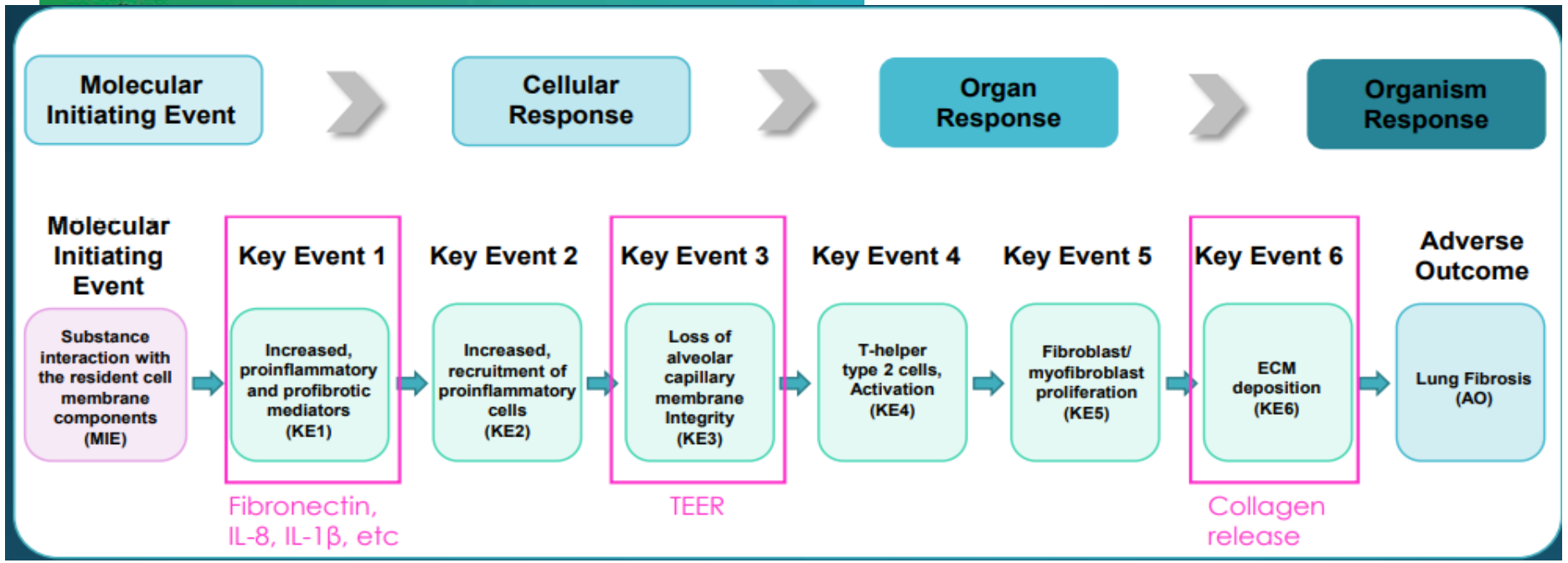
Integrated Chemical Environment

Estimate preliminary TRV from nearest neighbor, using ICE tanimoto score tool

Inhalation toxicity – predicting toxicity for poorly characterized chemicals



Surfactant effects
Irritation/Corrosion
Interaction with cell membrane
Physical injury



Clippinger 2016 – NICEATM webinar

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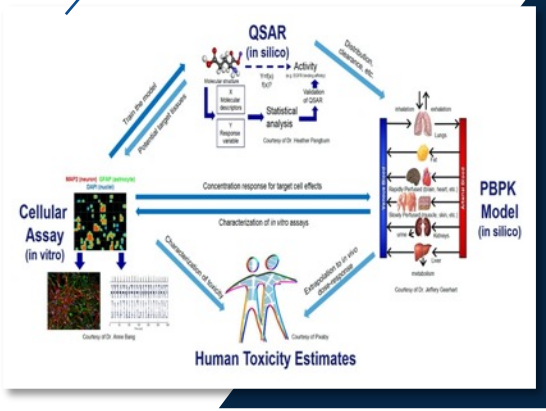

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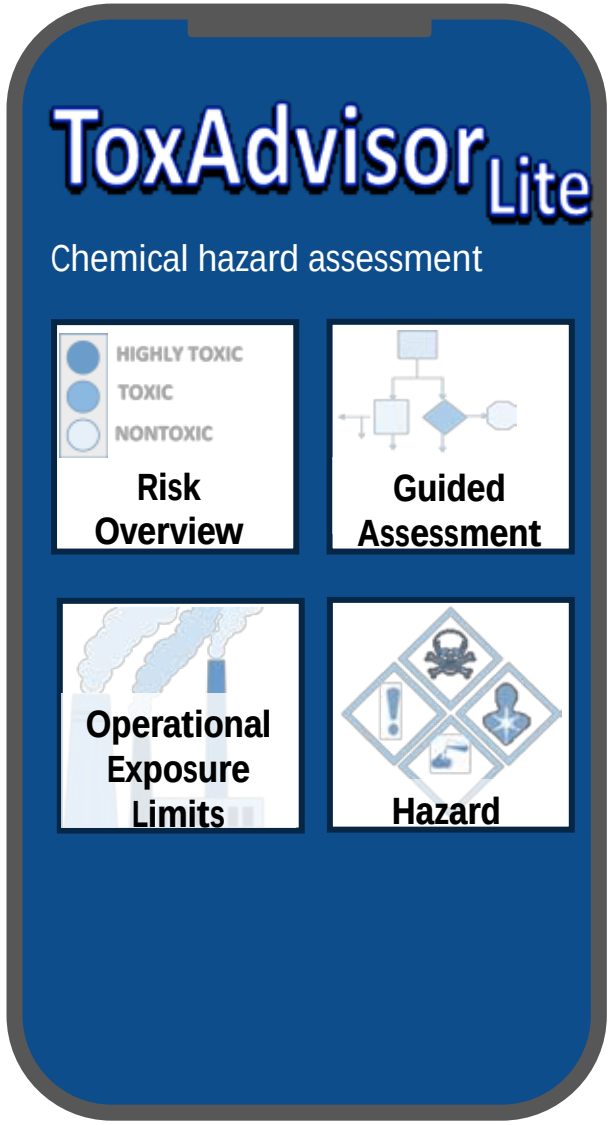
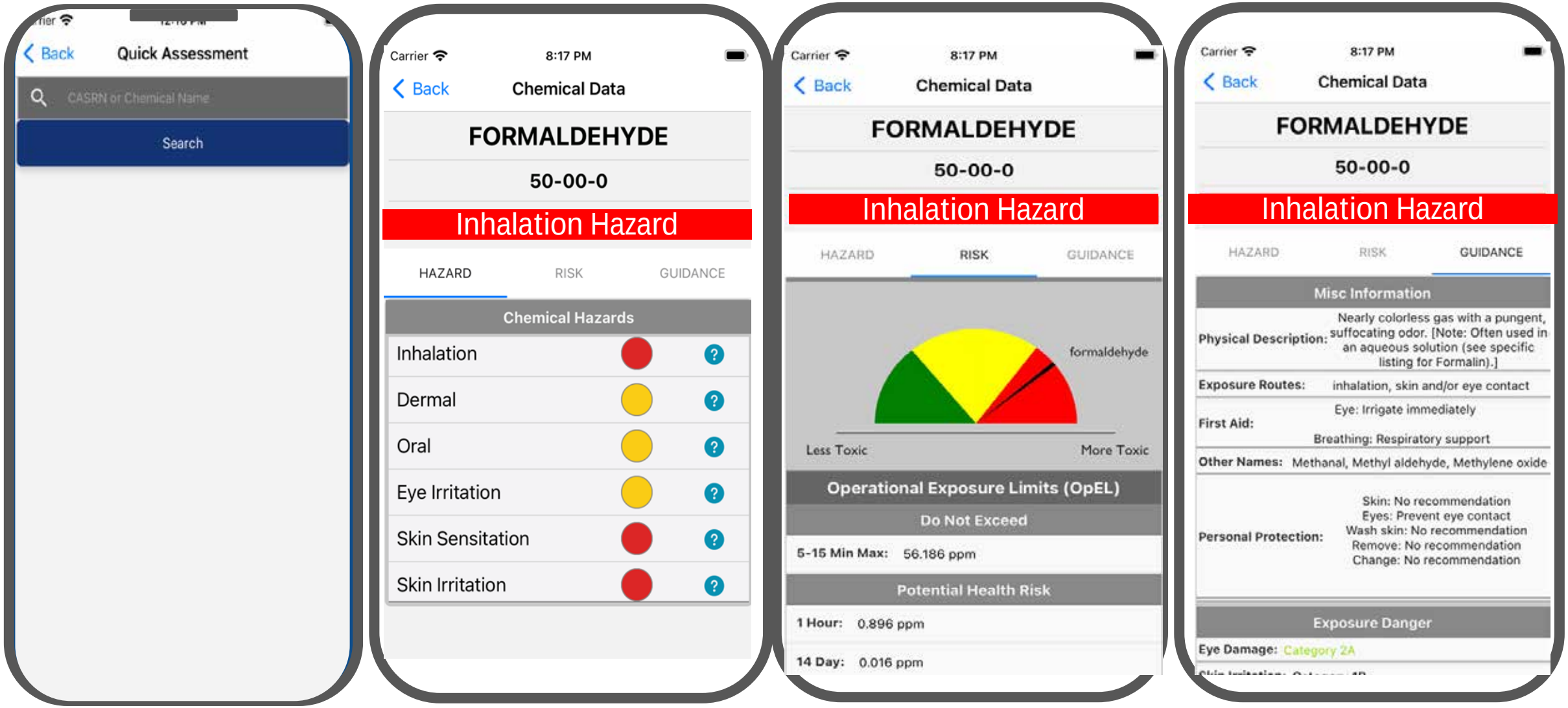
Wireframe of Mobile App – **Home page**



Possible homepage includes:

- Risk overview – allows 1-click results for OpEL/Hazard
- Guided assessment provides user assistance in decision-making
- More detailed information if desired
- User guidance
  - Provide context, recommendations for next steps

Screenshots from Beta version of ToxAdvisor-lite App



Mobile App – **Output and utility**

Results provide data & context:

- Requested endpoint actual value vs. predicted
  - If only predicted is available, user alert will call attention to the fact this is a predicted value
- Graphic provides context:
  - Comparison to well known “benchmark chemicals”
  - Rank order to show relationship to benchmark chemicals and greater chemical database
  - Color coding indicates relative toxicity classification
- Automated professional judgement

Current Activities

	Database	Predictive Models
Toxic Effect	**GHS labels** ***In vivo* data** - EPA, NIH/NTP/NICEATM - ECHA/REACH, DoD/DTIC ***In vitro* data#** - HT assays (ToxCast, OECD) - Organotypic assays (DoD, published, collabs) - Cardiac, lung*, CNS*	**6-pack acute toxicity model*** **QSAR-based structural alerts#** - Acute toxicity - Allergic contact dermatitis# - Skin/eye corrosion, etc. **Read-across** **Machine learning models#** - Neurotoxicity* - Lung toxicity*
Risk Level	**Toxicity Reference Values** - AEGLs, MEGs, TLVs, etc **GHS classifications (1-5)** ***In vivo* NOELs/LD50s** ***In vitro* NOELs/EC50s#**	**TTC categories (1-3)** **Read-across** **Systems biology models#**
Exposures	**Historical data** - Common AF scenarios	**JH/APL OE model#** **Other exposure models**
Dosimetry	**Chemical properties** **Particulate characterization**	**HTTK, rapid PBPK models*** **Chemical-specific PBPK***

Risk Assessment

Risk assessment workflows
+ AF-relevant exposure scenarios
+ Standardized process
+ Improved traceability
+ Increased efficiency

Acknowledgements

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QUESTIONS?