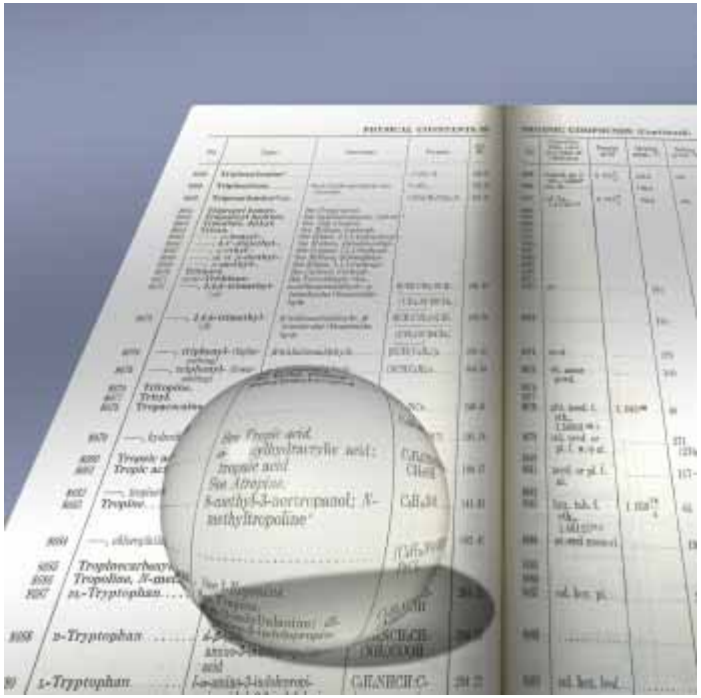
Read Across, SARs and QSARs for Acute Inhalation Toxicity



Tiffany Bredfeldt
Carla Kinslow
Roberta Grant

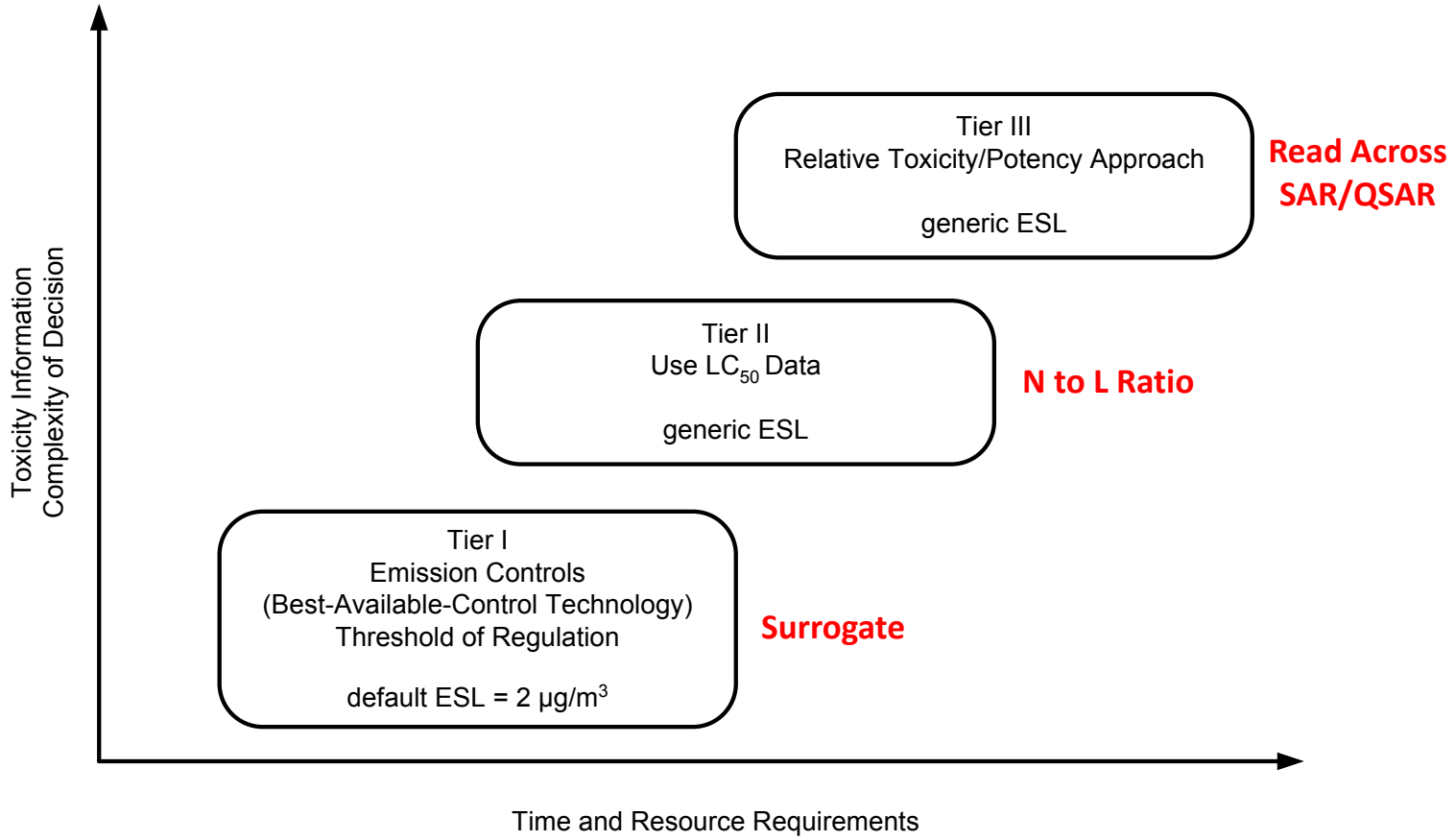
Problem Formulation

- Many chemicals have little or no toxicological data
- Concern regarding potential toxicity of chemicals
- Newer legislation regarding chemical safety
- Need to derive toxicity factors for limited toxicity data(LTD) chemicals
- Sustainable methods and reduced animal testing
  - Generic approaches
  - Read across or extrapolations
  - SAR/QSAR

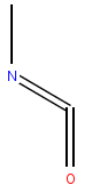
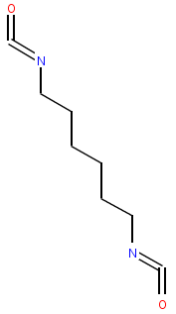
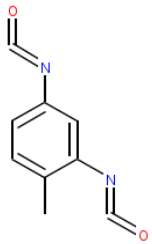
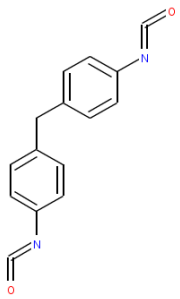
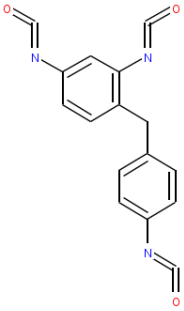
TCEQ Approaches for LTD Chemicals

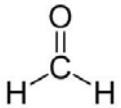
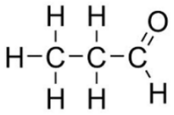
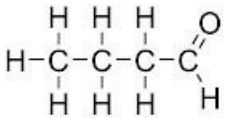
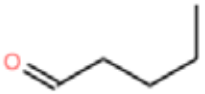
- Structural Surrogate
- Tiered Approach
- Route-to-Route Extrapolation
- N-L Ratio
  - Calculate LC50 by N-L (NOAEL-LC_{50} Ratio)
  - Grant et al., 2007

TCEQ Approaches for LTD Chemicals



Former Case Study

Structure					
CAS #	624-83-9	822-06-0	584-84-9	101-68-8	51944-41-3
Name	methyl isocyanate	hexamethylene diisocyanate	2,6 - toluene diisocyanate	4,4’ diphenyl methane diisocyanate	4-Cyanodiphenyl-methane diisocyanate
Physiochemical Properties	MW = 57.05 VP = 531 mm Hg 25 C°	MW = 168.22 VP = 0.05 mm Hg 25 C°	MW = 174.15 VP = 0.05 mm Hg 25 C°	MW = 250.25 VP = 0.0003 mm Hg 25 C°	MW=291.26 VP = 0 mm Hg 25 C°
LC50 (rat) 4 h (experimental data)	7 ppm	18.2 ppm	13.9 ppm	16.5-18 ppm	ND
LD50 (rat) (TEST-experimental data)	51.56 mg/kg	737.7mg/kg	5793.93 mg/kg	9191.97 mg/kg	20012.93 mg/kg
TEST Software- Nearest Neighbor (LD50 rat)	381.65 mg/kg	4129.3 mg/kg	5065.71 mg/kg	6291.33 mg/kg	5942.61 mg/kg
TEST Software- Hierarchical Clustering (LD50 rat)	62.02 mg/kg (24-162)	1054.17 mg/kg (810-1371)	3913.86 mg/kg (2471-6200)	10298.44 mg/kg (6478-16370)	18895.13 mg/kg (11684-30558)
RD50 (ppm)	ND	0.35 (1h, mice)	0.39 (1h, mice)	4.8 (1h, mice)	ND

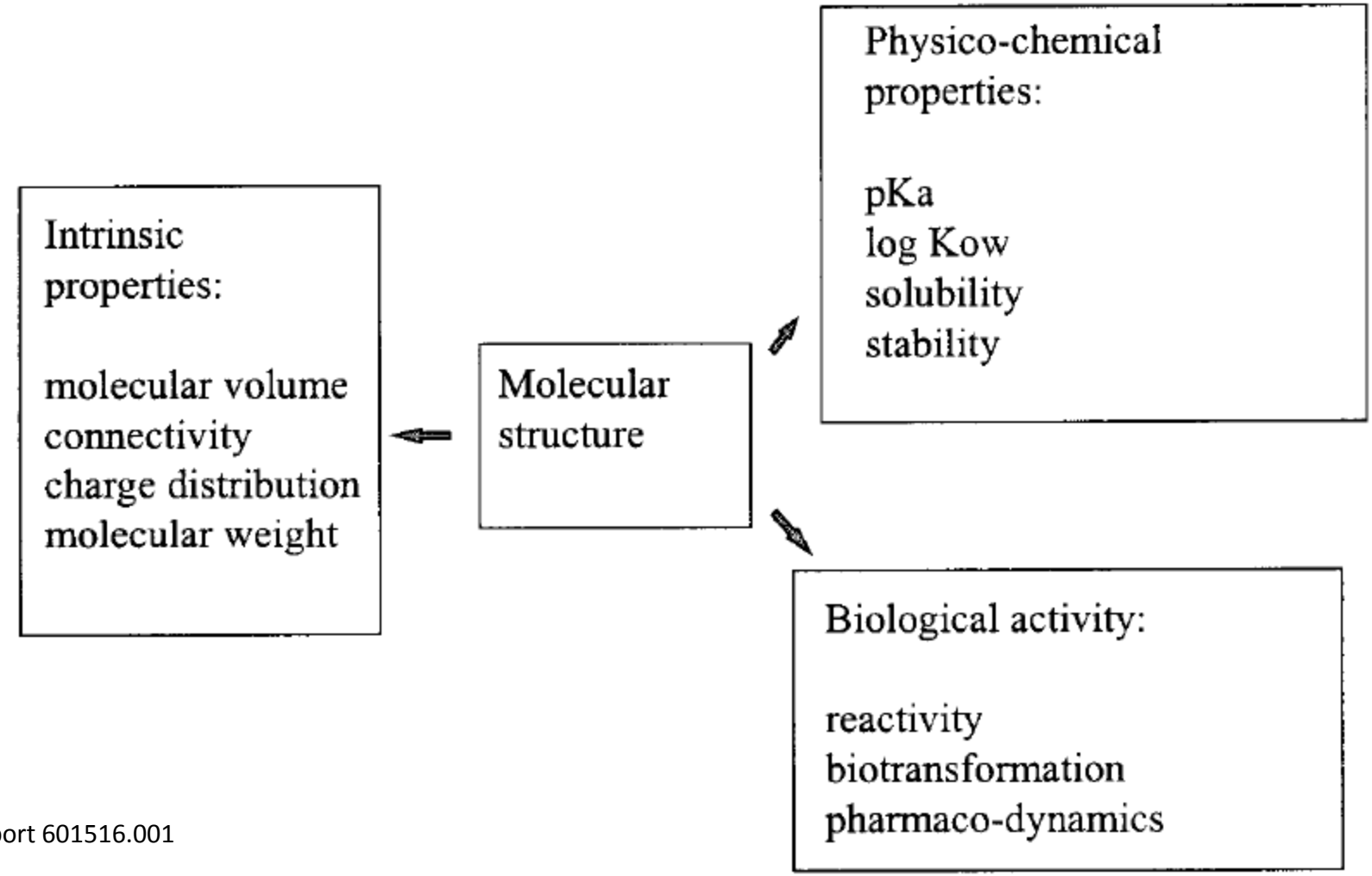
Structure					
CAS #	50-00-0	75-07-0	123-38-6	123-72-8	110-62-3
Name	formaldehyde	acetaldehyde	propionaldehyde	butyraldehyde	valeraldehyde
Physiochemical Properties	MW = 30 VP = 3890 mm Hg	MW = 44 VP = 902 mm Hg	MW = VP = mm Hg	MW = 72 VP = 72 mm Hg	MW=86 VP = 50 mm Hg
LC50 (rat) 4 h (experimental data)	83.5 ppm	13344 ppm	3250 ppm	7500 ppm	ND
LD50 (rat) (TEST- experimental data)	ND (reported: 100 and 2020 mg/kg)	660.76 mg/kg	1409.62 mg/kg	2489.18 mg/kg	4584.11 mg/kg
TEST Software- Nearest Neighbor (LD50 rat)	1594.25 mg/kg	1044.83 mg/kg	134.1 mg/kg	859.12 mg/kg	2116.36 mg/kg
TEST Software- Hierarchical Clustering (LD50 rat)	190.19 mg/kg (23.35-1548.86)	433.38 mg/kg (4.13-45451.06)	458.01 mg/kg (236.60-886.63)	2006.86 mg/kg (1161.46-3467.60)	4584.11 mg/kg (1718.58-3973.22)
RD50 (ppm) 10 minute exposure	3 ppm (rat) 13.8 ppm (rat)	2932 ppm (rat) 4946 ppm (rat)	2078 ppm (rat)	1532 ppm ** 1015 ppm**	1121 ppm** 1190 ppm**

By definition from the Haz-Map page – RD50 Concentration producing a 50% decrease in respiratory rate in experimental animals following a 10-minute exposure.

**REF = http://www.inchem.org/documents/sids/sids/110623.pdf They did not provide durations for RD50

Approaches for LTD Chemicals: Conclusions

- Derivation of a toxicity factor for an LTD chemical is dependent on available resources
- Approaches are designed to be conservative and produce generic toxicity factors that are health protective
- Inhalation can be highly variable
- Oral toxicity trend do not necessarily inform inhalation exposure concerns
- Available QSAR models are not particularly predictive of inhalation toxicity



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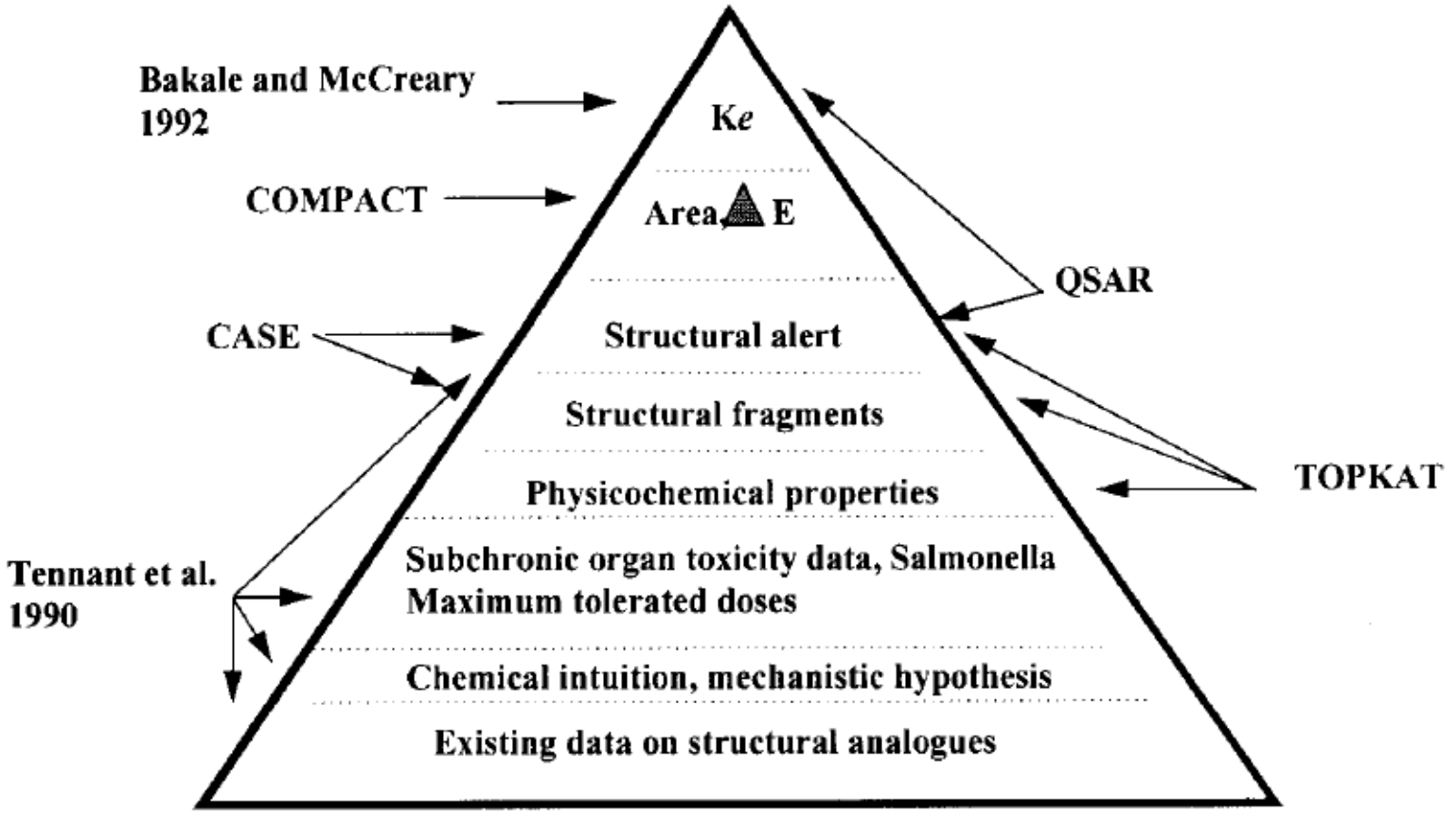


Area = the calculated molecular planarity, which is an indication for the three dimensional structure

E = measure for the oxidative activation potential by P450 system

Ke = electrophilicity parameter, indicative for directly acting carcinogens

SARs/QSARs: Strengths and Limitations

- Estimate toxicity
  - Select least toxic chemical suitable for industrial use
  - Estimate toxicity in case of emergency
  - Determine whether emissions would be a potential risk
- Direct toxicity testing
  - What data is missing? Prioritization?
- End point specific
  - Does a QSAR based on LD50 or LC50 data inform other endpoints?
  - Inhalation endpoints?
- Inaccuracy in model
  - Oral data not predictive of inhalation toxicity
  - Is the model predictive?
  - Database used to generate QSAR model:
    - Limited, heterogeneous data points
  - Representativeness of database to chemical of concern/interest

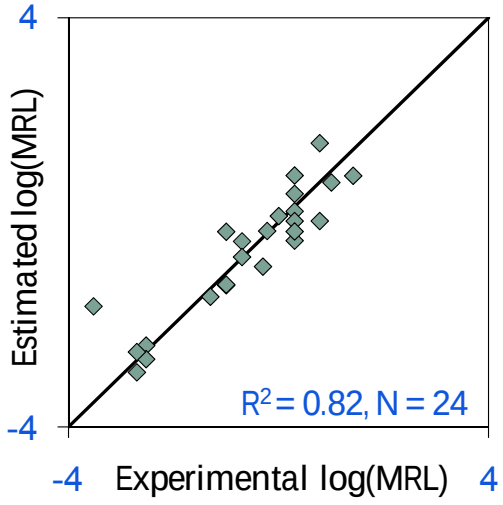
Data for QSAR Development

- Based on quality data
  - Systematic evaluation
  - Applicability
  - Heterogeneity
- Well chosen set of chemicals
- Best categorization of data
  - Structural, physicochemical, or MOA?
- What is a well-balanced training set?
  - Range of chemicals
  - High quality studies
  - Validated by comparing experimental data to predicted data
- Uncertainty

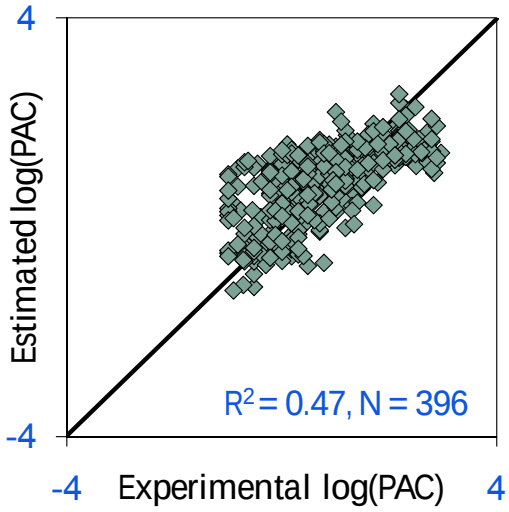
Exploratory ATSDR Models

for Inhalation Health Guidance Values

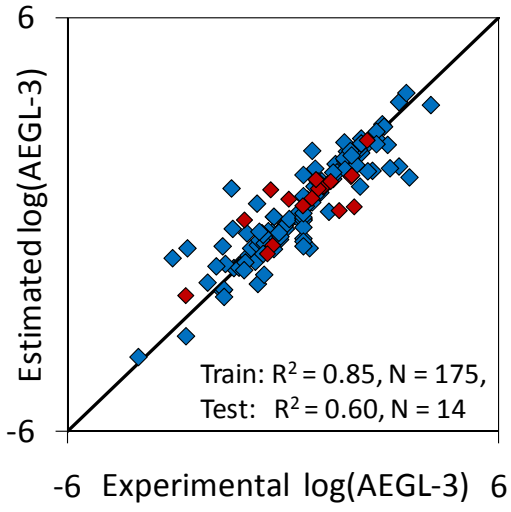
ATSDR MRLs



DOE TEELs



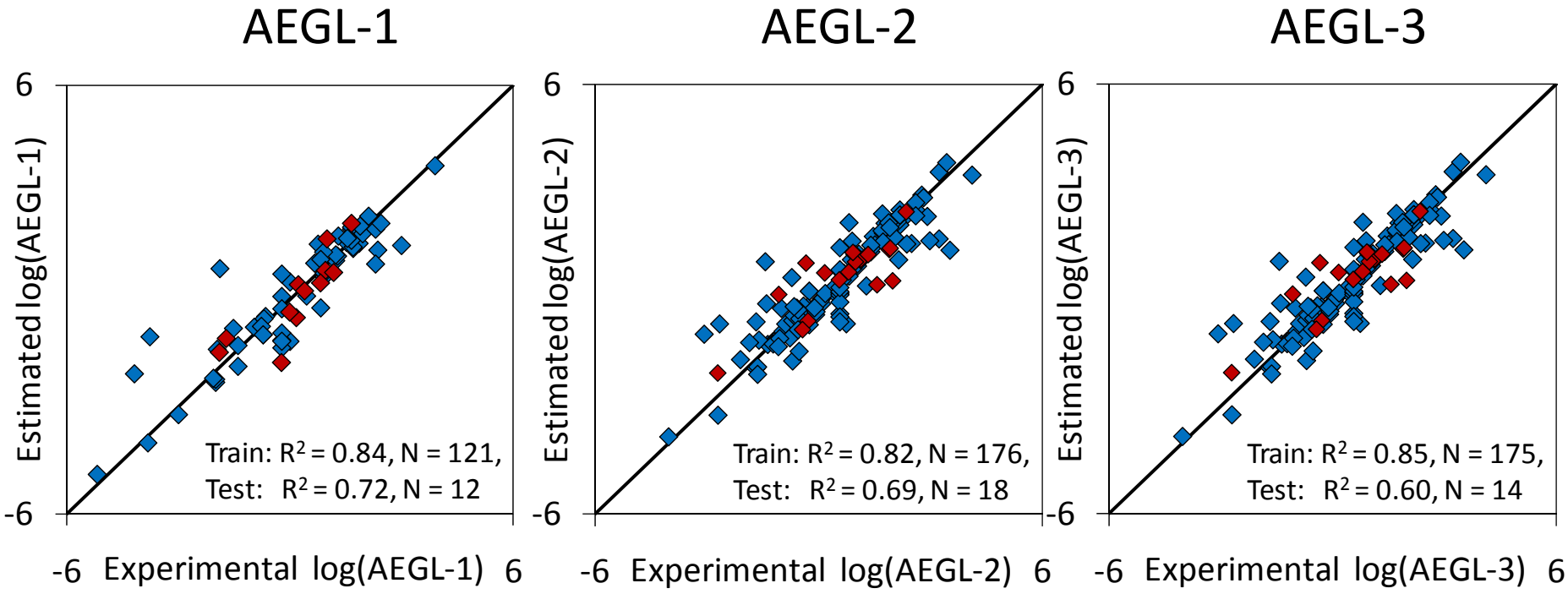
EPA AEGLs



Data Quantity:	few	ample	sufficient
Data Quality:	high	poor	high

Exploratory ATSDR Models

for Acute Exposure Guidelines Levels at 8 hour duration of exposure



ATSDR: Conclusions

- Available inhalation health guidance values can be modeled using QSAR methods
- The quality of QSAR estimates can not be better than the quality of experimental data using which the models were built
- AEGLs/ERPGs represent the most promising source of data for modeling

ATSDR/TCEQ: Future Directions

- Parameters of the models need to be optimized to achieve the best performance
- The chemical domain of model applicability needs to be explored and additional data recruited to improve coverage, as needed
- Confidence and prediction intervals for the estimates need to be derived
- Mode-of-action, species, and uncertainty-factor stratification of the data needs to be explored
- HGV cross-extrapolation dependencies need to be determined, e.g. exposure durations and severity levels

Acknowledgements

TCEQ

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Tracy Tie, Ph.D.

Mydzung T. Chu, MSPH

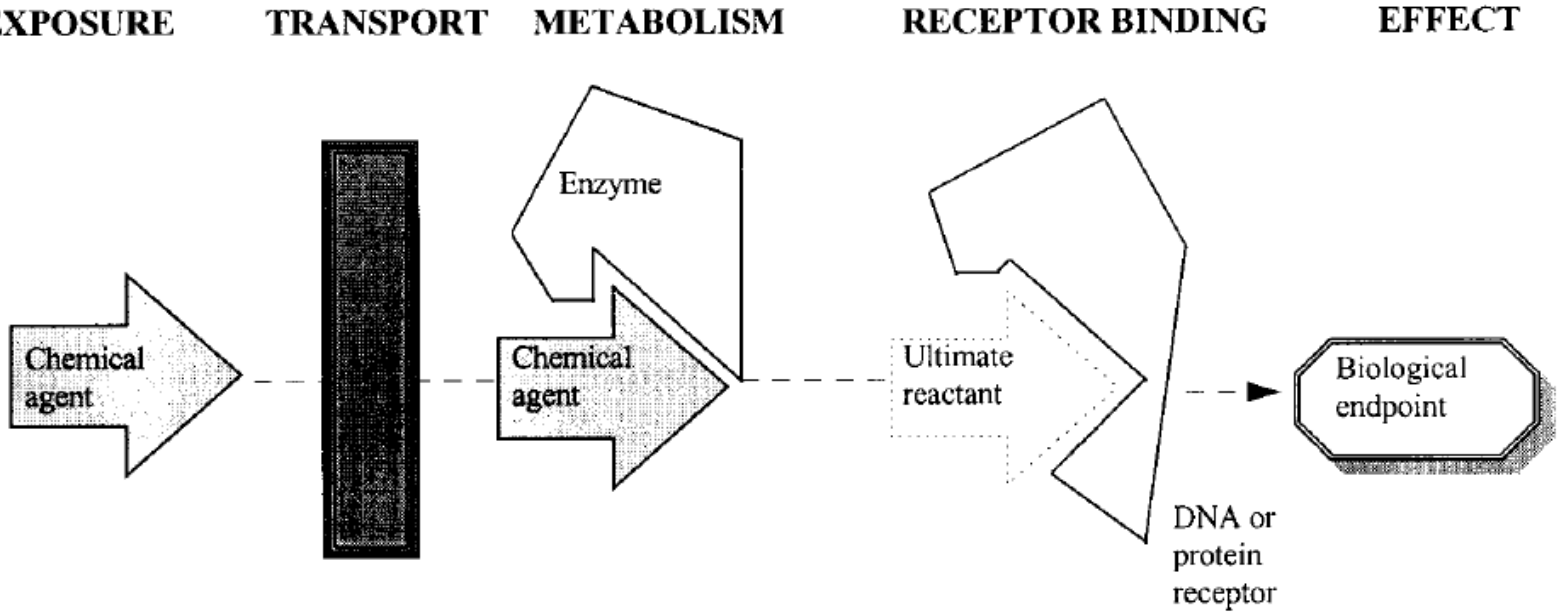
TCEQ Toxicology Division

ATSDR Computational Toxicology Group

EPA (TEST Software)

TERA

Questions/Comments??



SAR PROPERTIES	*partition coefficients, size, shape parameters*	*reactivity parameters: energies, 3D structures, functional groups, steric parameters, electronic properties*		CARCINOGENICITY GENOTOXICITY TERATOGENICITY NEUROTOXICITY CYTOTOXICITY
CHEMICAL CLASSES	Alcohols	PAHs halocetic acids chlorofluoromethanes nitrosoamines	dioxins PAHs PCSs steroids	

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QSAR Modeling Methods: Choices, Choices, Choices