Strategies to Integrate Exposure, PBPK Models and Data on Metabolism to Predict Plasma Levels of Compounds and their Metabolites that are Directly Comparable to *In Vitro* Toxicology Results

Tim Pastoor, Syngenta

On behalf of

Paul Price, The Dow Chemical Company


Paul Price

Measurement of dose in toxicology is now divided

Carrick-A-Rede Rope Bridge

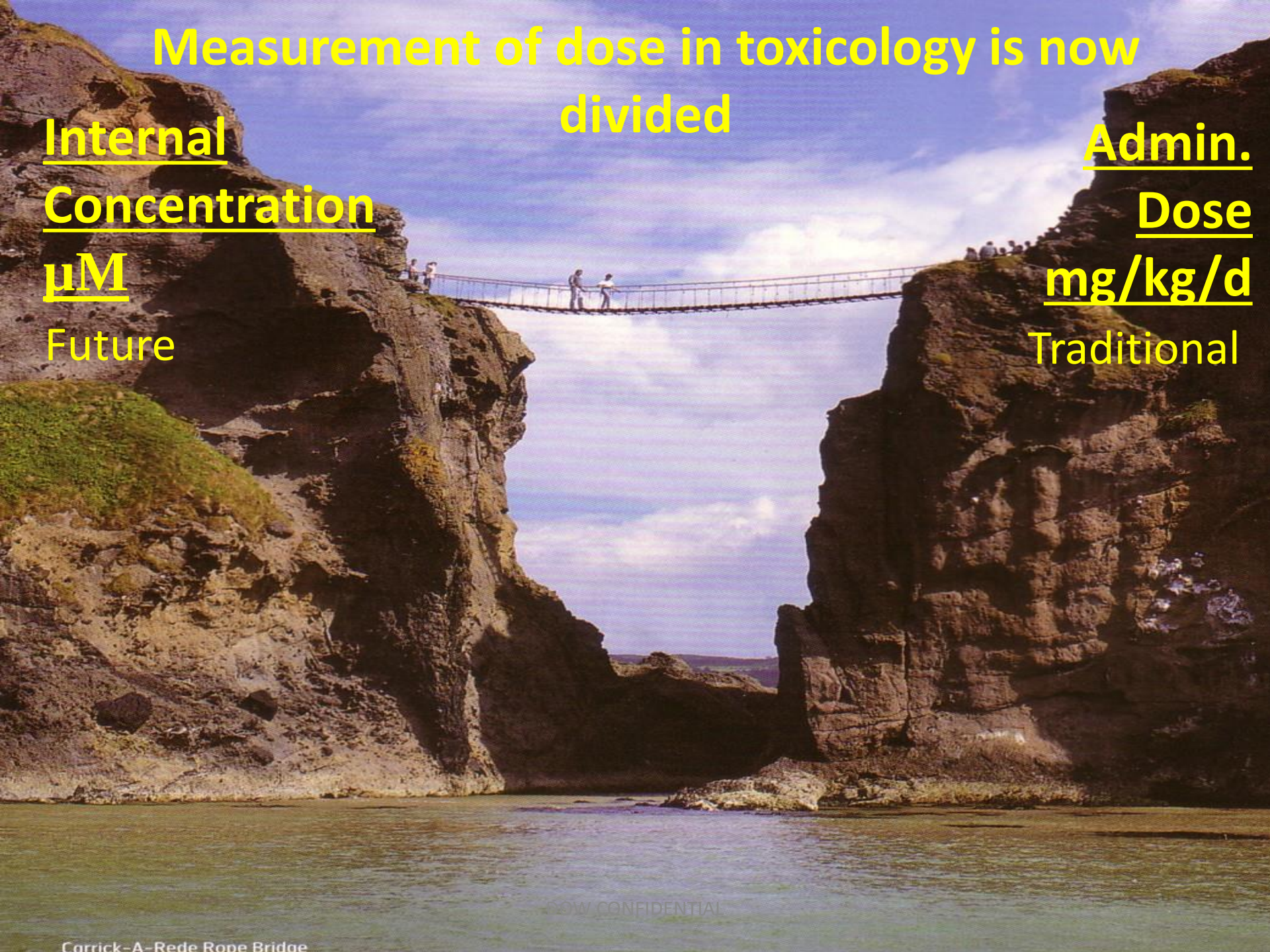
Measurement of dose in toxicology is now divided

Internal Concentration µM

Future

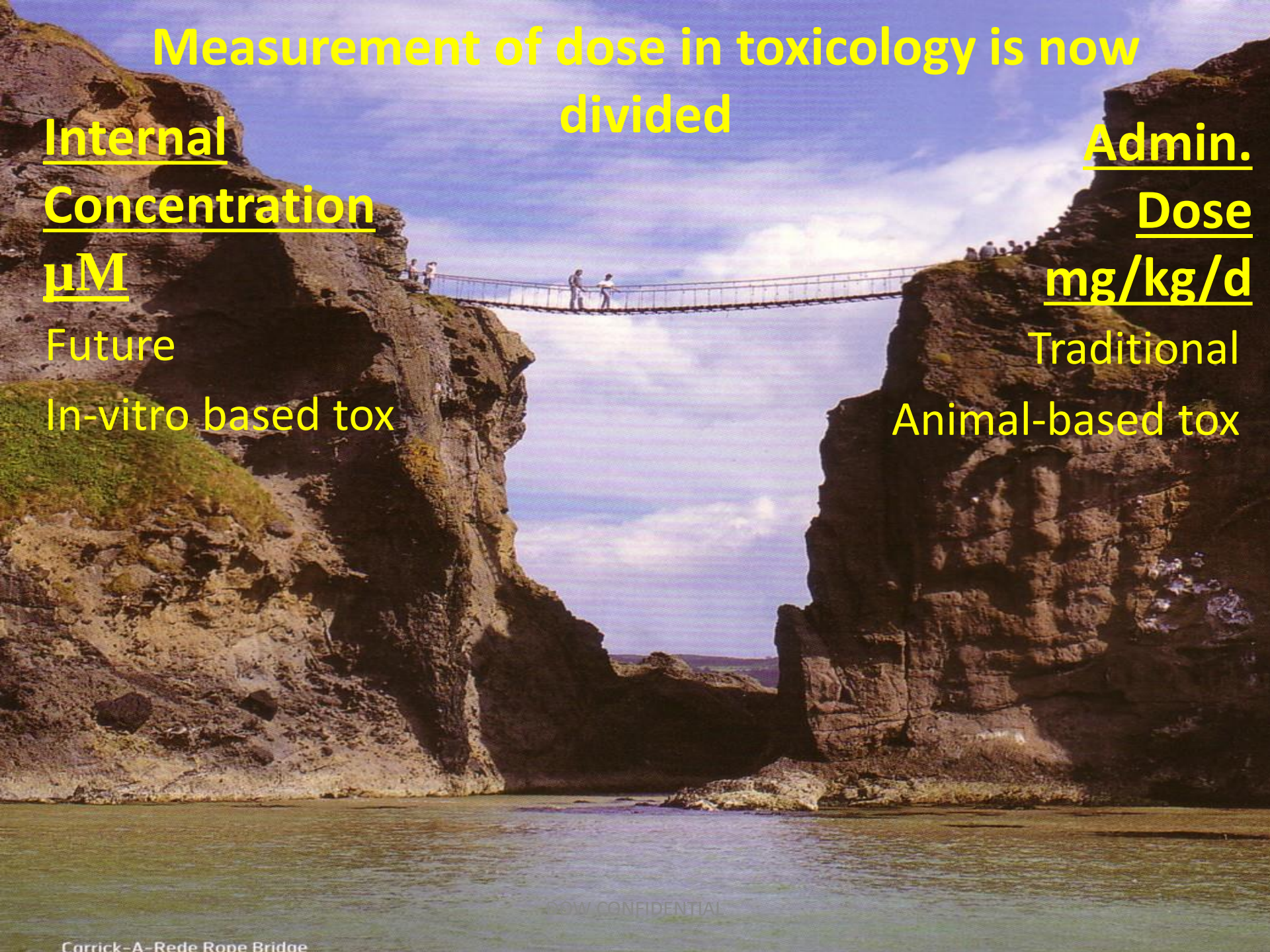
Admin. Dose mg/kg/d

Traditional



Carrick-A-Rede Rope Bridge

Measurement of dose in toxicology is now divided



Internal Concentration µM

Future

In-vitro based tox

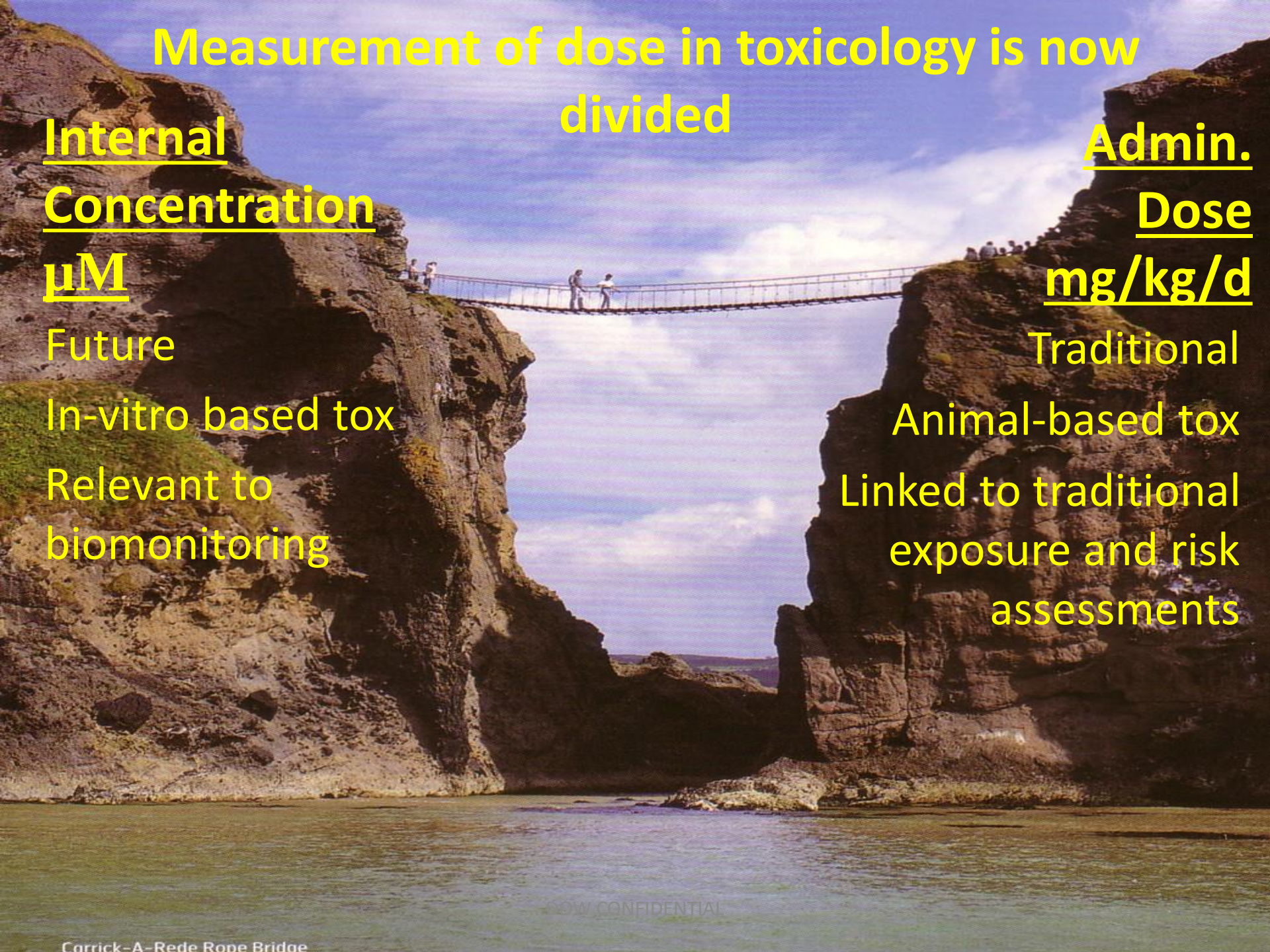
Admin. Dose mg/kg/d

Traditional

Animal-based tox

Carrick-A-Rede Rope Bridge

Measurement of dose in toxicology is now divided



Internal Concentration µM

Future

In-vitro based tox

Relevant to biomonitoring

Admin. Dose mg/kg/d

Traditional

Animal-based tox

Linked to traditional exposure and risk assessments

Carrick-A-Rede Rope Bridge

Measurement of dose in toxicology is now divided

Internal Concentration µM

Future

In-vitro based tox

Relevant to biomonitoring

Integrates doses from multiple routes and time-varying exposures

Admin. Dose mg/kg/d

Traditional

Animal-based tox

Linked to traditional exposure and risk assessments

Avoids dealing with ADME

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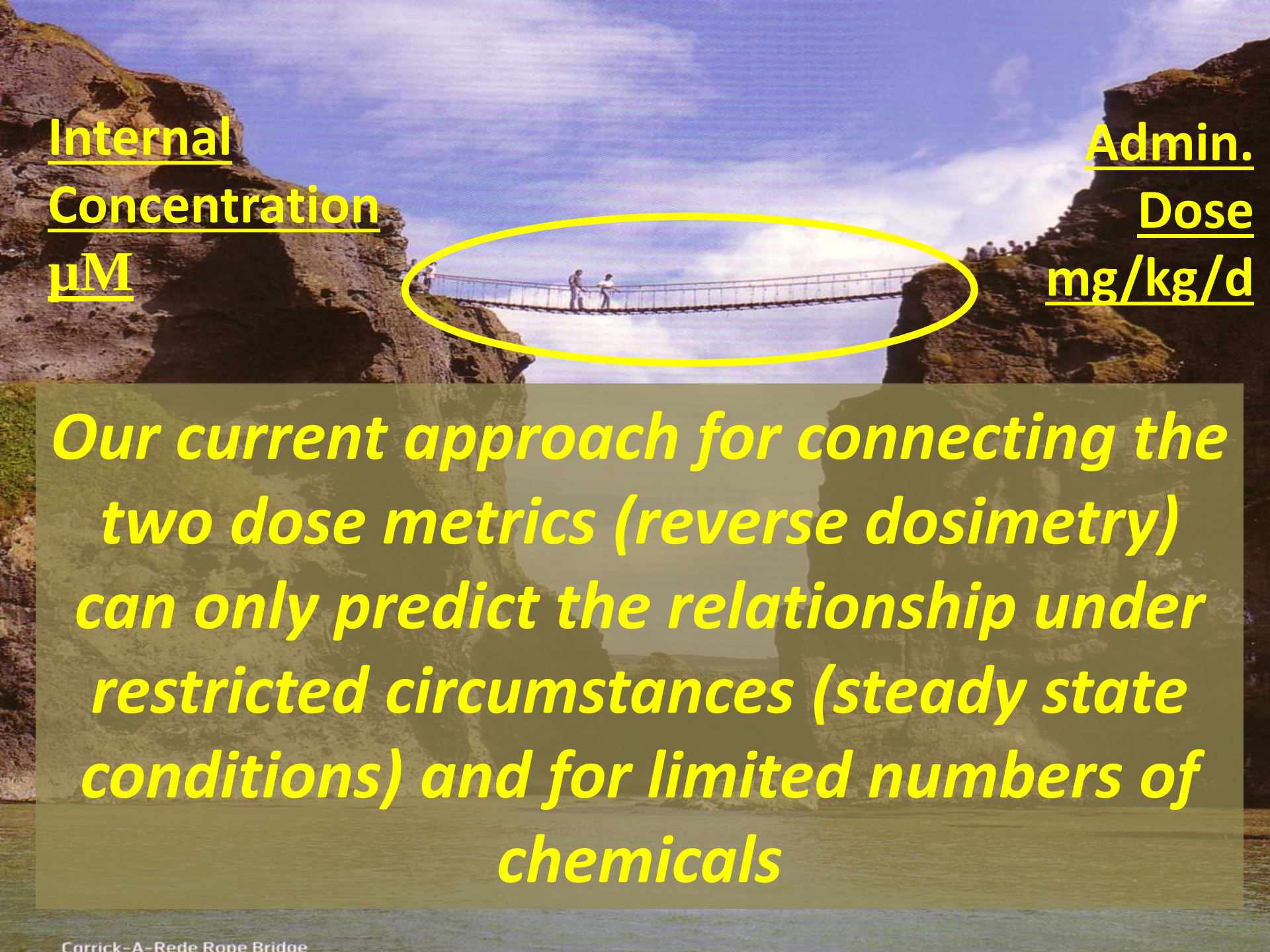

Internal Concentration µM
Admin. Dose mg/kg/d
Our current approach for connecting the two dose metrics (reverse dosimetry) can only predict the relationship under restricted circumstances (steady state conditions) and for limited numbers of chemicals
Carrick-A-Rede Rope Bridge

Goals of Project

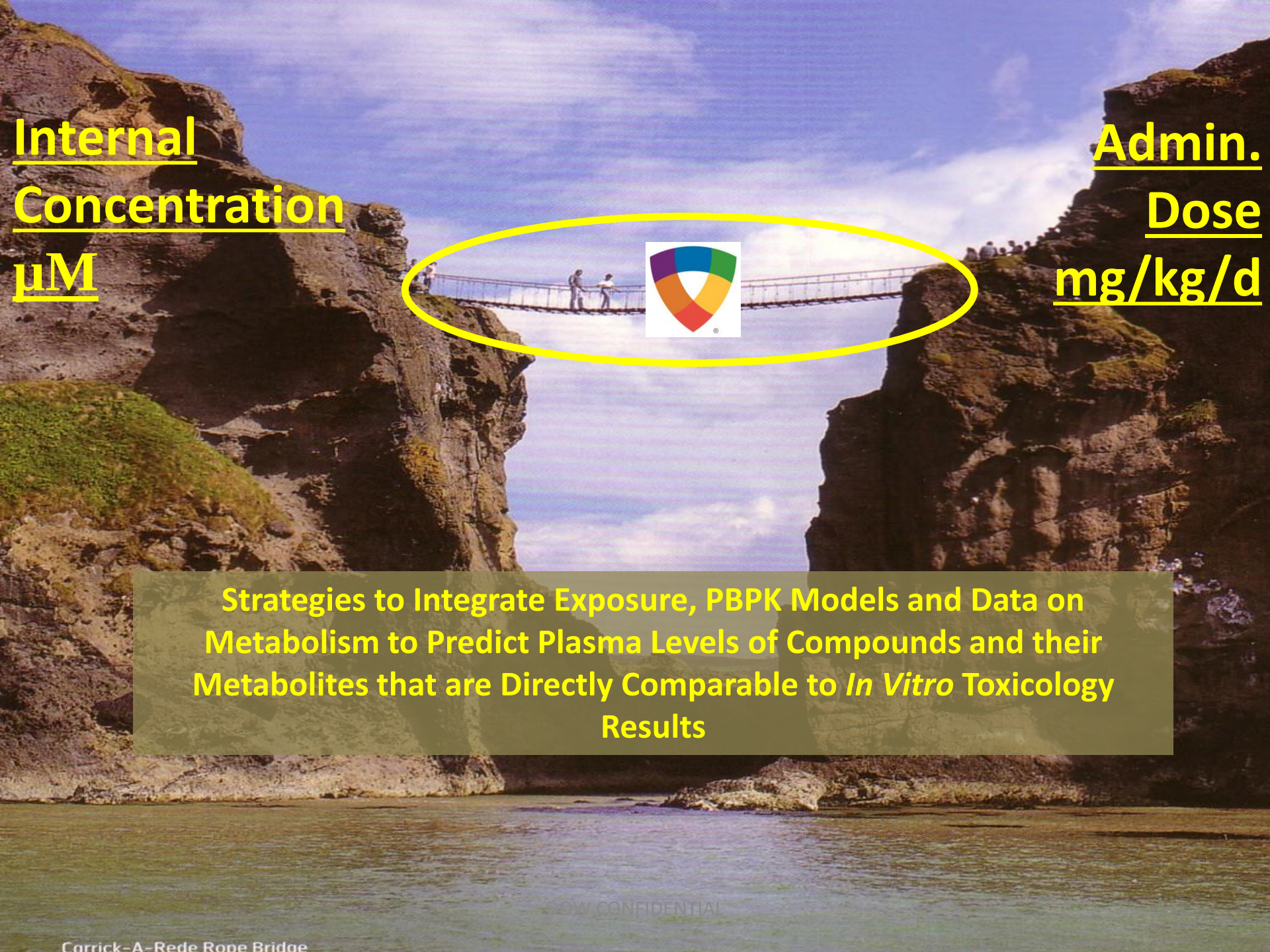
- Goal 1:
  - Tiered high throughput tools
  - Predict the time course of blood concentrations
- Goal 2: Metabolism in HTS risk assessments
  - Which chemicals
  - Assays

Resources

- Government, academia, and industry recognize the need to better connect internal and administered doses.
- Publications.
- RISK21 IVIVE subgroup.
- Structure-based predictions of metabolism and parameters required by PK and PBPK models are becoming more available.

Benefits

- Improved HTS risk assessments
  - More effective screening out low concern uses of specific chemicals
  - Ability to identify chemical-specific critical data for performing higher-tiered assessments
- Coordinate and establish best practices for the various groups working in this area.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