

# uncertainties using genomic information for evidence-based regulations

pasky pascual

uncertainty quantification in scientific computing  
august, 2011

Pulitzer Prize Winner

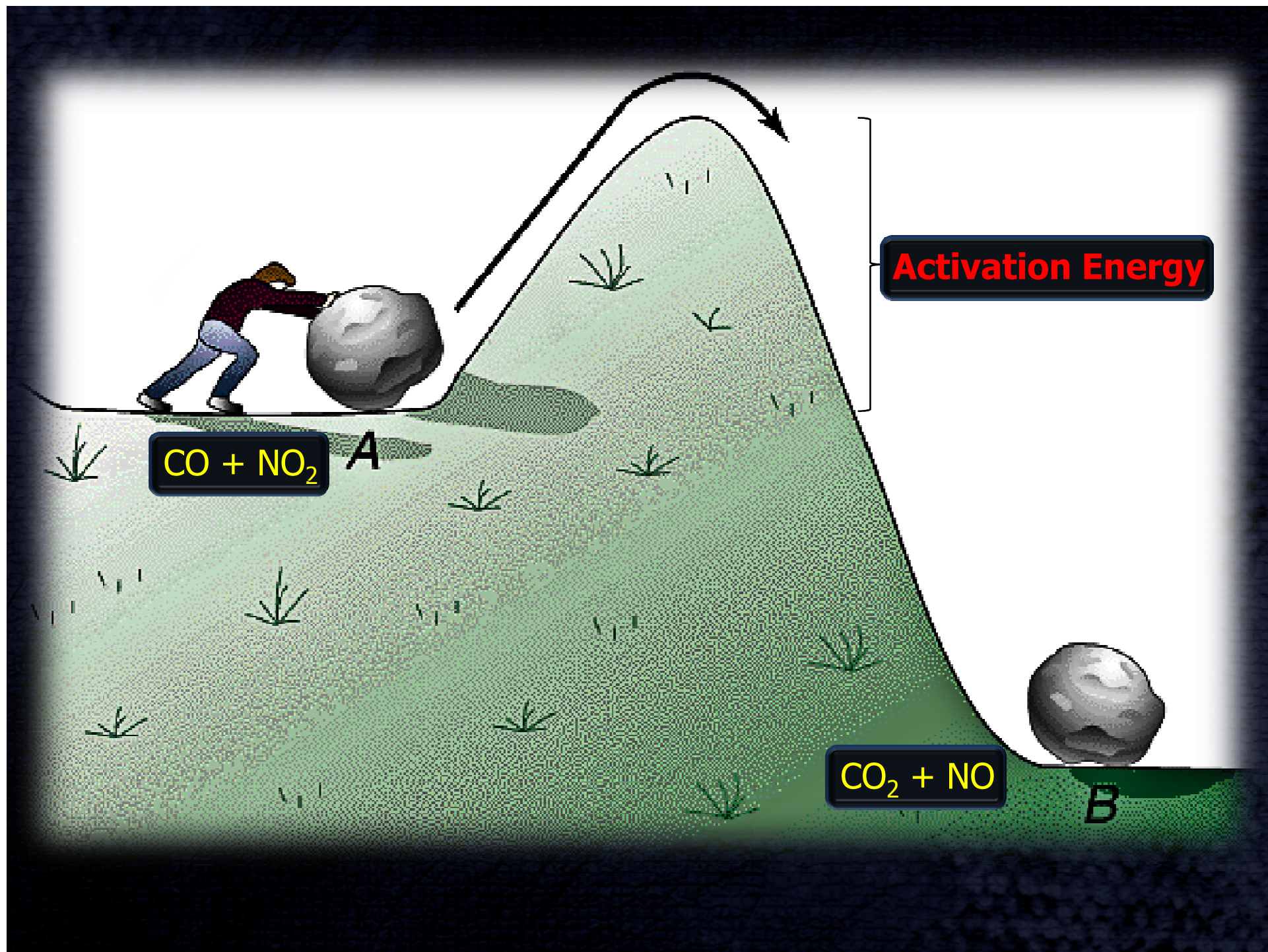


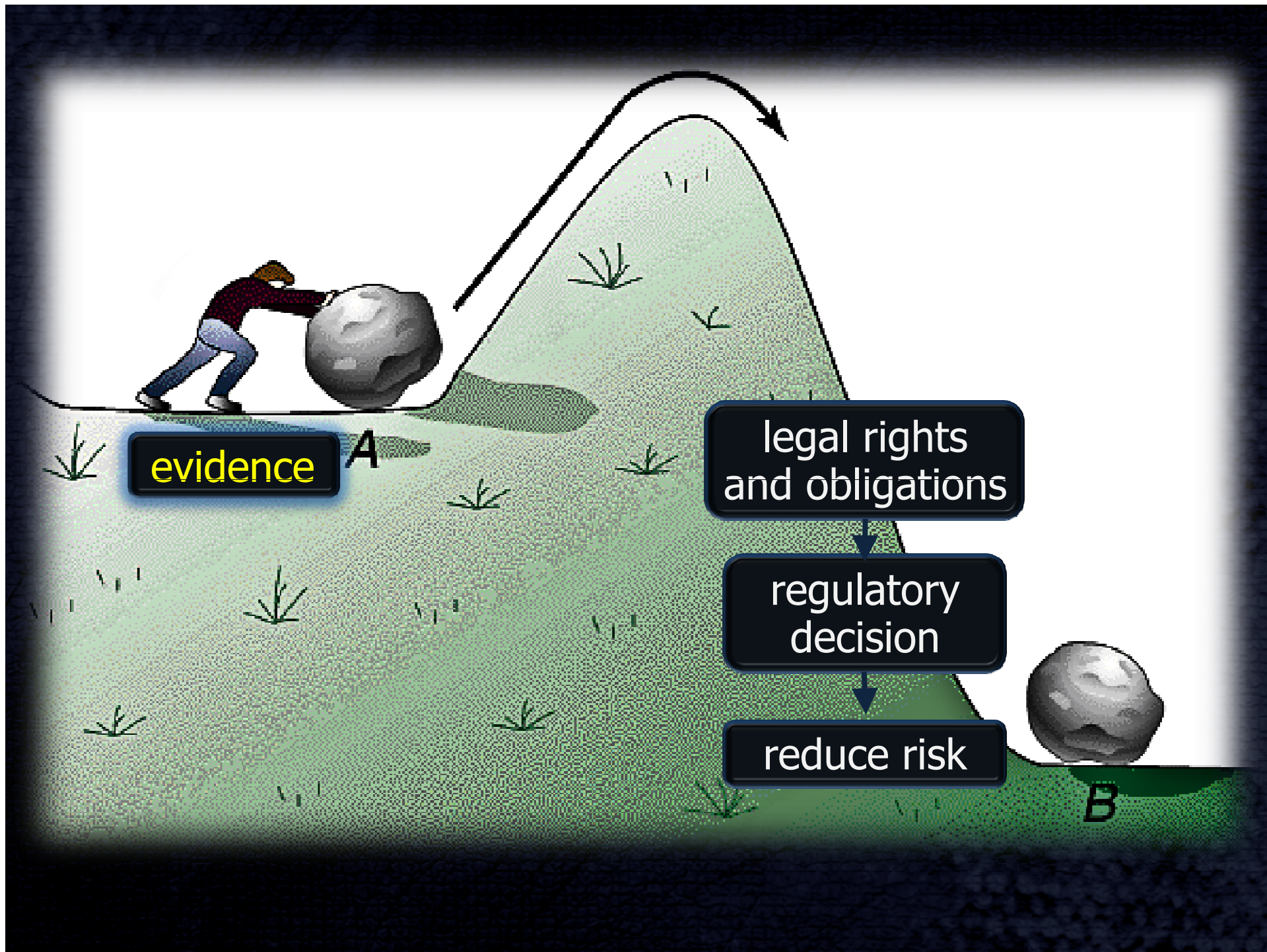
# GÖDEL, ESCHER, BACH:

||||| *an Eternal Golden Braid* |||||

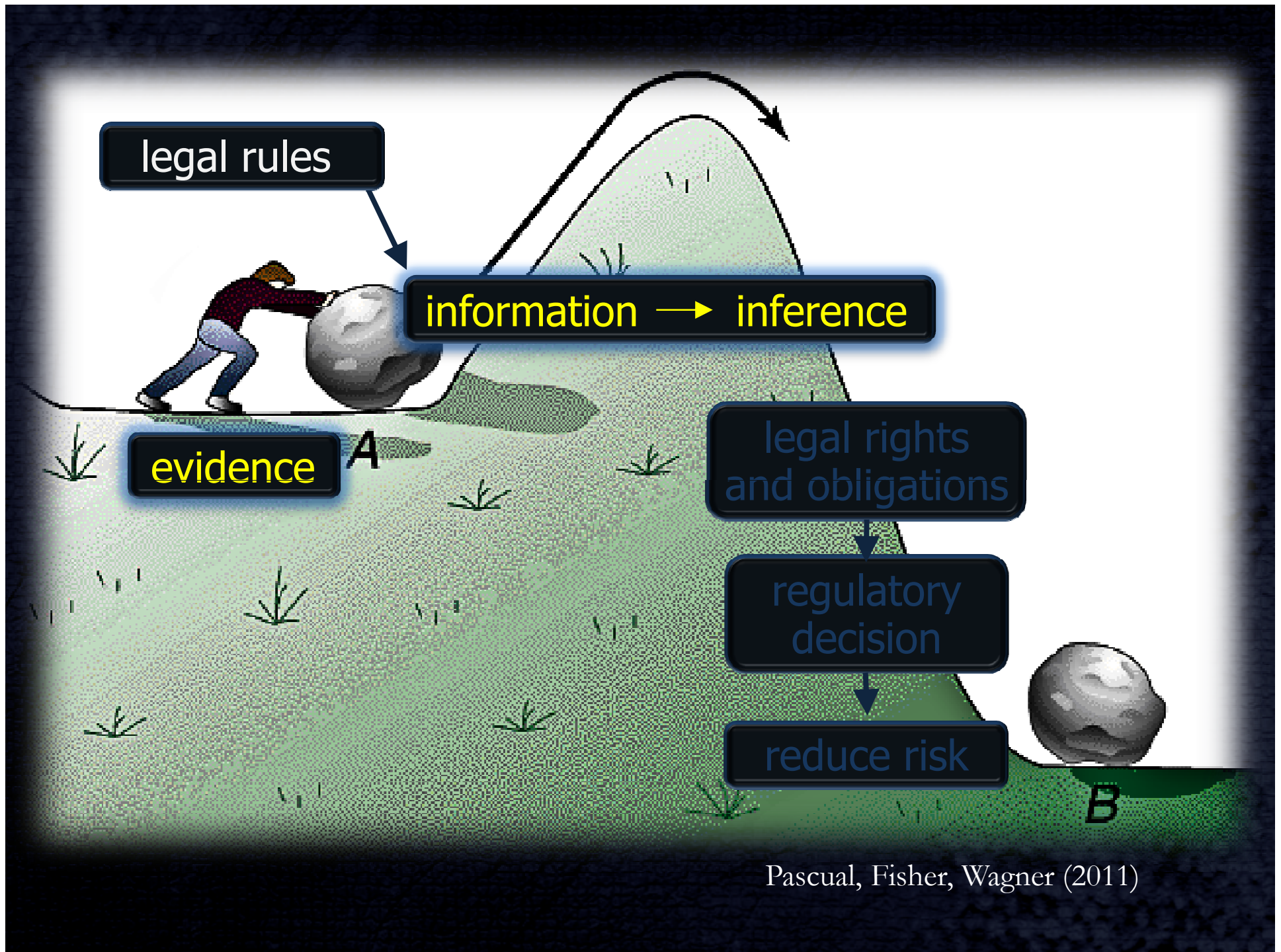
DOUGLAS R. HOFSTADTER











# evolution of FDA's evidentiary basis



**expert opinion**

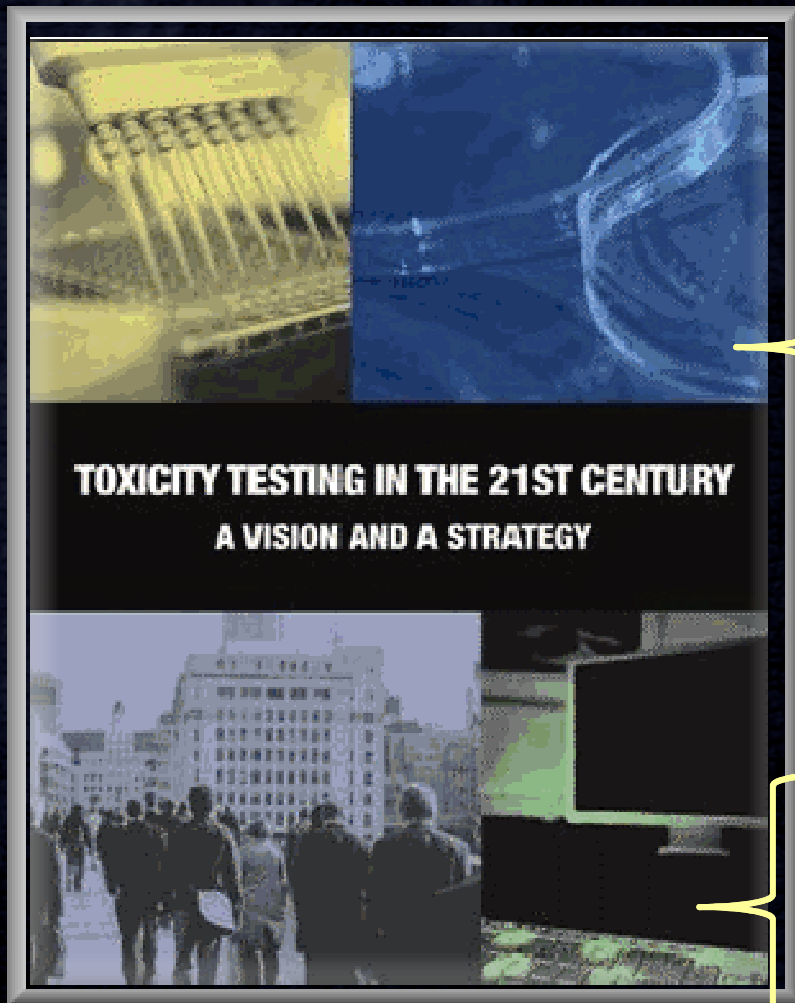


**randomized clinical trials**



**any and all information**





...toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could

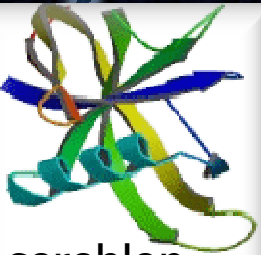
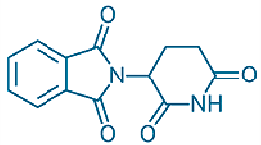
transform toxicity testing from a system based on **whole-animal testing** to one founded primarily on **in vitro methods**

that evaluate changes in biologic processes using cells, cell lines, or cellular components...

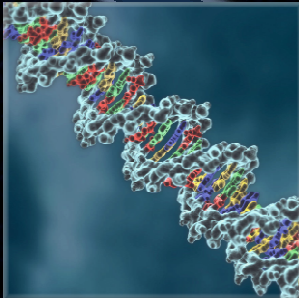
**toxicity pathways**

Cellular response pathways that, **when sufficiently perturbed**, are expected to result in adverse health effects...

thalidomide



cereblon



biology's central dogma





# risk information submitted to EPA

## multiple:

- chemicals
- bio endpoints
- dose levels
- dose durations

clofentazine  
CAS 74115-24-5

### NOTE DE SERVICE

SECURITY - CLASSIFICATION - DE SÉCURITÉ
OUR FILE — N / RÉFÉRENCE
YOUR FILE — V / RÉFÉRENCE
DATE July 27, 1988

SUBJECT  
OBJET

#### Pesticide Submission:

Clofentazine: 17/07/86, 26/08/86,  
17/7/87, 8/9/87, 15/12/87, 8/2/88, 23/6/88.

#### Name of Product:

Clofentazine miticide (Apollo)

#### Manufacturer/Distributor:

Nor-Am.

#### Previous Reviews:

13/03/86.

#### Existing Uses:

none

#### Proposed Uses:

on apples.

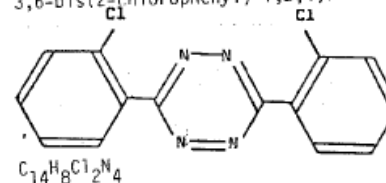
#### Requested Residue Limits:

1.0 ppm MRL.

#### Purpose of the Submission:

Toxicological data submitted in support of  
clofentazine registration.

3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine.



# alea iacta est



- $prob(\text{endpoints}) = \text{systematic} + \text{random variability}$
- $prob(E_1, E_2, E_3, E_4, E_5, E_6)$

↑ link function

$(W_1, W_2, W_3, W_4, W_5, W_6) = \text{latent variables}$

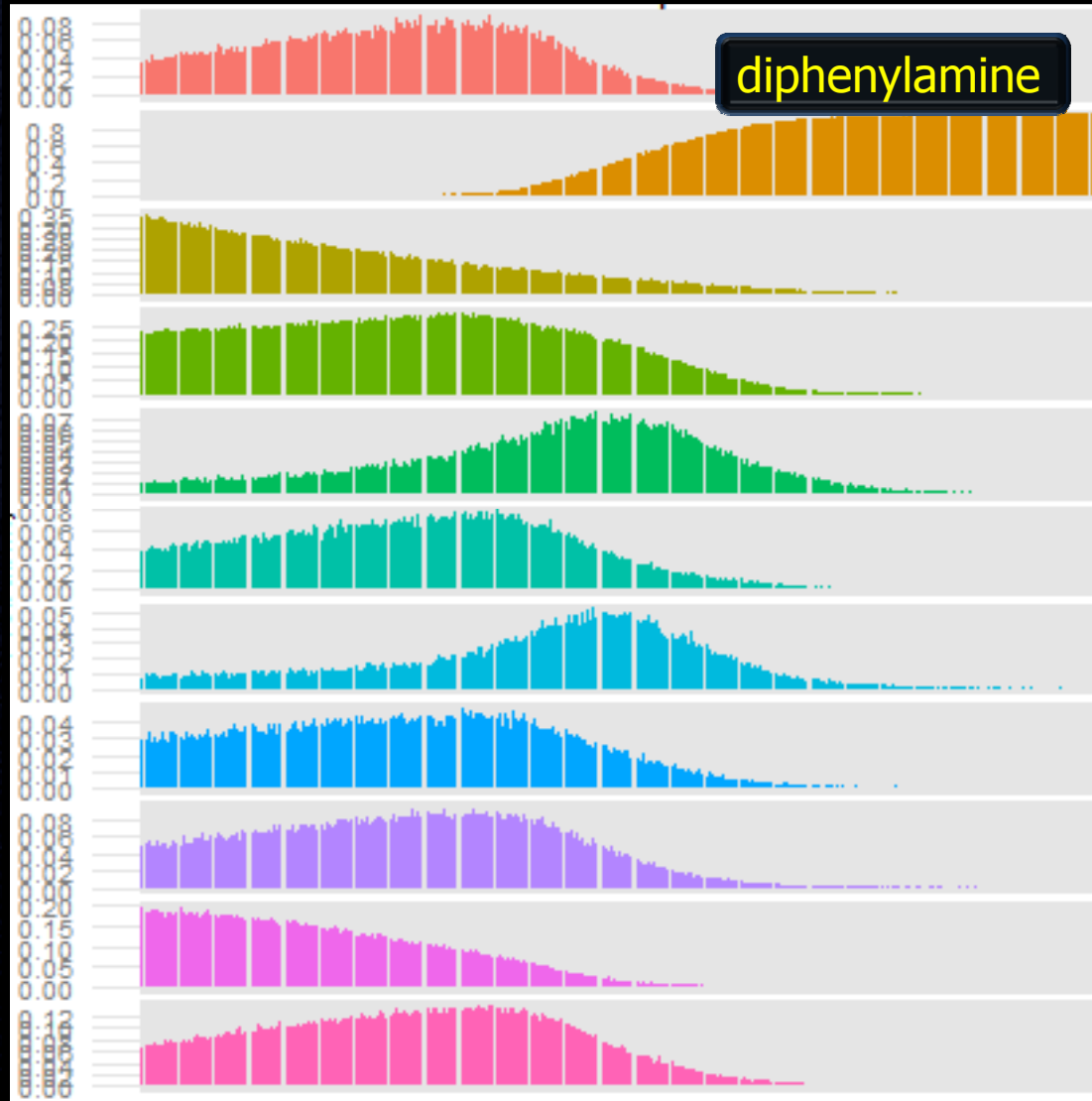
where  $W = f(X\beta + \varepsilon)$

↑  
and  $X = (\text{dose}, \text{duration}, \text{gender}, \text{dose} \times \text{duration})$



# simulated response for males, 24 month duration

prob



diphenylamine

Body Weight//In-Life Observations

Clinical Chemistry//Pathology (Clinical)

Clinical Signs//In-Life Observations

Hematology//Pathology (Clinical)

Kidney//Organ Weight

Kidney//Pathology (Non-neoplastic)

Liver//Organ Weight

Liver//Pathology (Non-neoplastic)

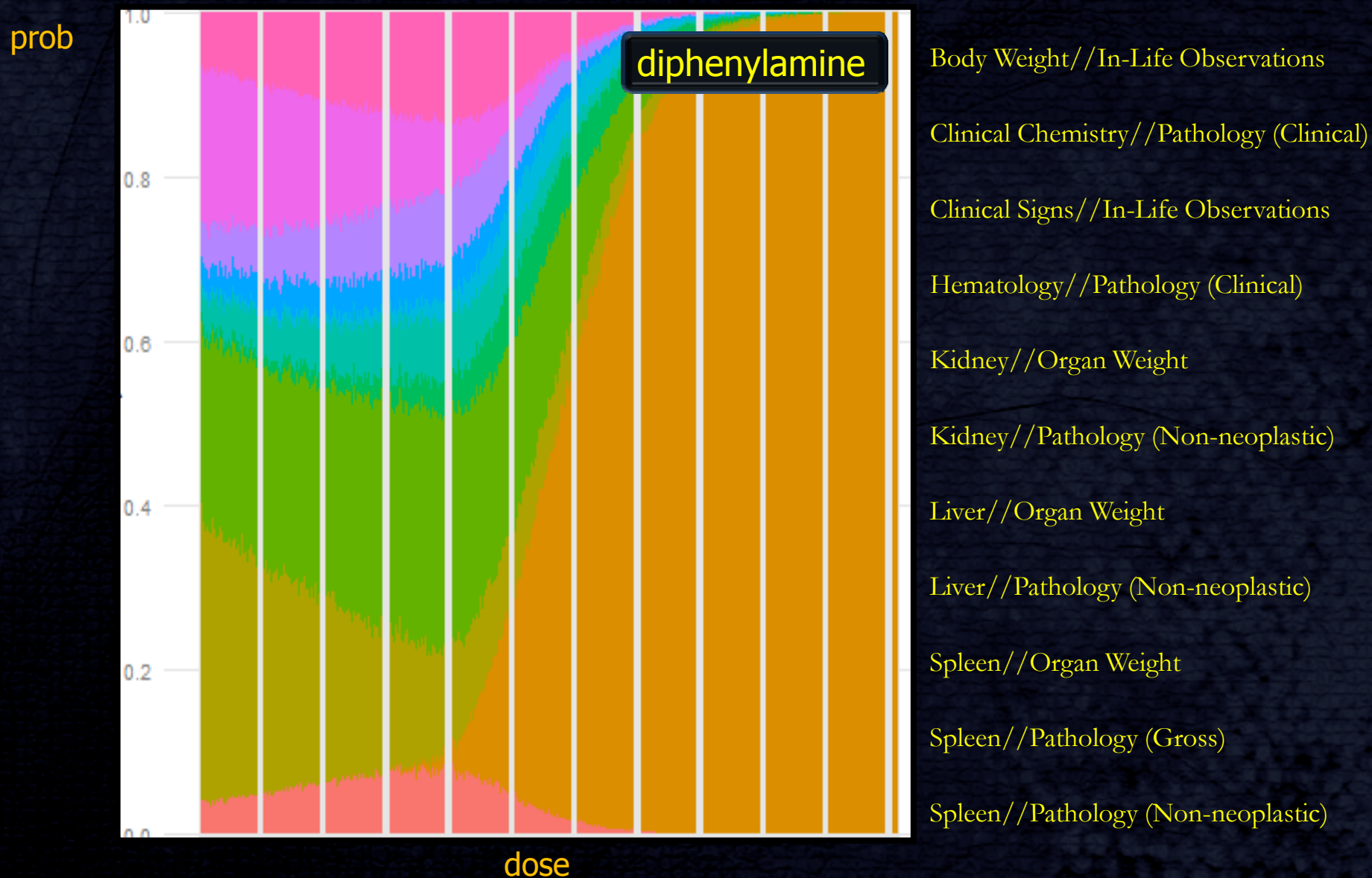
Spleen//Organ Weight

Spleen//Pathology (Gross)

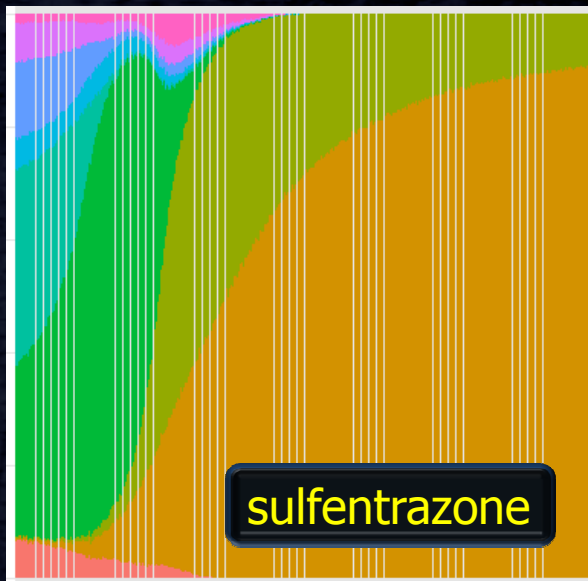
Spleen//Pathology (Non-neoplastic)

dose

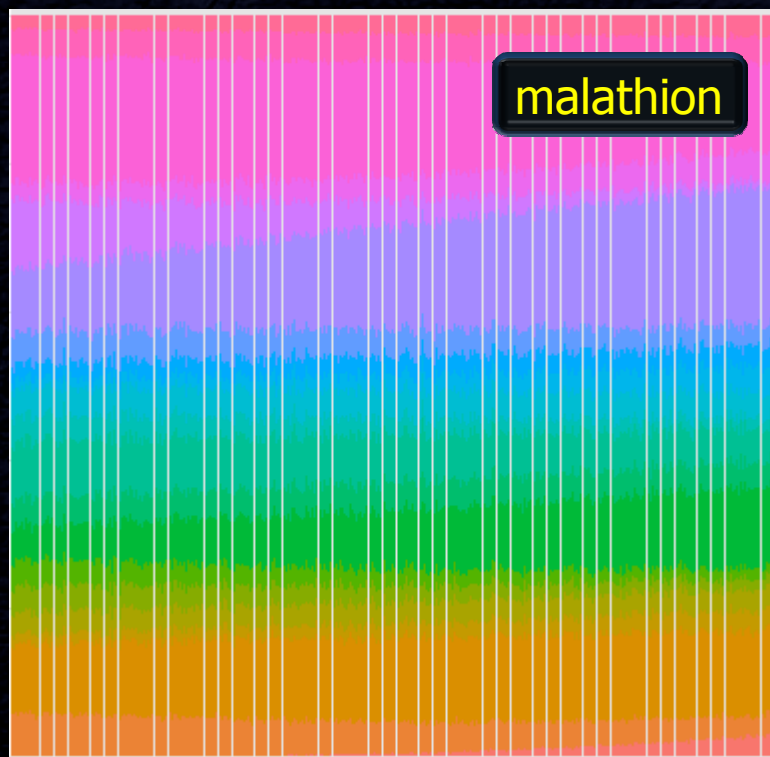
# bio profile: endpoints + $prob(\text{endpoints})$ as $f(\text{dose})$







Blood//Pathology (Non-neoplastic)  
 Body Weight//In-Life Observations  
 Clinical Signs//In-Life Observations  
 Hematology//Pathology (Clinical)  
 Kidney//Pathology (Non-neoplastic)  
 Liver//Pathology (Non-neoplastic)  
 Lung//Pathology (Non-neoplastic)  
 Spleen//Organ Weight  
 Spleen//Pathology (Non-neoplastic)



Body Weight//In-Life Observations  
 Bone Marrow//Pathology (Non-neoplastic)  
 Clinical Chemistry//Pathology (Clinical)  
 Clinical Signs//In-Life Observations  
 Eye//Pathology (Non-neoplastic)  
 Harderian Gland//Pathology (Non-neoplastic)  
 Heart//Pathology (Non-neoplastic)  
 Hematology//Pathology (Clinical)  
 Kidney//Organ Weight  
 Kidney//Pathology (Non-neoplastic)  
 Lacrimal Gland//Pathology (Non-neoplastic)  
 Liver//Organ Weight  
 Liver//Pathology (Non-neoplastic)  
 Lung//Pathology (Non-neoplastic)  
 Lymph Node//Pathology (Non-neoplastic)  
 Nose//Pathology (Non-neoplastic)  
 Parathyroid Gland//Pathology (Non-neoplastic)  
 Spleen//Pathology (Non-neoplastic)  
 Stomach//Pathology (Non-neoplastic)  
 Thyroid Gland//Organ Weight  
 Thyroid Gland//Pathology (Non-neoplastic)

## clusters of bio profiles

malathion

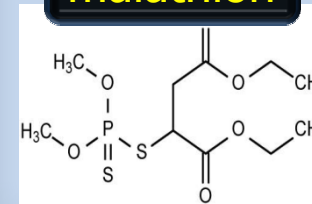
flufenacet

sulfentrazone

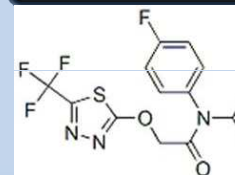
diphenylamine

## clusters of chem attributes?

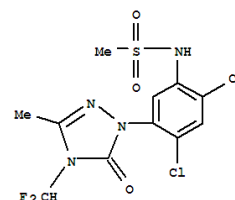
malathion



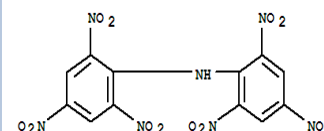
flufenacet



sulfentrazone



diphenylamine



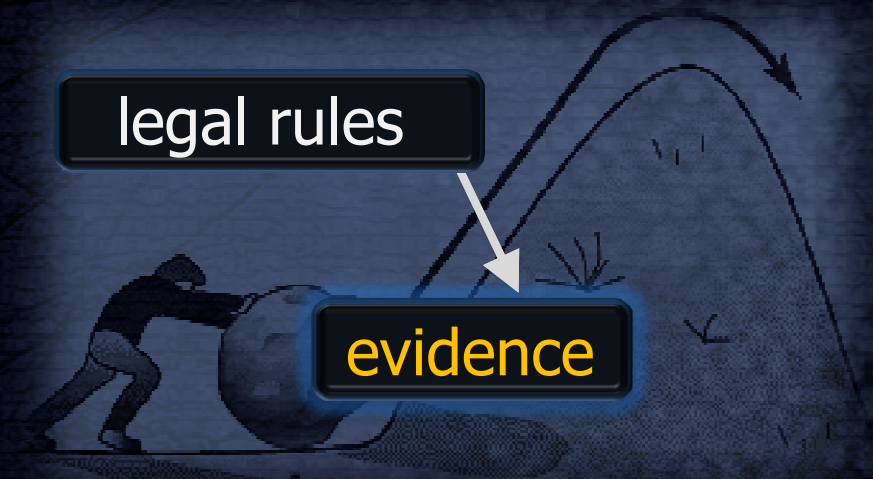




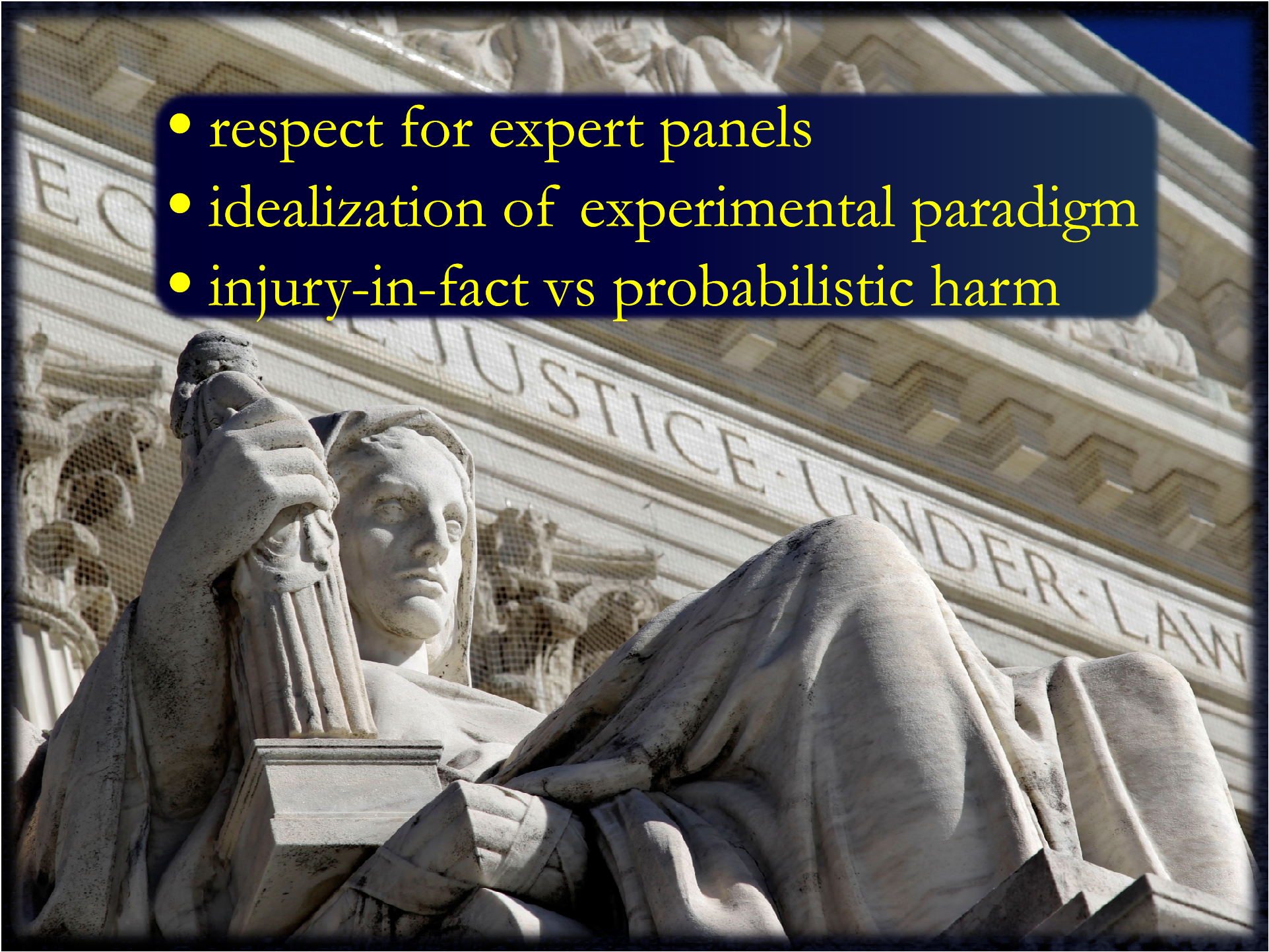
- use best available science
- provide a rational basis



arbitrary and capricious actions  
run counter to the evidence





- 
- A photograph of a classical statue of Lady Justice, blindfolded and holding a scale of justice, positioned in front of a building. The building's facade features the inscription "EQUITY UNDER LAW" in large, carved letters. The statue is made of light-colored stone and is shown from the waist up, seated. The background shows the architectural details of the building, including columns and carvings.
- respect for expert panels
  - idealization of experimental paradigm
  - injury-in-fact vs probabilistic harm



[epa.gov/ncер/rfa/2011/2011\\_star\\_comptox.html](http://epa.gov/ncер/rfa/2011/2011_star_comptox.html)



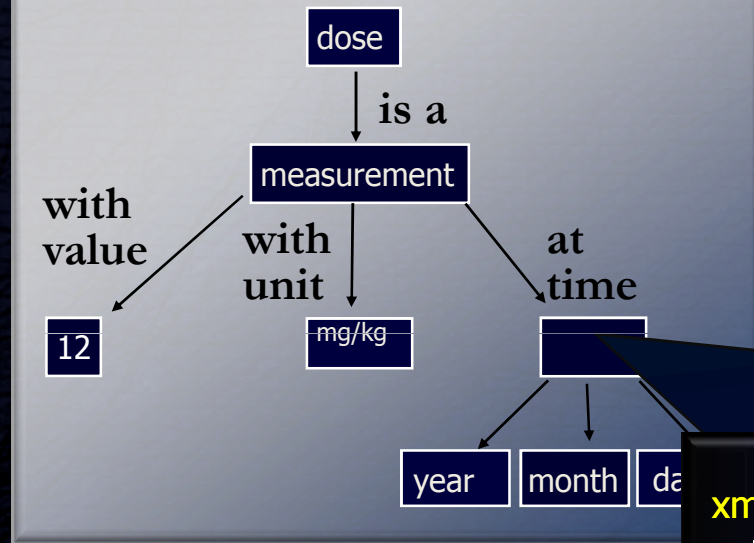
evidence

information → inference









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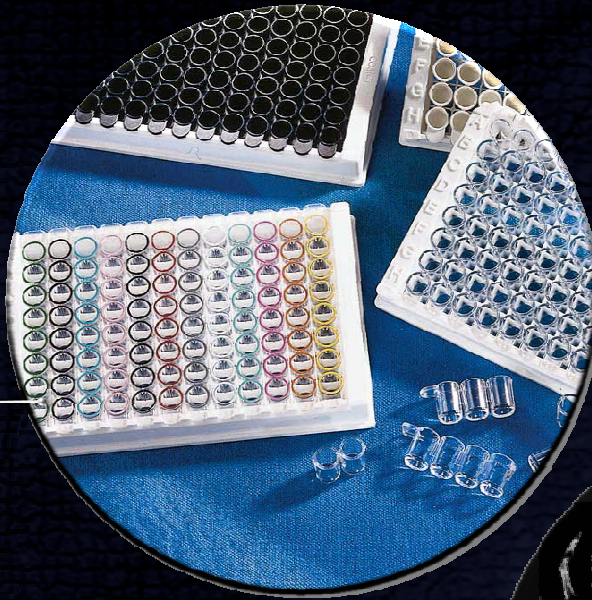
<owl:Class rdf:ID="Day">



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Pascual (2009)



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