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A Review of Data Fusion Methodology & Applications

Dose Response & Human Health Risk Assessment

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OpenTox InterAction Meeting
Innovation in Predictive Toxicology
In Vitro and In Silico Modelling, Applications, REACH, Risk Assessment
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Technical University of Munich, Germany

Canada

Disclaimer:

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Science and Decisions (NAS 2009) short term (2-5 years) and long term (10 yrs) recommendations towards a unified approach to Dose Response Assessment (Toxicology)

- Over the next 5 years, the committee recommends that EPA further develop the issue of vulnerability by gathering data and developing a broad array of human-vulnerability information from the biomedical literature, focusing on diseases that are likely to interact with the MOAs of prevalent-exposure and high-priority chemicals (for example, pulmonary, cardiovascular, hepatic, and renal diseases and various cancers). This could involve working with clinicians, biochemists, epidemiologists, and other biomedical specialists to develop preclinical-disease biomarkers as upstream indicators of vulnerability to toxicant MOAs.

- The committee recommends computational research that applies systems-biology techniques to analyze how -omics end points might inform the development of distributions outlined in Table 5-1. For example, analyzing data from high-throughput screens with genomics end points may result in interpretable upstream indicators of disease vulnerability. The biochemical processes that lead to pathologic conditions or functional loss could be described by continuous parameters that may be suitable as disease biomarkers in the population. These approaches could also provide interpretable biochemical end points reflective of key steps in a toxicant's MOA.

Data Fusion Human Health Risk Assessment Framework (DF – HHRA)

Petroleum Hydrocarbon Examples:

- Benzene (C6H6 - Cancer End Point)
- F1 Hydrocarbons (C6-C10) - Complex mixture of Aliphatics and Aromatics; Neurotoxicity and other potential health effect end points)

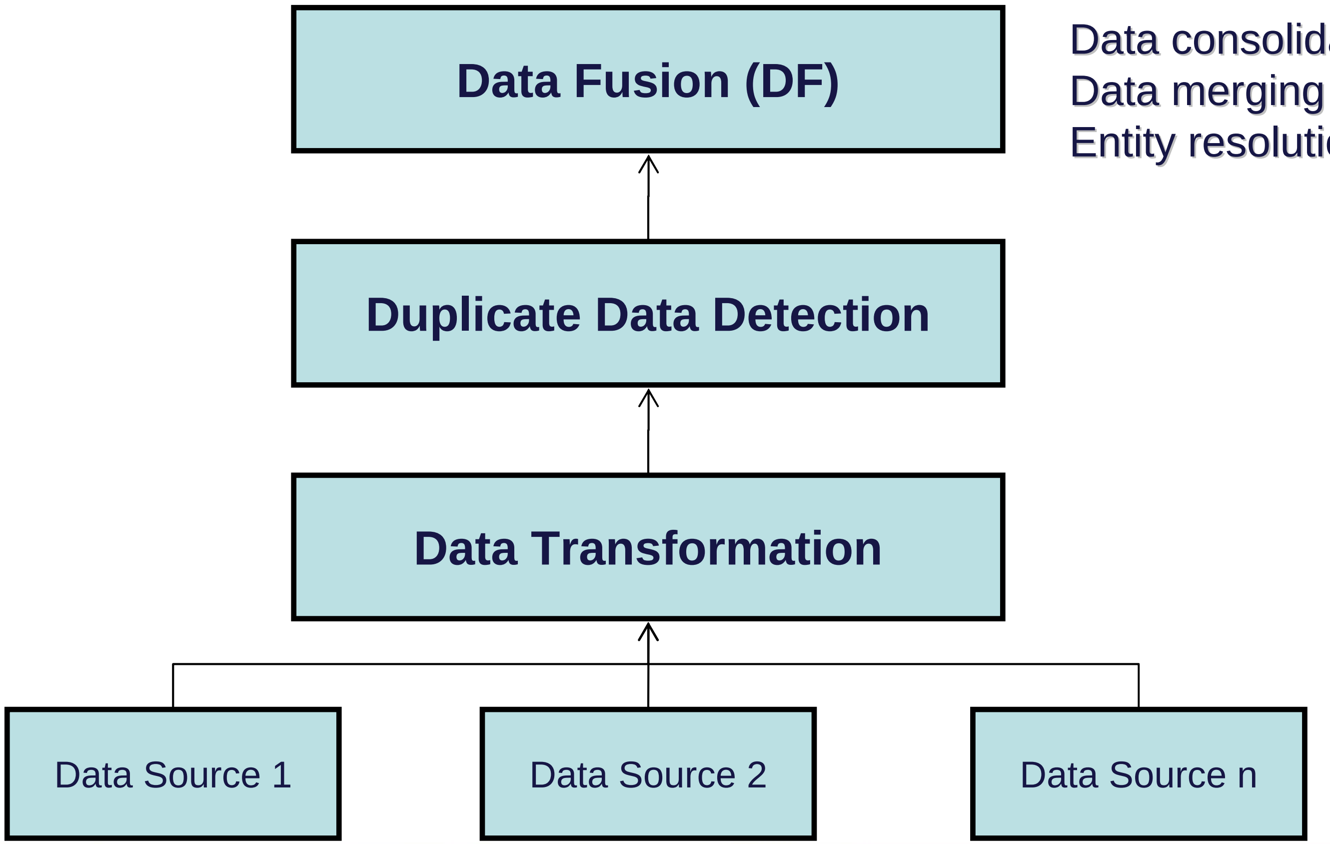
Mode and Mechanism of Action:

- Early and Late Key Events
- Regulatory Risk Assessment Applications
- Can we address data gaps by using Predictive Tox Tools and Data Fusion Tools?
- Can **SWIFT-DART*** help? Can we build such a platform and a tool for Public Health Risk Assessment Applications?
- What are some of the issues and challenges?

*** SWIFT DART is a work in progress to build a semantic web enabled informatics tool platform for the purpose of Dynamic Analysis of Risk Tools**

Data Integration

Data refinement and improving data quality
Additional inferences and increasing benefit from data
Improving understanding and decision



Data consolidation
Data merging
Entity resolution

Key Components of an HHRA

PROBLEM FORMULATION
- Chemicals of concern
- Receptors
- Pathways

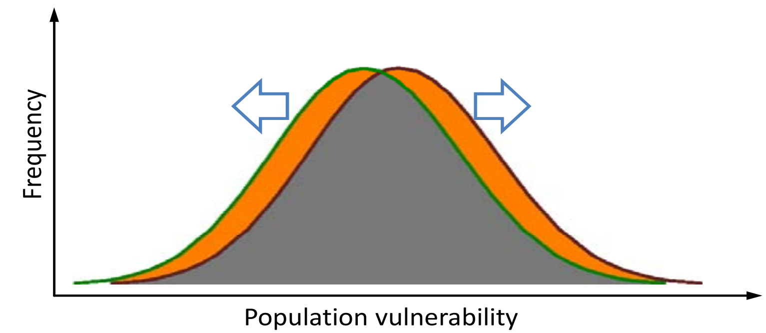
TOXICITY ASSESSMENT
- Dose/response

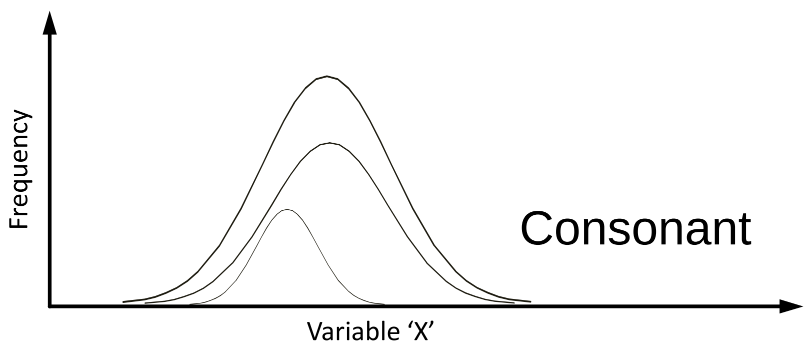
EXPOSURE ASSESSMENT
- Exposure calculations

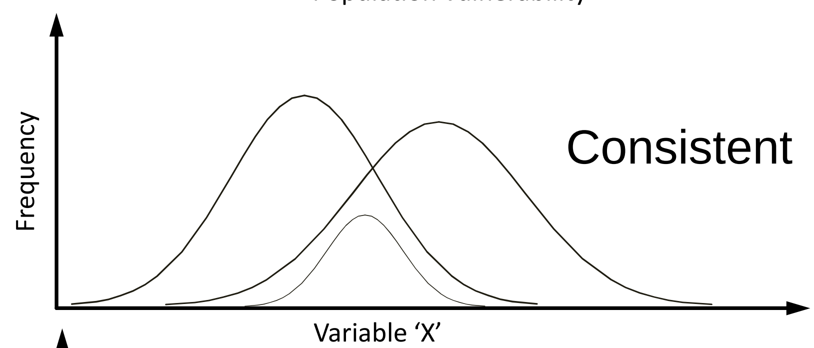
RISK CHARACTERIZATION
- Estimate of risk

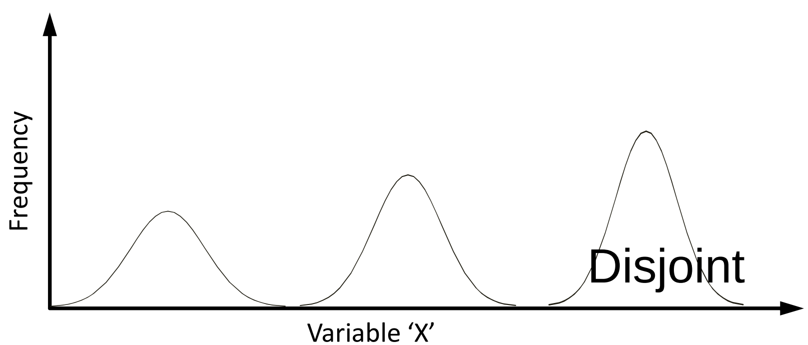
Conflict

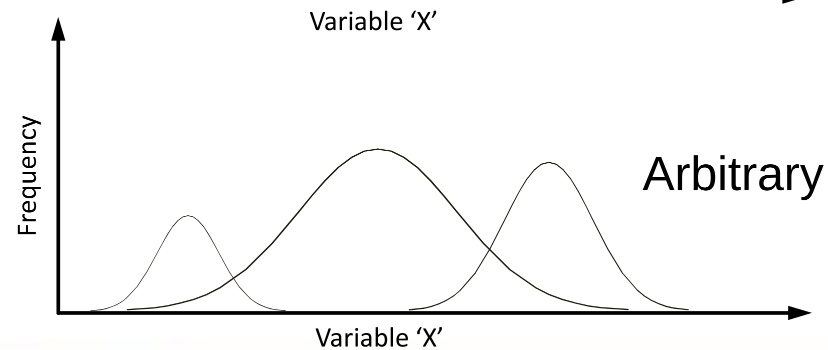
disagreement among data



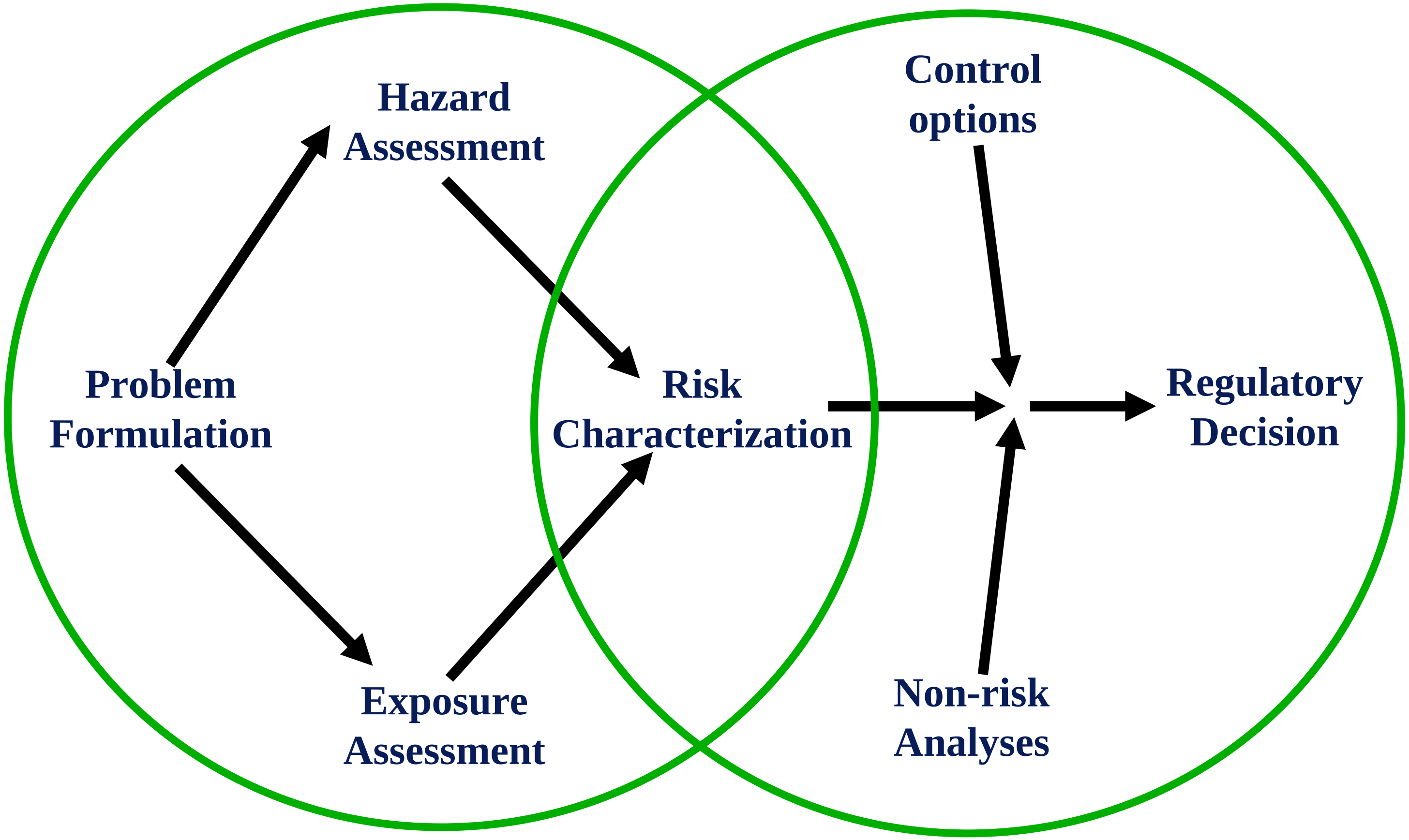




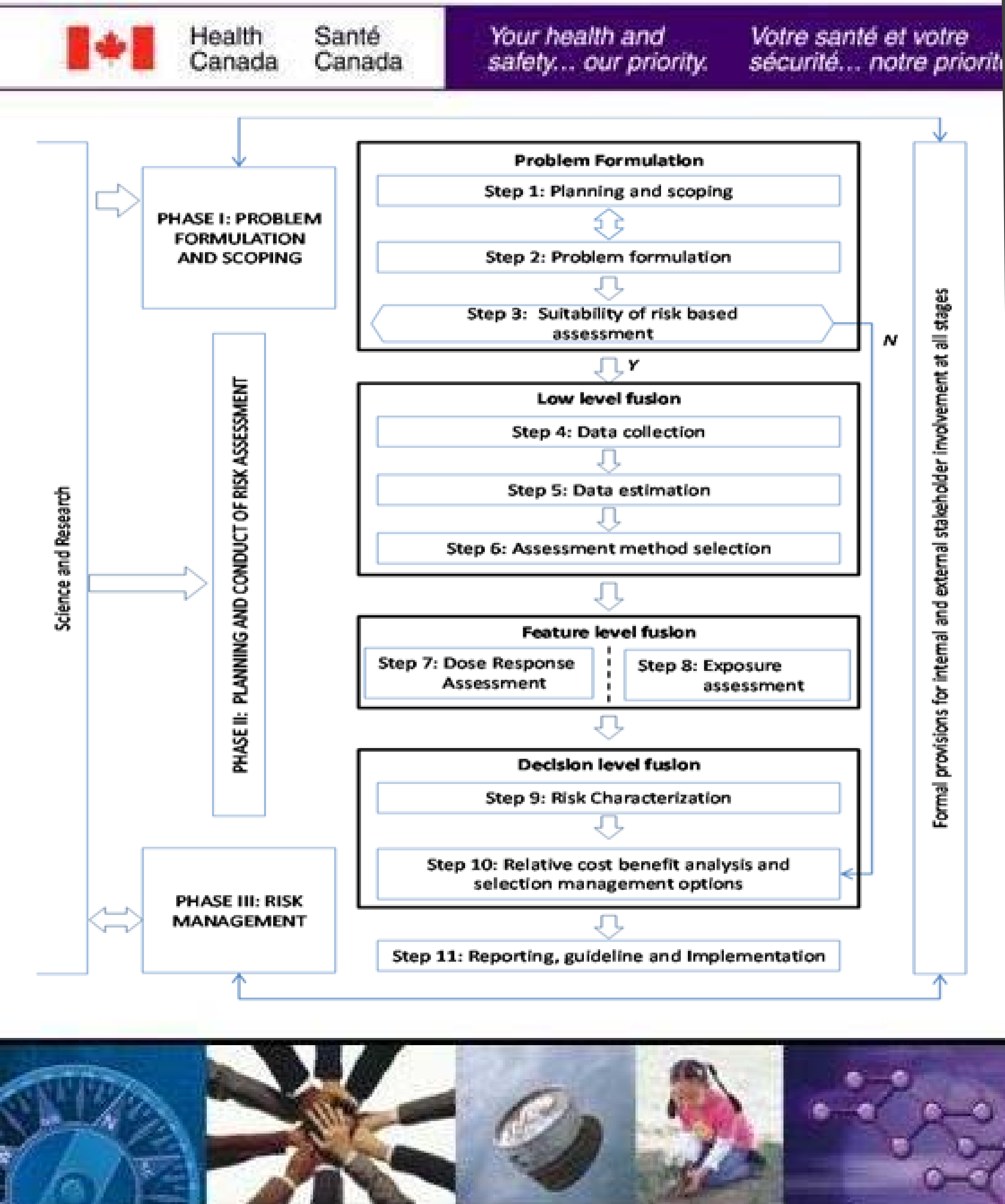


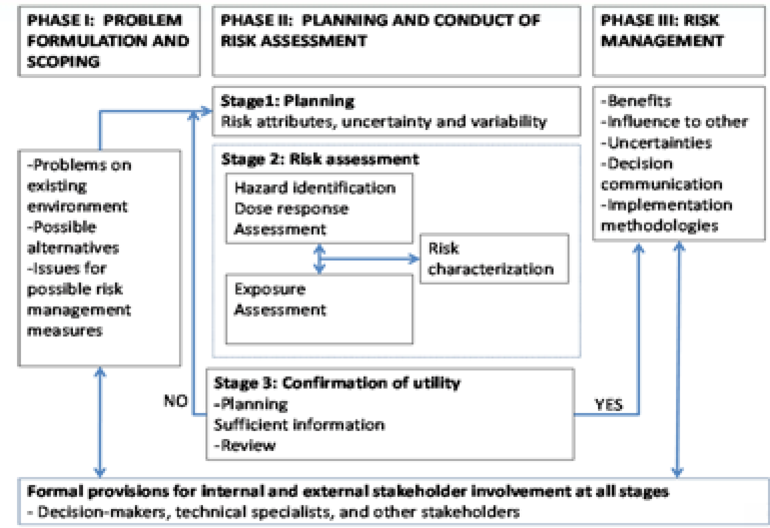


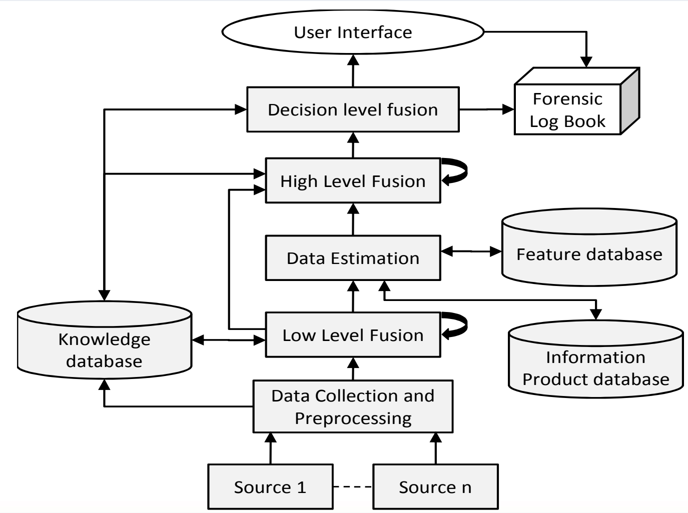
Risk Assessment *vs.* Risk Management



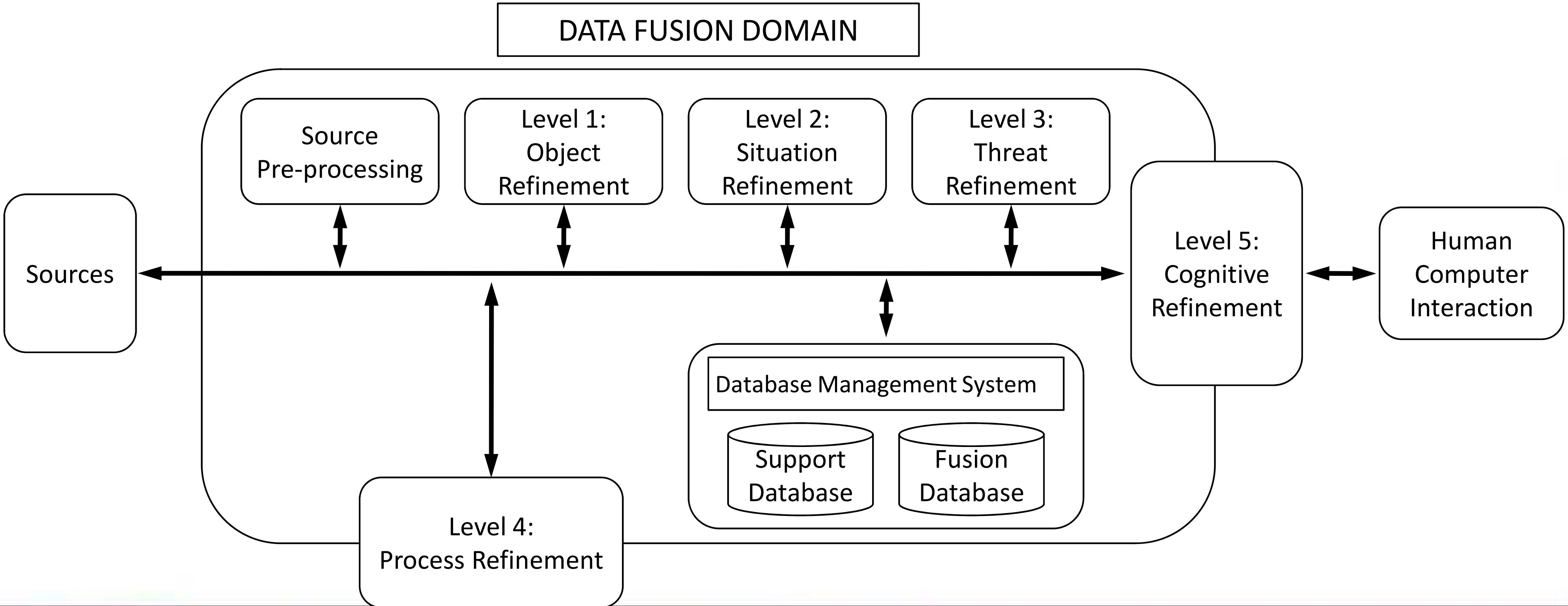
Proposed DF Framework



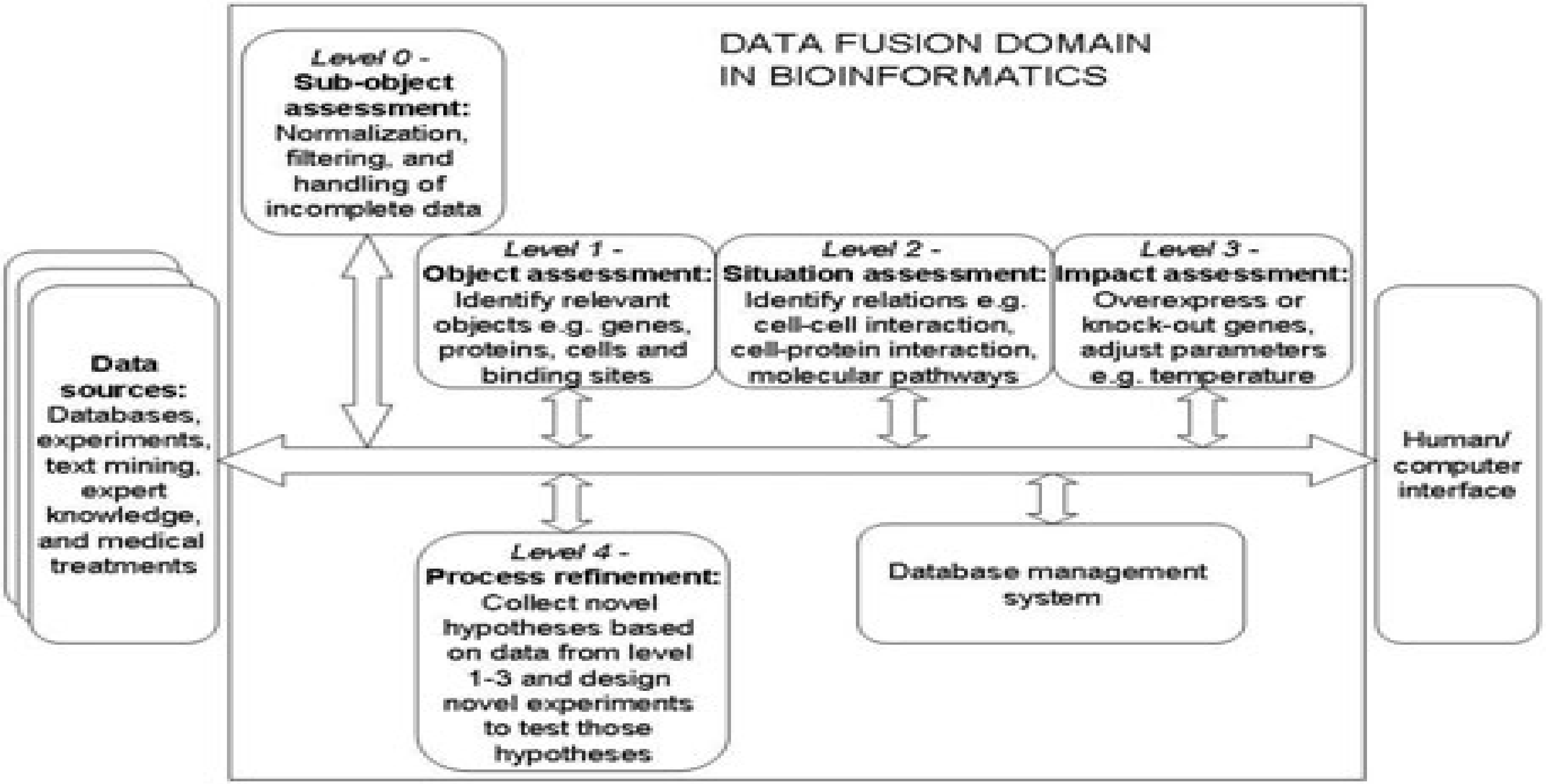




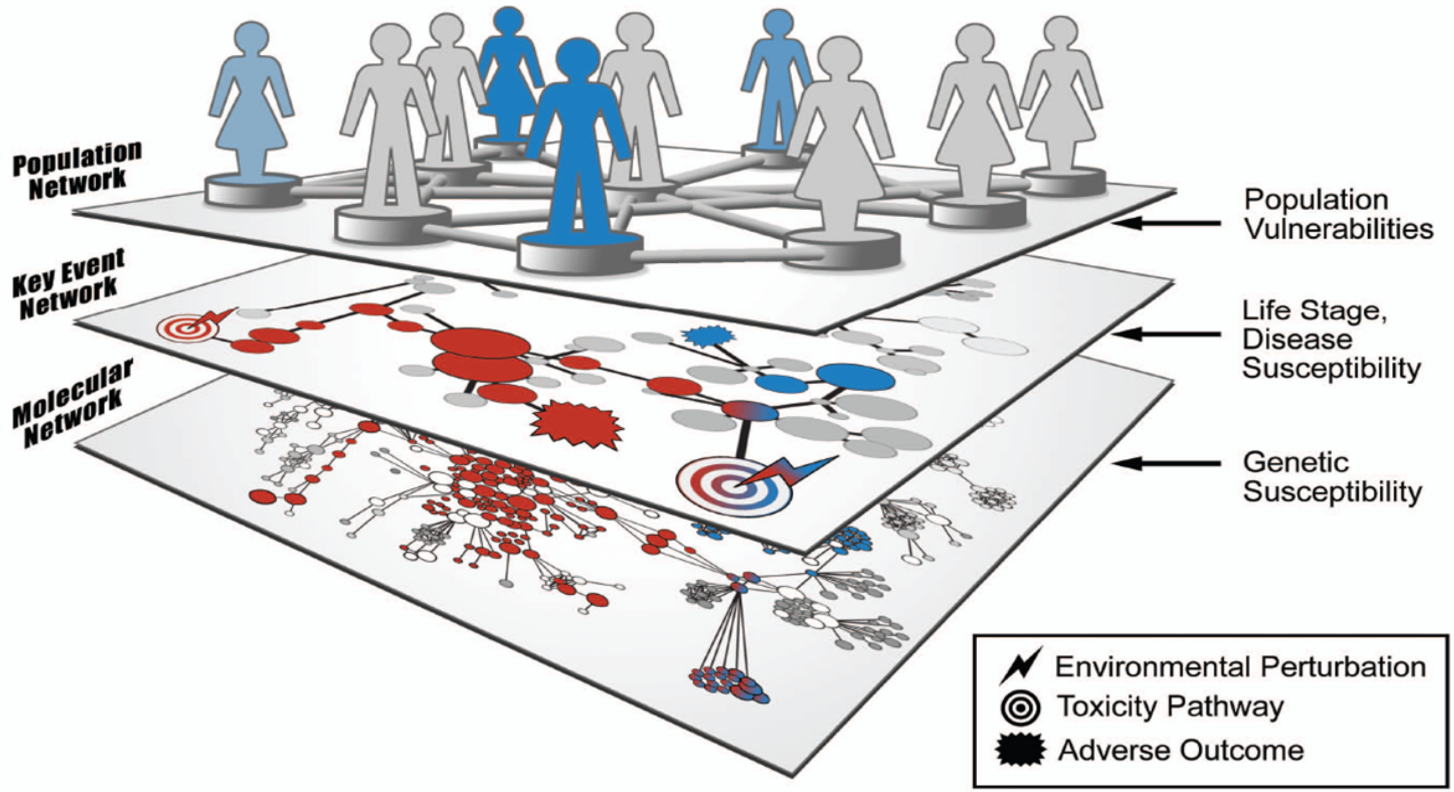
The Joint Directors of Laboratories (JDL) Data Fusion (DF) architecture



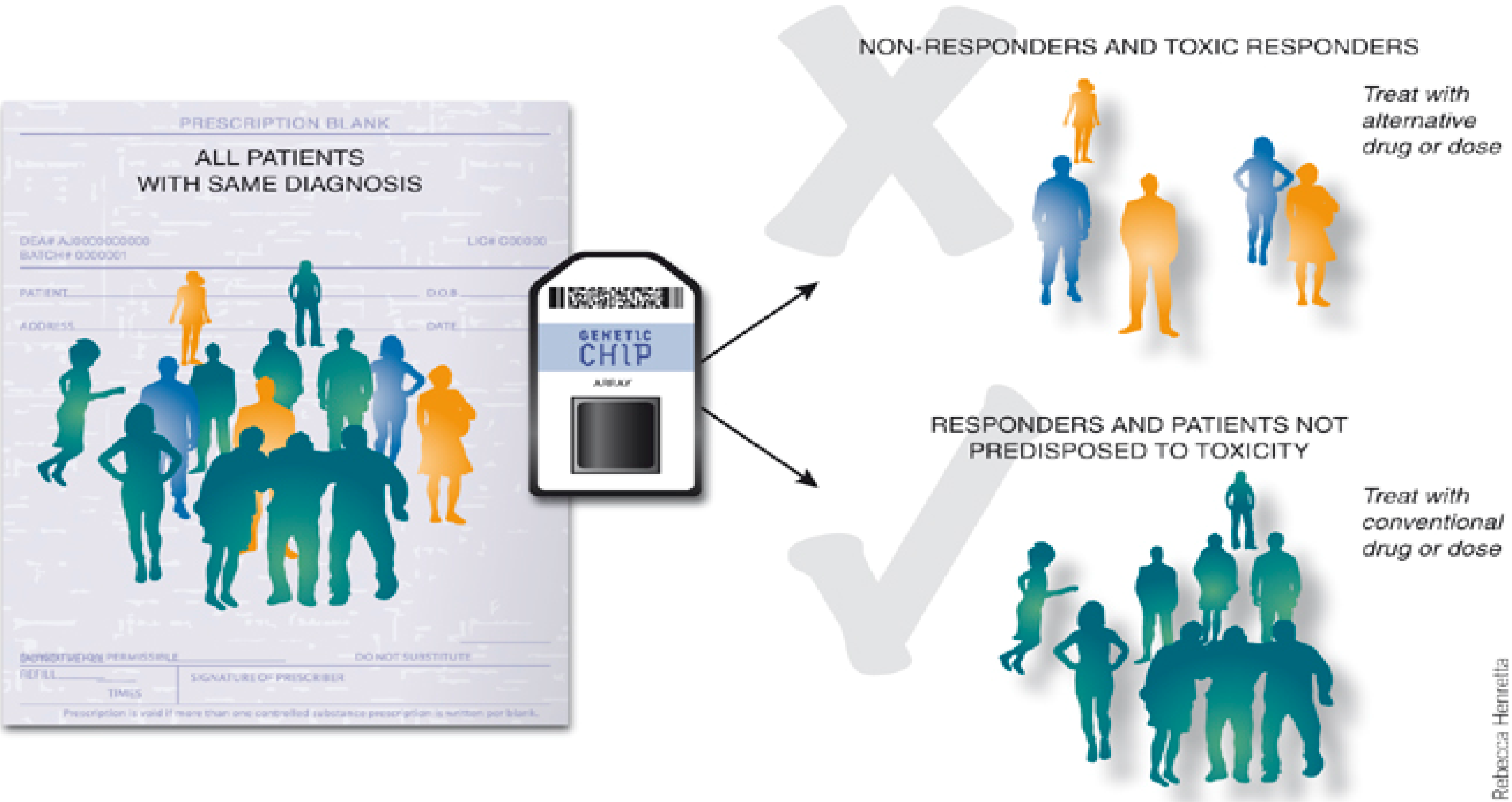
JDL Data Fusion Architecture Applied to Bioinformatics



Extent of Proposed Framework



Adapted from Edwards & Preston (2008), Tox Sci, 106(2):312-318


PRESCRIPTION BLANK
ALL PATIENTS
WITH SAME DIAGNOSIS
GENETIC
CHIP
ARRAY
NON-RESPONDERS AND TOXIC RESPONDERS
Treat with alternative drug or dose
RESPONDERS AND PATIENTS NOT PREDISPOSED TO TOXICITY
Treat with conventional drug or dose
Rebecca Henretta

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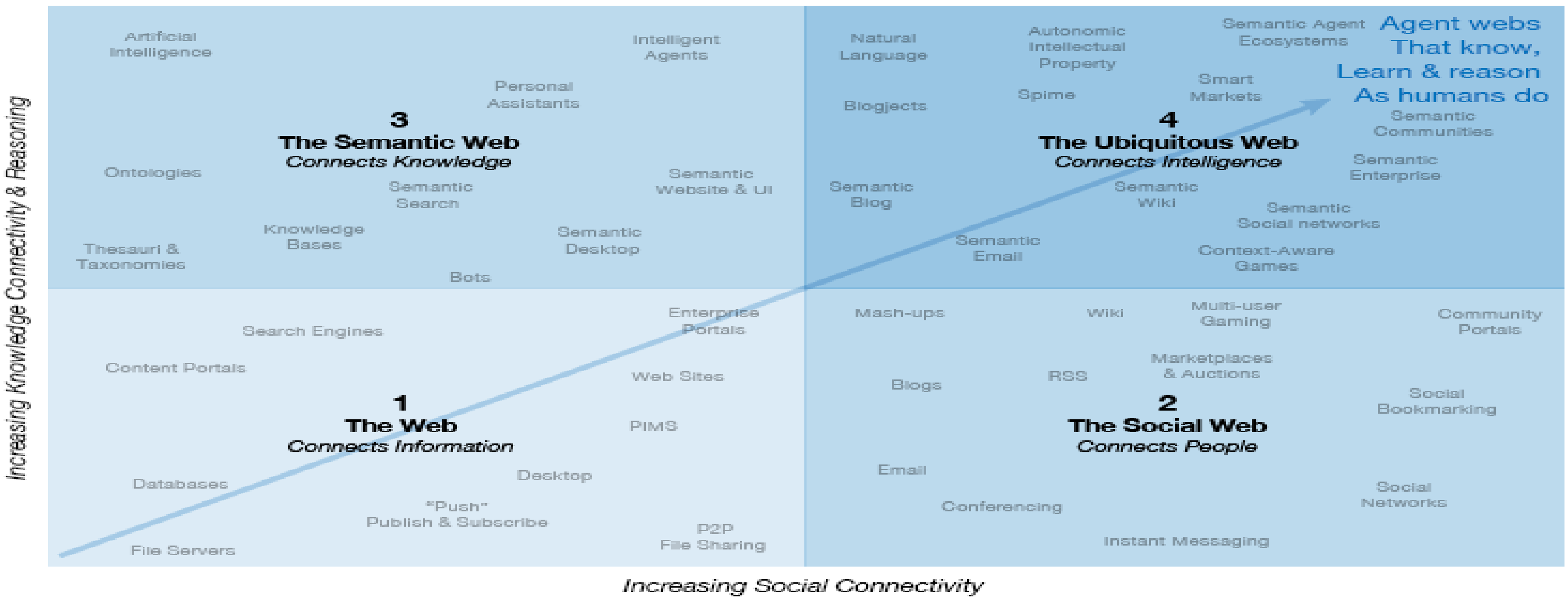
Below:
What is the Evolution of the Internet to 2020?



Source: Nova Spivak, Radar Networks; John Breslin, DERI; & Mills Davis, Project10X

Objective

Further Telescoping of the Evolution of Information Technology Revolution and Artificial Intelligence Application

Canada

DF Techniques

Fusion technique	Identity fusion	Feature-level fusion	Decision-level fusion
Cluster Analysis	X	X	
Classical Inference	X		X
Bayesian Inference	X	X	X
Dempster-Shafer Theory	X	X	X
Voting Strategies			X
Expert Systems	X	X	X
Logical Templates		X	X
(Adaptive) Neural Networks	X	X	X
Fuzzy Logic	X		X
Blackboard			X
Contextual Fusion			X
Syntactic Fusion			X
Estimation theory	X		
Entropy	X		
Figure of Merits	X		
Templates	X		
Generalized evidence processing theory			X

DF in the Context of HHRA

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Data fusion technique	Application area(s)	Methods	HHRA area	Sources
Statistical and kernel inference	Genomic data fusion	Kernel-based statistical-learning; different data types/formats are transformed into kernels; to combine kernels, it uses semi-definite programming to minimize the statistical loss function	TA	(Lanckriet, *et al.* 2004a)
	Transcription factor target gene prediction	Statistical inference coupled with additional sources	TA	(Xiaofeng *et al.* 2010)
	Biomedical data fusion	Optimization of the L_2-norm of multiple kernels	TA	(Yu *et al.* 2010)
Bayesian inference (BI)	Multi-study and multi-endpoint BMD	Combines mechanistically informed model results with empirical data to derive several endpoints; combines multi-endpoint BMDs to derive BMDL	TA	(Schmitt 2006)
	Wide-area assessment of UXO contamination	Generates PDFs of features extracted from survey maps, uses BI methods to combine features with auxiliary information and data quality features	EA	(Johnson *et al.* 2009)
	Syndrome surveillance	Uses Bayesian conditional autoregressive (CAR) models to combine symptom data collected from a network for early outbreaks detection	TA	(Banks *et al.* 2009)
Dempster-Shafer theory (DST)	Risk assessment of water treatment	Transferable belief models (TBM) input diverse data such as fuzzy, interval probabilities and statistical data to produce a belief network		(Demotier *et al.* 2006)
	Drinking water quality (WQ)	Uses disjunctive operator for the interpretation of overall WQ in the distribution system and the development of a WQ index	EA	(Sadiq and Rodriguez 2005)
	Microbial water quality in distribution network	Four DST fusion rules are applied to fuse weak information from two microbial water quality data sources, results in four p-boxes	EA	(Sadiq *et al.* 2006)
	Prediction of breast cancer tumours	Fuses the outputs of multiple classifiers from different diagnostic sources	TA	(Raza *et al.* 2006)
Artificial neural networks (ANN)	Surface WQ estimation	Combines optical data and microwave data to estimate surface WQ	EA	(Zhang *et al.* 2002)
Fuzzy sets theory	Analysis of gene expression data	Transforms gene expression values into qualitative descriptors that are then evaluated using a set of heuristic rules	TA	(Woolf and Wang 2000)

TA: toxicity assessment and EA: exposure assessment

DF Techniques

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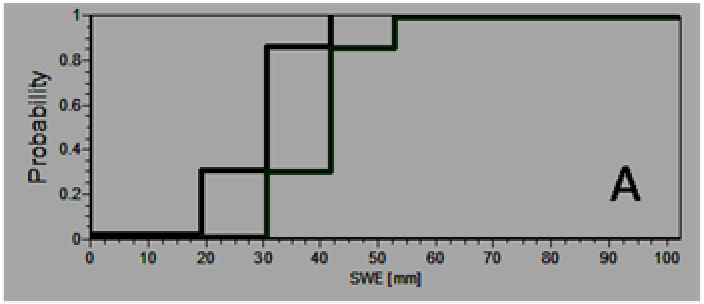
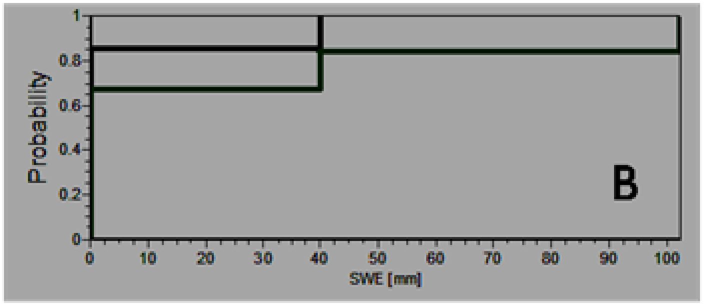
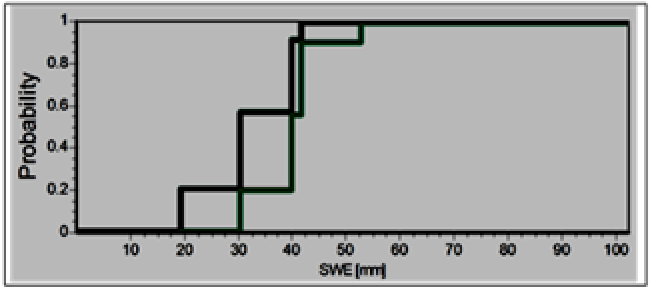
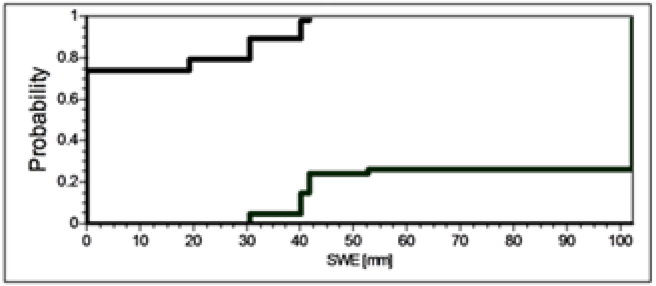




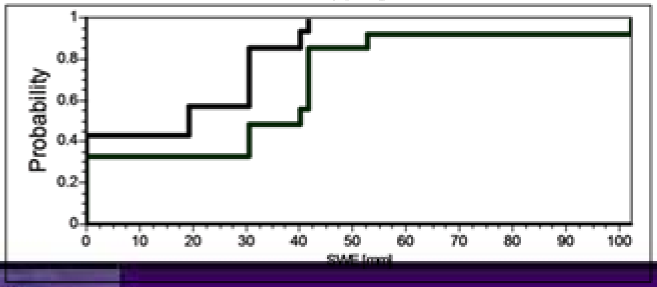
Dempster



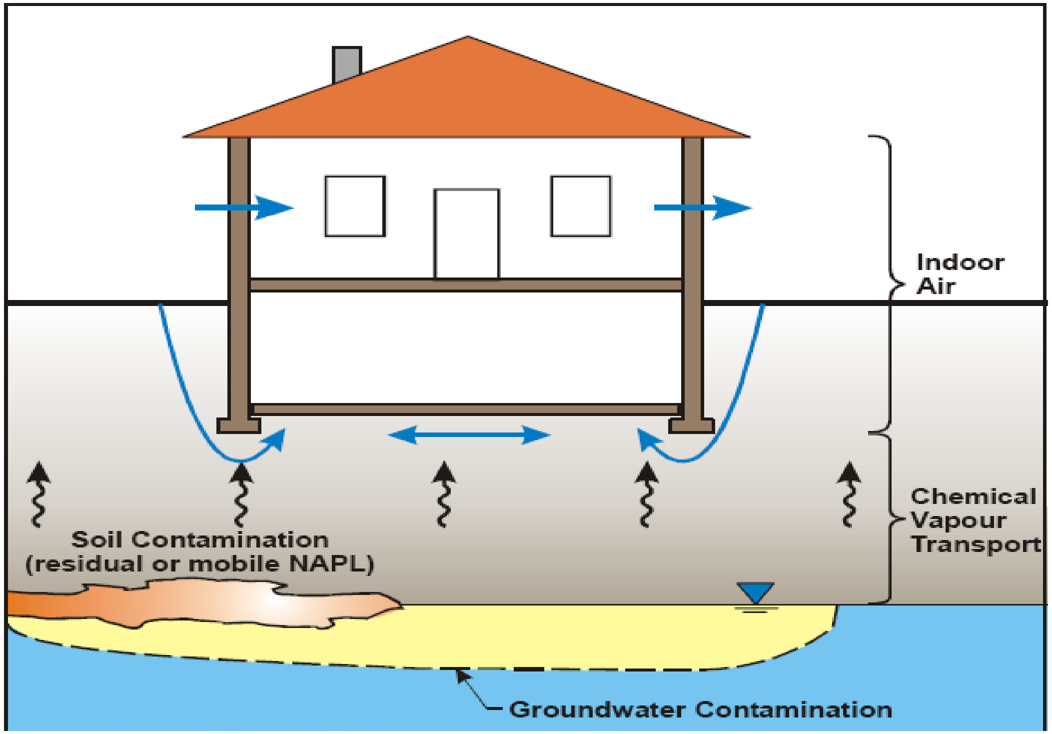
Yager



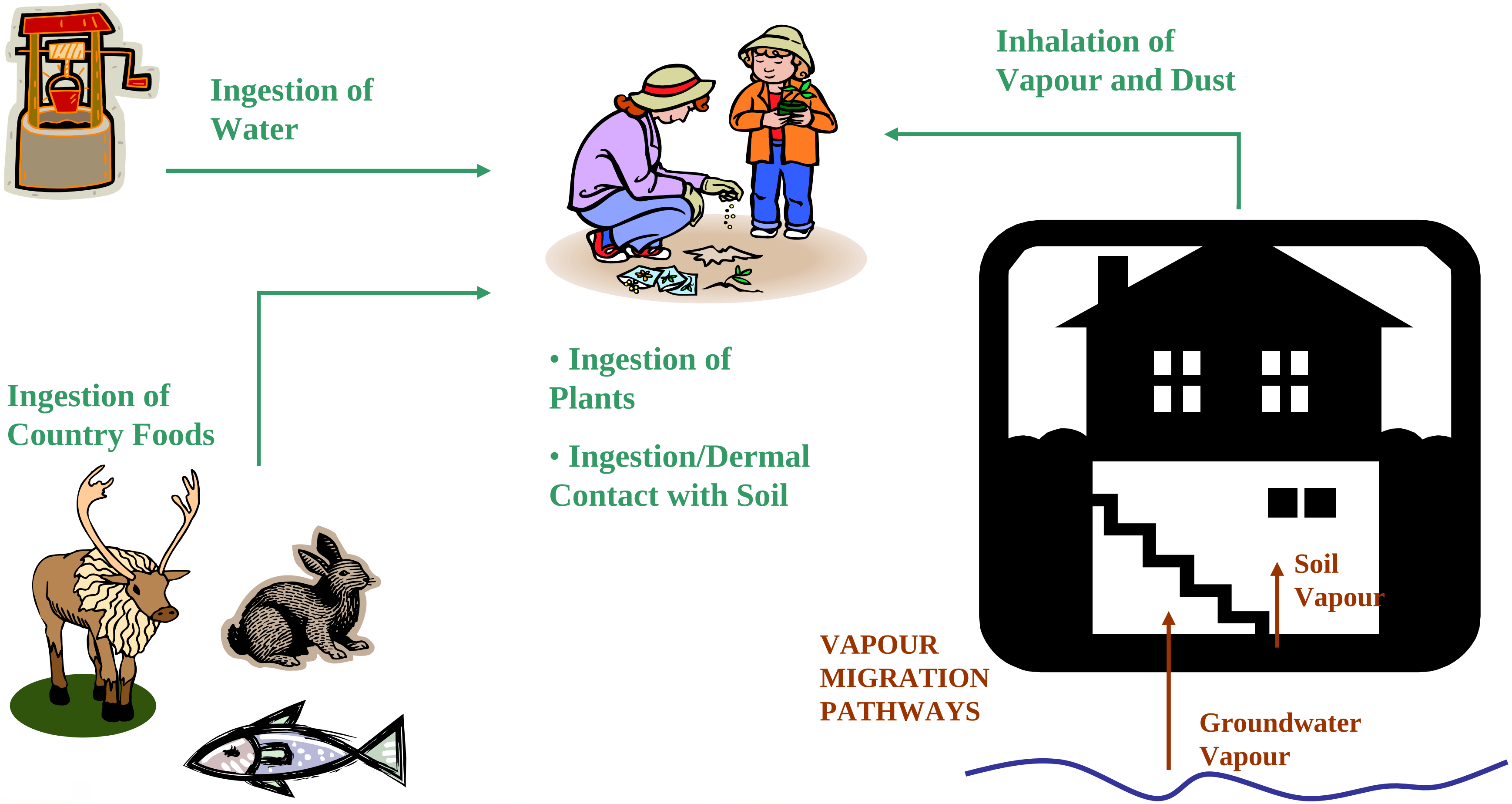
Mixture



Exposure Pathway Vapour Intrusion Modelling



Are All Pathways Considered?



Benzene Example

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Standardized Mortality Ratios (SMRs) for leukemia among Pliofilm workers based on the estimated cumulative exposures

Table 6. Standardized mortality ratios for leukemia in Pliofilm workers[a] by cumulative exposure at all locations.

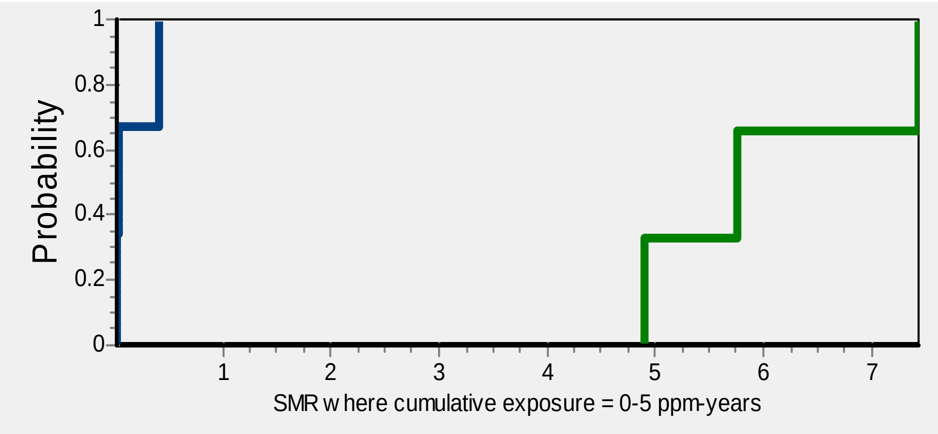
Exposure estimates	Cumulative exposure, ppm-years	Person-years	Observed	Expected	SMR[b]	95% CI
Rinsky	0–5	18,178	3	1.52	1.97	0.41–5.76
	>5–50	13,456	3	1.31	2.29	0.47–6.69
	>50–500	8,383	7	1.01	6.93**	2.78–14.28
	>500	328	1	0.05	20.00	0.51–111.4
Crump	0–5	12,974	1	1.14	0.88	0.02–4.89
	>5–50	13,951	4	1.23	3.25	0.88–8.33
	>50–500	11,448	6	1.23	4.87*	1.79–10.63
	>500	1,972	3	0.29	10.34**	2.13–30.21
Paustenbach	0–5	9,645	1	0.75	1.33	0.03–7.43
	>5–50	12,882	2	1.12	1.79	0.22–6.45
	>50–500	14,095	4	1.43	2.80	0.76–7.16
	>500	3,723	7	0.59	11.86**	4.76–24.44

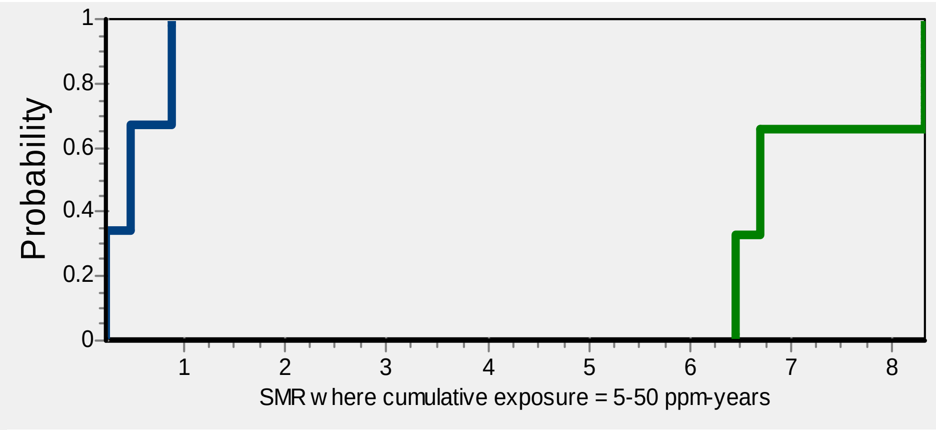
[a]White male wetside workers. [b]*p*-Value by two-sided Poisson test: * $p<0.05$; ** $p<0.01$.

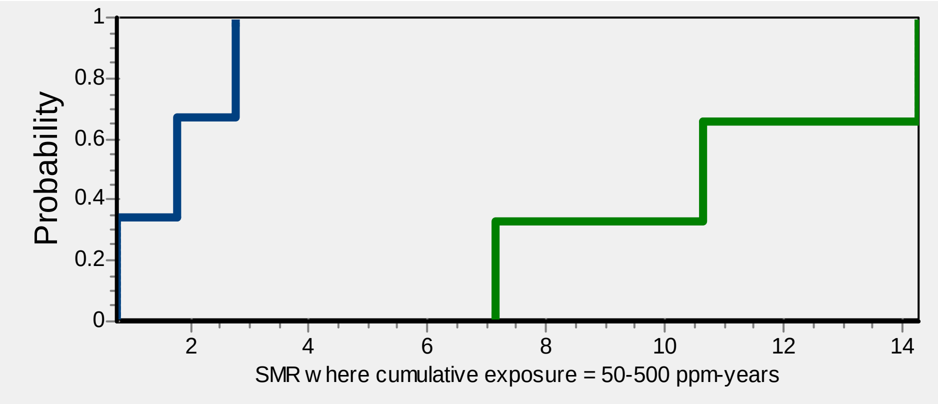
Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort

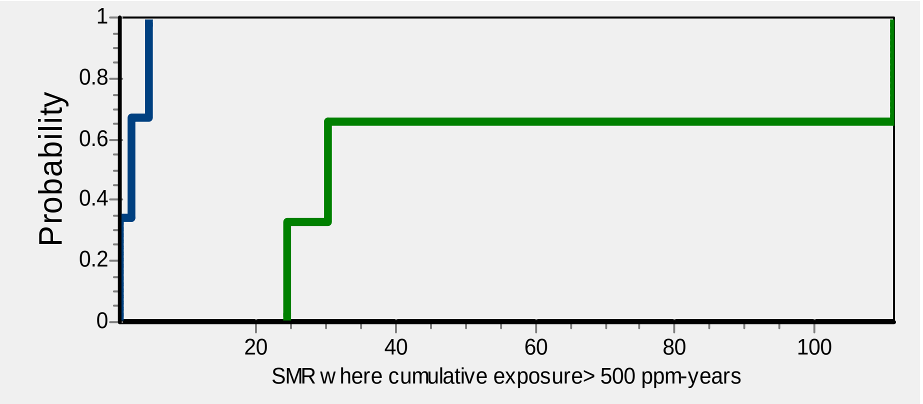
Mary Burr Paxton

Benzene Example





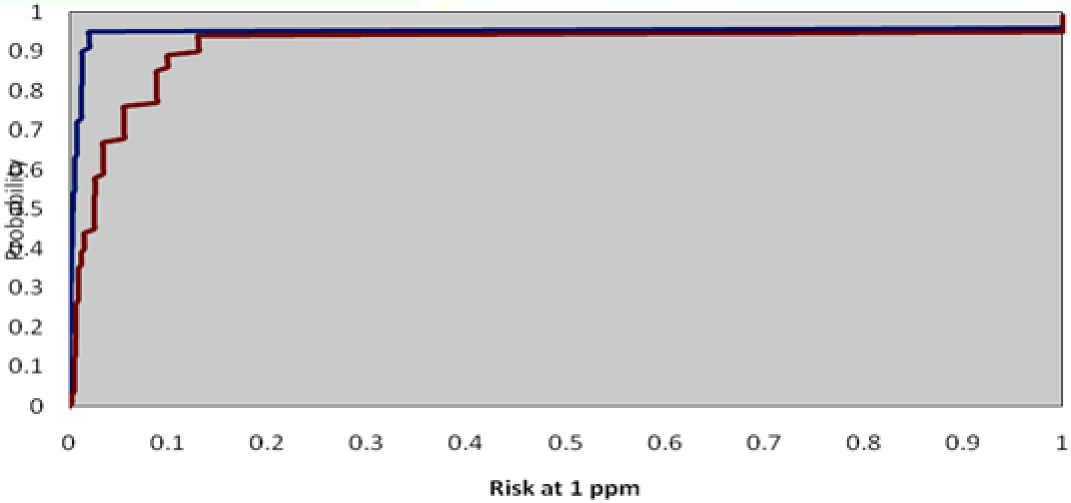


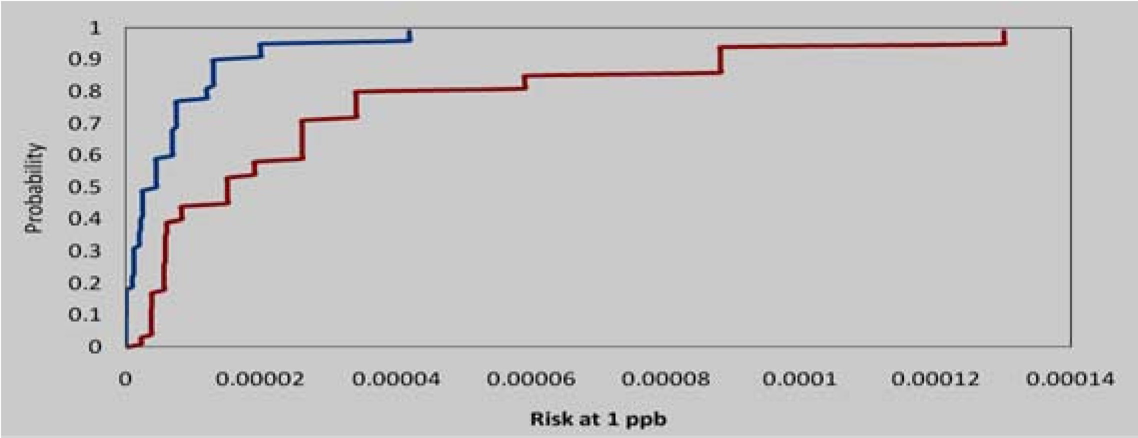


Benzene Example

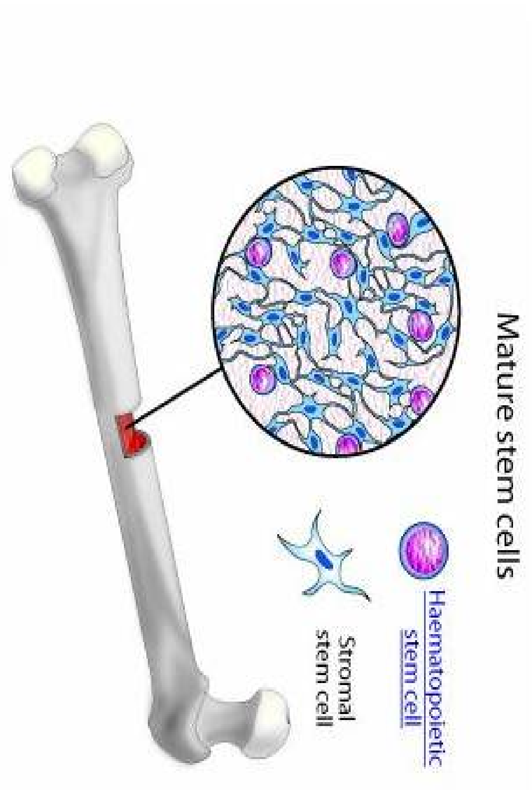
Source	Risk at 1 ppm	Risk at 1 ppb	Reference & model
US EPA (1985)	0.018 (7.5E-3, 3.4E-2)	0.000018 (7.5E-6, 3.4E-5)	Crump and Allen, additive risk
	0.041 (1.3E-2, 8.8E-2)	0.000041 (1.3E-5, 8.8E-5)	Crump and Allen, relative risk
Brett *et al.* (1989)	4.0E-3 (1.0E-3, 1.2E-2) to 2.5E-2 (2.5E-3, 9.9E-2)	3.6E-6 (9.5E-7, 6.9E-6) to 1.1E-5 (2.2E-6, 1.9E-5)	Crump and Allen, conditional logistic
	2.2E-1 (1.2E-2, 1.0) to 8.4E-1 (1.5E-2, 1.0)	2.4E-5 (6.9E-6, 4.2E-5) to 3.4E-5 (8.2E-6, 5.9E-5)	Rinsky, conditional logistic
Paxton (1992)	0.0022 (3.8E-5, 4.9E-3)	0.0000019 (3.7E-8, 3.7E-6)	Crump and Allen, proportional hazard
	0.0046 (1.3E-3, 9.0E-3)	0.0000035 (1.2E-6, 5.8E-6)	Paustenbach, proportional hazard
	0.018 (3.0E-3, 5.5E-2)	0.0000089 (2.5E-6, 1.5E-5)	Rinsky, proportional hazard
Crump (1992; 1994)	1.1E-2 (2.2E-3, 2.0E-2) to 2.5E-2 (6.0E-3, 1.3E-1)	1.1E-5 (2.2E-6, 2.0E-5) to 2.5E-5 (6.0E-6, 1.3E-4)	Crump and Allen, linear
	5.4E-3 to 2.5E-2	4.5E-6 to 2.6E-5	Crump and Allen, nonlinear
	7.1E-3 (2.0E-3, 1.2E-2) to 1.5E-2 (3.8E-3, 2.6E-2)	7.2E-6 (2.0E-6, 1.2E-5) to 1.6E-5 (3.8E-6, 2.6E-5)	Paustenbach, linear
	8.6E-5 to 6.5E-3	8.6E-11 to 5.6E-6	Paustenbach, nonlinear

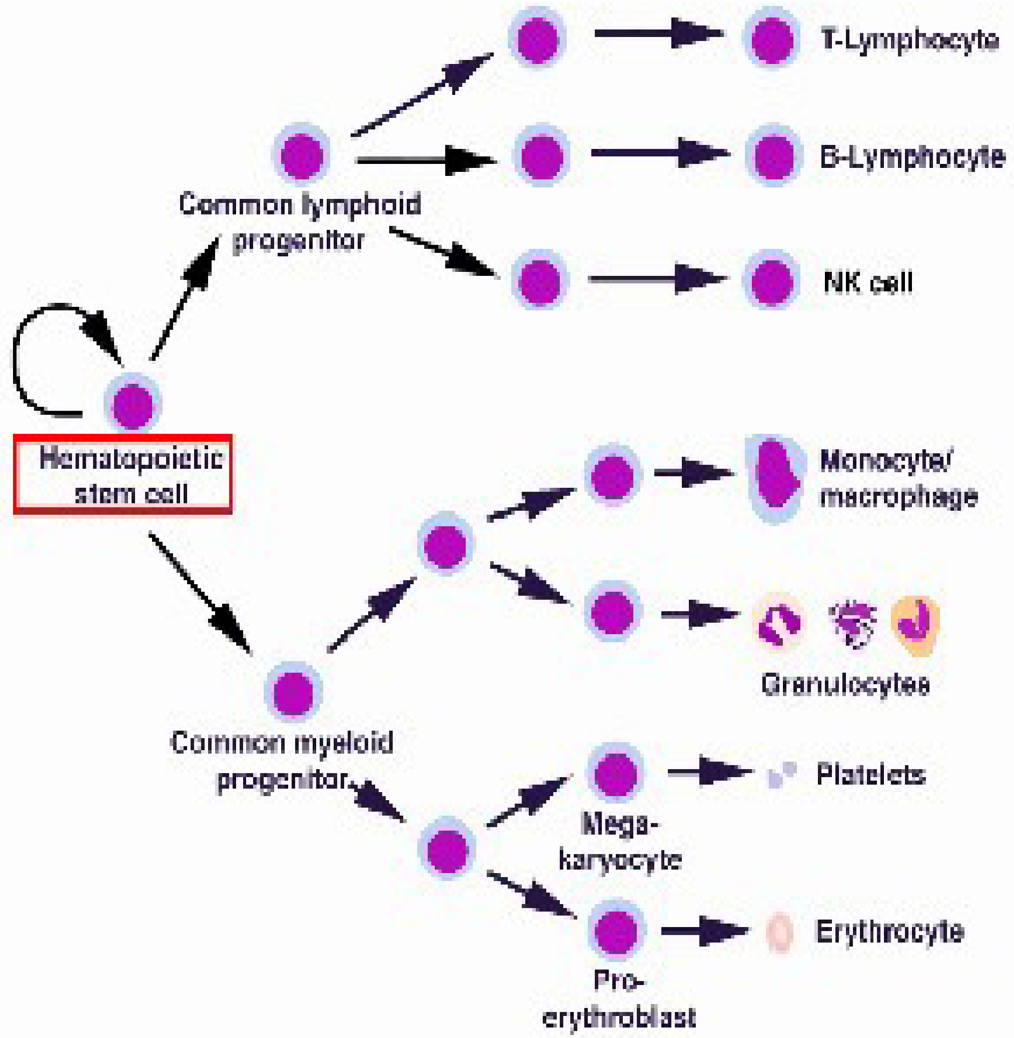
Benzene Example



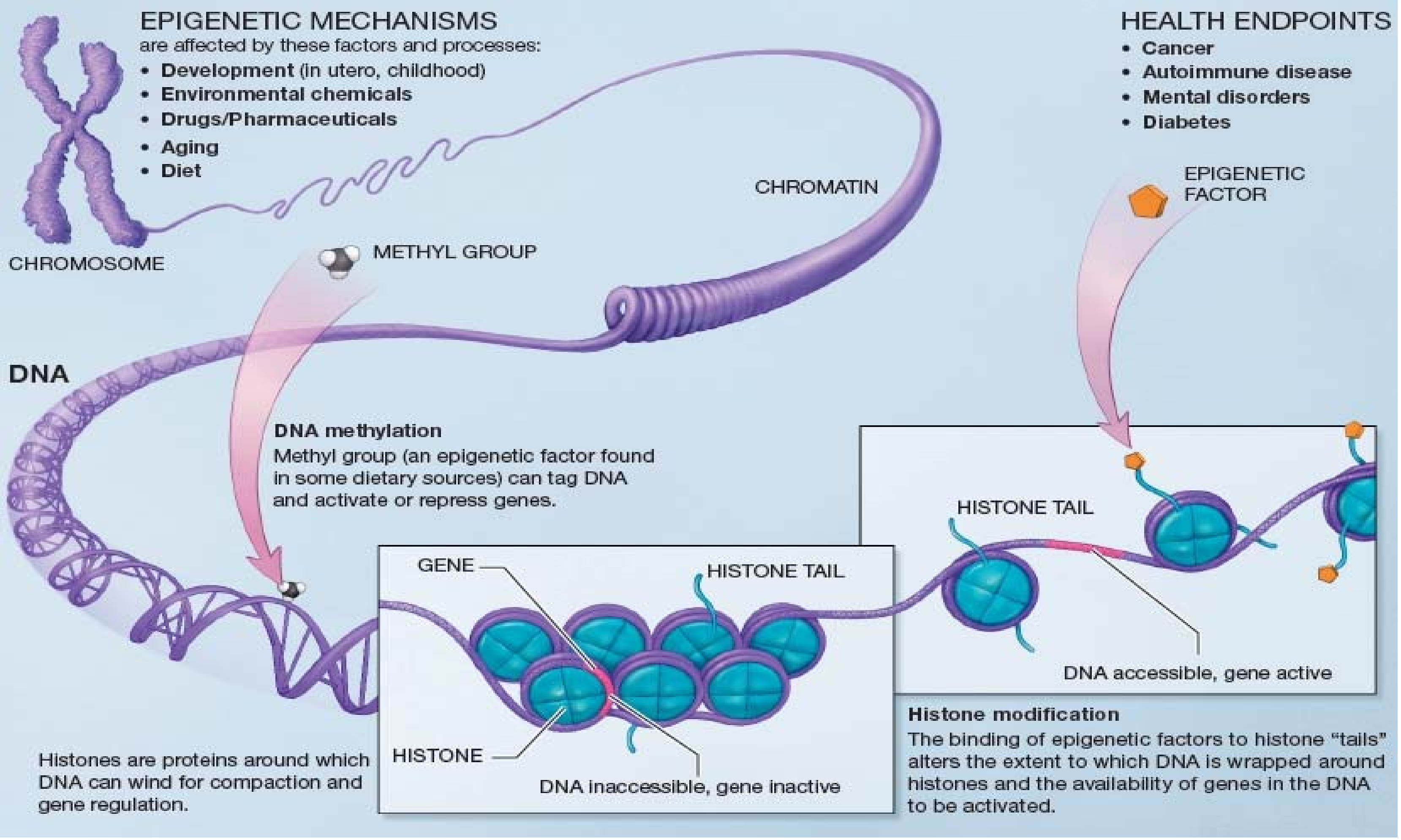


Hematopoietic System



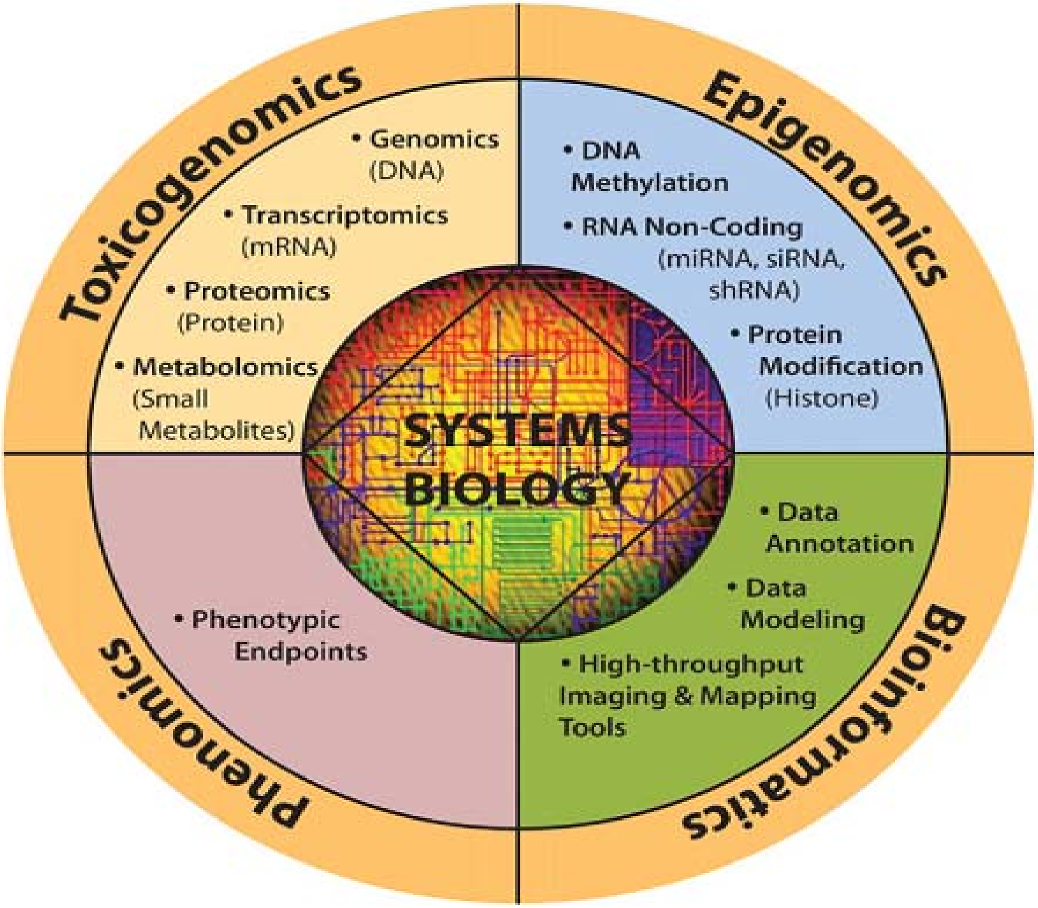


Epigenomics



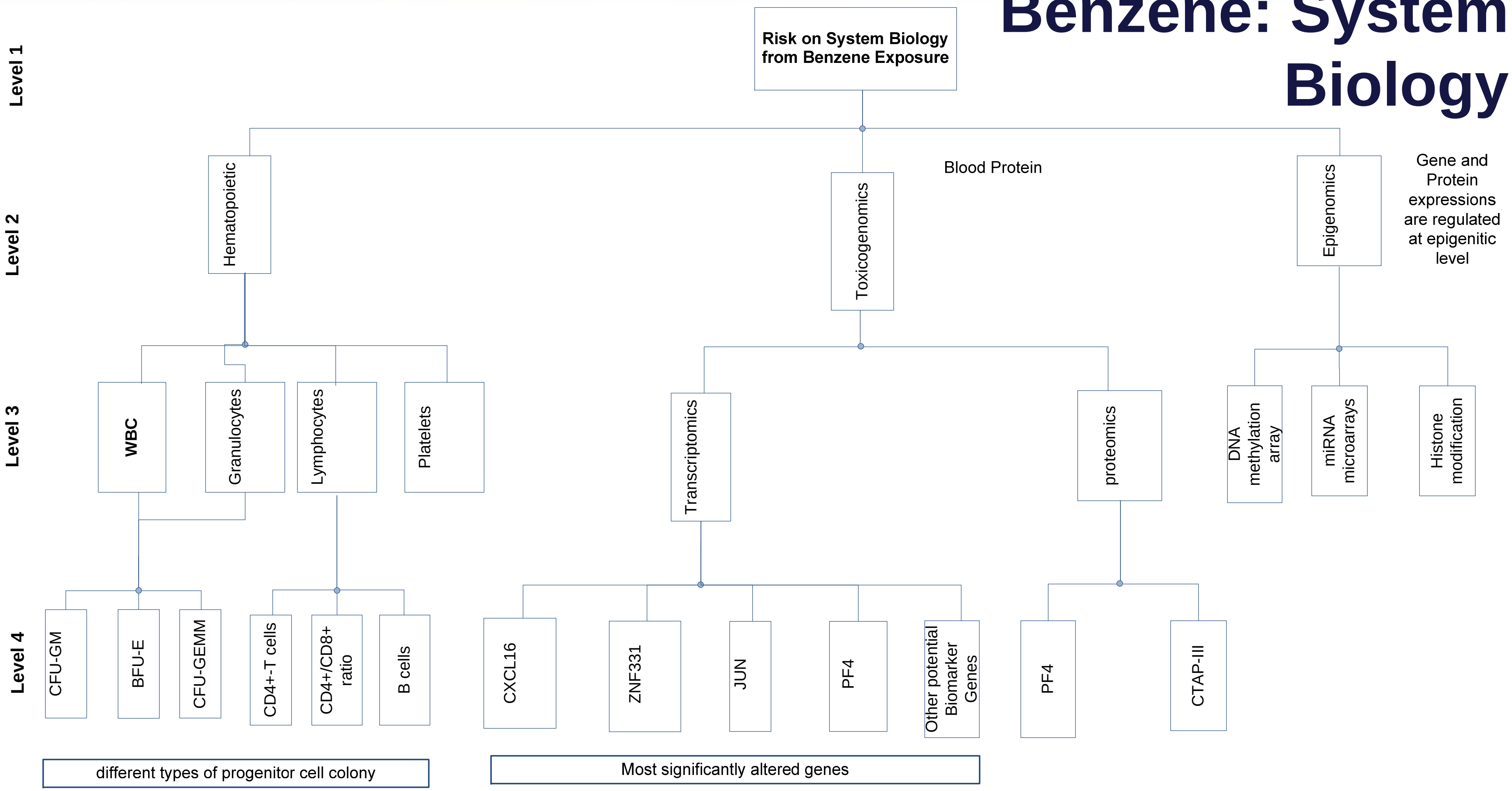
From Laura, B. (2008)

Overview of Systems Biology based Computing



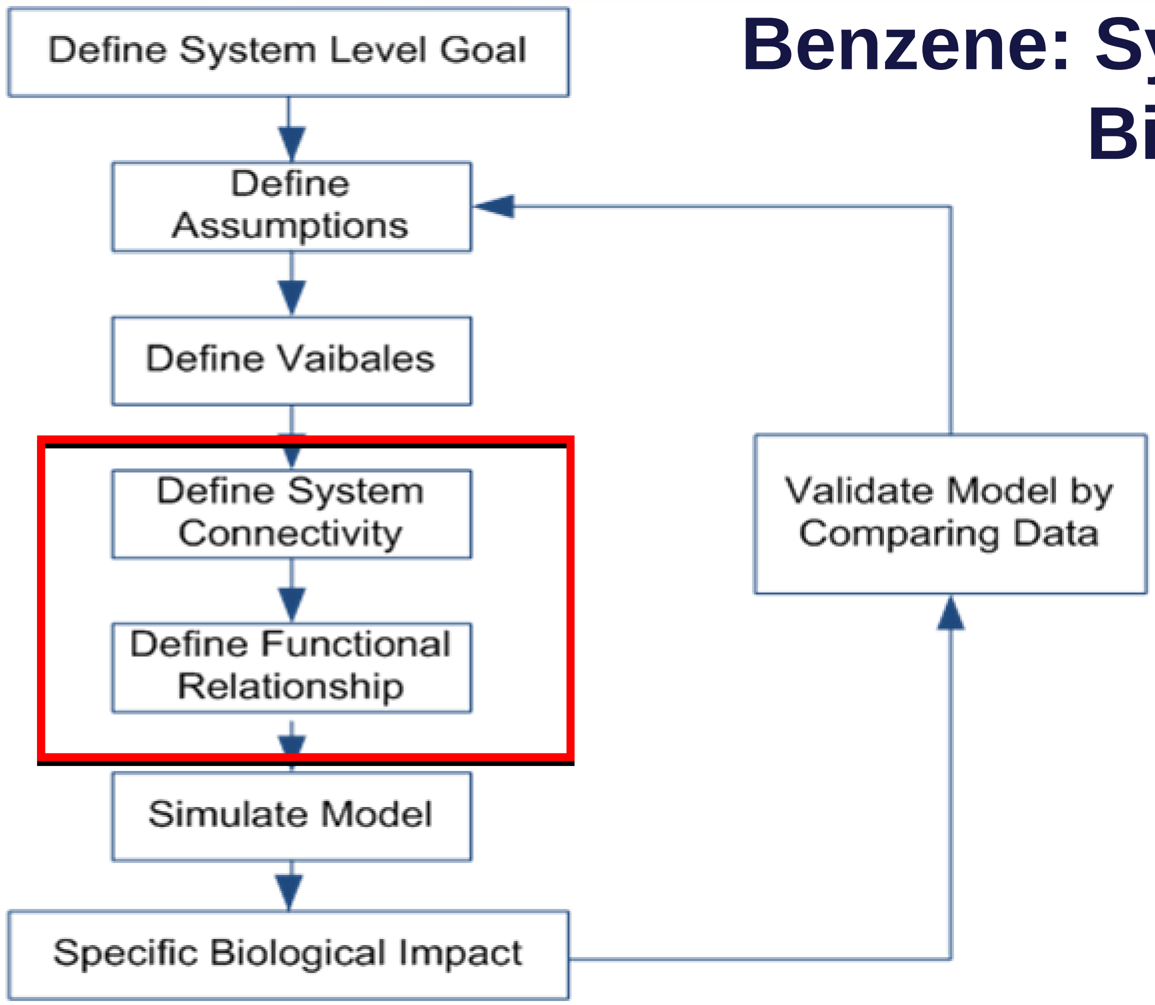
Adapted from Zhang et al. 2010

Benzene: System Biology



Benzene: System Biology

Mathematical Modelling of a Biological System



Benzene: System Biology

Comparative Toxicogenomics Database

400 interacting genes - at least a dozen highly interacting genes

Six most altered genes (based on Benzene (gene-cell-tissue-disease) Problem Formulation (with a disease focus – Leukaemia)

Literature Extraction – 115 peer reviewed publications

Overall objective: Probability of failure of biological systems identified in the Benzene System Biology flowchart (Overall impacts to Hematopoietic components).

Benzene: System Biology challenges

- Huge amount of sequence data
- Huge amount of genomics data
- Complex connectivity
- Understanding toxicological interactions
- Prediction of protein-coding genes
- Cell-cell interaction
- Cell-tissue-gene level interactions
- **Genome has a multi-dimensional structure**

F1-Hydrocarbon Example

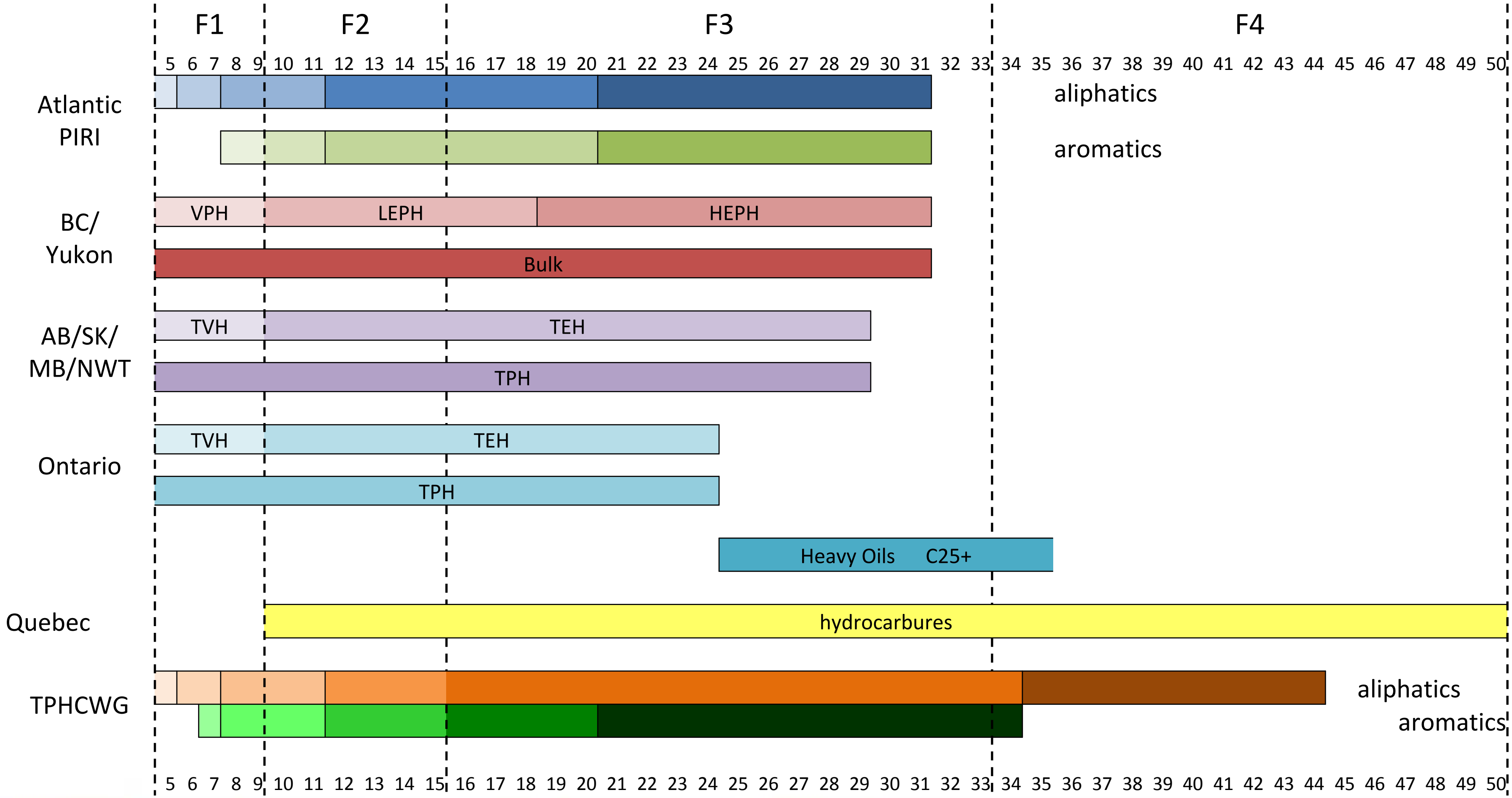
F1 hydrocarbon mixture

- **55%C6-C8 aliphatics**
  (n-hexane may vary between 3% to 12% or more?)
- **36% C8-C10 aliphatics**
- **9% C8-C10 aromatics**

F1 PHC = [F1 –BTEX]

n-hexane is used as a surrogate

F1-Hydrocarbon Example



F1-Hydrocarbon Example

Fraction	Equivalent Carbon #	Corresponding TPHCWG subfractions		TDI (mg/kg·d)	RfC (mg/m³)	Critical Effect used by TPHCWG to derive criteria
F1	C_6 to C_{10}	aromatics	$C_{>7}$-C_8	-[a]	-[a]	-[a]
			$C_{>8}$-C_{10}	0.04	0.2	hepatotoxicity, neurotoxicity
		aliphatics	C_6-C_8	5.0	18.4	neurotoxicity
			$C_{>8}$-C_{10}	0.1	1.0	Liver and blood changes
F2	$C_{>10}$ to C_{16}	aromatics	$C_{>10}$-C_{12}	0.04	0.2	decreased body weight
			$C_{>12}$-C_{16}	0.04	0.2	decreased body weight
		aliphatics	$C_{>10}$-C_{12}	0.1	1.0	Liver and blood changes
			$C_{>12}$-C_{16}	0.1	1.0	Liver and blood changes
F3	$C_{>16}$ to C_{34}	aromatics	$C_{>16}$-C_{21}	0.03	NA[b]	nephrotoxicity
			$C_{>21}$-C_{34}	0.03	NA[b]	nephrotoxicity
		aliphatics	$C_{>16}$-C_{21}	0.1	1.0	hepatic granuloma
			$C_{>21}$-C_{34}	2.0	NA[b]	hepatic granuloma
F4	$C_{>34}$ to C_{50}	aromatics	$C_{>34}$	0.03	NA[b]	nephrotoxicity
		aliphatics	$C_{>34}$	20.0	NA[b]	hepatic granuloma

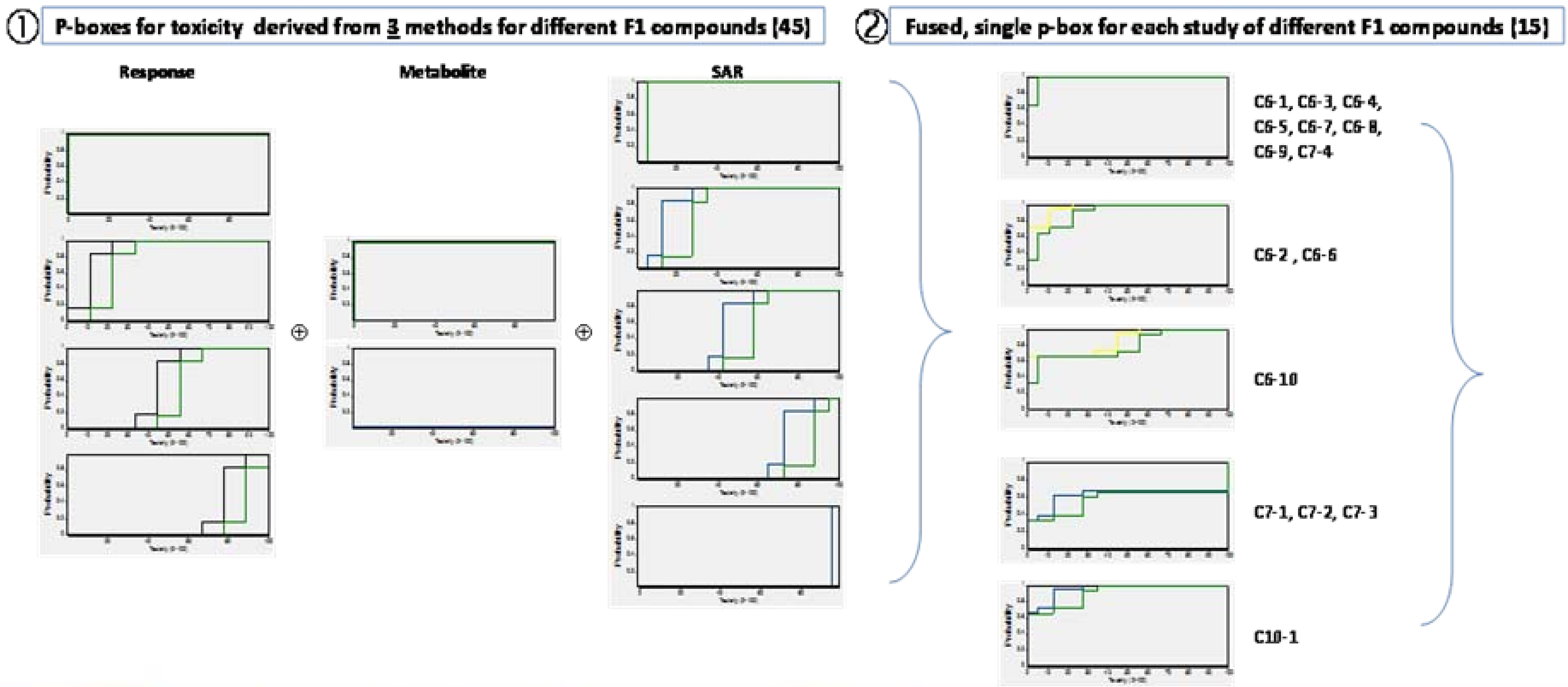
CCME (2008) & Edwards (1997)

Review of neurotoxicity studies for F1

Compound	Author	Subjects	Duration	Delivery	Dose	Effects	Response	med
Heptane	(Takeuchi et al. 1981)	Rat		12h/d,7d/w, 16w		3000	no histopathological signs of neurotoxicity	no
	(Frontali et al. 1981)	Rat		9h/d,5d/w 30 wks		1500 ppm	no evidence of histopathological neurotoxicity	no
	(Bahima et al. 1984)	female rat		6h/d, 5d/w, 12 wks		2000 ppm	no clinical signs of neurotoxicity	no
2-methyl Hexane	(Perbellini *et al*. 1985; Sayre *et al*. 1986)	human/rat					neurotoxic metabolites detected	no
3-methyl hexane	(Valentini et al. 1994)	Human	8-10 hr		case study exposure	36ppm heptane 16ppm 3-methyl hexane	peripheral neuropathy, induced by MEK?	med*
Methyl cyclo hexane	(Parnell et al. 1988)	Rats	every second day for 14d		0.8g/kg by gavage		Histopathologic examination of the rat kidney slices indicated only very slight traces of nephropathy,	NA
C7 Mixtures	(MacEwen and Vernot 1985)	dogs, rats, mice, hamsters	.Year-long exposures			0, 400, 2000 ppm	mean body wt depression in hamsters and male rats. Only significant lesions noted was progressive renal nephropathy seen in virtually all of the male rats	NA

F1-Hydrocarbon Example

Multi-study & multi-compound inference for F1 neuropathic toxicity using Dempster-Shafer mixture fusion (averaging)

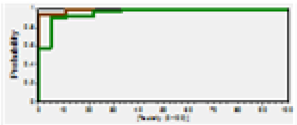


F1-Hydrocarbon Example

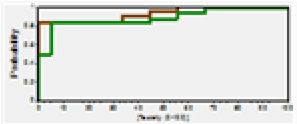
③ **Fused p-boxes for 7 F1 compounds (various)**

④ **Assign weights as per 7-compound mass composition (percentage)**

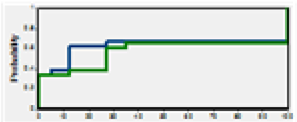
⑤ **Fused p-box for F1**



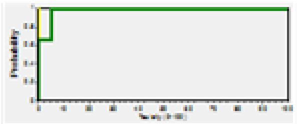
2-methylpentane, 28.72%
3-methylpentane 18.35%



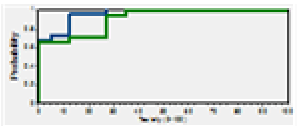
cyclohexane 6.19%



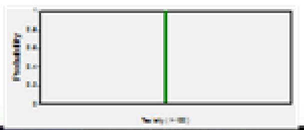
heptane 9.78%



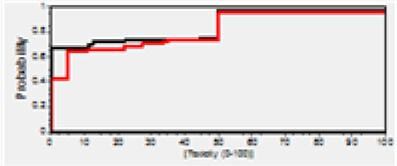
2-methylhexane 12.35%



n-decane 2.23%



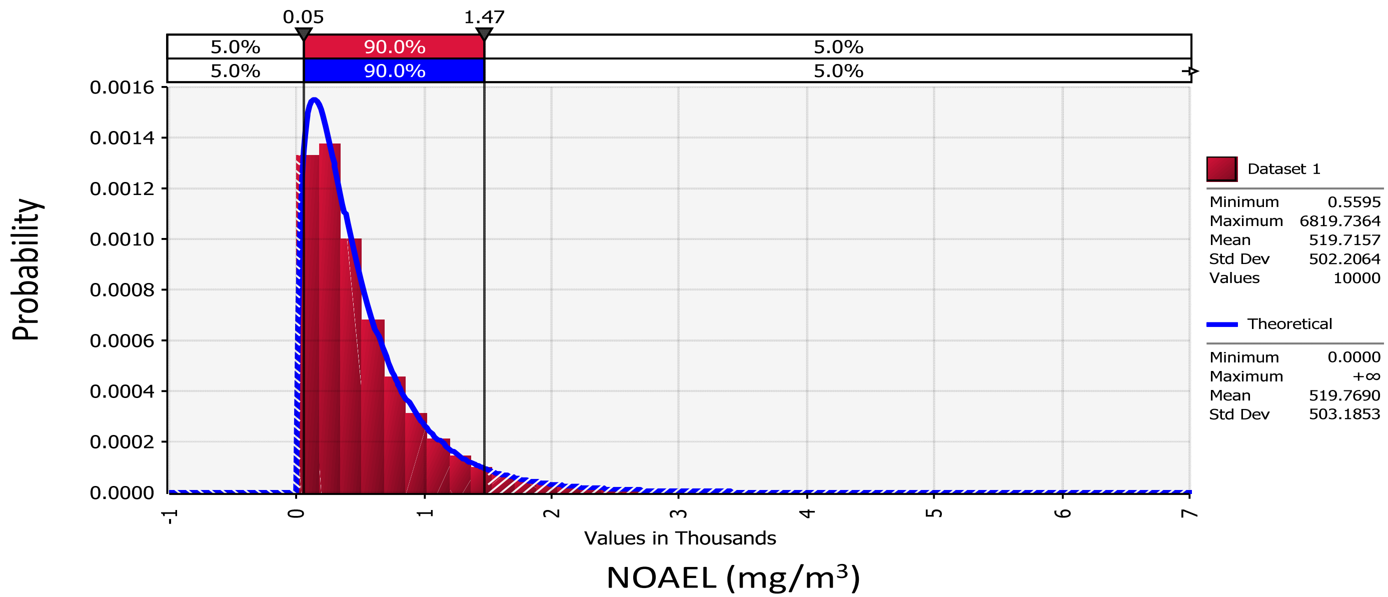
n-hexane 22.38%



F1-Hydrocarbon Example

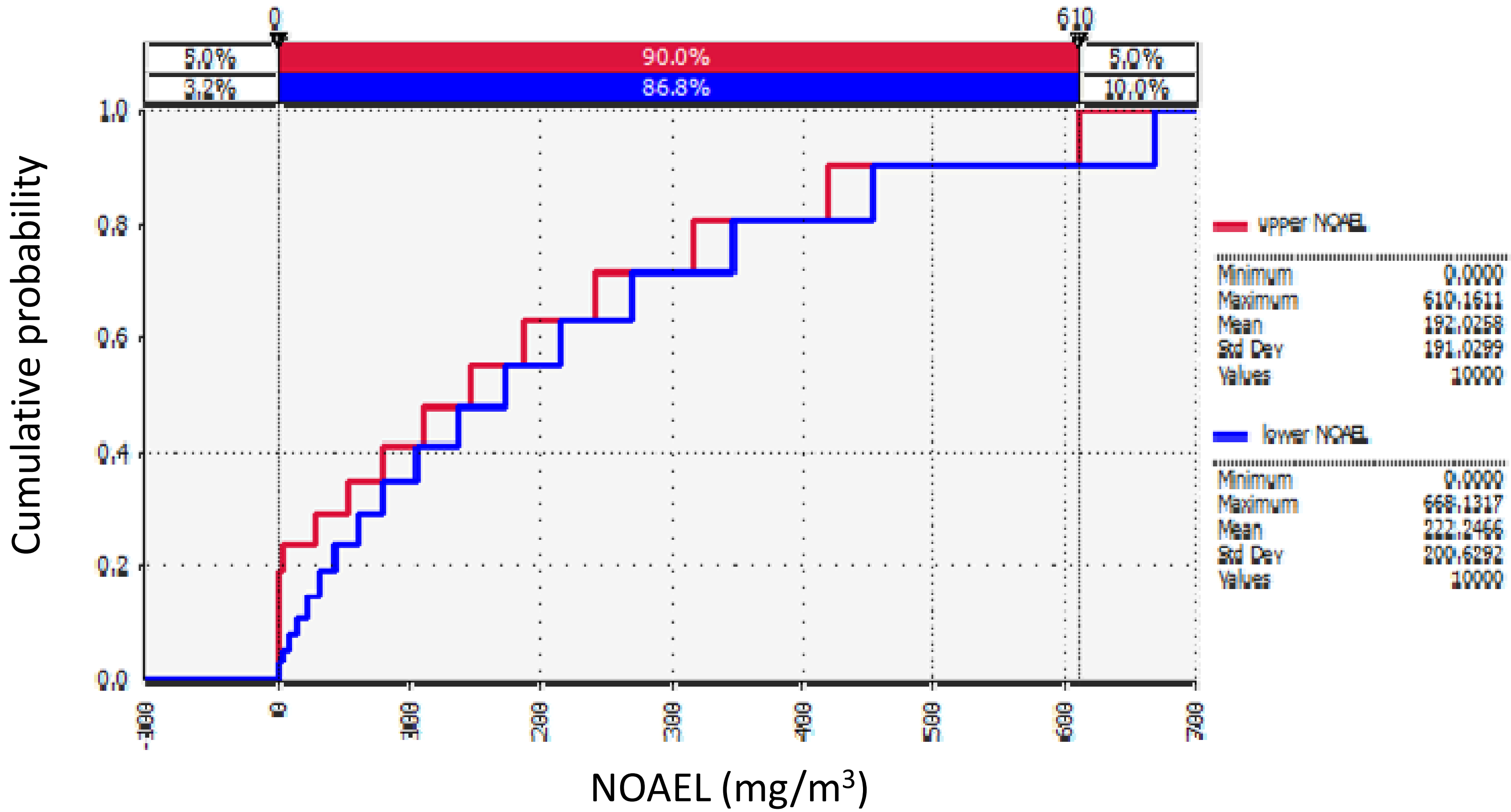
Feature Level Data Fusion: Dose-Response assessment

The toxicity of each compound was applied to the probability density function of the NOAEL concentrations from studies on n-hexane, for which there was much more toxicity data.



PDF of NOAEL from n-hexane subchronic neurotoxicity studies

F1-Hydrocarbon Example



p-box for neurotoxicity NOAEL for all of F1

F1-Hydrocarbon Example

Decision Level Data Fusion: Risk Characterization

The NOAEL from the dose-response assessment applies for rats in a sub-chronic study. Where NOAEL values were not available, the LOAEL values were divided by an uncertainty factor of 10. Other uncertainty factors that can be applied include:

- 10 for inter-species differences
- 10 for intra-species differences
- 3 for deficiencies in the data set.

No uncertainty factor is being used for the severity of toxic effects: a factor was included in calculating the combined NOAEL for F1.

Alternative Endpoints

F1-Hydrocarbon Example

Whether Current Inhalation Reference Concentrations are protective against irritancy for C_6-C_8 aliphatics?

Is this the most sensitive end point? Other health effect endpoints are being evaluated

Limited preliminary analysis of system biology datasets

F1 surrogate (n-hexane) Preliminary System Biology dataset analysis

n-hexane datasets were requested for curation from the Comparative Toxicogenomics Database for preliminary analysis and integration of system biology datasets in 2009.

Key interacting genes

BAX, BCL2, CASP3, CYP1A1, and CYP1A2 in rats;
CYP2E1 in mice, and
CYP2B1, CYP2B6, and CYP2E1 in humans

Additional analysis were conducted for **altered protein expression, metabolic changes, and gene polymorphisms in CYP2E1 leading to potential chemical susceptibility to n-hexane exposure.**

Further analysis of other health effects end points such as respiratory irritancy, respiratory lining and lungs inflammation, peripheral nervous system and hepatic diseases may be required.

Some preliminary results were presented at the Alliance for Risk Assessment workshops in the USA.

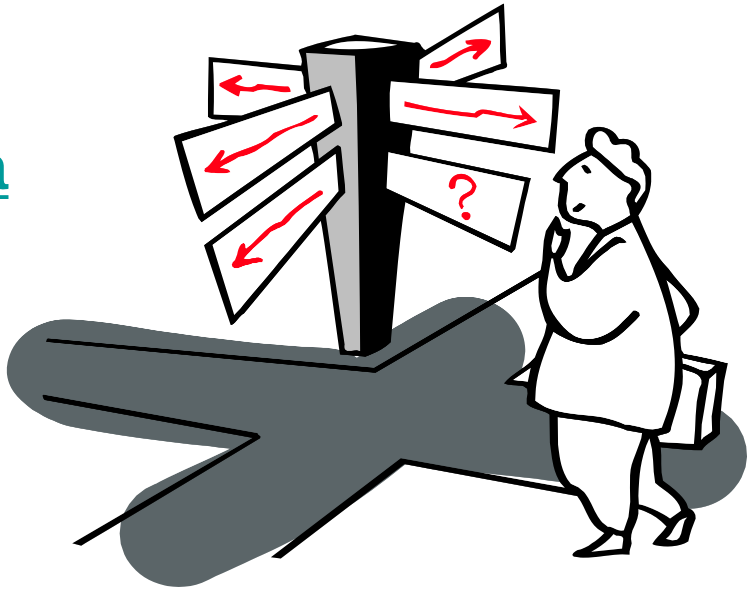
Paradox of Risk Management

“You always got to be prepared, but you never know for what”

“Sugar Baby” Bob Dylan

Predictive Toxicology Tools and Data Fusion can bridge the gap and help detect patterns and novel relationships so that risk assessment, risk management and risk communication can operate in a dynamic manner.

Thank you!



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