A Risk Assessment Approach for Chronic Obstructive Pulmonary Disease

presented at the Society of Risk Analysis, Europe Meeting, Den Hague, The Netherlands, June 2007

Hans-Jörg Urban, Rolf Weitkunat, Gerd Kallischnigg, Edward Sanders & Hugh Browne

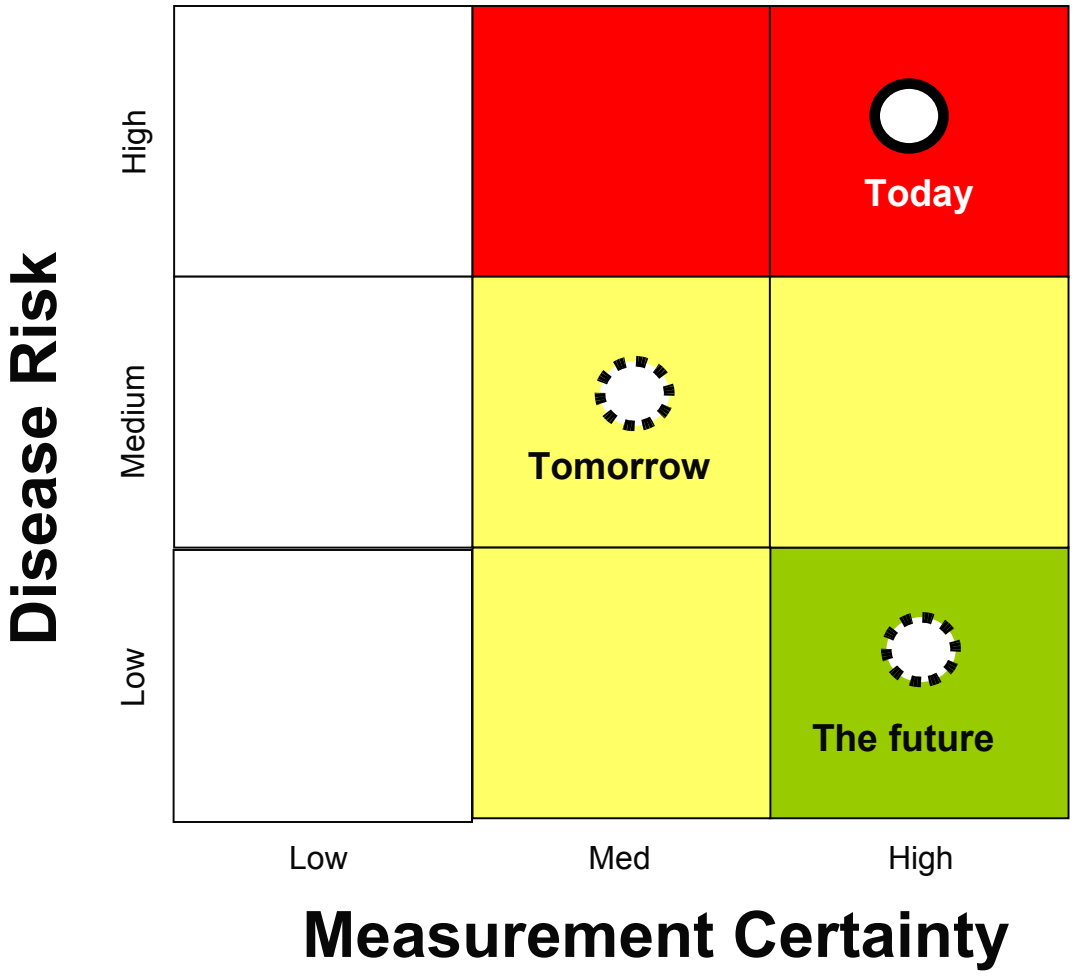
Philip Morris Product SA, PMI Research & Development, Product Risk Management
Quai Jeanrenaud 56, 2000 Neuchâtel, Switzerland

Purpose & Outline

1. Present a Risk Assessment Approach for COPD.
2. Structure the Presentation in two Parts:

Part I: Disease Risk Index

Part II: Measurement Certainty



What is COPD ?

- A respiratory disease characterised by irreversible airflow obstruction
- Three classic pathologies:
  - ***Emphysema*** (airspace enlargement and destruction of lung parenchyma)
  - ***Chronic Bronchitis*** (mucus plugging of the airways)
  - ***Chronic Obstructive Bronchiolitis*** (obstruction of small airways)
- Associated with an abnormal inflammatory response of the lungs to noxious particles or gases

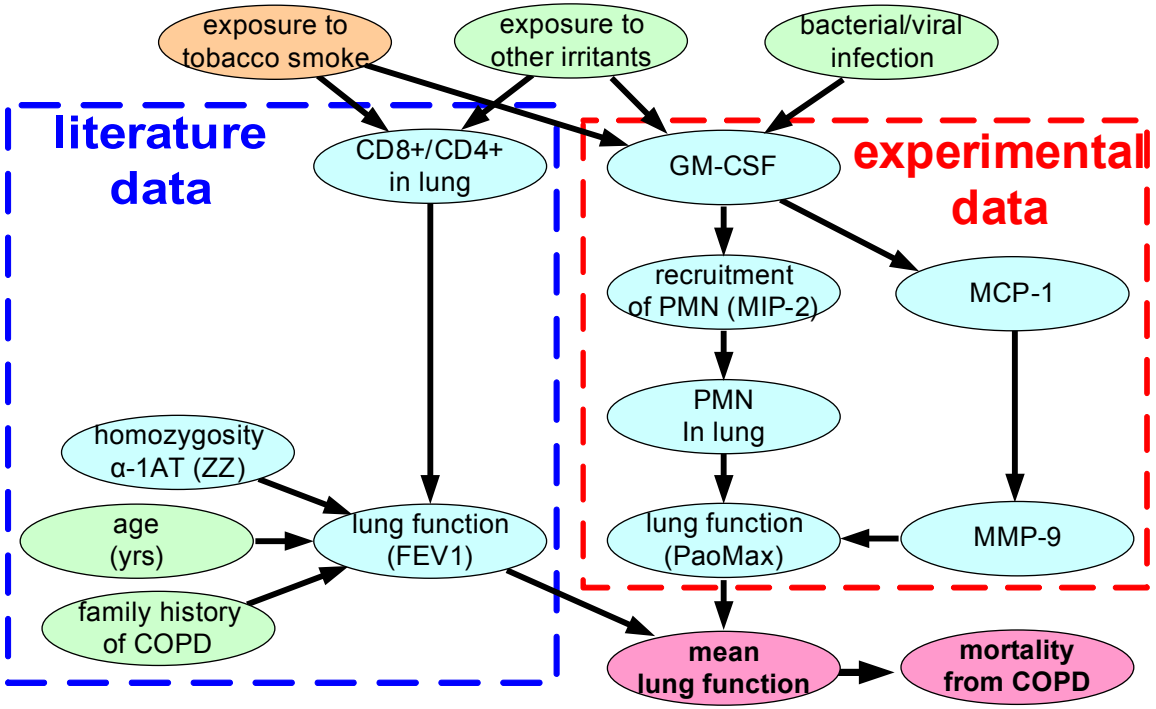
➔ **Cigarette smoking is the most important risk factor**

PART I: The Preliminary (Vers. 1) Model: presented at the SRA in Baltimore, 2006

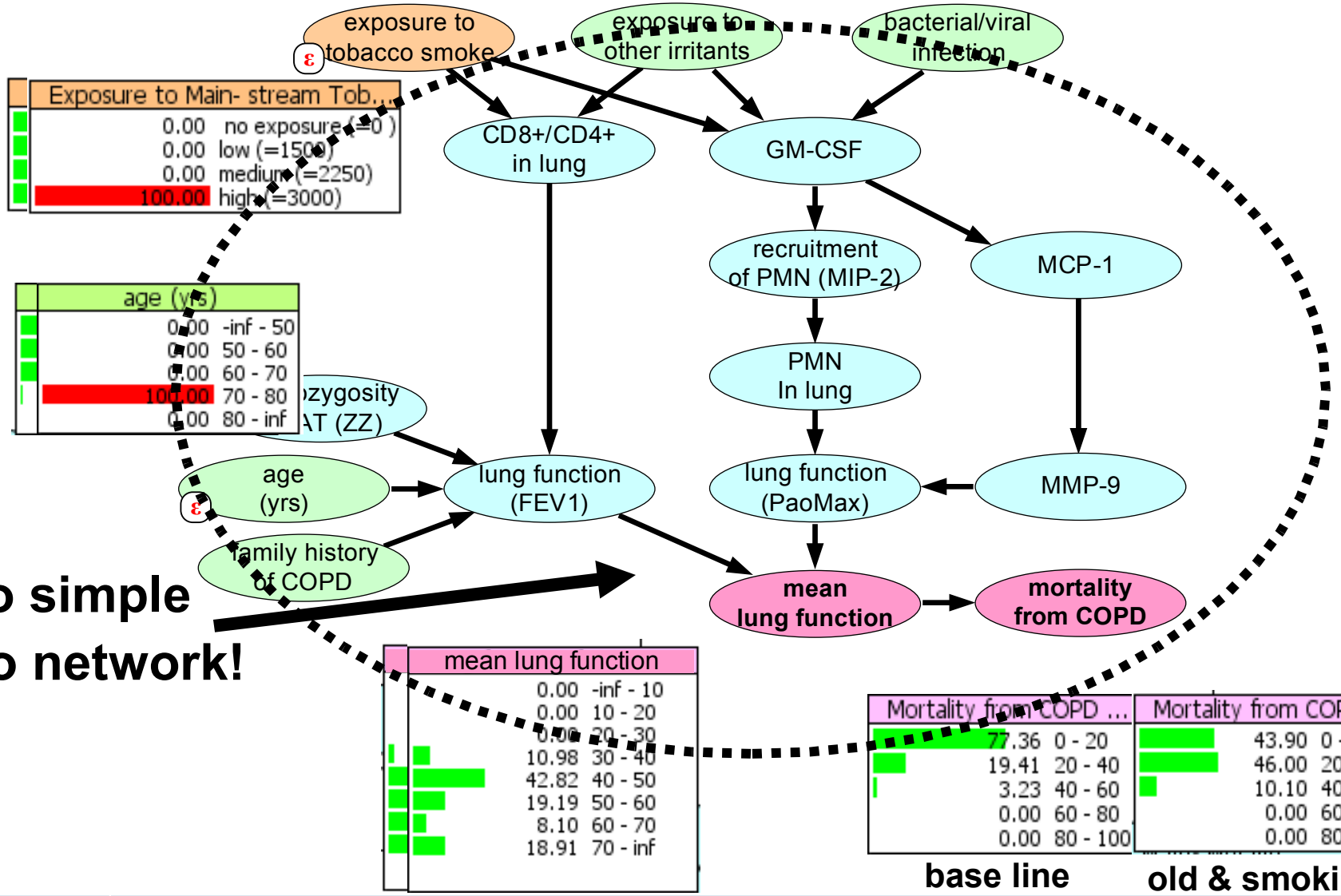
Data for Modeling Key Events in Emphysema:

- **Literature analysis** reveals that a number of key biological events may be associated with the development COPD
  Example: Recruitment of neutrophils to the lung triggers the release of proteases that can lead to emphysema

- **Data**: Emphysema study using A/J-mouse
  - Three months exposure to air or cigarette smoke at 3 smoke doses
  - End points: e.g. inflammatory cells and mediators



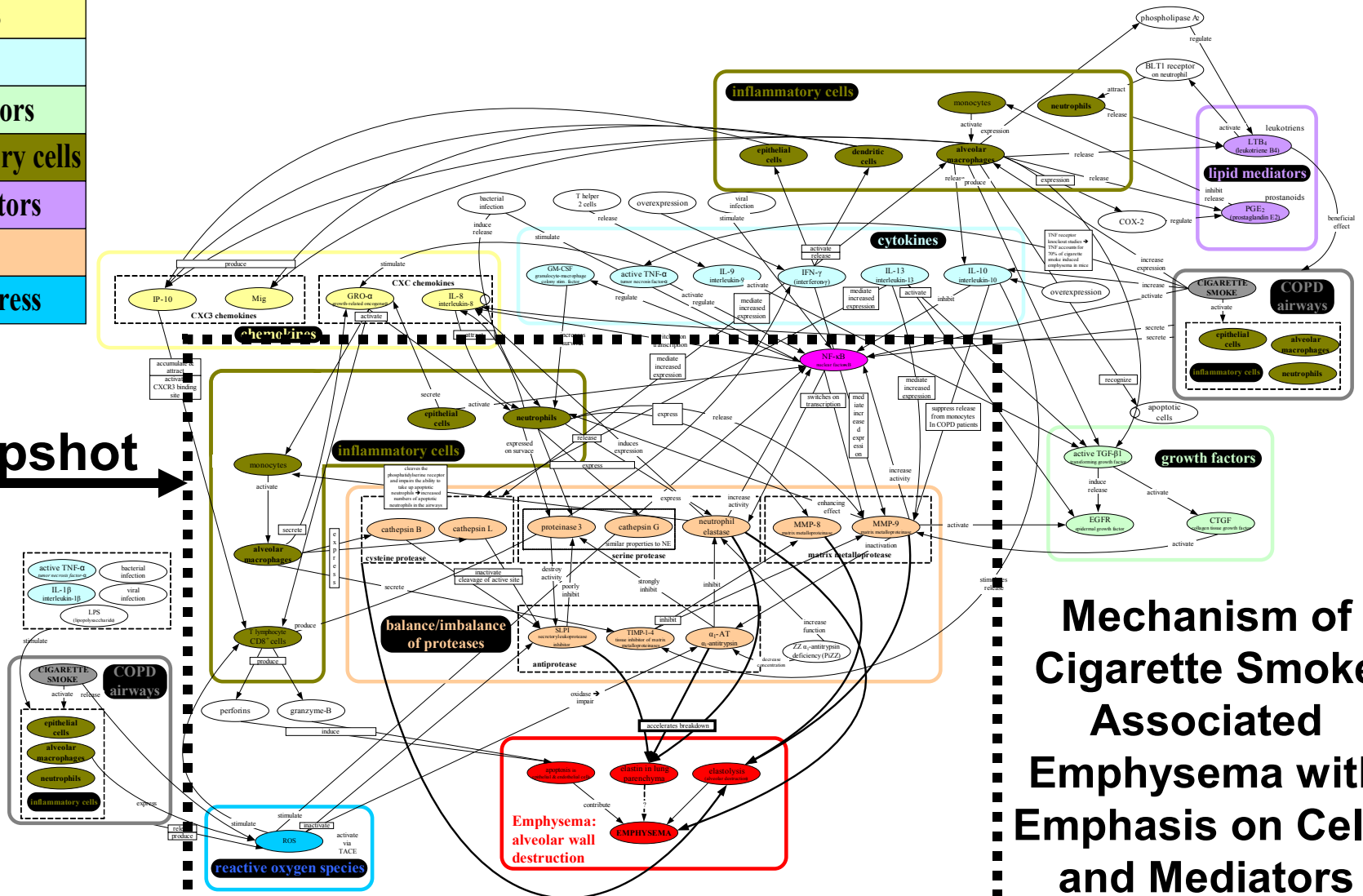
The Vers. 1 Model :
Model Emphysema Mortality with Hugin Expert



The Vers. 2 Model : Disease Mechanism Network Based on Literature

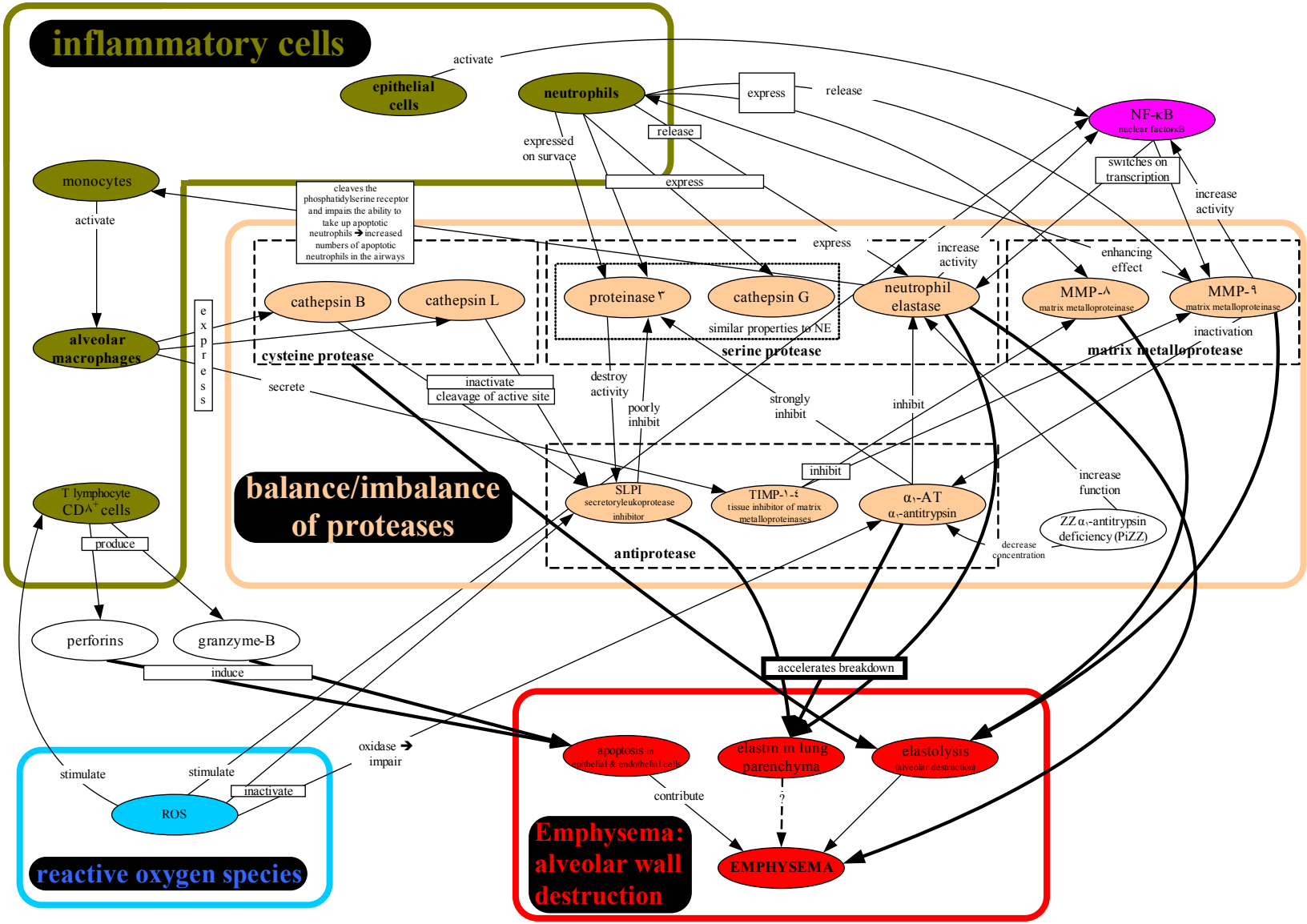
- chemokines
- cytokines
- growth factors
- inflammatory cells
- lipid mediators
- proteases
- oxidative stress

Snapshot



Mechanism of Cigarette Smoke Associated Emphysema with Emphasis on Cells and Mediators

The Vers. 2 Model : Transforming the Disease Network into a Bayesian Network

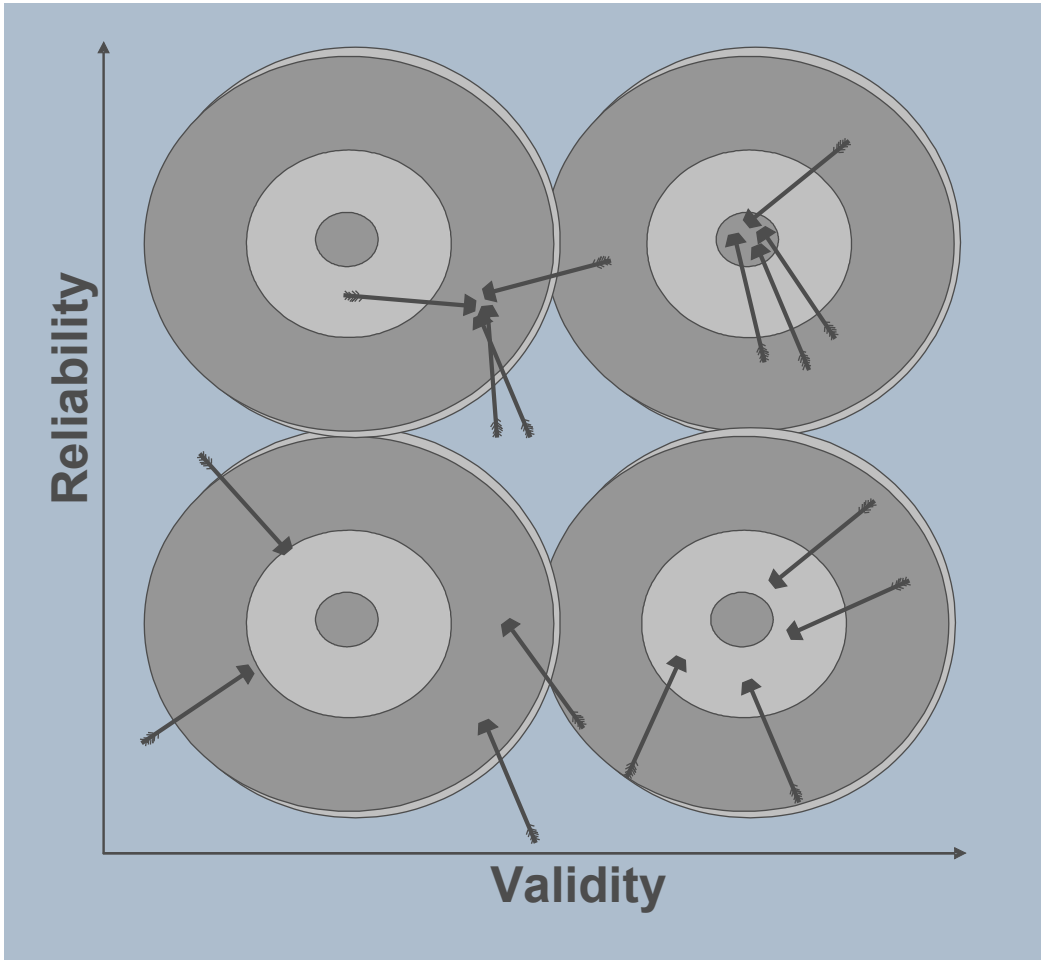


PART II: Measurement Certainty
Some Sources of Measurement Uncertainty

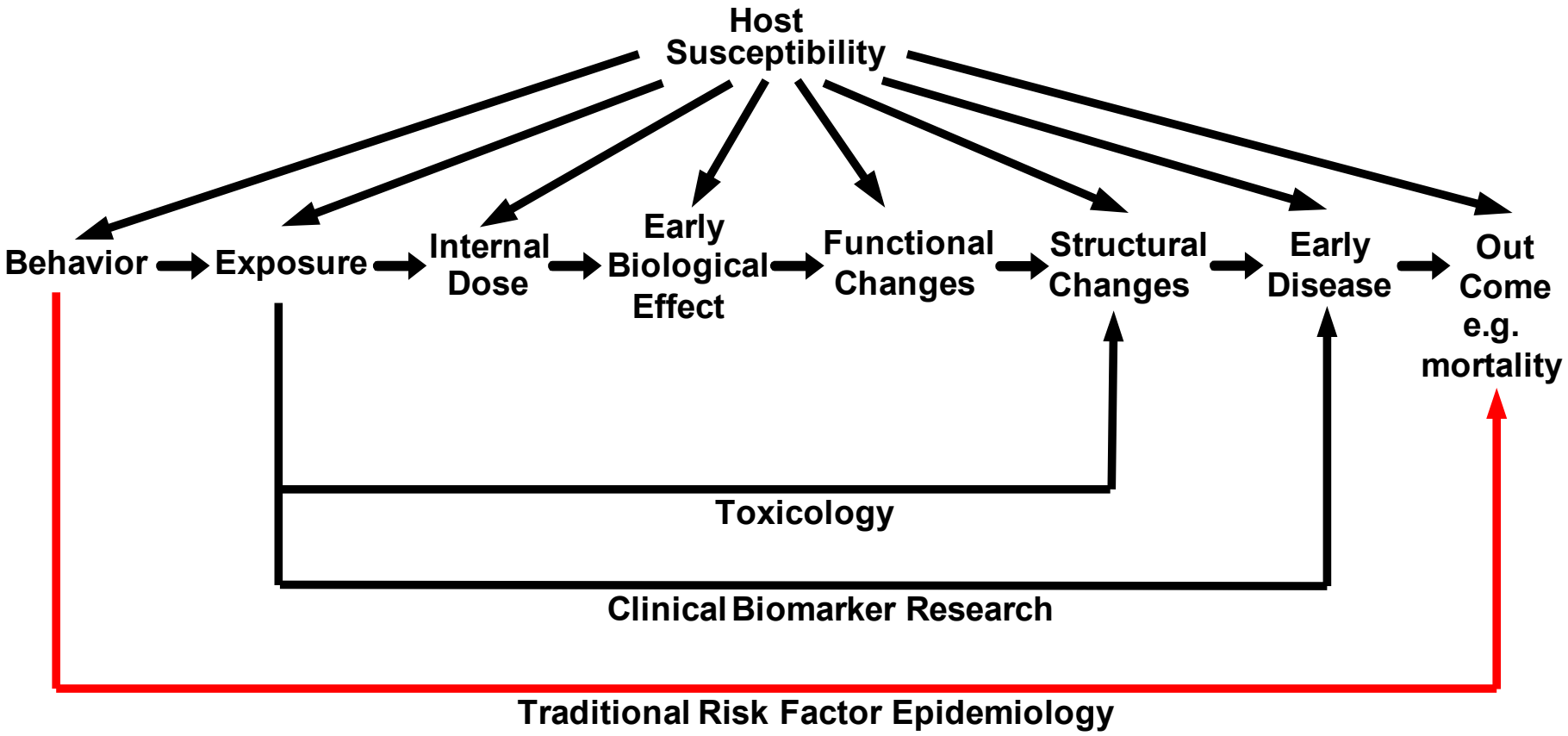
- incomplete definition of the measure
- biased sample
- environmental factors
- human factors (lab personnel)
- insensitive assay/equipment
- data processing error
- random error (background noise)

Reliability and Validity

- Reliability is about precision
- Validity is about truth



Generic Pathophysiological Model

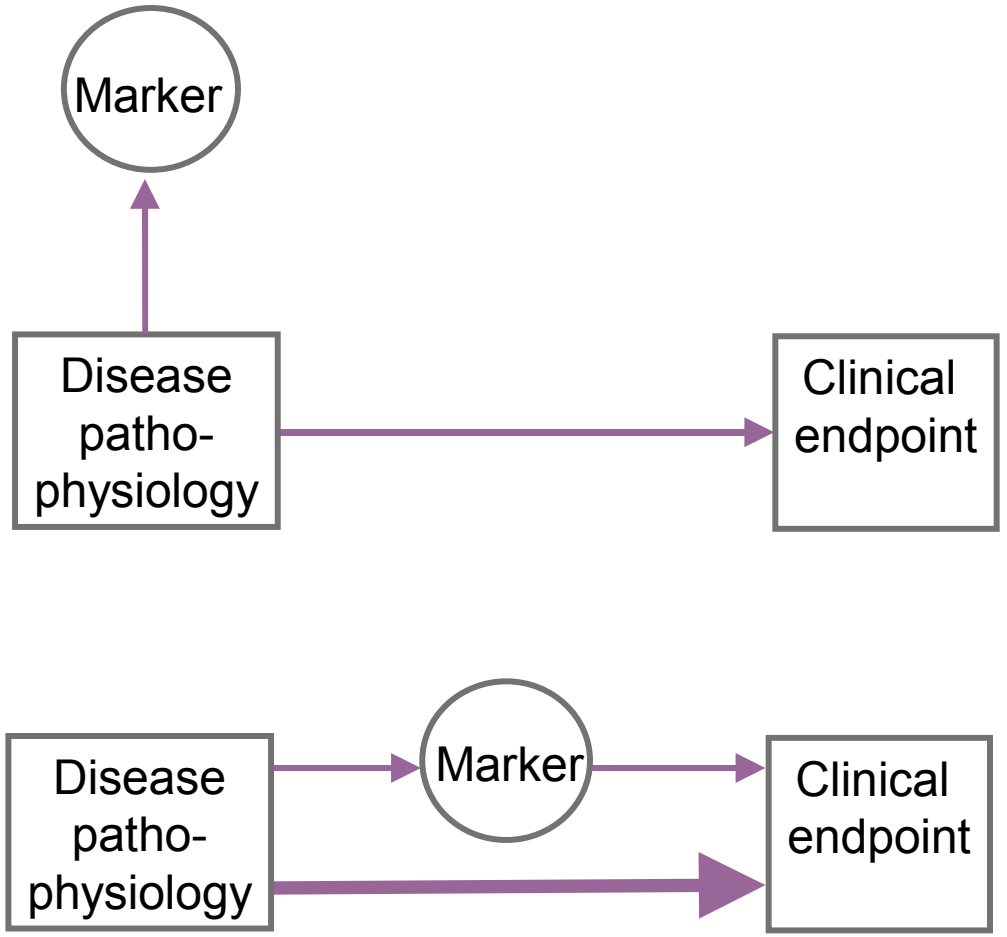


Validation: Caveats and Pitfalls

- Even a close association of a marker with a health-outcome (phenotype) does not prove a causal relation.
  ➔ "a correlate does not a surrogate make" (Fleming & DeMets, 1996.

- A marker must not necessarily be in the causal pathway of the disease process

- There might be other, more important pathways leading to the disease



Our Measurement Certainty Metric (MCM)

Reliability (R) - Precision of measurement **(P)**

- Quality of study **(Q)**

$$R = P \bullet Q$$

Validity (V) - Impact of measurement **(I)**

- Design of study **(D)**

$$V = I \bullet D$$

$$MCM = R \bullet V = P \bullet Q \bullet I \bullet D$$

Certainty Criteria

Measurement Precision (P)	
5	established stand. measurement procedure, nearly completely precise
4	established stand. measurement procedure
3	stand. measurement principle, literature evidence supporting reliability
2	standard. & practical meas. principle, internal evidence supporting reliability
1	standard. & practical measurement princ. Insufficient evidence on reliability available
0	none of the above

Study Quality (Q)	
5	all major and most minor quality criteria fulfilled
4	study conclusive, not all major quality criteria fulfilled
3	study partially conclusive, some major quality criteria fulfilled
2	study partially conclusive, serious methodological flaws
1	some but inconsistent evidence, replication required
0	none of the above

Measurement Impact (I)	
5	parameter proximate to health outcome (establ. clinical endp.)
4	parameter assoc. with organic functioning (establ. surrogate endpoint)
3	parameter rel. to organic functioning or established consistent literature evidence (established biom.)
2	parameter assoc. with pathogenetic mechanism, (new biomarker)
1	parameter assoc. with pathogenetic mechanism, lack of evidence on funct. relevance (new assay)
0	none of the above

Study Design (D)	
5	collection of cohort and/or case control health-outcome studies
4	health-outcome study (cohort or case-control)
3	experiment in humans (clinical study)
2	animal study
1	experiment in-vitro
0	none of the above

Certainty Criteria: Range & Example

R = P • Q : 0 – 25

V = I • D : 0 – 25

MCM = R • V : 0 - 625

MCM% = MCM/625 • 100

$V_1 = I \bullet D = 5 \bullet 5 = 25$

$V_2 = I \bullet D = 1 \bullet 5 = 5$

Measurement Impact (I)		Study Design (D)	
5		**5**	
4		**4**	
3		**3**	
2		**2**	
1		**1**	
0		**0**	

Pilot Study

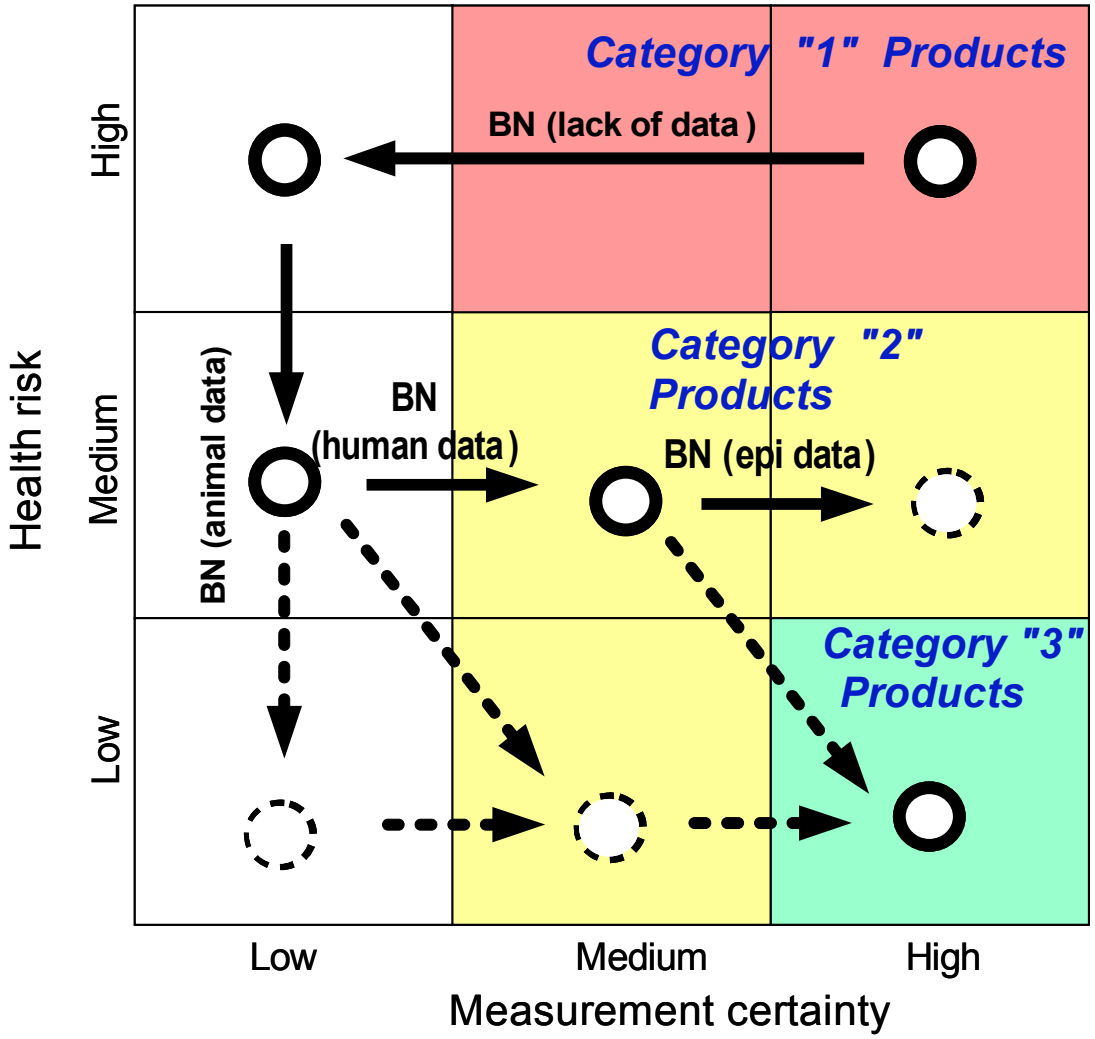
- February/March 2007
- Four different study reports
- Application of the multidimensional Measurement Certainty Metric (MCM)
- Five assessors with different scientific background

Summary Statistics of Pilot Study

$$\frac{\Sigma\left(\frac{SD}{mean\_MCM}\right)}{4}$$

	in vitro (AMES)	animal study	clinical study	clinical study	coefficient of variation
Quality	4.8	3.8	4.6	3.7	0.24
Precision	4.4	4.8	4.4	4.6	0.14
Reliability	*21.3*	*18.8*	*20.6*	*17.6*	
Design	1	2	3	3	0.00
Impact	3.2	3.2	1.9	2.9	0.37
Validity	*3.2*	*6.4*	*5.7*	*8.7*	
CERTAINTY (MCM %)	11.0	18.8	17.8	26.3	

4. Where will we be using the Bayesian Network and reliable epidemiological studies?



The End