Discussion

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Reduced Risk Evaluation

Objective: Address IOM Regulatory Principle 4

"(b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects" *

Reality: The path to 'reasonable expectation' is undefined

Filling the gaps in knowledge will take:

- Better mechanistic understanding (disease/exposure/complex mixture interactions)
- Additional biomarkers
  - "…because definitive evidence that a new PREP actually reduces harm will often be unavailable, short-term markers that reflect long-term outcomes are needed." *
  - "…the use of intermediate markers does not replace long-term follow-up and epidemiological surveillance, but it can be a basis for estimating effects before direct evidence from epidemiological studies is available." *
- Engagement
- Process definition

*Institute of Medicine, 2001, Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction

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Potential Non-clinical Assays Related to Disease

General	Cancer	COPD	CVD
➢ Superoxide dismutase ➢ Lung inflammation in BALF, (i.e. neutrophils) ➢ GSH in biological fluids ➢ HO-1 assay	➢ Mutagenicity assay ➢ Gap junction assay ➢ Micronucleus assay ➢ Hprt mutation assay with rat lung fibroblast ➢ Cytokeratin expression in rat lung tumors ➢ Dermal carcinogenicity model (Sencar mouse) ➢ Comet assay ➢ Chronic inhalation model for lung cancer ➢ Lung tumor progression in transgenic mouse strains	➢ Inactivation of antiproteases ➢ Macrophage activation in BALF ➢ CD4/CD8 lymphocytes in murine lung tissue ➢ Lymphocyte differentiation in murine in lymph nodes ➢ Myeloperoxidase in biological fluids ➢ Early biomarker of lung damage (CC16) ➢ Lung mechanics in rat and mouse models ➢ Mouse models of emphysema	➢ Endothelial cell assay ➢ Angiogenesis assay ➢ Cardiac telemetry ➢ Atherosclerosis model (Apo E deficient mouse strain) ➢ Cardiovascular disease model (Guineas pigs) ➢ Thrombosis model (Apo E-/-) ➢ Cardiac function and myocardial hypertrophy (SHHF and JCR stroke prone rat)

Note: Intended to list assays under consideration for use

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Biomarkers of Potential Harm

Biomarker of Potential Harm	Biomatrix	Pathogenic Mechanism	Health Effect
von Willebrand Factor	plasma	endothelial cell dysfunction	atherosclerosis
microalbumin	urine		atherosclerosis
nitrate+nitrite, exhaled breath NO	plasma		
cellular adhesion molecules *(VCAM-1, ICAM-1, E-selectin)*	blood		
homocysteine (SAM, SAH)	blood		
endothelium-dependent vasoreactivity *(arterial, venous)*	N/A		atherosclerosis
white blood cell count *(total, subpopulations)*	blood, BALF	inflammation	
interleukins-6, -8 (-10)	blood, BALF		
fibrinogen	plasma		
hs C-reactive protein	blood		atherosclerosis
sCD40 L	blood		
tumor necrosis factor α	blood		
nuclear factor kappa beta (NF-kB)	blood		
epidermal growth factor-1 (egr-1)	blood		
N-carboxymethyl lysine	blood		
bilirubin	serum	oxidative stress	
superoxide dismutase (SOD), catalase	blood		
8-epi-prostaglandin $F_{2\alpha}$	urine		
15-keto-dihydro-prostaglandin $F_{2\alpha}$	urine		
isoprostane $F_{2\alpha}$-VI	urine		
H_2O_2	exhaled breath condensate		

rapid-response **slow-response**

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Biomarkers of Potential Harm *(continued)*

Biomarker of Potential Harm	Biomatrix	Pathogenic Mechanism	Health Effect
total, HDL-, LDL-cholesterol	serum	lipoprotein metabolism	atherosclerosis
triglycerides	serum		
non-esterified free fatty acids	serum		
lipoprotein lipase A_2	blood		
paraoxonase	serum		
11-dehydrothromboxane B_2	urine	platelet/coagulation status	
tissue plaminogen activator	blood		
hematocrit	blood	blood viscosity	
fibrinogen	blood		
von Willebrand Factor	plasma		
glucose	plasma	glucose metabolism	diabetes
insulin resistance	blood		
hemoglobin A1c	blood		

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Functional Tests

Parameter	Test	Health Effect
FEV1, FVC	spirometry	COPD
arterial elasticity	pulse-wave Doppler	
arterial wall thickness	carotid intima-media thickness	atherosclerosis
LV diastolic function	color Doppler echocardiography	
cardiopulmonary exercise performance	treadmill exercise test	atherosclerosis
blood pressure		sympathetic activation
heart rate *(variability)*		

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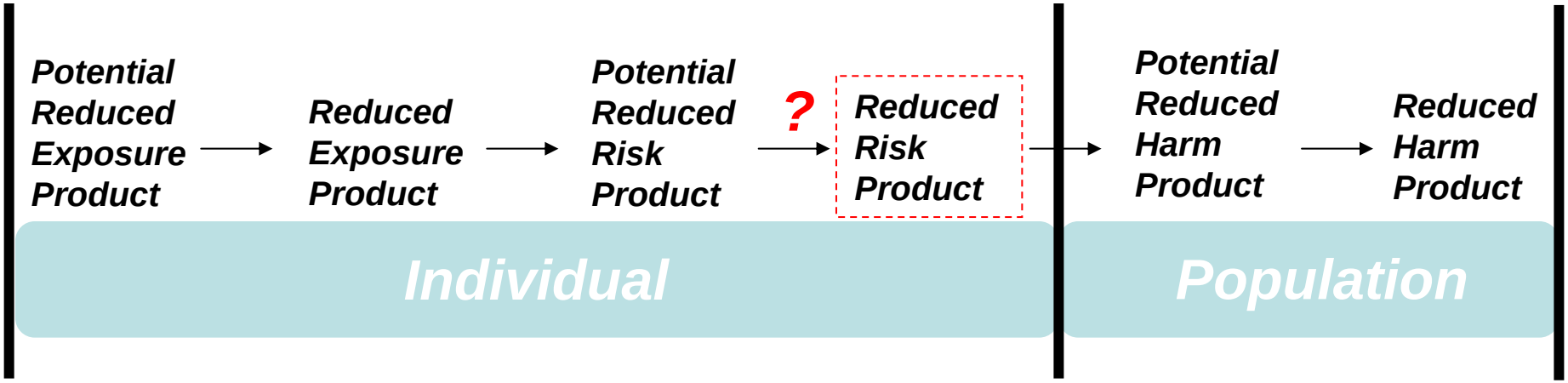
Focus on Risk Evaluation



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