

COMMENTS ON THE EVOLVING
ACES PROGRAM
(Evaluating new diesel technology)

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Analysis

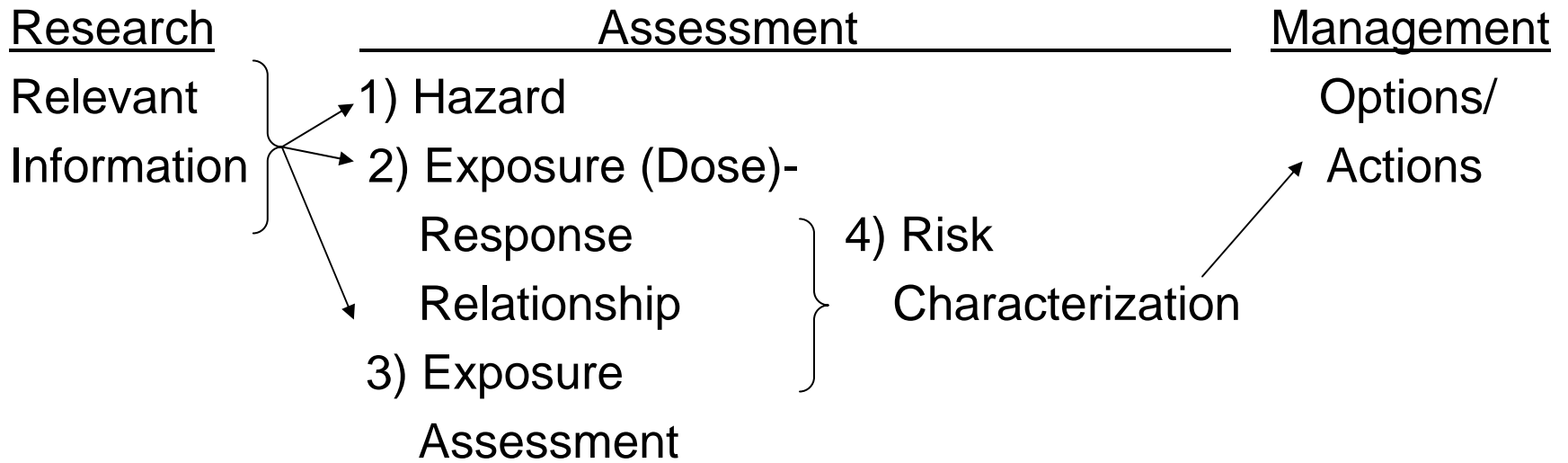
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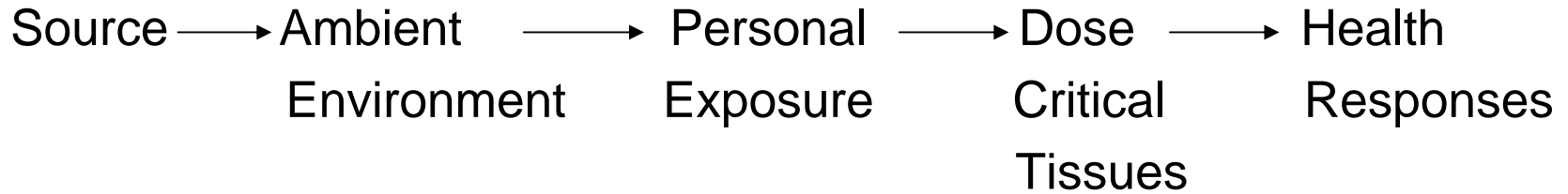
RISK PARADIGM



SOURCES OF INFORMATION TO ASSESS HUMAN HEALTH HAZARDS/RISK

- Human Data (use to maximum extent if available)
 - Epidemiological studies (will not be available for 2007 technology)
 - Clinical: Controlled exposures (must consider ethics of conducting human exposures)
- Whole Animal Studies
- Sub-Animal Studies
(Cells, Tissues)
- Chemical and Physical Characterization

CRITICAL LINKAGE



Individual studies must be considered within this framework to aid in planning and interpreting to achieve maximum value for assessing human hazard/risk

ISSUE RESOLVING RESEARCH PROGRAM NEEDS

Clear Objective

Well-developed Strategy

Defined Protocols

Careful Execution

Detailed Analysis



Quality Control/Quality Assurance

Thoughtful Interpretation

Peer Reviewed Publications

This needs to be a targeted research program, not a collection of loosely linked projects. Somewhat similar past HEI efforts were the CO Multi-Center Study and the HEI/NTP Collaborative Ozone projects

COMPARATIVE POTENCY MATRIX

	<u>Emission Sources</u>					
<u>Endpoints</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>E</u>	<u>F</u>
<u>In vitro</u>						
1						
2						
3						
<u>In Vivo</u>						
1						
2						
3						
4						
<u>Epidemiology</u>						
1						
2						

A, B, C, et. were different engines or other sources that had positive epidemiological findings, i.e., cigarette smoke, roofing tar and coke oven emissions. The goal was to estimate the human hazard/risk of exposure to diesel exhaust.

PROPOSED PROGRAM OBJECTIVE

Test the hypothesis: Exhaust emissions of 2007 technology (heavy duty diesel engines, ultra low sulfur fuels, and exhaust after treatment) pose reduced human exposure and health hazard (risk) compared to 1990s technology

ALTERNATIVE STRATEGIES

- (A) Compare health effects in sub-animal bioassays of equivalent dilutions of whole diesel exhaust from 2007 technology versus 1990s technology
- (B) Use exhaust constituent measurements as surrogate measure of human exposure and health hazard/risk
- (C) Compare health effects in animal bioassays exposed to diluted whole exhaust

I recommend against doing studies with collected particles that inevitably involve exaggerated “doses,” quantities instilled or present in 1 or 2 cc of culture media equal to what a human would inhale *in toto* over many days or weeks

STRATEGY REQUIRES FOCUS

Multiple Variables

- engines
- fuels
- after treatments

Results from studying many variables guide selection of few variables for intense study

Few Selected Technology Variables

1					
2					
3					
					34
					35
					36

2	7		
4			
			33

4		
		30

5	7
11	21

Chemical/Physical Measurements

- least expensive
- least sophisticated

Chemical/Physical Measurements

- most expensive
- most sophisticated

Short-Term Biological Assays

- least expensive
- shortest duration

Long-Term Biological Assays

- most expensive
- longest duration

*might be single life span bioassay

KEY ISSUES

Technology

- engine(s)
- fuel(s)
- after treatment(s)
- cycle

Bridging

- equal dilution versus equal mass
- temperature, humidity, O₂

Toxicology

- collected material applied to cells, tissues
- whole exhaust
 - species, strain, health status
 - exposure levels
 - study duration
 - endpoints (cancer, functional decrements)

Comparison of 2007 technology to older diesel technology may be done based on new studies of old technology or “desk-top” comparison with meta-analysis of prior studies. Stay alert to opportunity for comparisons with other sources of particulate material.

COST!!!

Importance of Relevant Exposure Levels

- Use dilutions of whole exhaust
 - Establishes “realistic” upper bound or maximum tolerated “dose” for assessing hazard
 - Dilution requires consideration of factors like temperature, humidity and O₂ content
- Example
 - 0.1 dilution (1970s and 1980s studies typically
 - 0.033 dilution involved about 1 to 10 dilutions)
 - 0.01 dilution
 - 0.0033 dilution
 - Control (likely to have 5-10 µg/m³ PM in cage)
- Caveat: Do not use PM_{2.5} concentrations below annual PM_{2.5} NAAQS multiplied by 168/42

LINKING NEW INFORMATION TO ISSUE/OBJECTIVES

- Must have integrated assessment that considers

(a) any changes in exposure* and (b) any changes in potency*

Surrogate for changes in human health response*

*Related to technology changes (definitely will have lower concentration of emissions, changes in potency, i.e., effect per unit exposure mass are unknown)

- Another set of hazard characterization data based on collected material for alternative technologies may provide information on potential changes in potency. However, it will not address the objective stated earlier.

RELEVANCE OF STUDIES OF LUNG CANCER IN RATS FROM EXPOSURE TO DIESEL EXHAUST FROM OLD TECHNOLOGY

Valberg and Crouch (1999)

- Meta-analysis of 8 long-term rat studies
- Threshold in range of 500-700 $\mu\text{g}/\text{m}^3$
- No evidence of positive slope below 600 $\mu\text{g}/\text{m}^3$

Mauderly (2000)

- Evaluated 8 most robust studies in rats
- Strongly suggest threshold at about 600 $\mu\text{g}/\text{m}^3$
- At 600-1500 $\mu\text{g}/\text{m}^3$ variable response
- Over 1500 $\mu\text{g}/\text{m}^3$ evidence of positive response related to “overload”

Recall the rats breathed whole exhaust, the PM measurements are a surrogate for the total exhaust, PM, NO_x, CO, volatile and semi-volatile hydrocarbons.

Relevance of Lung Tumor Findings in Rats

McClellan (1996), Mauderly (1996, 1997, 1998) concluded:

- Doubtful that rat lung tumor response is a useful indicator of lung cancer hazard for humans
- Lung tumor response of rats should not be used for quantitative estimates of lung cancer risk for humans

It follows logically from the above that -

If confidence is lacking in the validity of the above endpoints (lung cancer in rats) it follows that measures of putative precursor events observed exposed to high concentrations (low dilutions) of whole exhaust in rats are of questionable relevance to the human situation.

Studies of Lung Cancer in Mice and Syrian Hamsters from Diesel Exhaust

- Mice yielded, at most, an equivocal lung tumor response to diesel exhaust. Statistical power of largest study (Mauderly *et al*, 1996) was greater than largest individual rat study - yielded no excess lung tumors
- Diesel exhaust clearly not a pulmonary carcinogen in Syrian hamsters exposed under conditions carcinogenic to rats

Rationale for Rat Studies Below 600 $\mu\text{g}/\text{m}^3$

- Potential for detection of unique effects or potency of 2007 exhaust
- Limiting particle mass to less than 600 $\mu\text{g}/\text{m}^3$ (2400 $\mu\text{g}/\text{m}^3$ if exposed only one fourth of time – 42 hours/week rather than 168 hours) limited likelihood of producing lung tumors due to “overload phenomena.”

Use of second species such as mouse would match NTP protocol

Relevance of Studies of Non-Cancer Endpoints in Rats

Mauderly *et al* (1987, 1988), Henderson *et al* (1988)

At 73 $\mu\text{g}/\text{m}^3$ (350 $\mu\text{g}/\text{m}^3$, 7 hours/day, 5 days/week) – no effects on

- lung cell proliferation
- lung fibrosis
- lung clearance of particles
- lung function

Caveat: Could actually have higher “threshold” for NOAEL, next higher exposure level with effects was – 730 $\mu\text{g}/\text{m}^3$ (3500 $\mu\text{g}/\text{m}^3$, 7 hours/day, 5 days/week)

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This type of research requires coordinated planning to link all of the various elements of the program together. It requires substantially more management effort than required for a portfolio of individual research projects involving investigator identified goals, objectives and experimental designs.