

ACES Workshop

Health Effects Working Group
Report

November 7, 2003

Proposed hypothesis to be tested:

“Emissions from new diesel engine technologies (including fuel and aftertreatment) result in reduced human exposure and reduced endpoint-specific adverse effects when compared with earlier heavy-duty diesel technology”

Comparative Testing

Should ACES rely on published results or include an earlier engine in the testing?

Arguments

- Pro: older tests did not use the same conditions and were done on light-duty engines; end point assessment may be different (new assays)
- Con: Lots of information available, expensive

Health Endpoints to Be Considered

Priority:

- Cancer (most important because of history and regulatory classification)
- Cardiovascular (new for diesel because of PM effects)
- Respiratory disease
 - Allergy/asthma
 - Inflammation
 - Susceptibility to infectious disease in the lung

Health Endpoints to Be Considered

Emerging (possible additional endpoints to consider):

- Developmental
- Neurotoxicity

Removed from list: Reproductive

EXPOSURE ISSUES

- In vivo inhalation to whole exhaust
- In vitro exposure of lungs cells to whole exhaust
 - Why: more realistic, not enough particles in new emissions, composition changes when particles are collected and resuspended
- Primary versus secondary emissions
- Dose-response needed (maximum tolerated dose and dilutions thereof)

CANCER

- Long-term carcinogenicity bioassay (24 or 30 month)
- 2 species: rat and mouse
- Discussion item: use monkey? (also for other end points)
- Use sensitive species: p53 mouse (reduce to 6 month assay)?

CANCER

- Short-term assays: to be decided.

Possibilities:

- DNA reactivity, repair
- Mutagenicity
- Chromosomal aberrations in human lung cells

CARDIOVASCULAR

Human and animal studies

- Cardiac endpoints: arrhythmias, heart rate variability
- Vascular endpoints: clotting process and endothelial function

Human studies:

- Several studies in planning phase elsewhere
- Healthy adults, healthy elderly, diabetics

CARDIOVASCULAR

Animal models:

1. Cardiac infarction
2. Diabetic model
3. Atherosclerosis model (rabbit)
4. Thrombosis model (hamster)

RESPIRATORY ENDPOINTS

ASTHMA/ALLERGY

Humans:

- Non-clinical enhancement of response to allergens
- Inhalation of diluted exhaust

Animals:

- Induction and exacerbation
- Important to deliver to lung
- Mouse and rat models, choice of allergens

RESPIRATORY ENDPOINTS

INFLAMMATION/LUNG INJURY

Lung inflammation

- Biomarkers of airway inflammation (cytokines)
- Neurogenic inflammation?
- Morphological changes

Systemic inflammation (circulating neutrophils, C-reactive protein)

Good animal models: rats, monkeys?

RESPIRATORY ENDPOINTS

RESISTANCE TO INFECTIOUS DISEASE IN LUNG

Animal models: choice of pathogens

- Respiratory Syncytial Virus
- Pseudomonas
- Mycoplasma pneumonia

90-DAY SUBCHRONIC STUDY

- General toxicity
 - organ weights,
 - histopathology,
 - blood parameters
- Additional endpoints?

GENERAL ISSUE

Relevance of all assays of health endpoints and animal models to human diseases