Recent Respiratory Toxicology Investigations of Mineral Oils: Post-1990

W. E. Dalbey and R. W. Biles
ExxonMobil Biomedical Sciences, Inc.

ACGIH Symposium On Mineral Oils And Metal Processing Oils

October 2-4, 2002

Overview of Presentation

- Summary of acute inhalation toxicity data
- Summary of long-term inhalation studies prior to 1990
- Review of recent 4-week inhalation studies
- Review of recent 13-week inhalation studies on formulated products
- Conclusions

Key Messages

- No unique toxicity apparent in animal models
- Biological responses limited to lungs
- Recent studies support low toxicity of inhaled mineral oils

Mineral Oils/ Lubricant Base Oils

- Lubricant/specialty base oils prepared from crude oils
- Carbon numbers >15 (15-50) and boiling point ranges 300 to 600°C (570 to 1110°F); molecular weights > 280
  - ➢ Does not include low viscosity solvents, distillates
- Other nomenclature in the inhalation toxicology literature:
  - ➢ "lubricating oils"
  - ➢ "paraffinic oils"
  - ➢ "motor oils"
  - ➢ "white oils"
  - ➢ "fog oils"
  - ➢ "metalworking oils" (with / without additives)

Summary of Acute Inhalation Toxicity Data

- Toxicity/lethality not observed unless exposure very high (10^{3-5} mg/m^3)
- Irritation of respiratory tract only at high concentrations

Concentration	Material	Endpoint
250 mg/m^3	Lube Oil	G. Pigs - Breathing Pattern[1]
>100,000 mg/m^3	Three Mineral oils	RD50[2]
>1000 mg/m^3	Mineral oils	Est. human irritation[2]
53 mg/m^3	Mineral oil from a MWF	Est. human irritation[3]

- Reports of hypersensitivity pneumonitis and asthma
  - Water-based formulations
  - Possible role of endotoxin[4]

[1]*Costa and Amdur, 1979*
[2]*Schaper & Detwiler, 1991*
[3]*Schaper & Detwiler-Okabayashi, 1995*
[4]*Gordon, 1995 & 1997*

Summary of Long-Term Inhalation Exposures Prior to 1990

- Effects with 1-26 month exposures limited mainly to lung
  - Concentration-related retention of oil in lung and associated lymph nodes
  - Progressive accumulation of vacuolated macrophages in alveoli, terminal bronchioles, or lymph nodes
  - Occasional inflammatory response or granulomas (lipoid pneumonia)
  - Rat generally more sensitive than dog, mouse, hamster, rabbit, gerbil, or monkey

- No fibrosis or tumors reported at 100 mg/m^3 for 26 months in rat, dog, mouse, hamster, or mouse

- More recent studies in the rat confirm and extend these earlier results

Subchronic Inhalation Studies in Rats Since ~1990

Reference	Product	mg/m3	Time
Selgrade et al,1987	Light Lubricating Oil (Fog Oil)	0, 500, 1500	3.5 hr/d, 4 d/wk, 4 wk
Dalbey et al, 1991	Solvent-Refined Oil	0, 50, 210, 1020	6 hr/d, 5 d/wk, 4 wk
	White Oil	0, 50, 210, 980	
	Hydrotreated Base Oil	0, 47, 220, 980	
Selgrade et al, 1990	Light Lubricating Oil (Fog Oil)	0, 200, 500, 1500	3.5 hr/d, 4 d/wk, 13 wk
Formulations:			
Dalbey and Roy, 1997	Aluminum Roll Oil	0, 60, 170, 420	6 hr/d, 5 d/wk, 13 wk
Dalbey, 2001	Generic Cutting Oil	0, 50, 150, 500	6 hr/d, 5 d/wk, 13 wk
	Generic Gear Oil	0, 60, 150, 520	
	Commercial Engine Oil	0, 50, 150, 400	

Light Lubricating Oil

- **200 mg/m^3**
  - **13-wk: Minimal accumulation of macrophages in alveoli; minimal increase in lavaged protein**
- **500 mg/m^3**
  - **4 & 13-wk: Increased macrophages, lavaged PMNs, lung weight**
  - **13-wk: Macrophages in peribronchial lymph nodes**

Light Lubricating Oil (cont'd)

- **1500 mg/m^3**
  - **4 & 13 wk: Effects similar, but more pronounced**
  - **Multifocal pneumonitis with hypercellularity of alveolar walls & interstitial infiltration of inflammatory cells in some animals**
  - **Increased lavaged protein & cells, particularly PMNs**
  - **DL_{CO}[1] increased with 4-wk and not changed with 13-wk exposures**

- **Consistent with mild inflammatory edema**

Selgrade et al, 1987 and 1990

[1]Carbon monoxide diffusing capacity

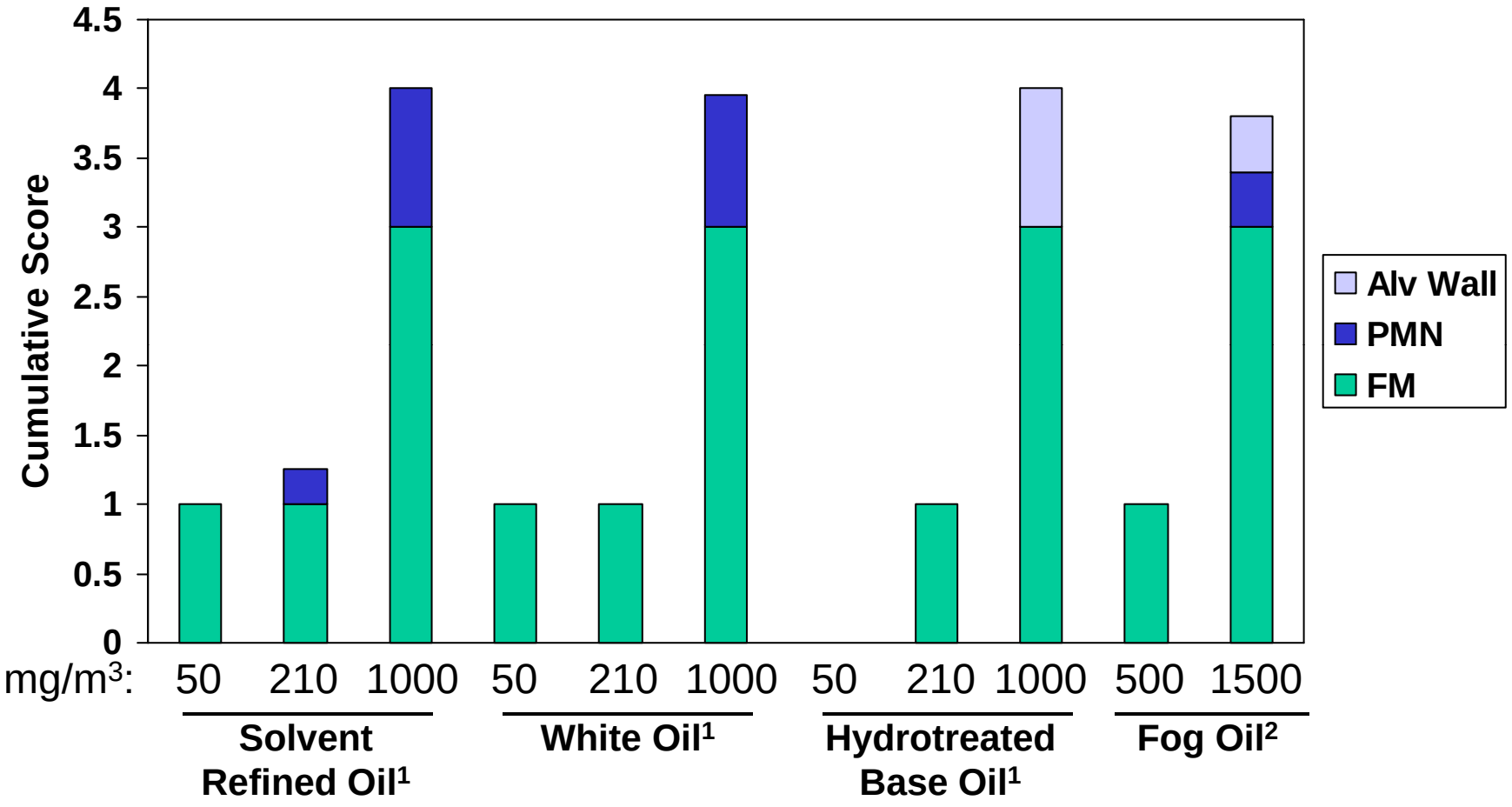
4-Week Inhalation Exposures Using Lubricant Base Oils

- **Three base oils**
  - **Severely hydrotreated and hydrocracked heavy paraffinic oil (HBO)**
  - **Solvent-extracted, catalytically dewaxed heavy paraffinic oil (SRO)**
  - **Severely hydrotreated and acid-washed white oil-USP (WTO)**
- **Endpoints: hematological profile, 22 serum clinical chemistry measurements, weight and histopathology of major organs**
- **General profile of results similar to those with light lubricating oil**

Pictures (Too large to include here)

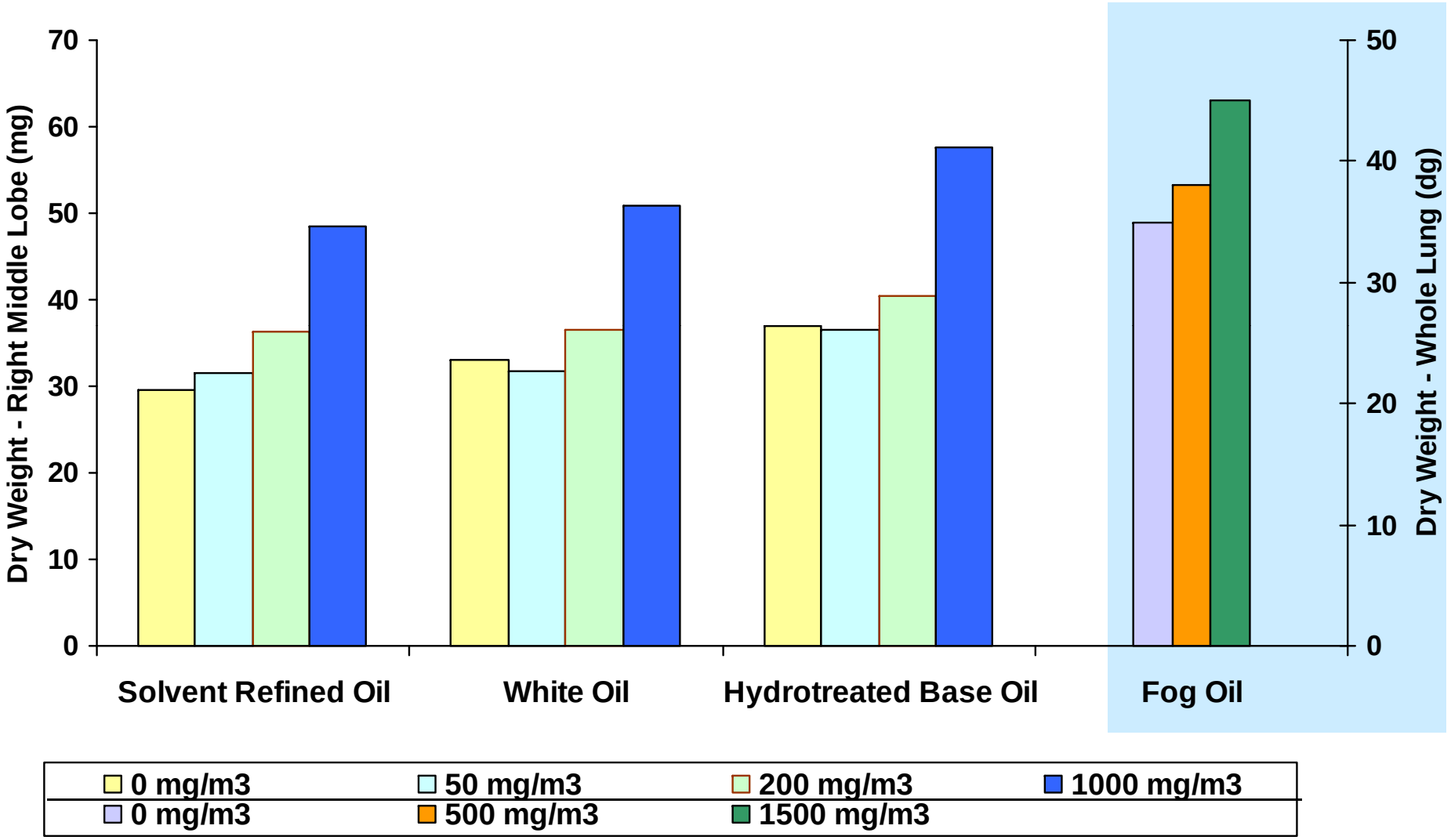
- Examples of 0 and 1,000 mg/m^3 SRO
- Example of Lung from Unexposed Control
- Example of Lung Following 4-Week Exposure to 1,000 mg SRO/m^3
- Example of Foamy Macrophage (FM)
- Example of Aggregates of Foamy Macrophages with 1,000 mg SRO/m^3

Cumulative Histology Scores After 4-Week Exposures to Various Mineral Oils



[1]Dalbey et al, 1991
[2]Selgrade et al, 1987

Lung Dry Weight After 4 Wks Inhalation Exposure to Various Mineral Oils



13-Wk Inhalation Exposures with Formulated Products

- **Aluminum roll oil[1]**
  - **70% severely hydrotreated naphthenic base mineral oil**
  - **25% proprietary ingredients, 5% triethanolamine**
  - **Generation by brief contact of 25% emulsion with aluminum at ~800°F**

- **Generic cutting oil-Straight MWF (GCO)[2]**
  - **85% heavy paraffinic mineral oil, 10% sulfurized choice white grease**
  - **3% proprietary additive, and 2% chlorinated wax**

[1]*Dalbey and Roy, 1997*
[2]*Dalbey, 2001*

13-Wk Inhalation Exposures with Formulated Products (cont'd)

- **Generic gear oil (GO)[2]**
  - **97% heavy paraffinic/naphthenic mineral oils, 3% additives**
- **Generic commercial engine oil (CEO)[2]**
  - **94% heavy paraffinic distillate**
  - **6% calcium sulfonates, zinc dithiophosphate, VI improver, etc.**

[2]Dalbey, 2001

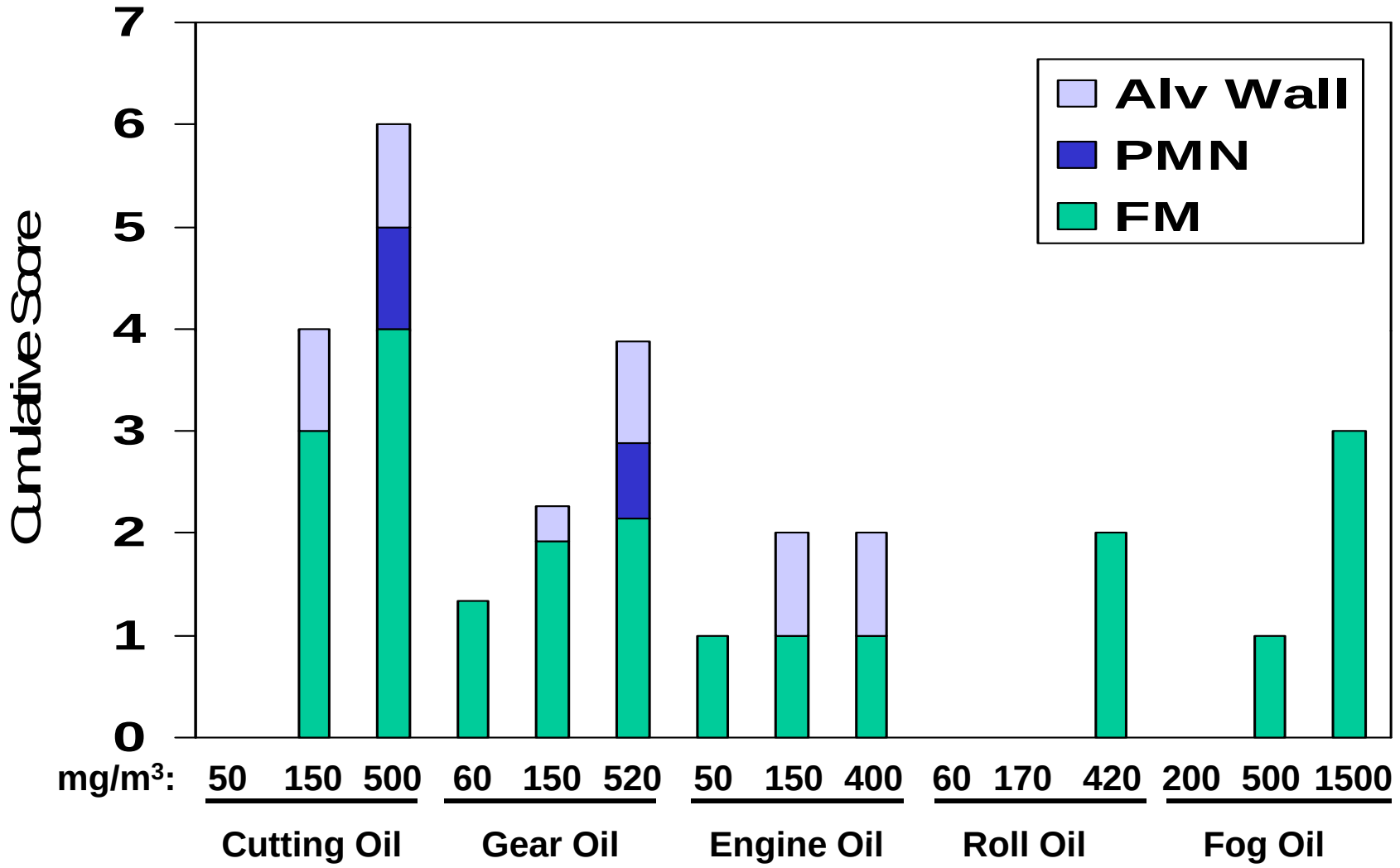
13-Wk Inhalation Exposures with Formulated Products (cont'd)

- **Endpoints: Hematology, serum chemistry, organ weights, histologic evaluation, pulmonary function, and pulmonary hydroxyproline.**

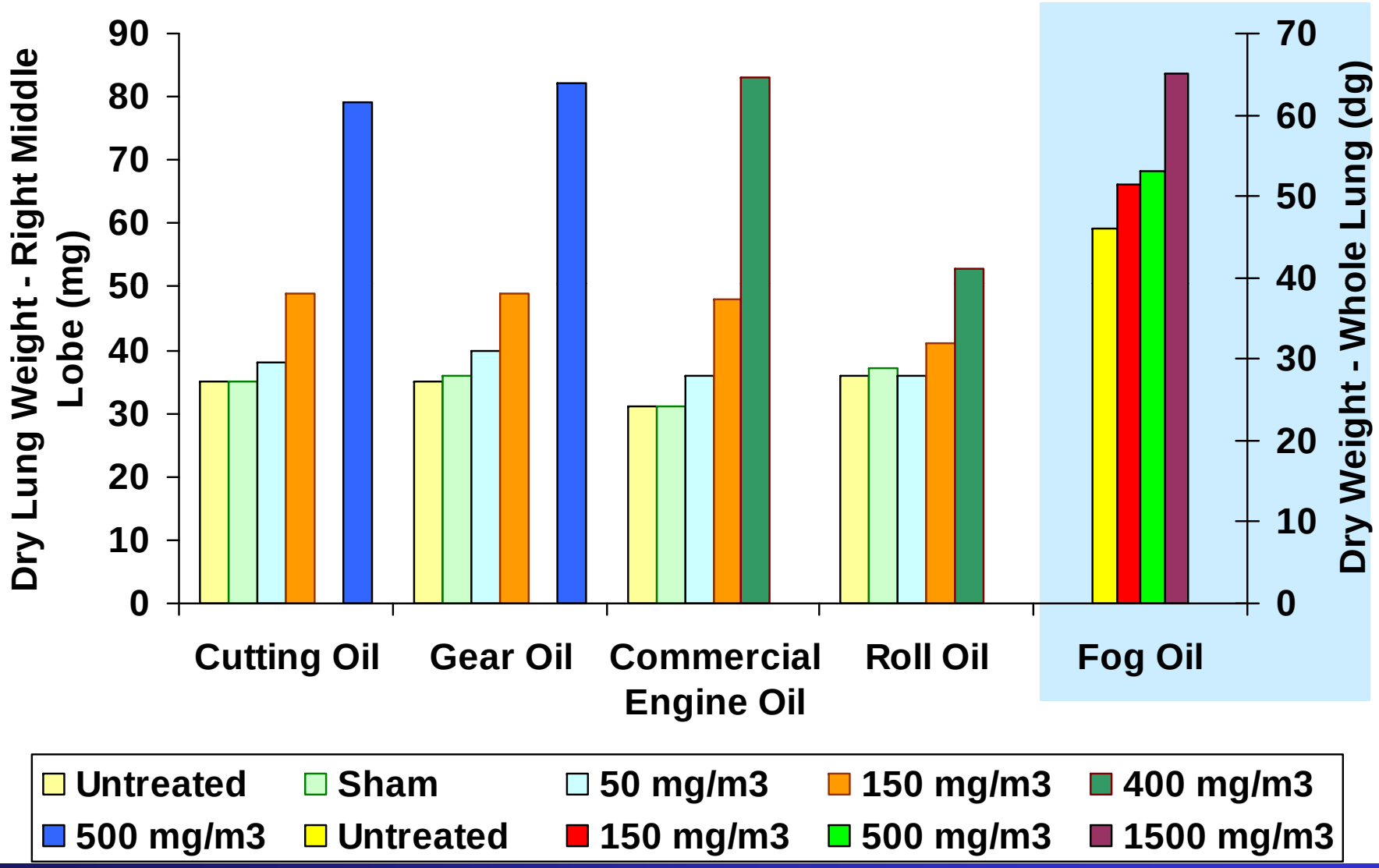
- **Effects limited primarily to lung and respiratory tract**
  - **Accumulation of FM in pulmonary alveoli and alveolar walls**
  - **Very mild thickening of alveolar walls due to FM and mixed cell infiltrate**
  - **Subtle epithelial hyperplasia**

- **Generic Cutting Oil (MWF) relatively more severe in effects over other oils**

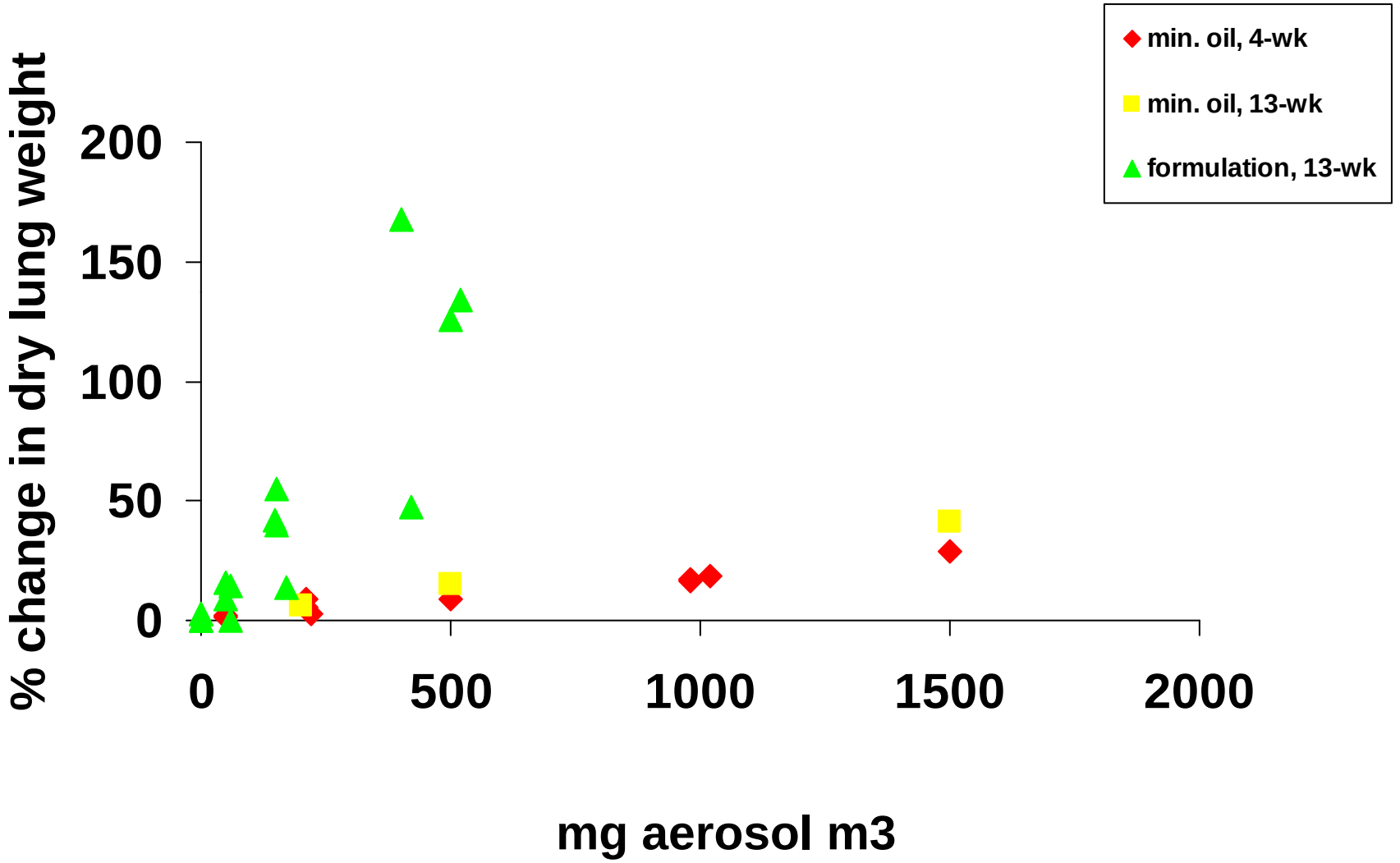
Cumulative Histology Scores After 13-Wk Exposures to Formulated Products



Lung Dry Weight After 13 Wks Inhalation Exposure to Formulated Products



Percent Change in Dry Lung Weight



Conclusions

- No unique toxicity apparent in animals exposed to high concentrations of aerosols from refined base mineral oils or formulated products
- Reactions limited mainly to lung and appear to be primarily nonspecific responses to deposited aerosol
- No tumors or fibrosis observed with chronic exposures to 100 mg/m^3
- NOAEL in rats for severely refined mineral oils (marginal/mild increase in FM & lung wt)
  Data support proposed TLV of 1992 and 1996 for severely refined mineral oil at 5 mg/m^3
  - 4-wk ~200-500 mg/m^3
  - 13-wk ~50-150 mg/m^3
- NOAEL for formulated products may be lower depending on composition