Presentation 9 – Mark Witten

Effect of JP-8 Jet Fuel Exposure on the Immune System and Lungs

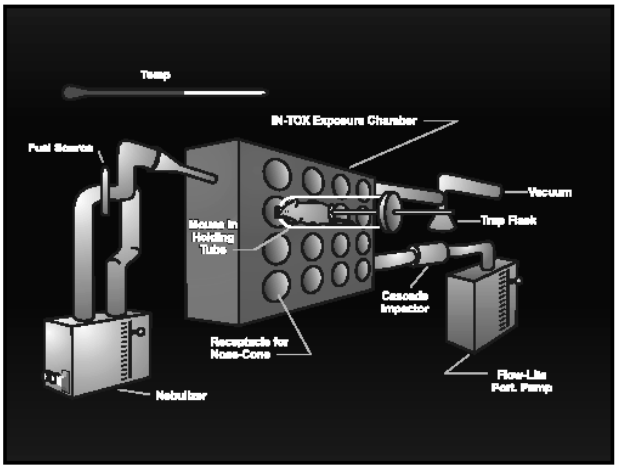
Mark L. Witten, Ph.D.
Joan B. and Donald R. Diamond
ung Injury Laboratory
e University of Arizona
of Medicine, Tucson, Arizona

Gulf War Illnesses Syndrome

- Visit to Saudi Arabia in June of 1995
- Talks with Saudi health officials
- Extent of air pollution from Kuwait oil fires
- Personal experiences of my cousin during Gulf War 1

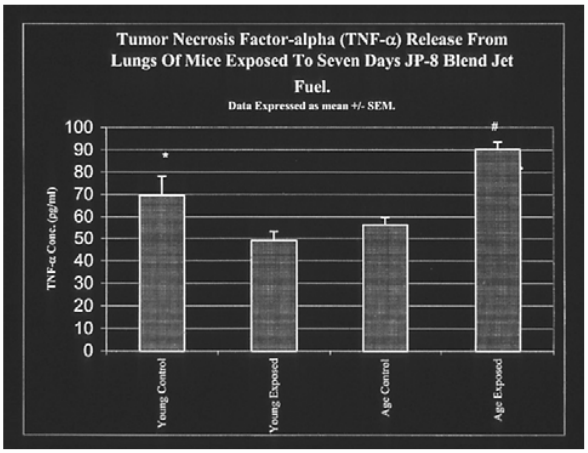
My talk will be divided into three segments

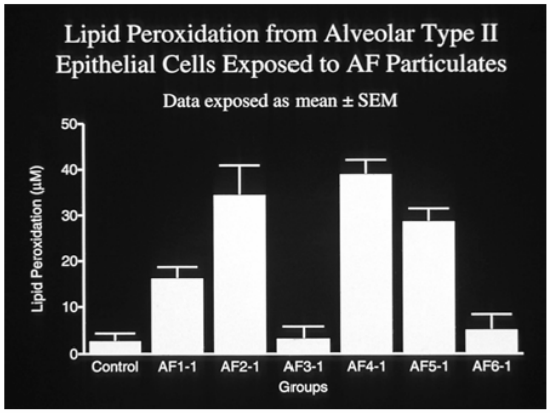
- Lung Immune Data
- Systemic Immune Data
- Skin Immune Data

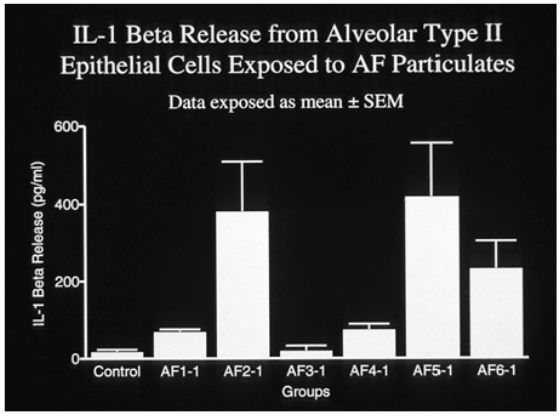


Age-Related Differences in Pulmonary Inflammation to JP-8 Jet Fuel Aerosol Inhalation

- C57BL/6 mice split into a young (3.5 month old) group and adult (12 months old) group.
- JP-8 jet fuel exposure at 1000 mg/m^3/hr for 7 days.
- JP-8 exposed young and adult mice had similar responses with regards to lung dynamic compliance, lung permeability, BALF cell count, and decreased PGE_2.
- Total lung cell counts in both the adult (<33%) and young (<50%) JP-8 jet fuel-exposed mice compared to controls. However, % PAM < in the adult mice while remained stable in the young mice.
- TNF♋ and 8-iso- PGF_2♋ responses varied between the adult vs.
young mice.







Immune System

- JP-8 jet fuel exposure for one hour/day
- 100mg/m^3 conc – Decrease in cellularity of the thymus.
- 500mc/m^3 conc – Decreased spleen weight and cellularity.
- 1000 mg/m^3 conc – Decreased ability of spleen cells to mediate immune responses.

- Adult Female B6C3F1 mice given JP-8 (olive oil carrier) by gavage ranging from 250-2500 mg/kg/day for 14 days.
- Thymus mass < at exposure levels ≥1500 mg/kg/day.
- Decreases in thymic cellularity were observed at exposure levels of 2000 mg/kg/day.

- Decreases in plaque – forming cell response were dose responsive at levels of 500 mg/kg/day.
- Alterations were detected in thymic and splenic CD4/8 subpopulations.
- Proliferative responses of bone marrow progenitor cells were enhanced in mice exposed to 2000 mg/kg/day of JP-8

Key Point

Humoral immune function is impaired with lower concentration of JP-8 than is required to affect primary and secondary immune organ weights and cellularity, CD4/8 subpopulations, and hematological endpoints.

JP-8 Jet Fuel Exposure of 1000 Mg/M By Female C57BL/6 Mice For One Day

- Decrease in thymus cellularity
- Decrease in spleen cellularity, but not as pronounced as thymus.
- Spleen immune cells associated with apoptosis (CD4/8,Mac 1, CD45R) were increased, Dec-205 was decreased and CD-16 was unchanged at one day post – exposure to JP-8.

Cytokines IFN gamma, IL-4, and IL-10 associated with CD4/8 and Mac-1 cells were increased at days +1 and +4 after JP-8 exposure.

Dermal Immune Responses

- Low (50 μl/day) JP-8 jet fuel administration of five consecutive days in C3H/HeN mice suppressed contact and delayed hypersensitivity responses, including depressing the protective effect of prior vaccinations.
- Hypothesis – IL-10 and PGE2 are produced by keratinocytes that distribute through the systemic circulation and down-regulate the cell-mediated immune response.

JP-8 Dermal Exposure for 4 Hours

- Increases in TNF and IL-8 in human keratinocytes.
- This is the same time-frame observed in rats for IL-1 and inducible nitrous oxide synthetase.

Potential Mechanism for JP-8 to Induce Keratinocyte Cell Necrosis

High intrinsic levels of Bcl-2 and Bcl-x(L) may prevent apoptotic death of keratinocytes at lower levels of JP-8 jet fuel exposure while perturbation of the balance between pro-and antiapoptotic Bcl-2 family members at higher levels may induce nectrotic cell death in human keratinocytes.

Conclusions

- JP-8 jet fuel is a toxic substance.
- Demonstrated immune system effects at levels of JP-8 as low as 100 mg/m.
- There are age related effects to the JP-8 response.
- Dermal exposure may have body wide immune system perturbations.