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**EFFECT OF DIESEL PARTICLES ON
HEALTH**

Epidemiological studies suggest particulate matter implicated in:

- Increased mortality:
 - Cardiopulmonary
 - Lung cancer
- Increased morbidity:
 - Hospital admissions for asthma and cardiovascular pathologies
 - Respiratory symptoms

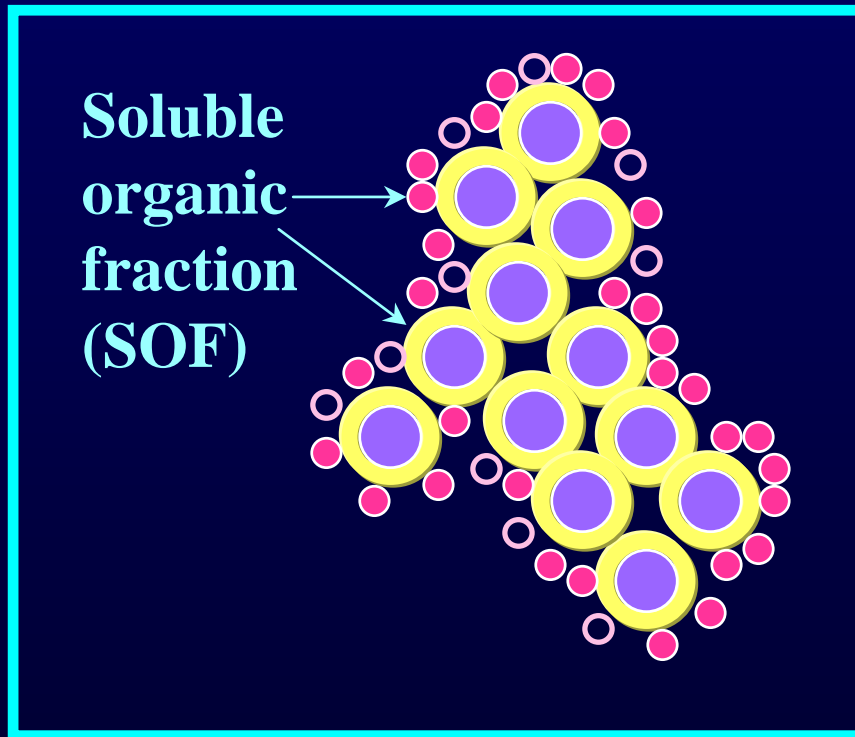
Role of Diesel exhaust particles?





- Increasing part of Diesel vehicles in Europe and in Japan, 50% in France.
- DEP account for a highly significant percentage of PM in many cities in the world
- About 80% of soots in PM 2.5 in Paris

Diesel emission:

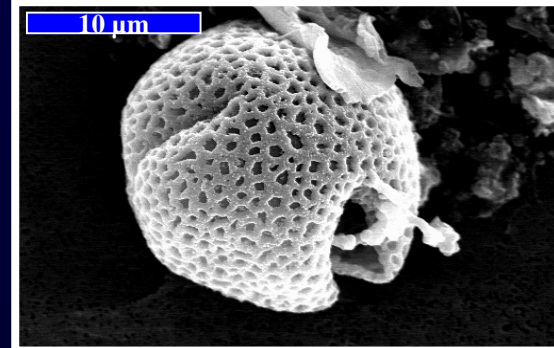
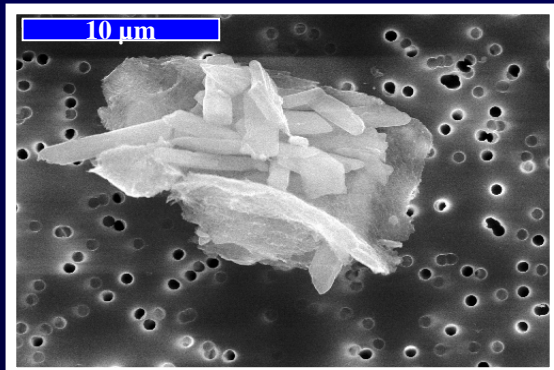
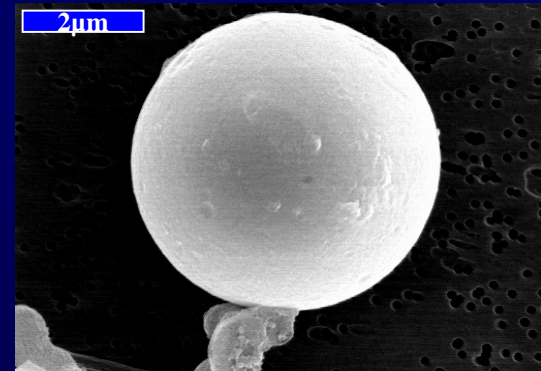
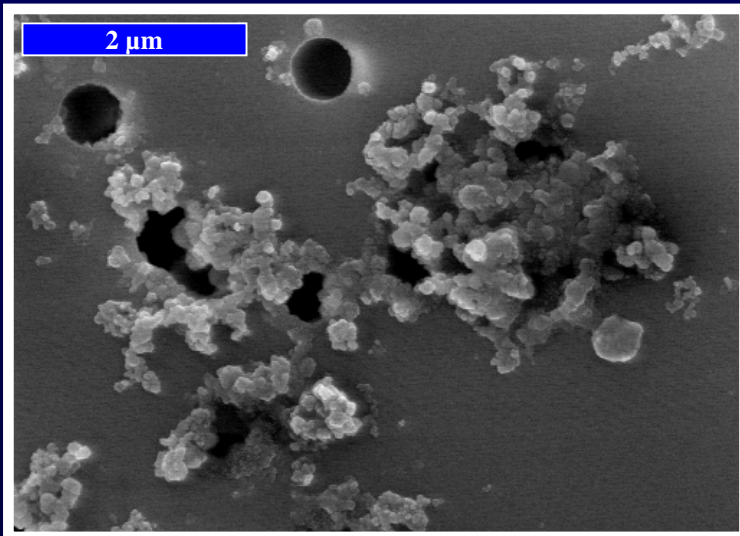
- **In motor vehicles : incomplete combustion \Rightarrow various gases and Diesel particles (DEP)**
- **DEP emission depends on vehicles and fuel composition**
- **DEP emission strongly decrease from 1975 (0.5g.km⁻¹ to 0,08 g.km⁻¹)**

SCHEMATIC OF DIESEL PARTICLES



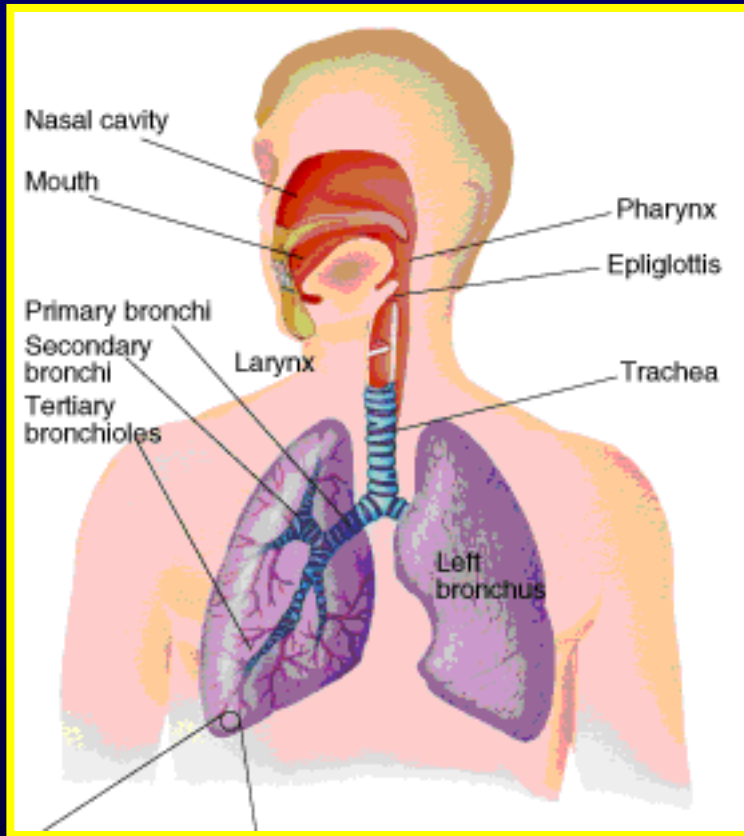
-  **Solide carbon spheres**
(0.01-0.08 μm)
form agglomerates (0.05- 1 μm)
-  **Adsorbed hydrocarbons**
-  **Liquid condensed hydrocarbon particles**
-  **Sulfate with hydratation**

PM collected in Paris



Soots represent about
~80% of PM

Particle deposition in lungs



← nasopharynx : $> 5\mu\text{m}$

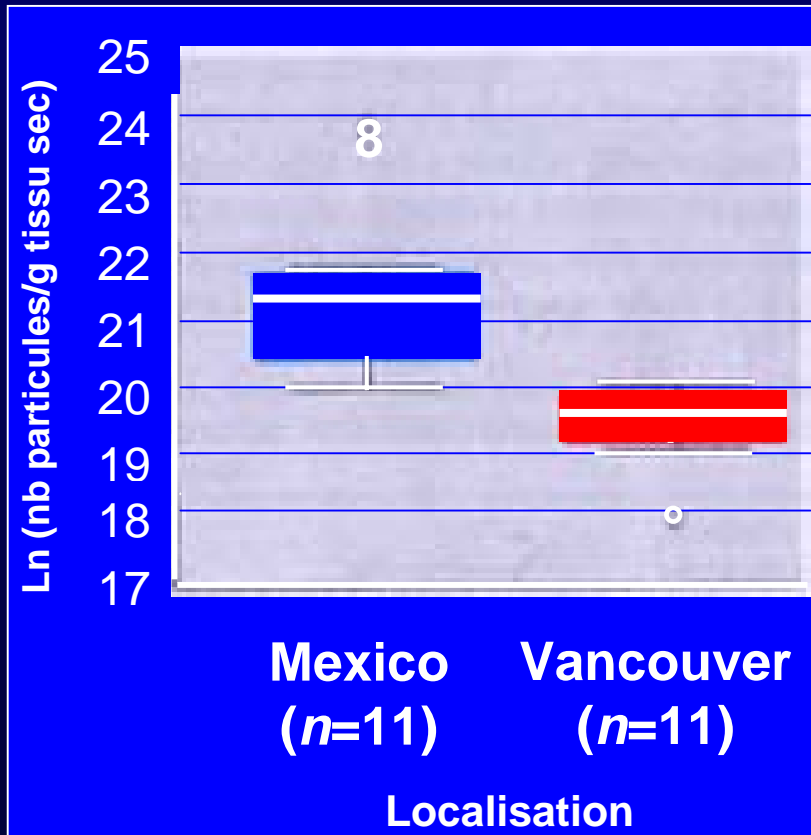
← trachea / bronchi : $1 - 5\mu\text{m}$

← bronchioles / alvéoles : $< 1\mu\text{m}$

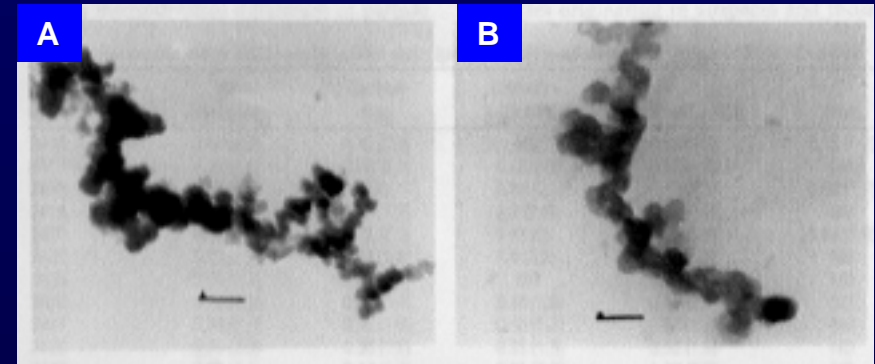
Clearance of DEP particles

- 30 % of inhaled DEP are deposited in respiratory tract.
- one third in pulmonary region
- clearance half time of 62 days in rats

Pulmonary biopersistence of fine PM (Brauer et al. 2001)



Mexico



A : Atmosphere PM B : lung PM

CONCLUSION :

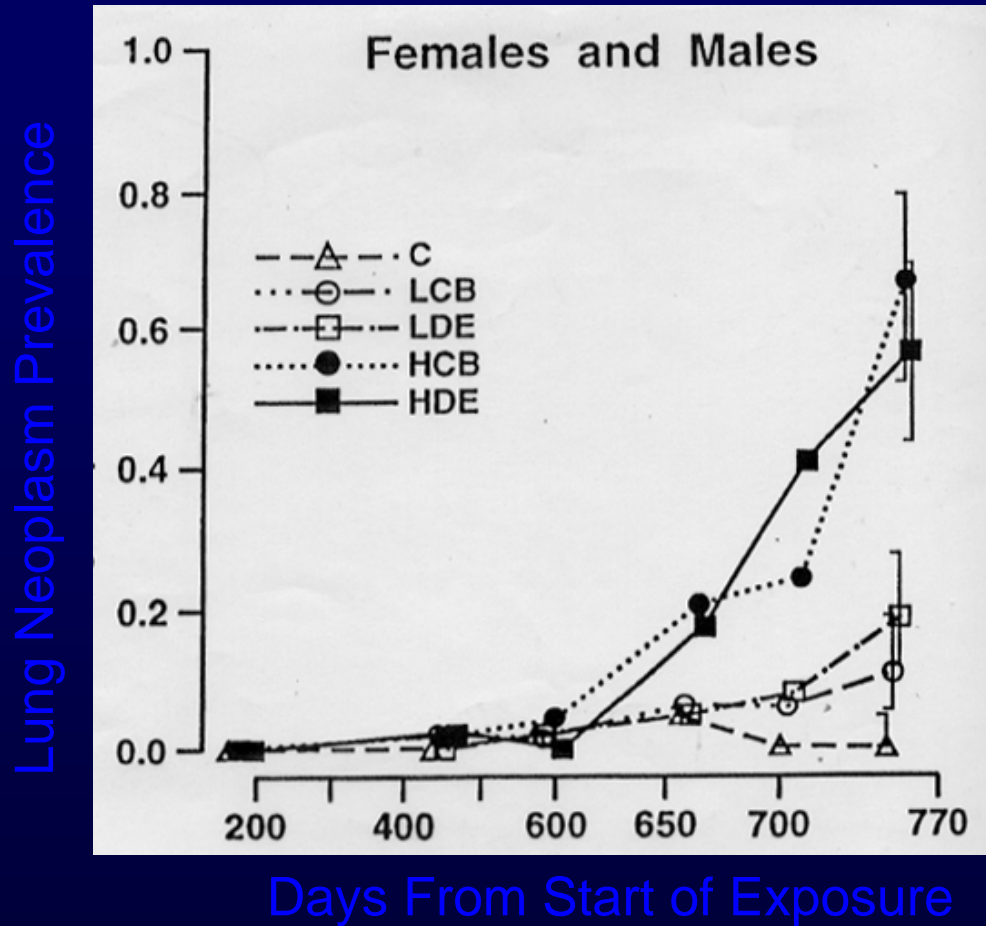
10 more fine PM in lungs at Mexico than at Vancouver

Research approaches on DEP biological effects

- **Long Term**
 - Rat and Mouse models (6 weeks- 2 years)
- **Short Term**
 - Exposure chamber studies (2hrs)
 - mouse, human volunteers
 - Nasal provocation challenges (bolus)
 - human volunteers
 - In vitro models

DEP and Lung cancer

Long term effects :carcinogenesis in rat



Lung tumors in rat after exposure to Diesel exhaust and carbon black (Mauderly 1994)

C : control LCB : 2,5mg/m³ NDC

HCB : 6,5mg/m³ NDC

LDE : 2,5mg/m³ PDI

HDE : 6,5mg/m³ PDI

Meta-analysis of Rat lung tumors from lifetime inhalation of Diesel exhaust

(Valberg and Crouch, EHP, 107, 693- 99, 1999)

- High concentrations of DEP(1000 μ g/m³) lifetime exposure result in excess lung tumors
- Treshold of response between 200 and 600 μ g/m³
- Low exposure data does not support a lung cancer risk at nonoverload conditions.

Are Diesel particles carcinogenic?

- Mechanisms?
 - genotoxic
 - epigenetic
- Variability related to species
- IARC classification : 2A
- Epidemiological studies concluded for a low risk for occupational exposure, negligible risk for environmental exposure (Stöber and Abel 1996)

Occupational exposure to Diesel exhaust and lung cancer

- **Meta-Analysis(M.Lipsett et al 1999 Am. J. Public.Health 89,1009-1017):**
 - Etiologic role to occupational Diesel exhaust exposure and lung cancer induction.
 - Pooled smoking adjusted relative risk of 1.47 (95% confidence interval= 1.29,1.67)

DEP as a cause of increased
asthma and allergy?

Short term effect of diesel exhaust on human lower airways (I)

- Sandström, Salvi and coworkers (1999, 2000)
- Restricted to normal healthy subjects
- Exposed non-smoking subjects for 1 hour to diluted diesel exhaust
- Perform lung biopsies and lavages before and after exposure

Short term effects of DEP on human lower airways (II)

- Increased number of inflammatory cells in the airways
- Increase in histamine levels
- Increased levels of inflammatory mediators
- Decreased macrophage function

Short term effects of DEP on human upper airways

- Nasal challenges of human (Diaz Sanchez et al., 1994, 1996)

Increase in number of inflammatory cells

- Increase in cytokine release
- Increase in specific IgE

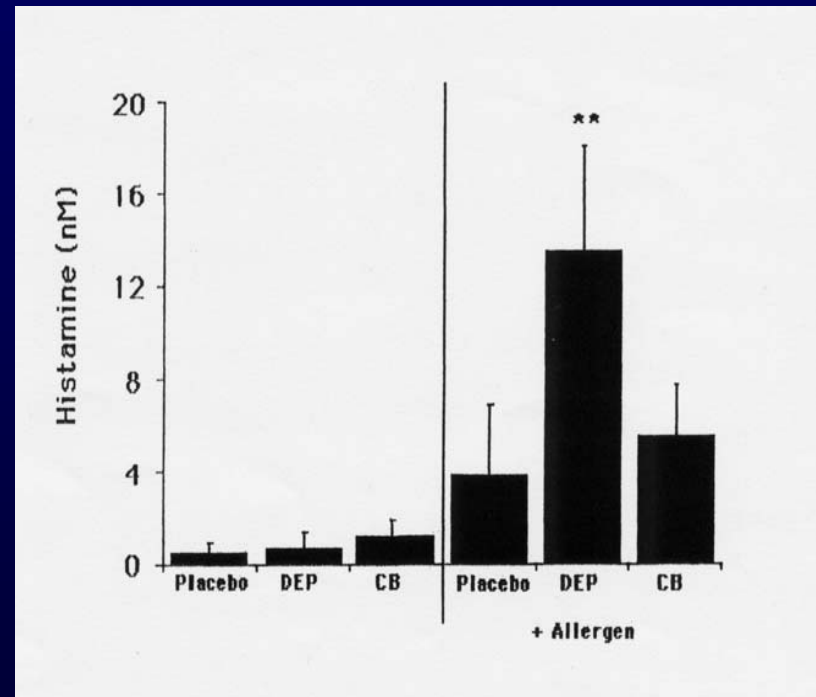
DEP induces an inflammatory response in the airways

Sensitization

- Cause an allergy to a substance which was previously « harmless »
- Can DEP make subjects allergic ?

Immediate effects

- Allergic subjects challenged nasally with pollen + 0.3 mg DEP
- Allergic mediators increased
- Diaz-Sanchez et al., J Allergy Clin Immunol.2000; **106**: 1140-46

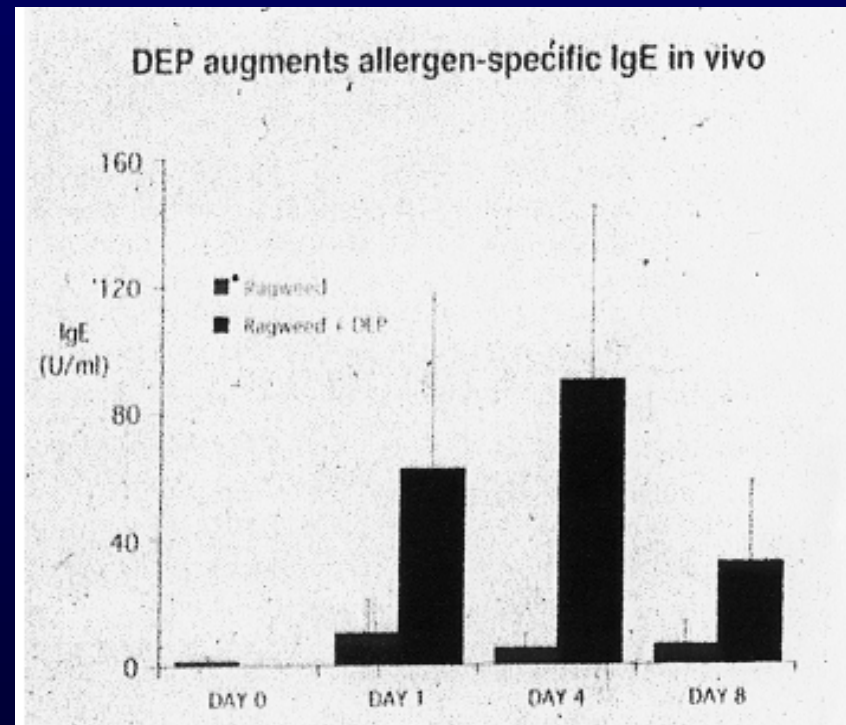


Exacerbation of allergic response

- Allergic subjects challenged nasally with pollen + 0.3 mg DEP
- Allergic antibody production is up to 50 times greater if DEP present

Diaz-Sanchez et al., J Immunol. 1997;

158: 2406-13



Mechanistic studies

- **To determine if the airway epithelial cells play a role in the inflammatory response.**
- **To understand the cellular and molecular mechanisms involved in this response.**
- **To evaluate the relative importance of the non extractable DEP core versus adsorbed organic compounds.**

INHALED AIR

Particles

Allergens

**bronchial
epithelium**



**INFLAMMATORY
RESPONSE**



CYTOKINES

GM-CSF

immun cells activation



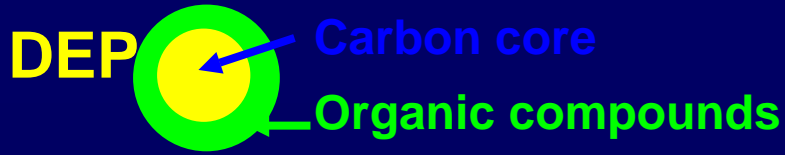
ALLERGIC RESPONSE - IgE PRODUCTION

Cell culture models

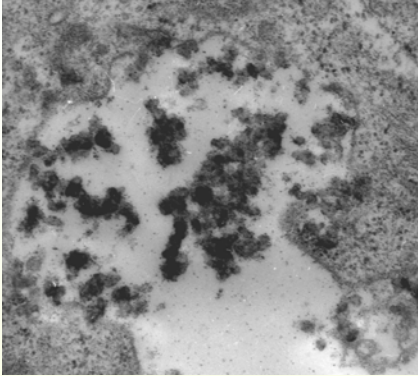
- **Primary cultures of human nasal epithelial cells**
- **Human bronchial epithelial cell line (16 HBE 14o-)**

Particules used

- **Native or extracted standard reference Diesel particles (SRM 1650)**
- **Carbon black particles (CB)**



phagocytosis

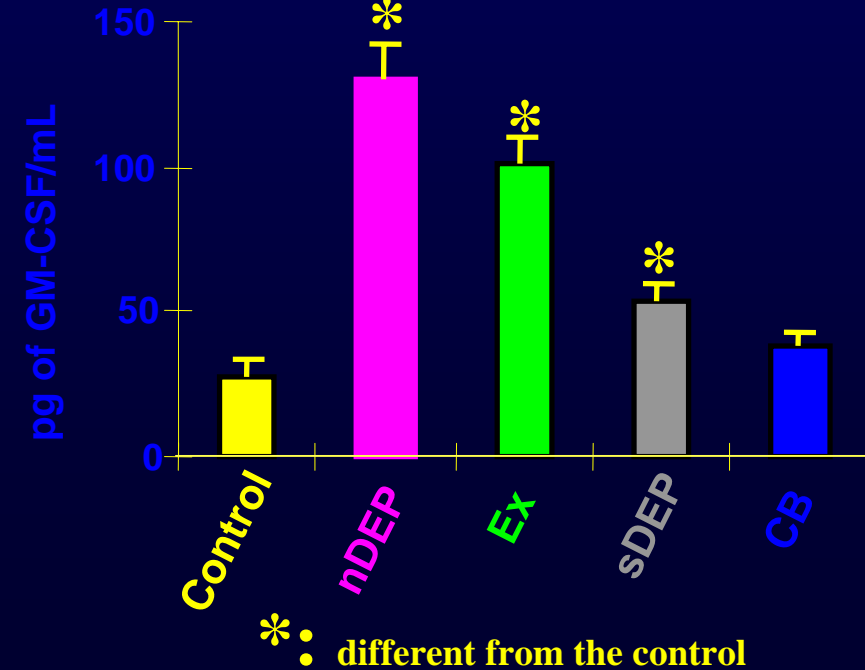
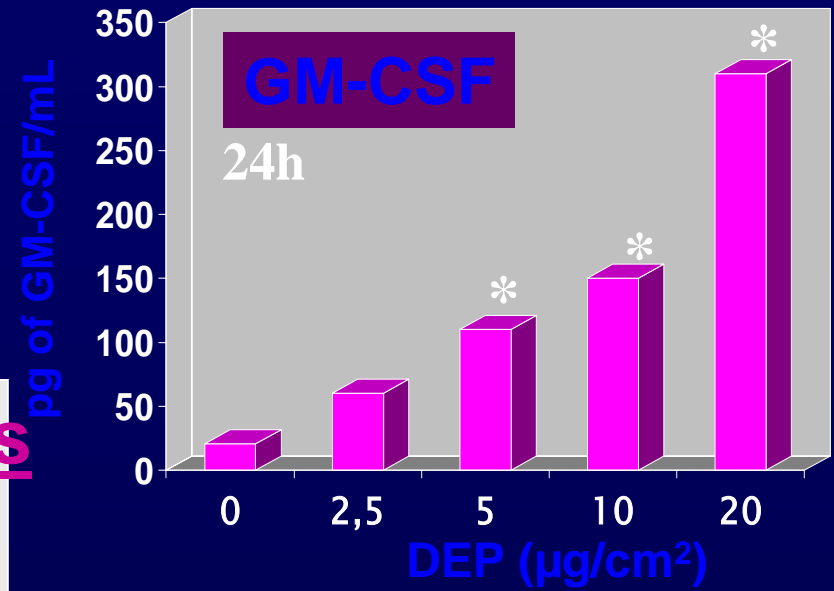


Cytokines

IL1 β
IL8
GM-CSF

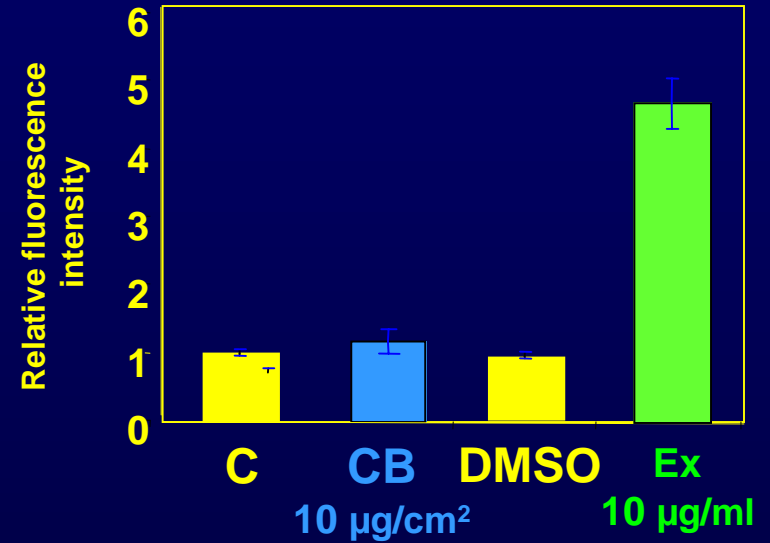
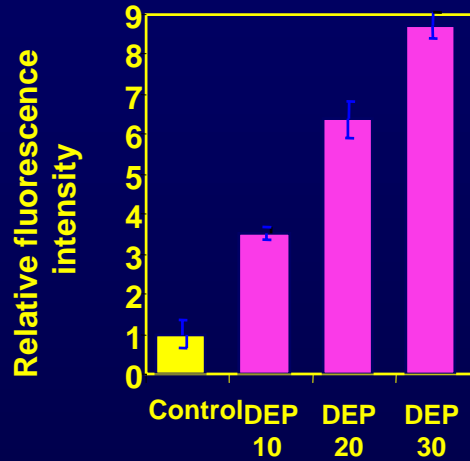
Cytokine gene

16 HBE cells

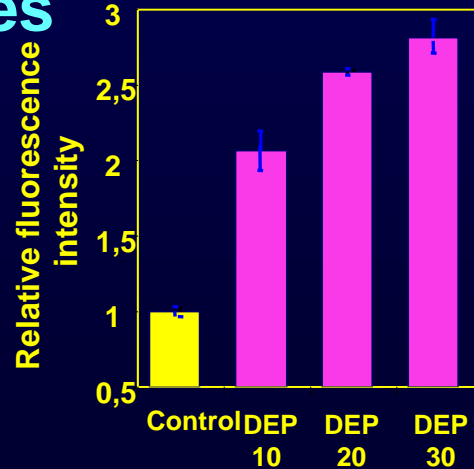


DEP induce a dose-dependent peroxides production

16 HBE cells

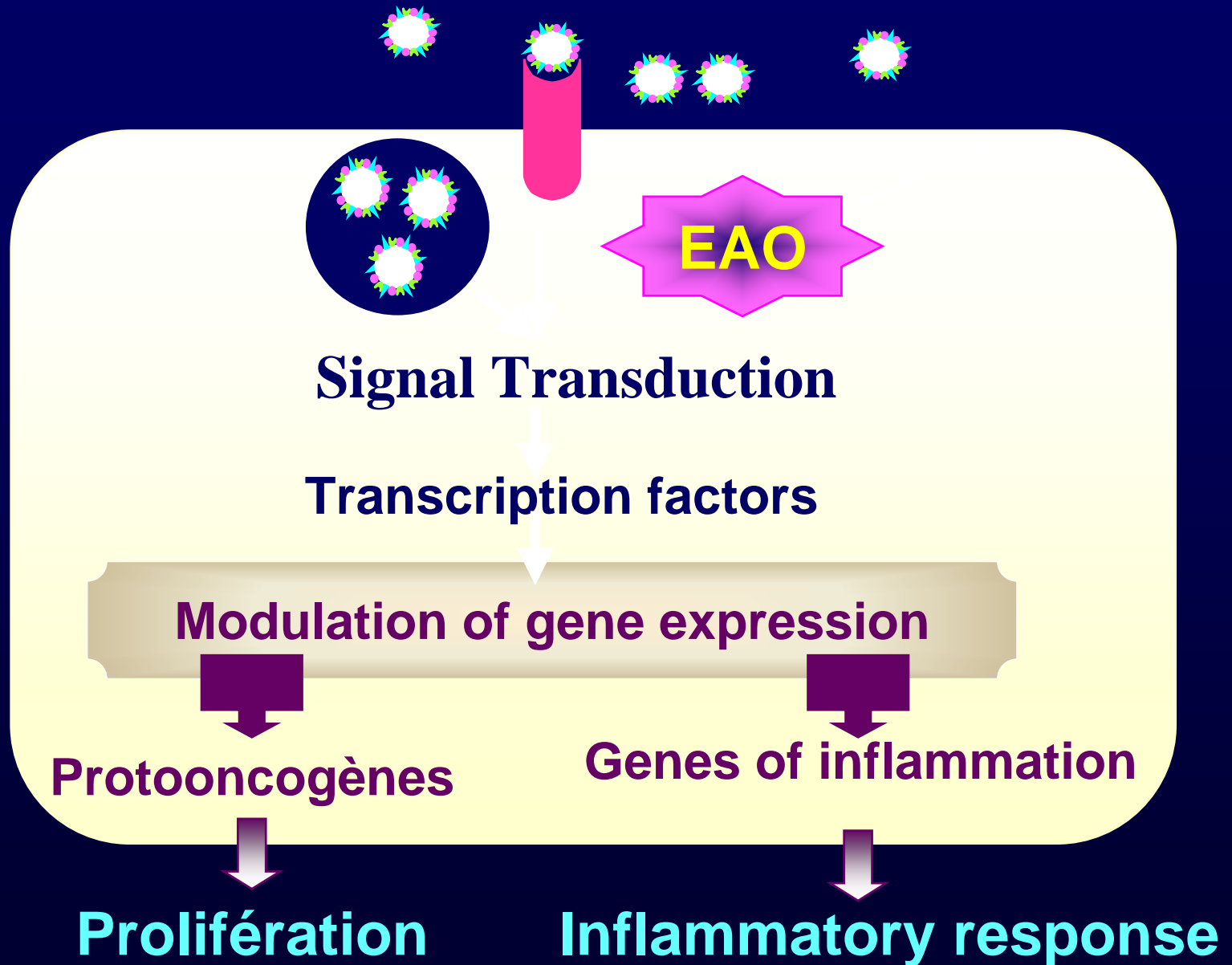


Primary cultures



concentration ($\mu\text{g}/\text{cm}^2$)

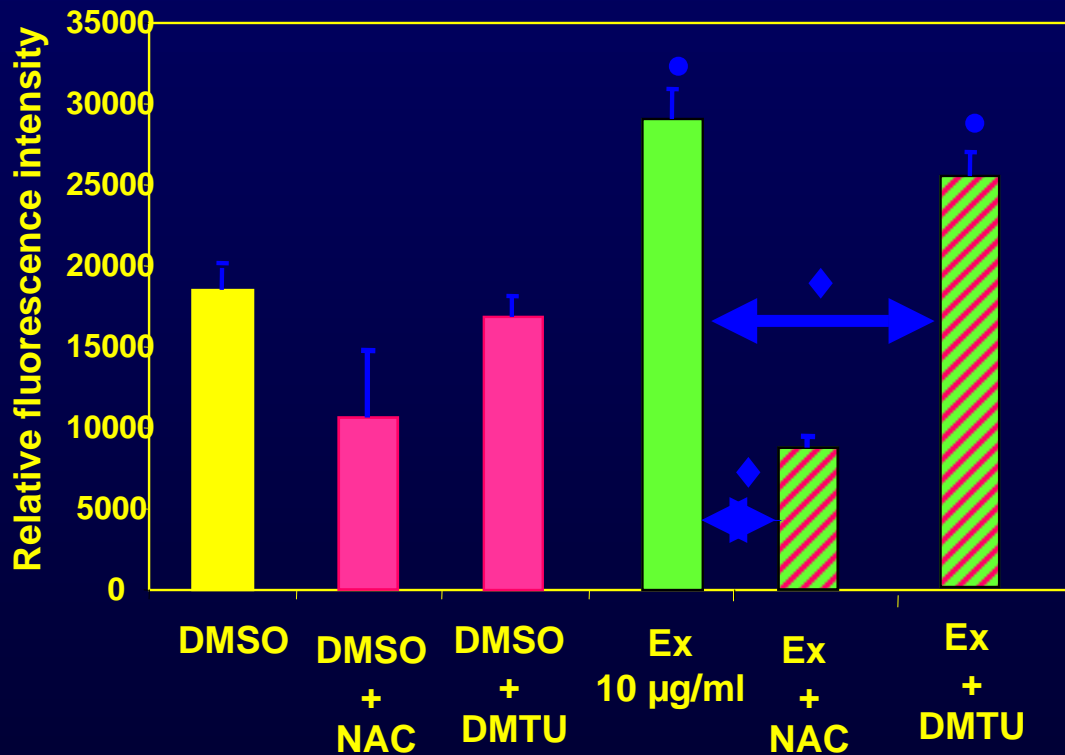
The "particle stress"



CONCLUSIONS

- DEP: induce an inflammatory response in the airways via an oxidative stress and increase the respiratory diseases
- Role of organic compounds in the response
- Induction of numerous genes i.e for inflammation and proliferation, role in cancer?
- DEP enhance the allergic response
- Systemic effects: translocation?
release of cytokines?

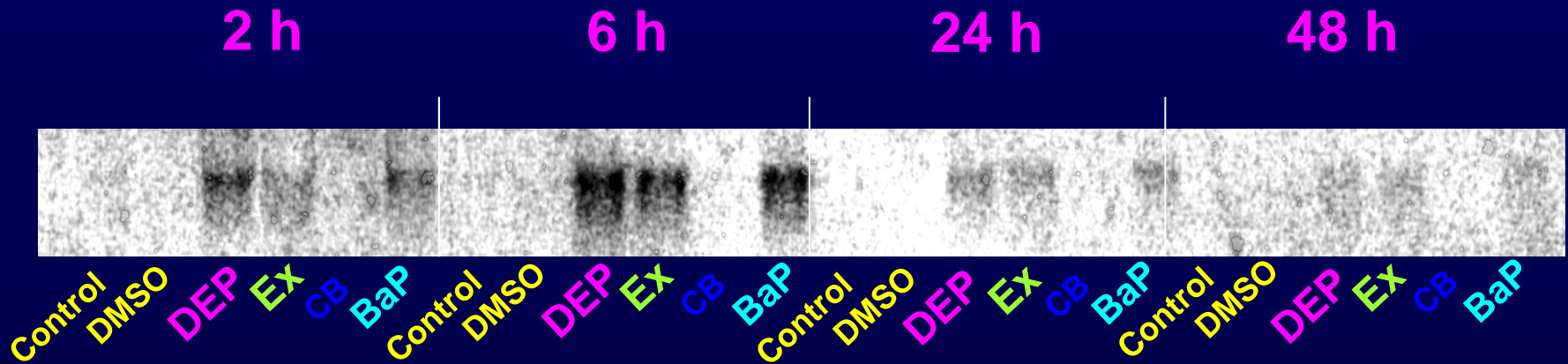
Organic compounds induced peroxides production is reduced by anti-oxidants



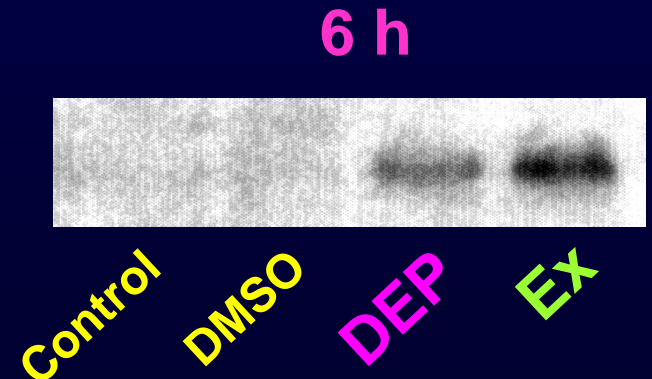
- ◆ different from toxic without antioxidant
- different from their relevant control.

CYP1A1 mRNA induction

16 HBE cells



Primary cultures of
human nasal turbinates



DEP-mechanisms of action

