role of ROS in the bioactivity of the fibres

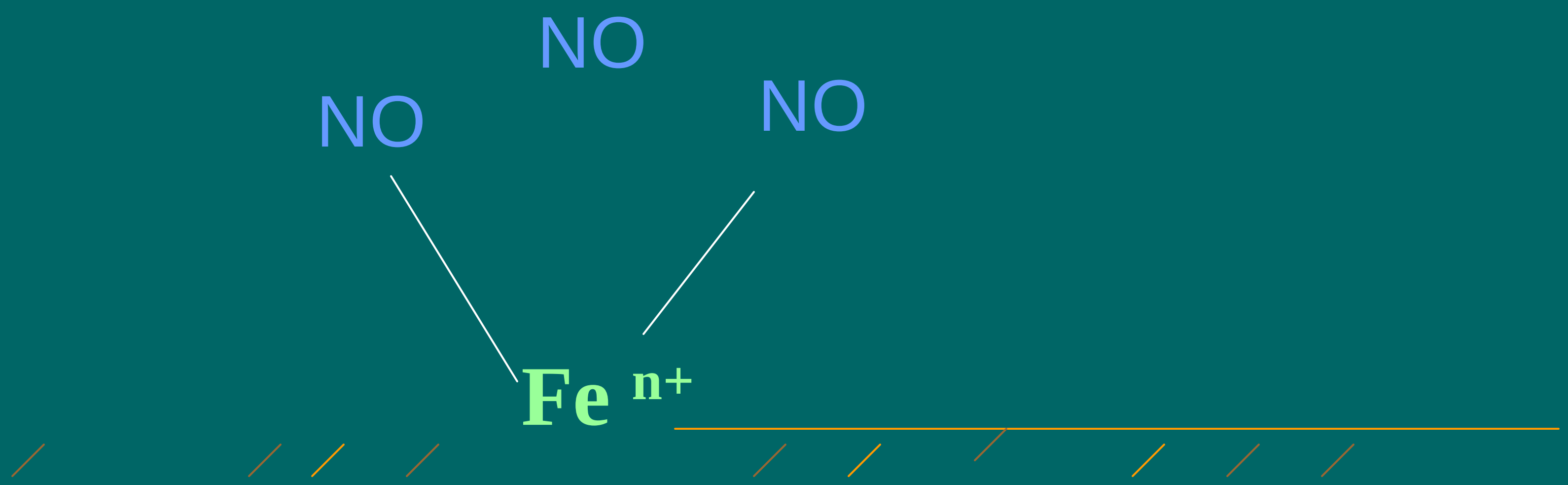
SOD, catalase, mannitol and other antioxidants ameliorate or inhibit the biological response to asbestos

ROS implicated in the pathogenic mechanism

long lasting mechanisms of pathogenicity

catalytic mechanism of ROS generation
or
surface sites regeneration

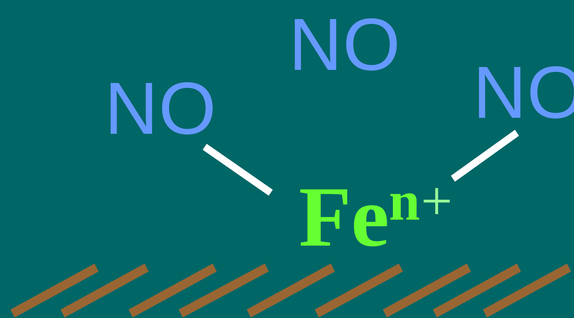
role of iron in the coordination of endogenous molecules

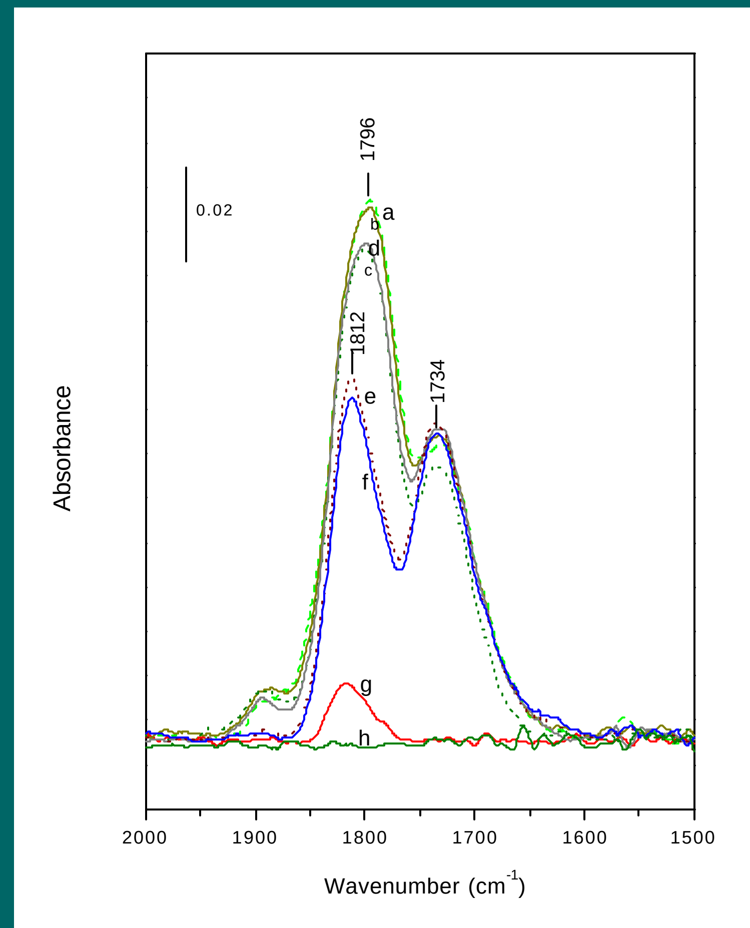


poorly coordinated surface ions bind ligands through free coordinative valencies

interaction with nitric oxide

FT-IR spectroscopy

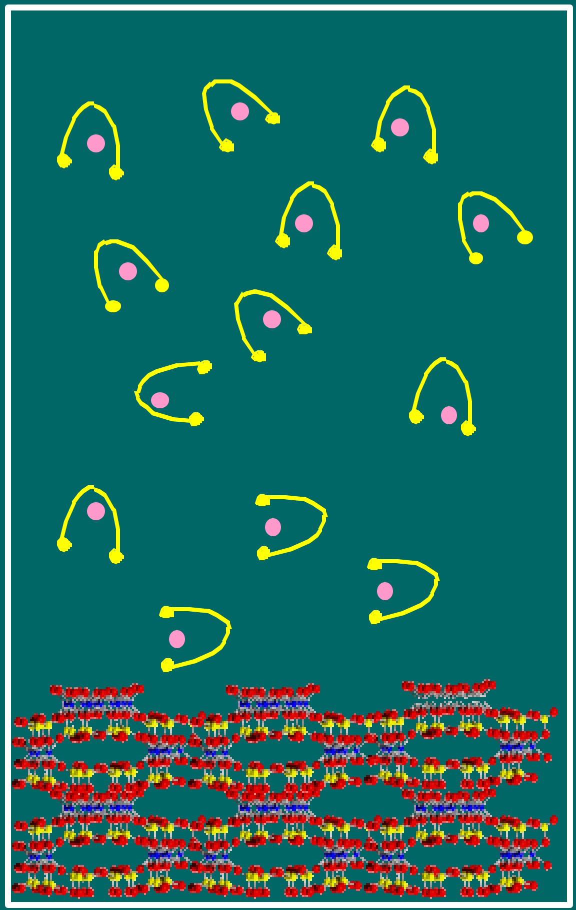


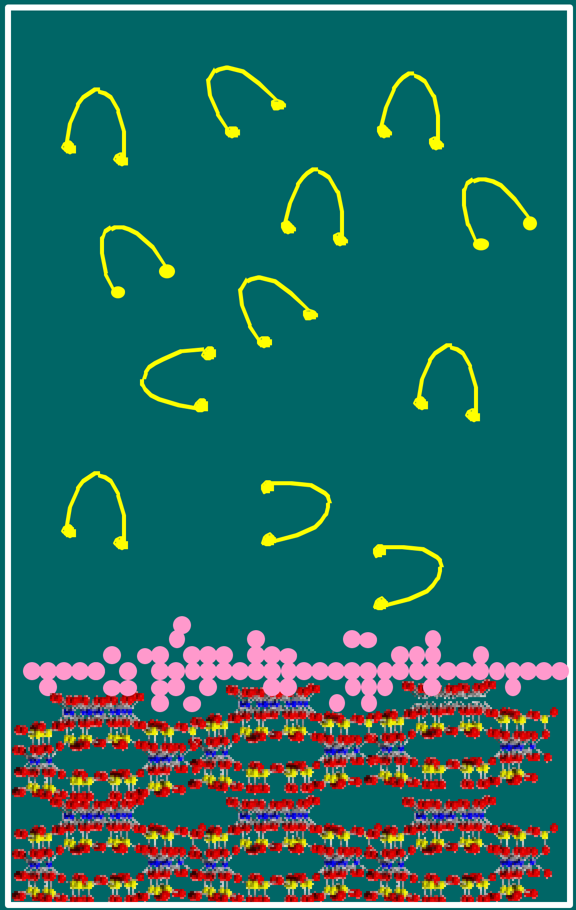


NO is strongly held at the surface

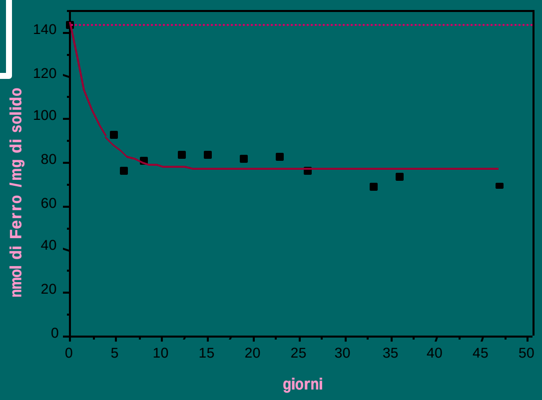
adsorption may interfere with iNOS activation

iron uptake by fibers



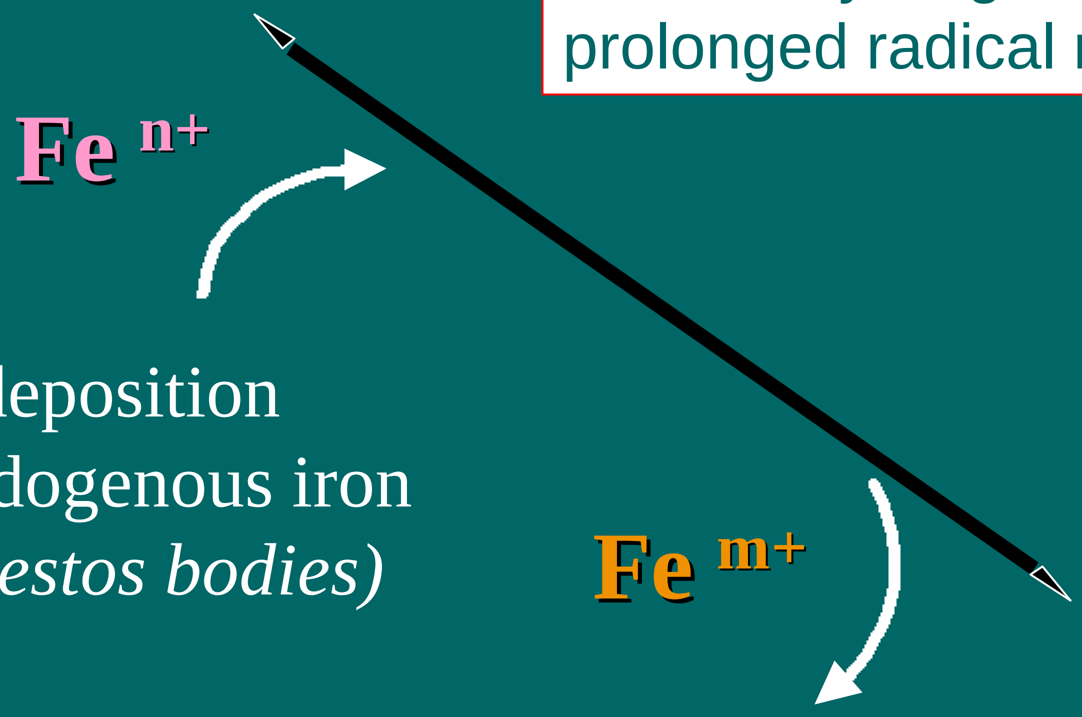


Fe-NTA



what may happen in vivo at the fibre surface

- mobilization and reuptake of iron ions.
- redox cycling of iron with prolonged radical release

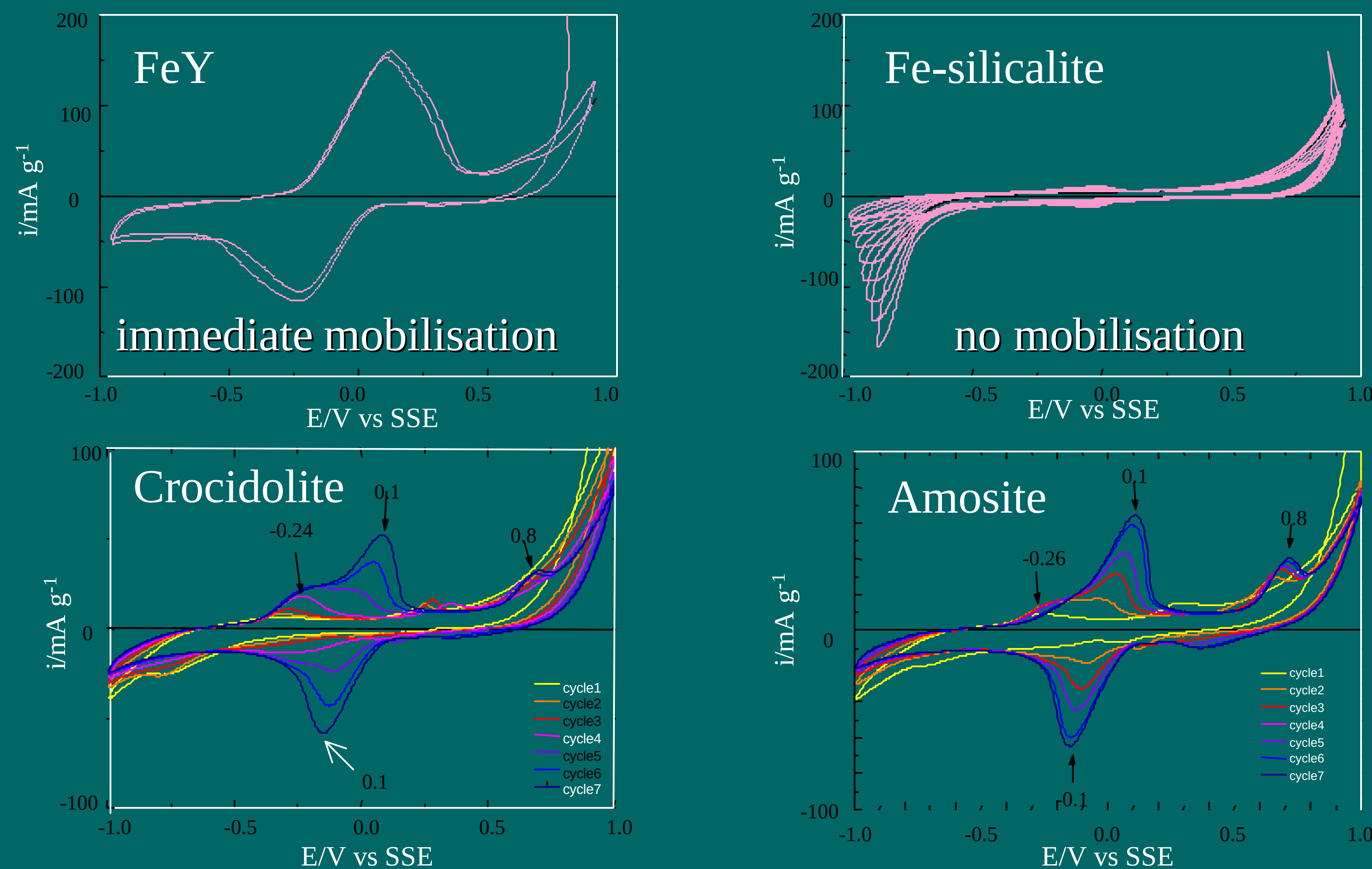


deposition
of endogenous iron
(asbestos bodies)

mobilization of iron by
endogenous chelators

electrochemical evaluation of iron mobility

cyclic voltammetry (neutral pH)



Fe partly mobilised in subsequent cycles

heterogeneity in iron surface sites *Prandi et. al., J.Mater.Chem* ***11****,1495-1501, 2001*

endogenous iron deposition

ferritin deposition and modification on asbestos fibres

348 B. FUBINI ET AL.

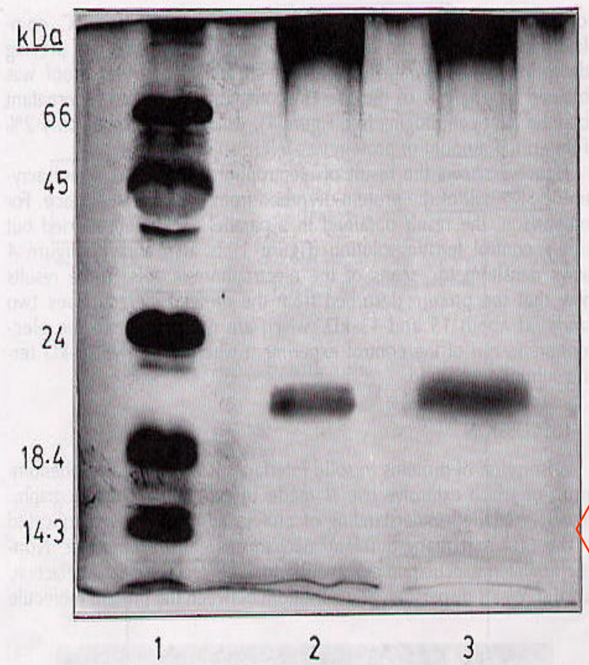


FIGURE 3. Polyacrylamide-SDS gel electrophoresis of horse spleen ferritin. The gel was stained with silver nitrate. Lane 1, molecular weight marker (LMW; Pharmacia). Lane 2, control experiment. Lane 3, protein recovered after being adsorbed onto amosite asbestos. Note the presence in lane 3 of two faint bands at about 15 and 13 kD, which are degradation products of the ferritin 20-kD subunits.

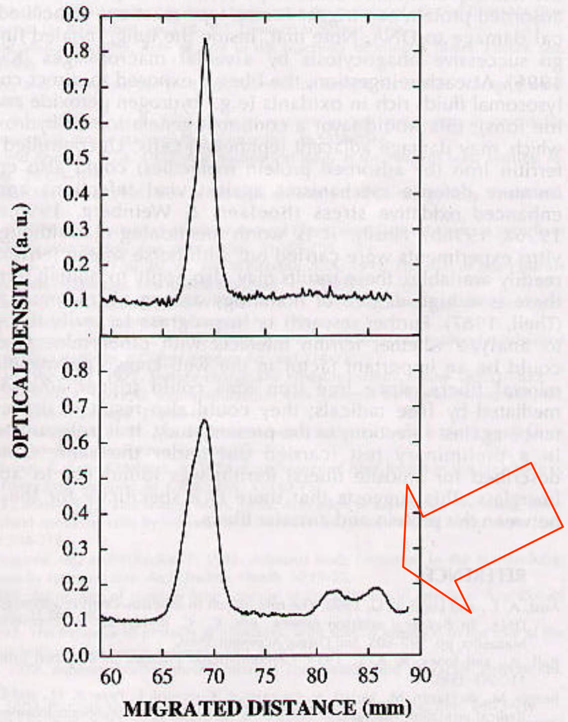


FIGURE 4. Densitometric scans of gels from electrophoresis: lanes 2 (top) and 3 (bottom) in Figure 3. The main bands correspond to the 20-kD subunit of ferritin, while the smaller bands in the bottom diagram reveal breakdown of the protein recovered after adsorption onto amosite fibers (15- and 13-kD bands in lane 3 of Figure 3).

Fubini et al. J .Toxicol. Envir. Health 52, 101- 110, 1997

are asbestos bodies a reactive center?

Iron in asbestos bodies damages DNA

Ferrhydrite similar to asbestos bodies deposited in vitro

A.E.Aust & coworkers 1994-2000

Ferritin is adsorbed and modified at the surface of amphibole asbestos (crocidolite, amosite)

Deposited ferritin is active in DNA damage

Fubini, Otero Aréan & coworkers, 1997-2000

open questions

Which iron is active? ⇨ ***at "active sites" on the surface***

mobilized

Under which circumstances iron becomes active?

⇨ ***when poorly coordinated***

Does extraction/inactivation of iron detoxify asbestos?

⇨ ***Yes, better destroy the surface site***

Which are the biochemical reactions involved

⇨ ***generation of ROS and reaction with NO***

outline

Physico-chemical characteristics which contribute to the biological activity of fibers

Role of form: physical, chemical and biochemical effects of fibers

Mineral composition: crystallinity, contaminants, active sites at the surface

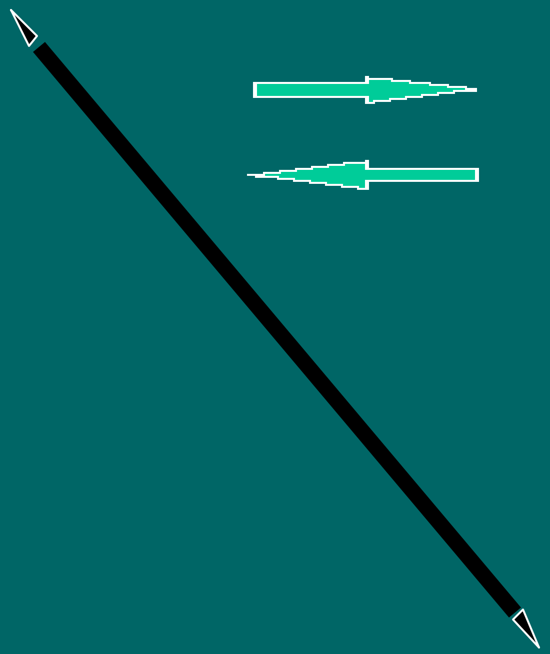
Chemical aspects in biopersistence

Reaction with endogenous substances

Which physico-chemical properties govern the various steps of the pathogenic process

Tentative association between physico-chemical features, hypothesized mechanisms and diseases

chemical aspects in biopersistence



Ca^{2+}, Mg^{2+}, Fe^{3+}, Fe^{2+}...

- abstraction of ions due to formation of low solubility compounds
  e.g. magnesium oxalate

- abstraction of ions from the fibre by action endogenous chelators
  e.g. [Fe (cysteine)]

chrysotile vs amphiboles

progressive increase in surface free energy during chrysotile disgregation

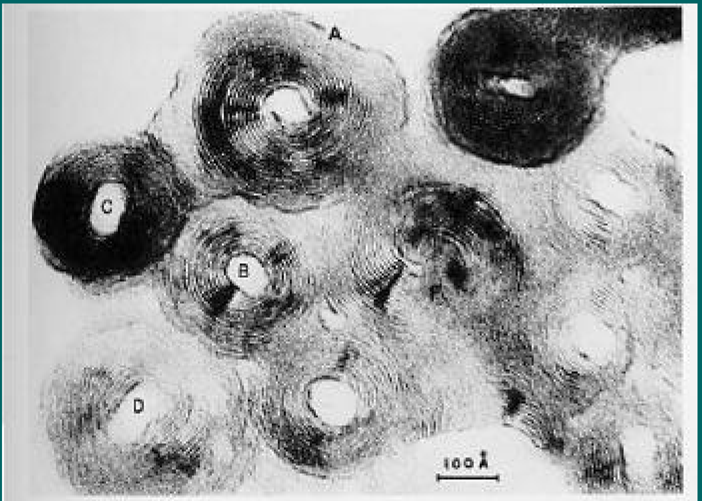


Fig. 2.4 Chrysotile asbestos sectioned perpendicular to the fiber axis. Electron micrograph showing typical lattice images of the layers of this serpentine mineral rolled into hollow cylinders (fibrils).

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Tentative association between physico-chemical features, hypothesized mechanisms and diseases

extracellular reactions

Reactions with glutathion and ascorbate

Brown et al., Ann.Occup.Hyg. 44, 101-108, 2000

Activation of the complement

Governa et al. J.Toxicol. Envir. Health 59, 539-552,2000

Adsorption of serum and membrane proteins

↳ …cell signalling pathways

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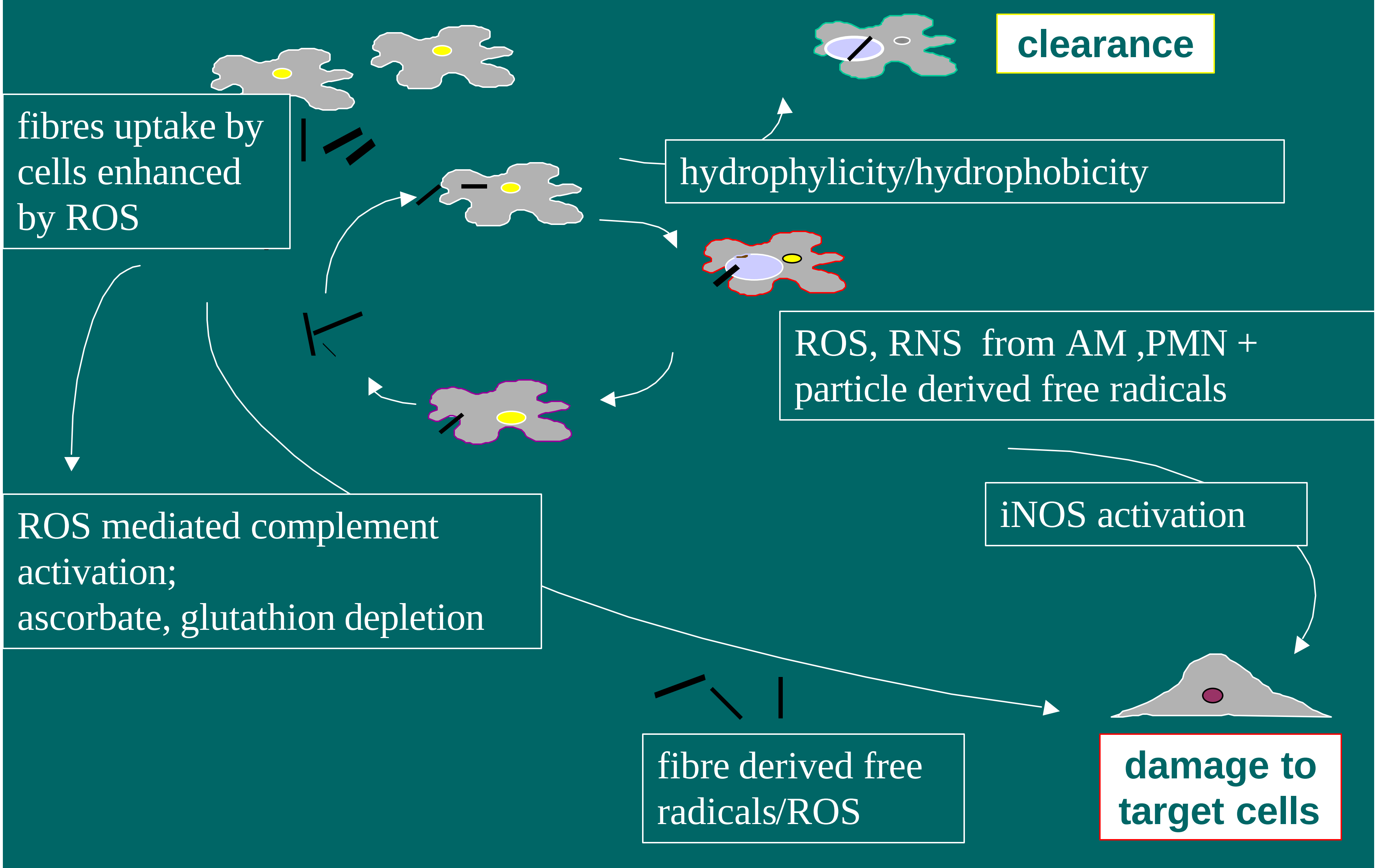
at which stage do surface properties play a role?



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tentative association between physico-chemical features, hypothesized mechanisms and diseases

epidemiology suggests different pathogenic mechanisms

bronchogenic carcinoma

Linear correlation with cumulative exposure

Slope industry-specific, but not correlated to the type of asbestos

Risk from tobacco smoking acts synergistically with asbestos exposure

pleural mesothelioma

Correlation with a power function of time since first exposure

Slope specific to industry and type of asbestos fibre

No effects of tobacco smoking

Boffetta, Med.Lav. ***89****, 471-480,1998*

physico-chemical features and diseases

pleural mesothelioma

long thin fibers
- *only caused by fibres, both in humans and, upon inhalation, on experimental animals*
- *fibres may attain the pleura*
- *long fibres are not cleared by macrophages*

biopersistentent fibers
- *dependence upon time since first exposure*
- *elevated risk 40 years since first exposure*

ROS
- *increased susceptibility of p53 deficient mice*

Fe at catalytic sites
- *in carcinogens, such as erionite, tremolite, ceramic fibres, iron only as trace contaminant*

physico-chemical features and diseases

bronchogenic carcinoma

fiber and cell derived
ROS and RNS
peroxinitrite

→ *cumulative lung loading*

(sustained inflammation?)

no different
carcinogenic potency
among the various
asbestos fibers

→ *no dependence upon type of asbestos*

fibrous habit ?

→ *non fibrous particles equally inflammogenic & fibrogenic?*

type of asbestos

pleural mesothelioma

amphiboles >> chrysotile

long, thin > short

iron in trace amounts

tremolite: active contaminant

dose: number of fibers? surface?

bronchogenic carcinoma

all asbestos

active surface iron to sustain inflammatory response

inflammatory dusts: active contaminant

dose: total surface exposed

asbestosis same as bronchogenic carcinoma