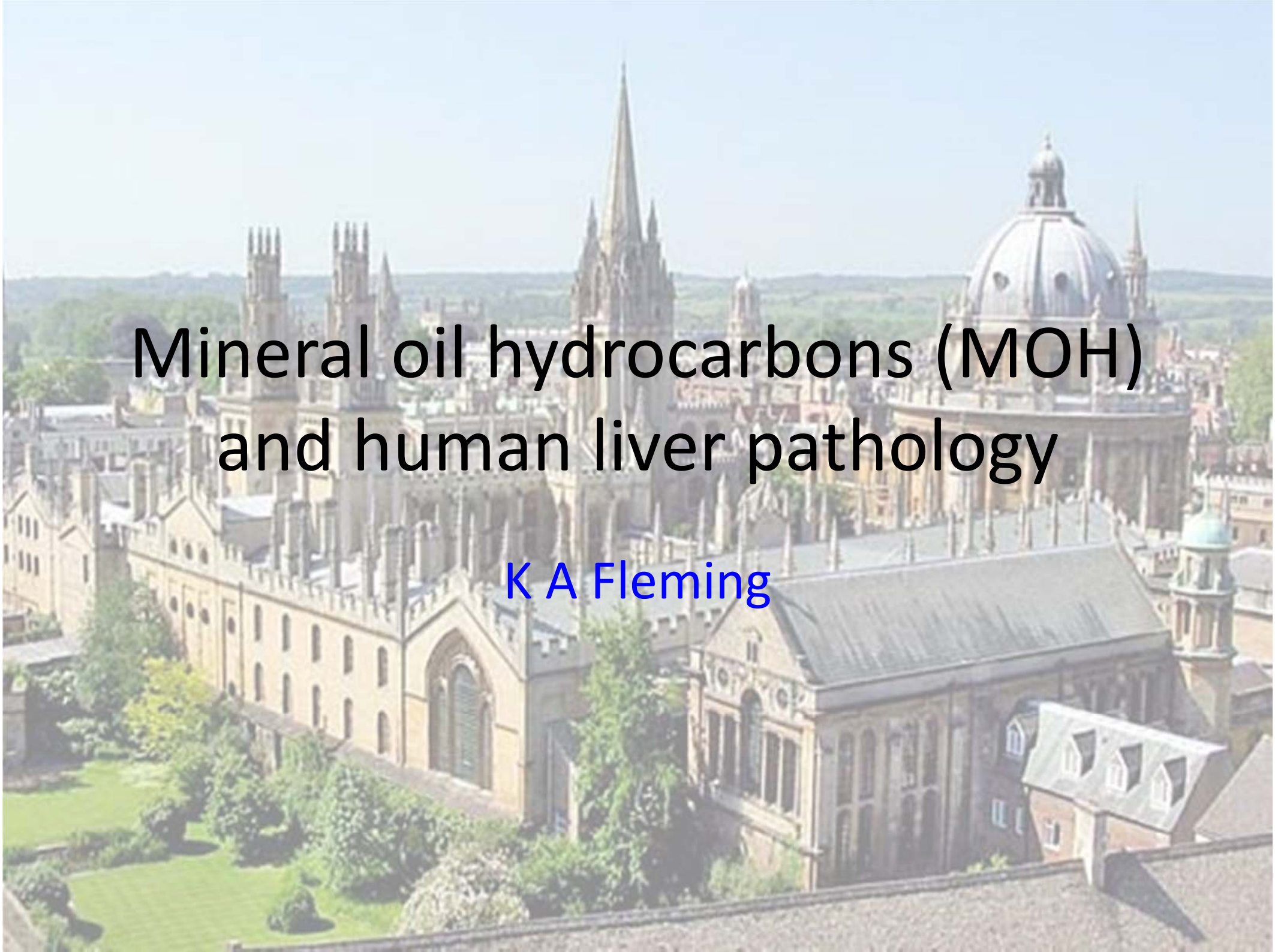


Mineral oil hydrocarbons (MOH) and human liver pathology

K A Fleming

Mineral oil hydrocarbons (MOH) and human liver pathology

Key question is;

does ingestion of mineral oil hydrocarbons (MOH) cause liver disease in humans?

Mineral oil hydrocarbons (MOH) and human liver pathology

Known already:

If feed various types of MOH, to various animals, for varying periods:

Dogs – no lesions

Long Evans, Sprague-Dawley rats – no significant lesions

Fischer 344 rats

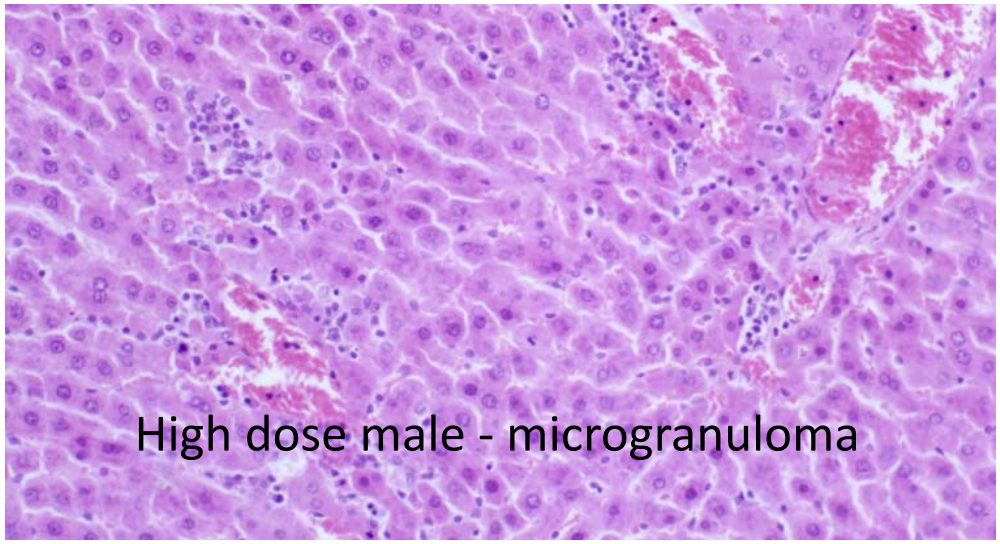
- high viscosity mineral oil and microcrystalline waxes
  – no lesions
- Lower viscosity mineral oil and low/intermediate melting point/low molecular weight wax
  - granulomas in mesenteric nodes, spleen and liver
  - LFT abnormalities.

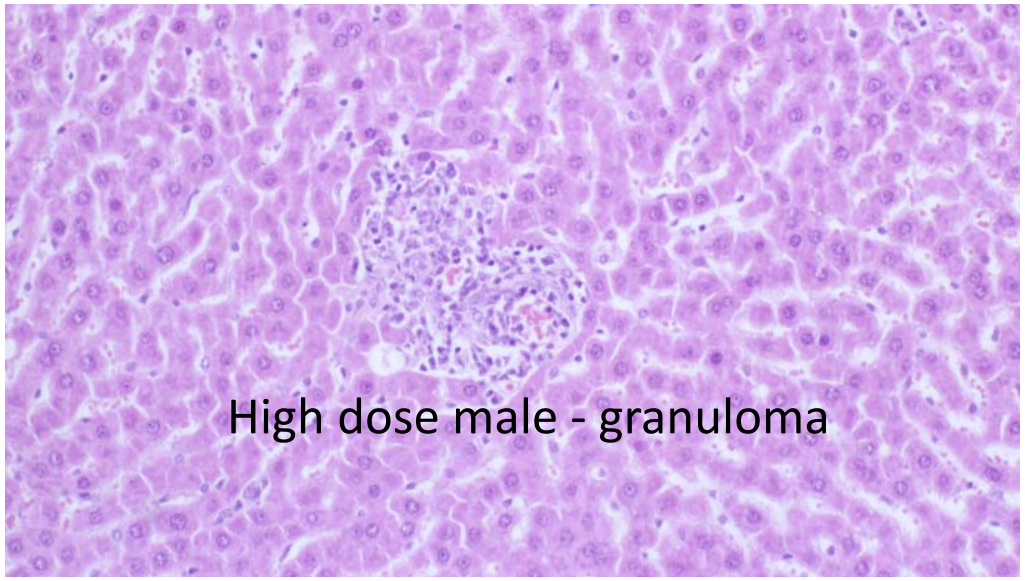
In liver, severity varies from minimal histiocytic microgranulomas to follicular granulomas with hepatocyte necrosis

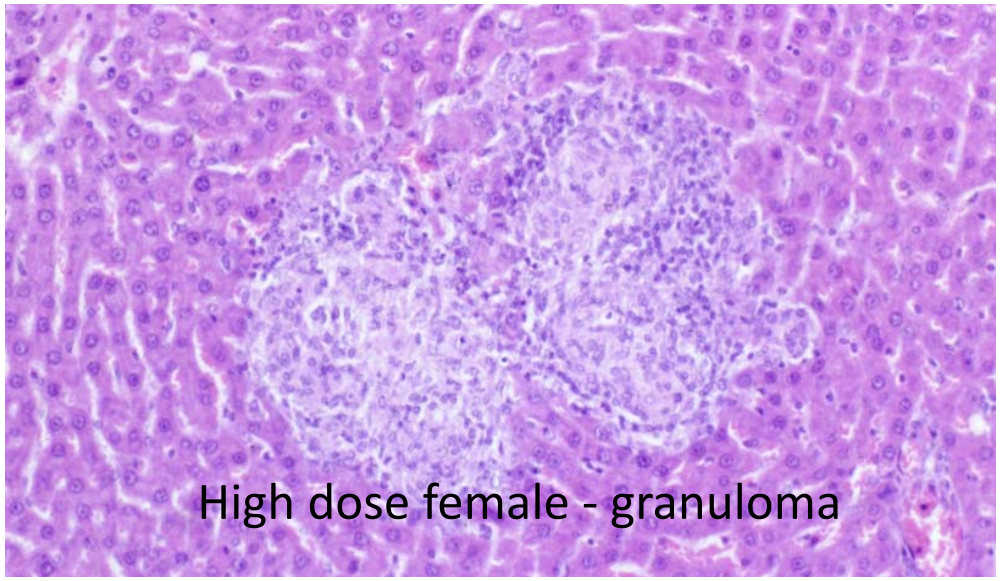
Severity related to dose, duration, type of oil and sex.

F344 rats (female) absorb more MOH than S-D rats.

Mineral oil hydrocarbons (MOH) and human liver pathology







Mineral oil hydrocarbons (MOH) and human liver pathology

- Histiocytic microgranuloma – small collection of macrophages/histiocytes

- Follicular granuloma
  - Large, discrete collection of epithelioid cells (altered macrophages) rim of lymphocytes, multi-nucleated giant cells
  - Can have central necrosis (caseous in TB)
  - Can be foreign material present

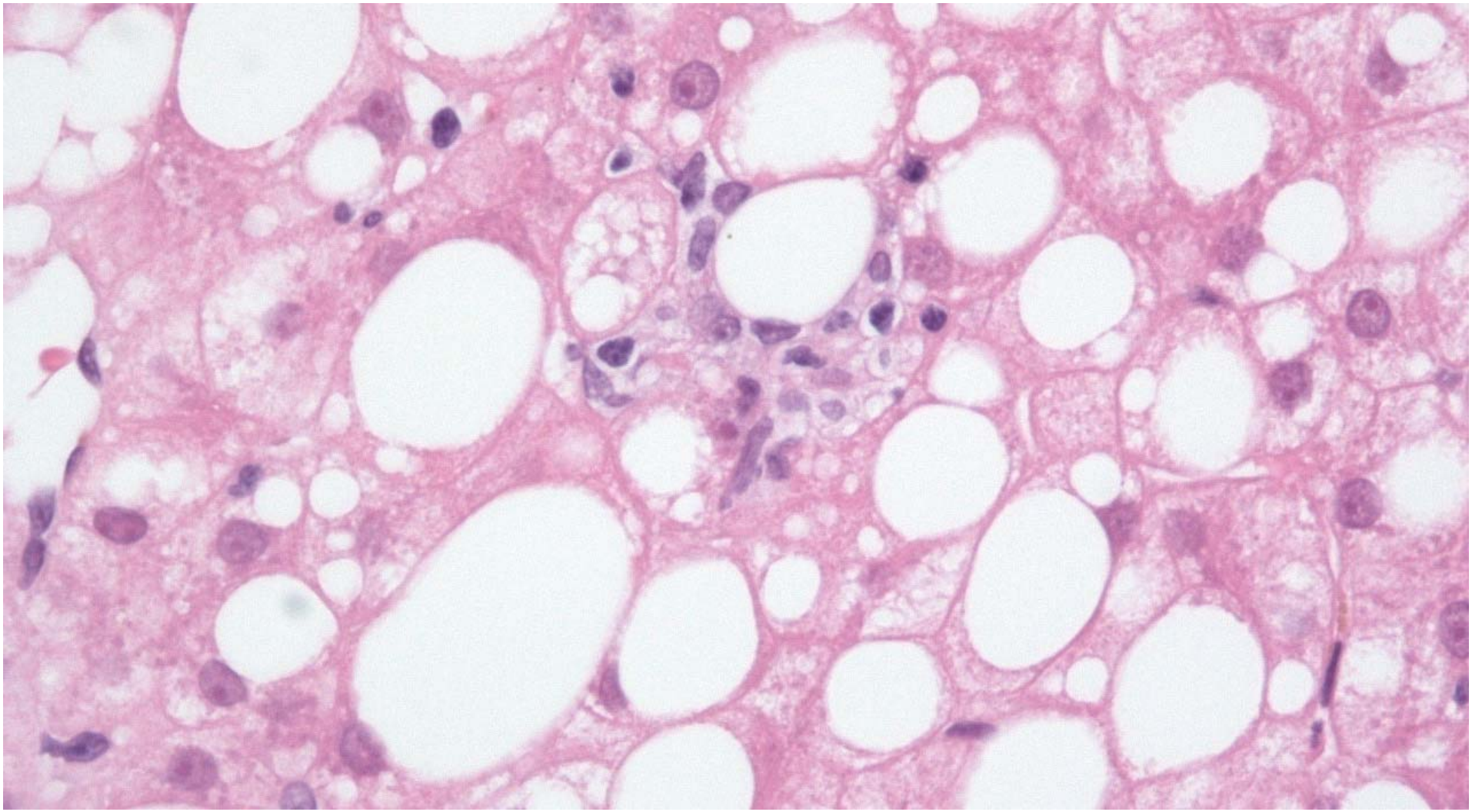
- Th1/2 immune response to antigen – lepromatous/tuberculoid leprosy

Mineral oil hydrocarbons (MOH) and human liver pathology

Relevance to humans

- Mineral oil granulomas in humans recognised for many years
- LNs (especially porta hepatis – 85%), spleen (24-75%), bone marrow (less common but up to 87% reported) and liver (up to 48%)
- Vacuolated macrophages, some lymphocytes
- Rarely, very mild fibrosis

Mineral oil granuloma



Mineral oil hydrocarbons (MOH) and human liver pathology

- Percentages increase with age, sex, geography
- Thought to be associated with laxative ingestion
- not associated with illness
- No real resemblance to rat lesions

So we can forget these?

Mineral oil hydrocarbons (MOH) and human liver pathology

If not related to recognised mineral oil granulomas, are the rat lesions related to any other human lesions?

Mineral oil hydrocarbons (MOH) and human liver pathology

How often do granulomas occur in human liver?

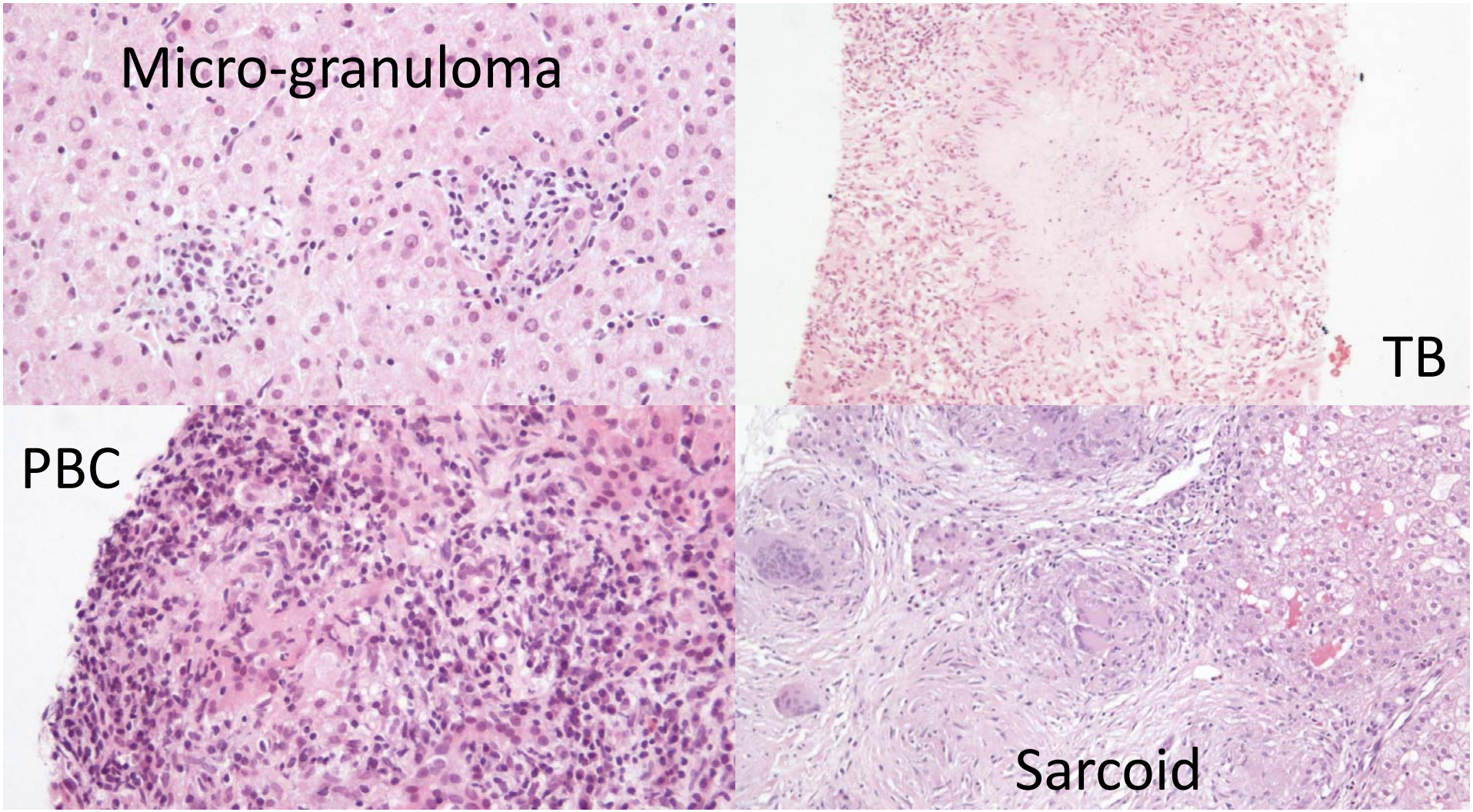
What are the causes?

What is the outcome?

Mineral oil hydrocarbons (MOH) and human liver pathology

- 5-10% Liver biopsies have granulomas
- Range of granulomas – histiocytic microgranuloma to large follicular, necrotising lesions

Mineral oil hydrocarbons (MOH) and human liver pathology



Mineral oil hydrocarbons (MOH) and human liver pathology

Causes of granulomas in human livers

INFECTIOUS DISEASES

Bacterial
- Actinomycosis
- Bartonella henselae[31]
- Borrelia (Lyme disease)[32]
- Botryomycosis
- Brucellosis
- Cat-scratch disease
- Granuloma inguinale
- Listeriosis
- Melioidosis
- Nocardiosis
- Proprioniosis
- Staphylococcal infections
- Syphilis (primary and secondary)
- Tularaemia[33]
- Typhoid
- Whipple disease
- *Yersinia enterocolitica*[34]

Mycobacterial
- Tuberculosis
- Atypical mycobacteria (e.g. *M. avium intracellulare*)
- BCG immunization and immunotherapy[35]
- Leprosy (lepromatous and tuberculoid)

Rickettsial
- Boutonneuse fever
- Q fever
- *Rickettsia conorii* infection

Chlamydial
- Lymphopathia venereum
- Psittacosis

Fungal
- Aspergillosis
- Blastomycosis (North and South American)
- Candidiasis
- Coccidioidomycosis
- Cryptococcus
- Histoplasmosis
- Mucormycosis
- Paracoccidioidomycosis

Viral
- CMV infection
- EBV—infectious mononucleosis[39]
- Hepatitis A[37]
- Hepatitis B[36]
- Hepatitis C[37]
- Varicella[38]

Parasitic
- Amoebiasis
- Ancylostomiasis
- Capillariasis
- *Enterobius vermicularis* infection[39]
- Fasciolíasis
- Giardiasis
- *Linguatula serrata*[40]
- Paragonimiasis
- Opisthorchiasis
- Pentastomiasis
- Schistosomiasis
- Strongyloidiasis
- Toxocariasis
- Visceral leishmaniasis (kala-azar)

HYPERSENSITIVITY
- Drugs (see Ch 14)
- Metals—beryllium, copper, gold

IMMUNOLOGICAL DISEASES
- Common variable immunodeficiency[41]
- Chronic granulomatous disease of childhood[42]
- Hypogammaglobulinaemia
- Polymyalgia rheumatica
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Rheumatic fever[43]
- Systemic lupus erythematosus
- Vascular diseases
  - allergic granulomatosis
  - necrotizing angiitis in drug abuse[44]
  - polyarteritis nodosa
  - temporal arteritis
- Wegener granulomatosis

FOREIGN MATERIALS
- Anthracotic pigments
- Barium
- Cement and mica dust
- Mineral oil—radiocontrast media, food additives
- Polyvinyl pyrrolidone
- Silica
- Silicone rubber—renal dialysis tubing[45]
- Starch
- Suture material
- Talc
- Thorotrast

NEOPLASMS
- Extrahepatic malignancy[46]
- Hepatocellular adenoma and liver adenomatosis[47]
- Hodgkin disease
- Non-Hodgkin lymphoma

MISCELLANEOUS
- Biliary tract obstruction—bile granulomas
- Chronic inflammatory bowel disease
- Eosinophilic enteritis[48]
- Jejuno-ileal bypass surgery
- Porphyria cutanea tarda[49]
- Sarcoidosis
- Lipiodolized neocarzinostatin[50]

Mineral oil hydrocarbons (MOH) and human liver pathology

Frequency of different causes of human liver granulomas

- Sarcoidosis 35%
- Tuberculosis 20%
- Undetermined 11%
- Misc. non non-infectious 9% *
- PBC 5%
- Other cirrhosis 5%
- Misc. Infections 5% **
- Schistosoma 2%
- Lymphoma 2%
- Brucellosis 2%
- Drug induced 2%
- Acute viral hepatitis 1%
- Fungal infection 1%

*Pancreato/biliary disease, berylliosis, malignancy, NASH, temporal arteritis, Crohn disease, Wegener granulomatosis, erythema nodosum, eosinophilic granuloma, starch, CVID, celiac disease.

**Typhoid fever, EBV, syphilis, other bacterial infection, otherviral infection, leprosy, toxoplasma, CMV, lymphogranuloma venereum, actinomycosis, influenza B, visceral larva migrans, BCG.

Mineral oil hydrocarbons (MOH) and human liver pathology

BUT

Mineral oil hydrocarbons (MOH) and human liver pathology

- 10-25% (50%) no cause found
- Therefore around 1% (0.5-2.5%) of all biopsies have unexplained granulomas

Mineral oil hydrocarbons (MOH) and human liver pathology

- Most of these (guess ~90%) have few, scattered histiocytic microgranulomas

- Some (guess ~10%) are follicular granulomas.

Mineral oil hydrocarbons (MOH) and human liver pathology

- So unexplained histiocytic microgranulomas may be found in about 0.9% of all liver biopsies and follicular granulomas in about 0.1% of all biopsies.
- Could either or both of these patterns be an atypical (?genetically determined) reaction to MOH?

Mineral oil hydrocarbons (MOH) and human liver pathology

Size of potential problem

- Oxford ~400 biopsies/year
- Therefore 20-40/year with granuloma
- ~4/year unexplained
- ~0.4/year may have unexplained follicular granulomas
- ~1 every 3 years

Mineral oil hydrocarbons (MOH) and human liver pathology

- UK-wide – number of liver biopsies unknown
- Guesstimate ~15,000 biopsies/year (7,000)
- So UK-wide (pop 60 million) ~150/year unexplained granulomas
- Europe (pop 500 million) ~1200/year
- Follicular granulomas ~120/year

These are guesstimates

Mineral oil hydrocarbons (MOH) and human liver pathology

- What happens to these patients?
  - follow up for some years, steroids for ~50%, no progression for all/most.
  - Very occasionally increasing liver/biliary damage and fibrosis – certainly <10%
- This would represent 12 patients/year in EU

NB - these is a guesstimate

Mineral oil hydrocarbons (MOH) and human liver pathology

Summary

- In most animals tested, MOHs show no toxicity
- F344 rats (especially females) show dose-dependent granulomas in liver and lymph nodes in response to certain types of MOH
- Laxative mineral oil produces frequent but clinically irrelevant histiocytic lesions in human liver
- No evidence of other MOH-induced human lesions

Mineral oil hydrocarbons (MOH) and human liver pathology

Summary

- However, around 1% of human liver biopsies contain unexplained granulomas
- Even if ***all*** unexplained granulomas were MOH-related, numbers very small (1200/year)
- Furthermore, all/most cases are non-progressive
- A **guess** is 12 cases/year in EU might show some progression

Mineral oil hydrocarbons (MOH) and human liver pathology

Conclusion

This suggests MOHs are not a major public health hazard