Mineral oil hydrocarbons (MOH) and human liver pathology

K A Fleming
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Key question is;

does ingestion of mineral oil hydrocarbons (MOH) cause liver disease in humans?
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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.
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- Male control
- High dose male - microgranuloma
- High dose male - granuloma
- High dose female - granuloma
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• 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
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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
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• 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?
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If not related to recognised mineral oil granulomas, are the rat lesions related to any other human lesions?
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How often do granulomas occur in human liver?
What are the causes?
What is the outcome?
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• 5-10% Liver biopsies have granulomas
• Range of granulomas – histiocytic microgranuloma to large follicular, necrotising lesions
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- Micro-granuloma
- PBC
- TB
- Sarcoid
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Causes of granulomas in human livers
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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%

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

**Typhoid fever, EBV, syphilis, other bacterial infection, other viral infection, leprosy, toxoplasma, CMV, lymphogranuloma venereum, actinomycosis, influenza B, visceral larva migrans, BCG.
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BUT
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• 10-25% (50%) no cause found

• Therefore around 1% (0.5-2.5%) of all biopsies have unexplained granulomas
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- Most of these (guess ~90%) have few, scattered histiocytic microgranulomas

- Some (guess ~10%) are follicular granulomas.
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• 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?
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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
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- 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*
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• 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*
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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
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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
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Conclusion

This suggests MOHs are not a major public health hazard