Author's response to reviews

Title: Experimental glomerulonephritis induced by hydrocarbon exposure. A systematic review

Authors:

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Author's response to reviews: see over
Reviewer's report
Title: Experimental glomerulonephritis induced by hydrocarbon exposure. A systematic review 1
Version:
Date: 21 August 2005
Reviewer: Paul Cockwell
Reviewer's report:

General
This review by Ravnskov comprises an overview of published studies that report the effect of various hydrocarbons on the development of glomerular disease in animals. The report is linked to human disease.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The search should be repeated for the key words 'renal disease' or 'tubulointerstitial disease', these studies should be then assessed for reports of glomerular pathology and the manuscript revised appropriately. I am concerned that important papers may be excluded on the basis of the failure to register glomerulonephritis as a key word by the search engines studied. It would also be useful to search against the term 'glomerulopathy'.

For many years it has been acknowledged that hydrocarbon exposure may cause tubulointerstitial disease, both in man and in animals. This has been documented in numerous case reports, clinical reviews and in countless animal experiments. Accordingly, using the key words “renal disease” or tubulointerstitial disease” results in a huge number of studies, but it is very unlikely that any of them should have found signs of glomerulonephritis without having used this word in the text, in particular because the large majority, if not all of these experiments have been performed to see if the clinical observations (eg. glomerulonephritis associated with hydrocarbon exposure) could be verified by experimental evidence. Even if I should have ignored an experiment having produced glomerulonephritis successfully, this should be a further support to my conclusions.

I included the term glomerulopathy in a new search as suggested, but found no new studies.

2. The table could be more informative: I would include separate columns for: length of study; light microscopy; immunohistochemistry; electron microscopy.

I have expanded the table as suggested.

3. The author should report whether there is any in vitro evidence to support a direct toxic effect of hydrocarbons on resident renal cells.

I am not familiar with that part of the literature. However, such findings are irrelevant because even if isolated renal cells may be harmed by hydrocarbons (which they most likely may be) this finding could neither support or contradict the notion that hydrocarbon exposure may produce glomerulonephritis. The clinicopathological picture of glomerulonephritis does not involve the damage of singular cells only, but is characterised by complex glomerular changes as well as clinical and laboratory abnormalities such as oedema, glomerular proteinuria and renal dysfunction.
4. Is there any supportive evidence for pathogenetic mechanisms from other organ systems?

I have referred to a review giving evidence that hydrocarbon exposure may be harmful to a number of immunological functions that are assumed to participate in the development of glomerulonephritis (ref. 32). Hydrocarbons are toxic to many other organs, for instance the liver and the brain, but these effects are not relevant for the issue.

5. Care should be taken in reporting the human literature. Is there any information on the comparative levels of hydrocarbons that humans are exposed with the animal models reported here? Critical analysis of the human studies should be made – how stringent were these, were they controlled for age, body mass, smoking history, socioeconomic group, analgesic use etc – that is factors that we know are important for the development of renal disease, but may not have been recognised at the time of these original studies.

I think that a more detailed reporting of the human literature is without the scope of the article. It should increase the volume of my paper considerably, and the issues mentioned by the reviewer have been evaluated extensively in several previous reviews. Thus, a whole issue of Toxicology has been devoted to the human literature (ref. 1), as has a 209 pages review from the German Federal Institute for Occupational Health, available on the web (ref. 2).

6. The paper needs editing in areas: for example, the workers don’t produce microscopic or histological changes directly, they report these patterns of findings in animals that they have treated with hydrocarbons.

I shall change the text as suggested

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

I disagree. This paper should be of interest to all clinical nephrologists. As I mentioned in Conclusions all case-control studies, that included patients with end-stage renal disease only, found that more than 50 % of the patients with glomerulonephritis reported about prolonged exposure to hydrocarbons. In many countries chronic glomerulonephritis is the most common cause of end-stage renal failure, which means that if such exposure could be discontinued at an earlier stage, end-stage renal disease could be prevented in a substantial number of patients. The reason why the large majority of clinical nephrologists have aimed little interest in the subject is scepticism against the association between hydrocarbon exposure and glomerulonephritis because it is said that such exposure produces tubulointerstitial disease, not glomerular. My review has shown that this is not true, and as experimental evidence is the strongest proof of causality, my paper might, hopefully, lead to
a better understanding of the issue and thus lead to a major improvement in the treatment of chronic glomerulonephritis including the prevention of end-stage renal disease.