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RHENIUM: SUMMARY REPORT ON A LITERATURE SEARCH FOR TOXICITY DATA

1 Introduction

A subacute/reproductive toxicity screening study (OECD TG422) is being conducted on ammonium perrhenate at dose levels of 0, 110, 330 or 1000 mg/kg/day. From day 10, clinical symptoms were seen in the high dose group (both males and females) which might be considered indicative of an immunological response. They consisted of transient swelling and reddening of the face, ears and paws, with recovery within 24 hours. The severity of the symptoms decreased following repeated exposure to the test material. Full details of the effects observed will be presented in the formal toxicity study reports from Charles River, Edinburgh, the laboratory undertaking the study.

On the basis of these findings, wca was requested to perform a literature search to identify if there are any published data referring to similar clinical symptoms after treatment with rhenium compounds, particularly in relation to possible immunological effects.

2 Literature search

It should be noted that general literature searches and data call-ins had been made some years ago by wca, bibra, and PMC prior to the preparation of the Phase III ITS report. At that time, only a relatively small number of hits were found, indicating the lack of published data on this group of substances. Although the current review focused specifically on potential immunological effects, a broader search (using the term 'toxicity' – see below) was also included to verify the limited data in the public domain.

The following databases were searched: PubMed (which also contains access to MEDLINE citations) and TOXNET (which searches TOXLINE as well as a number of other relevant databases). Both these databases would be expected to contain any relevant publications. The search terms used were:

> (rhenium OR *rhenate) AND ((toxicity OR allergy OR (type AND 1) OR urticaria OR hives OR IgE OR oedema OR edema OR sensit* OR histamine OR immunolog*))

3 Results

Using the above search terms, PubMed returned 439 hits, while TOXLINE returned 186 hits (note: TOXLINE also contains PubMed in its databases, but draws less hits than searching PubMed directly). As expected, there was an overlap in the papers identified using these two databases. In view of the relatively low number of hits, it was considered relevant to include the broad term 'toxicity' in the search.

The majority of papers cited that were not specifically focused on the pure chemistry of rhenium complexes, were mainly related to antibody-based tumour radioimmunotherapy using Re186/188, including metastic bone tumour pain relief. This type of therapy involves cytokine release and immune cell recruitment, particularly in severely compromised patients. Hence these papers do not provide any meaningful insight into potential mechanisms of toxicity of e.g. ammonium perrhenate.

One paper was identified that could be considered relevant, but has already been identified in earlier searches: **Haley, T and Cartright, F. Pharmacology and Toxicology of Potassium Perrhenate and Rhenium Trichloride, 1968, Journal of Pharmaceutical Sciences, vol 57 No 2**. A copy of this paper was retrieved from the files and further evaluated to see if it contained any useful information. The paper initially refers to earlier work from the 1930's, where an LD_{50} value for potassium perrhenate could not be obtained in mice or rats. Subsequently the authors performed an intraperitoneal LD_{50} test and the value quoted for $KReO_4$ was 2.8 g/kg. Symptoms were sedation and severe ataxia, with death or recovery within 7 days. The value for Re_2Cl_6 was 280 mg/kg, where sedation was also seen. Pharmacological effects of $KReO_4$ were evaluated following intravenous administration in cats. Transient hypertension with tachycardia was seen at 10 – 50 mg/kg, while hypotension, bradycardia, and bradypnoea occurred at 60 – 70 mg/kg. Death from cardiovascular collapse was observed at the latter levels. Control studies indicated that the potassium ion played no major part in the responses seen. No repeat dose studies were reported.

The conclusion by the authors was that their work showed the low order of toxicity of potassium perrhenate compared to rhenium trichloride. There are no clear conclusions to be drawn from this paper regarding the mechanism of toxicity, and no obvious relationship to the clinical signs seen with ammonium perrhenate in the current OECD TG422 study.

A further paper of potential relevance from its title was **Elinder, C and Zenz, C. Other Metals and their compounds, 1994, Occupational Medicine, 3rd Edition, Ed Mosby, Year Book Inc., St Louis, pp 595-616.** The abstract of this section is:

> The production of, uses of, and health effects associated with exposure to several metals encountered in diverse mining settings were reviewed. These included barium (7440393), bismuth (7440699), boron (7440428), copper (7440508),hafnium (7440586), iron (7439896), lithium (7439932), magnesium (7439954), molybdenum (7439987), palladium (7440053), platinum (7440064), **rhenium** (7440155), rhodium (7440166), silver (7440224), strontium (7440246), tantalum (7440257), thallium (7440280), tin (7440315), titanium (7440326), zinc (7440666), and zirconium (7440677). Experimental and/or human evidence of **toxicity** has been reported following exposure to these metals or their compounds with the exceptions of palladium, **rhenium**, rhodium, and inorganic tin compounds. Molybdenum and hafnium and their compounds have been thought to have few, minor toxic effects especially in humans. These metals and their compounds have

not been reported to have carcinogenic effects, although a possible role for iron oxides as cocarcinogens has been suggested.

This abstract indicates that no experimental and/or human evidence of toxicity has been reported following exposure to rhenium or its compounds. The original reference therefore has not been obtained.

One other reference was identified in PubMed:

34. QJM. 2012 Apr;105(4):379-80. **Epub 2011 Mar 3.Leg oedema in a young female. Fernández-Fernández FJ, Caínzos-Romero T. Department of Internal Medicine, Hospital Arquitecto Marcide, Ferrol, Spain.** fjf-fernandez@terra.es PMID: 21372108 [PubMed - indexed for MEDLINE]

However, the original paper has not been sought at this time since it is unlikely to have major relevance.

Additionally, a review of the limited proprietary data considered in the preparation of the ITS included an acute oral toxicity study on rhenium(VII) oxide. The LD_{50} value obtained was >500 - < 2000 mg/kg. The clinical symptoms as described did not clearly match those seen in the current OECD TG422 study, particularly in relation to oedema and skin reddening. An acute oral toxicity study in rats on ammonium perrhenate is currently under discussion with regard to its accuracy, and no relevant toxicity information was observed from this study.

4 Conclusion

The literature search conducted using public databases to see if any useful information relating to possible immunological effects of rhenium ions failed to identify anything significantly relevant. Very little data are published specifically on the hazards associated with rhenium salts, and most information relates to the use of radiolabelled antibodies for treatment of malignancies. The abstracts obtained by searching PubMed and TOXLINE are available for review if required.

Paul Whitehead

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