PRECIOUS METALS CONSORTIUM RHENIUM REACH PROJECT: PHASE I

FINAL REPORT FROM WCA ENVIRONMENT LIMITED TO THE PRECIOUS METALS CONSORTIUM

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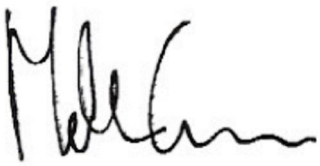
Document Quality Checked by		28 November 2008

Introduction

The Precious Metals Consortium (PMC) commissioned wca environment and bibra to provide consultancy work for Platinum Group Metals (PGMs) and Rhenium REACH Registration projects. The two projects are based on five phases of work, as follows:

- Phase I: Literature work; preliminary data gap analysis; formal report of findings.
- Phase II: Test derogation assessments and the design and progression of any enabling tests (such as bioaccessibility determinations) relevant to Intelligent Testing Strategies and test waiving.
- Phase III: Main test programme design, test conduct, test monitoring and reporting (per REACH Annexes).
- Phase IV: Production of Chemical Safety Assessments/Chemical Safety Reports.
- Phase V: Compilation of IUCLID 5 files and Registration Dossiers.

The objectives of Phase I of this project are to:

1. Produce a data matrix which clearly identifies tonnage-relevant IUCLID 5 endpoints for which there may be no data, tonnage-relevant endpoints for which valid data potentially exist for PGMs and rhenium, and any other toxicity data on these compounds that could be useful in later phases (e.g. when writing data waivers).

2. Provide a preliminary identification of data gaps and endpoints for which grouping and read-across may be possible, and identify any appropriate reference substances on the basis of chemical, physical and biological behaviour in relation to other group members (i.e. any trends across groups).

3. Use experience gained through the understanding of previous metals risk assessments, undertaken through the TCNES[1] process, to assess potential read-across conditions.

4. Perform a REACH Annex III assessment to identify any substances for which it is predicted that establishing only a physico-chemical dataset will be required.

This short report plus accompanying Excel files present the results of Phase I for rhenium.

Literature searching methodology

The PMC supplied a list of the names and CAS numbers of the chemicals of interest to wca. Nine rhenium substances were identified.

The chemical names and CAS numbers supplied to us were checked to ensure that they referred to the same compound, and any common synonyms were identified. Literature was searched for in TOXNET (this includes all the databases and databanks) and Web of Science using chemical names, CAS number and the agreed search strings.

[1] European Union's Technical Committee on New and Existing Substances

Box 1: Search Strings

- () AND (Environmen* OR Pollution OR Exposure OR Health OR Safety OR Poison* OR Work*) – **Exposure**
- () AND (Toxicant OR Toxicology OR Toxicity OR Acute OR Chronic OR Oral OR Dermal OR Inhalation OR Vision OR Hearing OR Irritant OR Irritation OR Sensitisation OR Sensitiser) – **Mammalian Tox 1**
- (Endocrine OR Endocrinology OR Immunotoxin OR Immunotoxicity OR Neurotoxin OR Neurotoxicity OR Toxicokinetics OR Metabolic OR Metabolism OR Metabolite) – **Mammalian Tox 2**
- () AND (Cancer OR Carcinogen OR Carcinogenic OR Mutagen OR Mutagenic OR Cytotoxic OR Cytotoxicity OR Genotoxic OR Genotoxicity OR Leukemia OR Leukaemia) - **CMR 1**
- () AND (Repro* OR Pregnan* OR Fertility OR Developmental) - **CMR 2**
- () AND (Environment OR Environmental OR Work* OR Epidemiology OR Epidemiological) - **Epidemiology 1**
- () AND Case AND Epidemiolo* - **Epidemiology 2**
- () AND (Environment OR Environmental OR Toxicology OR Toxicity OR Toxicant OR Ecotox* OR Pollution OR Acute OR Chronic OR Fish OR Invertebrate OR Algae OR NOEL OR NOAEL) - **Environmental**
- () AND (Asthma OR Allergen OR Allergic OR Allergy OR "DNA Interaction" OR "DNA Damag*" OR NOEL OR NOAEL OR Pathology OR Corrosive OR Corrosivity) - **DNA**

Items in () are substance specific CAS No and substance name e.g. (7440-15-5 OR rhenium). Names in bold text are wca search identifiers.

Searches of the bibra TRACE and USEPA ECOTOX databases were also conducted on the chemical name and CAS number. The references from each source were merged into a single file for each compound and duplicates were removed. The total number of references identified for each substance is shown in Table 1.

Table 1. Number of references identified in TOXLINE and Web of Science for each substance. The name of each substance is kept as originally supplied to wca.

Name of the substance	CAS number	Number of references identified
Rhenium	7440-15-5	2697
Perrhenic acid	13768-11-1	38
Ammonium perrhenate	13598-65-7	109
Dirhenium heptaoxide	1314-68-7	7
Sodium rhenate	13472-33-8	80
Calcium perrhenate	13768-54-2	12
Dirhenium heptasulphide	12038-67-4	2
Rhenium-containing scrap (searched as rhenium)		2697
Ion-exchanger polymer (searched as rhenium)		2697

Some members of the PMC supplied lists of published references to wca that they believed to hold useful information. These lists were compared with the results of the literature search. Any references not already identified by wca were added to the lists of potentially useful literature.

wca screened the references located for each compound to identify those which looked relevant to IUCLID endpoints in chapters 4 (physico chemical), 5 (environmental fate), 6 (ecotoxicology) and 7 (mammalian toxicity). At this stage we have been as inclusive as possible in order to identify as many references as possible that may contain relevant information. We have therefore identified references that may be relevant to all REACH endpoints, regardless of the tonnage band of the substance. The references that were identified as relevant were transferred to a new work sheet, and grouped by endpoint in order of REACH Annex information requirements.

Because of the variety of different sources from which references were gathered there are differences in the amounts of information available and the format in which they are presented. For example,

- some references have abstracts, others do not;
- the journal name, volume and page numbers may be in a single column or six separate columns;
- the references may be reported in lower case or upper case;
- some alphabetical symbols are not represented correctly in Excel (and may be missing or replaced with a different symbol, e.g. a % sign).

We have tried to make the lists of references reasonably consistent but at this stage it should not be necessary to spend a large amount of time formatting these files. These lists of references are for use by wca, bibra and the PMC during later phases of the project and will not be provided to other parties. We believe that they are sufficient to show the references that have been identified as potentially useful, the REACH information requirements to which these references may relate, and where there may be data gaps for some substances.

Proprietary data for some of the compounds were supplied to wca by members of the PMC. These studies were anonymised by changing the owner/authors of these studies to a code number and they were then added to the non-proprietary data for the test compound. Code names for proprietary data consist of the elemental symbol followed by a two digit number.

Results of literature searches

The results of the literature search fulfil the first objective of Phase I of this project, to produce a data matrix which clearly identifies tonnage-relevant IUCLID 5 endpoints for which there may be no data, tonnage-relevant endpoints for which valid data potentially exist for rhenium, and any other toxicity data on these compounds that could be useful in later phases.

The results sheets are supplied as Excel files named as 'CAS number_PMC list.xls'. Different substances have different amounts of information available. References are grouped by REACH endpoint and ordered by REACH Annex. If no references were identified as potentially relevant to a specific endpoint then this is indicated by a blank row and highlighted in red bold text.

If no references were found for a substance during the literature searches this is recorded as 'no references found' in the Excel file. If none of the references found were clearly relevant to the REACH endpoint requirements this is recorded as 'no references selected as relevant' in the Excel file.

Defining categories

Annexes VII-X of REACH identify the data requirements on a per substance basis. However, Annex XI allows for evaluation under REACH to be conducted by grouping chemicals into categories. The use of a category approach has several advantages. Data from one of more chemicals can be interpolated or extrapolated to other category members, removing the need to test every endpoint for every chemical. This reduces the cost to the registrant, reduces the need for animal testing, may help in the evaluation of compounds that are difficult to test using standard protocols and can provide time savings. All compounds in a category can potentially contribute some data, so that - in theory - the category evaluation might be based on a greater amount of data than evaluation for a single compound. This could increase the confidence in the risk assessment, and may identify potential effects for compounds that would otherwise be overlooked. However, in order for a category approach to be helpful to the risk assessment process the definition of the categories must be well justified.

The use of chemical categories in hazard and risk assessment is an established technique for metals. The underlying assumption is that properties are likely to be similar, or follow a trend, as a result of a common metal ion. The bioavailability of the metal ion must also be considered carefully, as it is the bioavailability that in most cases determines the effects seen. Information to assess bioavailability can range from a simple measure of solubility to more complex measurements of *in vivo* uptake and toxicokinetics. For example, effects data from a water soluble metal compound could be used as a conservative estimate for a compound with lower solubility or to identify a need for classification or nonclassification.

In addition, when defining a category it is also important to consider other factors that could influence how similar effects are likely to be. For transition metals the chemical speciation and valency/oxidation state may be critical in determining ecotoxicity and toxicity. We must also consider whether the metal itself belongs in the same category as compounds of that metal. The toxic potential of organometals may be underestimated if we assume that the metal ion is the sole source of toxicity. Alternatively, an organometal that rapidly degrades to the metal ion in the environment may fit well in the metal ion category.

REACH guidance is available on how to define a chemical category (ECHA (2008) Guidance on information requirements and chemical safety assessment Chapter R6

QSARs and grouping of chemicals). The guidance is provided as a stepwise approach to the formation of categories.

Step 0: Check whether the chemical is a member of an existing category
Step 1: Develop category hypothesis and definition, and identify individual members of the category
Step 2: Gather data for each category member
Step 3: Evaluate available data for adequacy
Step 4: Construct a matrix of data availability
Step 5: Perform a preliminary evaluation of the category and fill data gaps
Step 6: Propose and perform testing
Step 7: Perform a further assessment of the category
Step 8: If the category appears adequate, document the final category and its rationale.

None of the compounds included in this project have been identified as category members under existing risk assessment programmes (e.g. USEPA, OECD or EU). We therefore need to develop a category hypothesis and definition and identify which of the compounds fall into each category.

We have used oxidation state as the basis for category formation, as speciation in environmental waters and biological fluids is likely to be similar for compounds with the same oxidation state. As data gathering on additional endpoints that will inform the category definitions begins in Phase II the use of oxidation state is a reasonable starting point at this stage in the project. In Phase II we will consider whether the different oxidation states exist and are stable in environmental media. This will inform the category groupings further.

Where applicable, we have also included an assessment of the possible toxicity of the counter ion in order to identify compounds that may require a separate category. If there are five different toxic counter-ions they may all require a separate category, although we may be able to group some. If we can demonstrate that the counter ion is not toxic, or that the effects are the same as the metal ion, then the substances could join the general category for that oxidation state.

The results of this preliminary grouping are shown in Table 2. Categories are named by the elemental symbol followed by the oxidation state. Where the counter ion is likely to have significant impact e.g. on (eco)toxicity in addition to the metal ion these have been placed in a separate category marked with an A, as currently only an ammonium complex has been identified as such. An X indicates that we do not currently have enough information to place the compound into a category.

Table 2. Preliminary category definitions based on oxidation state and counter ion toxicity.

Category	Name of the substance	CAS number
Re0	Rhenium	7440-15-5
Re7	Perrhenic acid	13768-11-1
Re7	Dirhenium heptaoxide	1314-68-7
Re7	Sodium rhenate	13472-33-8
Re7	Calcium perrhenate	13768-54-2
Re7	Dirhenium heptasulphide	12038-67-4
Re7A	Ammonium perrhenate	13598-65-7
ReX	Rhenium-containing scrap	
ReX	Ion-exchanger polymer	

Compounds identified as intermediates have been included in the formation of categories as, although they may not be registered as part of a category, there may be data for these compounds that could be used to confirm the adequacy of the category or that could be used for read-across to other compounds.

This is scientifically as far through the process of category definition as we can go at this stage of the project. Category definition is an iterative process and will continue throughout the project. The next step is to gather data for each category member and this will form part of Phase II. The bioavailability of the metal will form a key part of this reassessment of the categories and we will then proceed to address special cases (for example, the halogen complexes and certain organic ligands may need to be separated out once we begin assessing data). After examining the data some categories may be merged, or split further. The categories suggested here are therefore subject to change and should not be regarded as final.

Preliminary data gap analysis method

We produced a matrix of data availability for the preliminary categories identified above which allowed us to highlight possible data gaps and the potential for read across.

We have only looked at REACH Annex VII and VIII requirements because these encompass the tonnage bands for these substances. We have assumed that calcium perrhenate, dirhenium heptasulphide, rhenium-containing scrap and the ion-exchange polymer would fall in the same tonnage bands as those provided for the other rhenium compounds (i.e. up to 100 tonnes). Note, however, that for completeness references that may be relevant to REACH requirements at higher tonnage bands are still retained in the results of the literature searches for all compounds. Note also that the references identified for rhenium-containing scrap and ion-exchanger polymer are the same as those identified for Rhenium. Specific identifiers for rhenium containing scrap and ion-exchanger polymer (e.g. CAS numbers) were not supplied by the PMC and searches on

these terms did not provide relevant information. Therefore, results for these three substances are identical.

Results of preliminary data gap analysis

The results of the preliminary data gap analysis fulfil the second and third objective of Phase I of this project to provide a preliminary identification of data gaps and endpoints for which grouping and read-across may be possible and to use experience gained through the understanding of previous metals risk assessments, undertaken through the TCNES process, to assess potential read-across conditions.

The results of this are supplied as an Excel file named 'data analysis matrix Rhenium 181108.xls'. The matrix indicates the endpoints for which information may be available with a 'Y'. We have annotated the matrix to identify opportunities for data waiving or read-across. Any cells in the matrix left blank indicate a data gap.

This matrix highlights the following:

1. We did not find references that obviously provide data on specific individual physico-chemical endpoints for any of the categories, but some general reviews were identified that may provide information on some of these endpoints. In addition, many of the physico-chemical endpoints required under REACH are of minor importance or are not relevant for inorganic compounds. We expect that for the majority of these rhenium compounds the endpoints vapour pressure, surface tension, partition coefficient, flash point, flammability, explosive properties and self ignition temperature could be addressed by derogation. Test derogation/data waivers will be prepared under Phase II of this project.

2. Only a very limited amount of mammalian toxicity data was identified. The mammalian toxicity data on acute oral toxicity and skin irritation all relate to proprietary tests conducted with ammonium perrhenate. Some general reviews of rhenium toxicity were also identified and these may contain further information which may be useful for data requirements under REACH. Currently, therefore, the data matrix represents what hopefully could be a "worst-case" scenario as regards data availability. Full awareness of what is available (and thus what data gaps exist) will only be known once the various reviews, other references and proprietary reports are obtained and examined.

3. Only one short-term aquatic invertebrate test study was identified, which tested the toxicity of rhenium to the sediment dwelling crustacean *Hyalella azteca* (depending on the form of rhenium in the test solution this may be more relevant to other categories). Short-term aquatic invertebrate studies were not identified for any of the other proposed categories, nor did we identify algal or fish studies for any of the rhenium compounds. These aquatic ecotoxicity tests may be waived if there are mitigating factors that indicate that aquatic toxicity is unlikely to occur, for example if the substance is highly insoluble in water or if the substance is unlikely to cross biological membranes. The possibility for derogation will be considered in detail in Phase II.

4. We found no references which related to the required environmental fate endpoints for any of the proposed categories. However, some endpoints, such as biodegradation, are not required for inorganic substances and so may be waived. Consideration of the stability of different Re oxidation states in environmental media may be more relevant than a hydrolysis study and HPLC screening for adsorption/desorption is unlikely to be successful, so information on solubility, redox, precipitation, charge etc, may be adequate at a screening level.

5. Overall, only limited potential data sources were identified for the rhenium compounds.

It must be recognised that this initial category formation and data gap analysis has been conducted before any data have been looked at in detail. During Phase II of this project we will assess the quality and relevance of each of the references identified during Phase I. These data may lead us to revise the category groupings, identify data where we thought there may be a data gap, or identify further data gaps where potential information sources prove inadequate to fulfil REACH data requirements.

Experience of the TCNES process under the Notification of New Substances Regulations and Existing Substances Regulations suggests that ECHA and its supporting Risk Assessment Committee (which includes several former members of TCNES) will make decisions that are evidence-based, but conservative in the face of any residual uncertainties. The attitude of TCNES to different industries was clearly influenced by whether they believed that an industry was making an honest and timely attempt to collate or generate sufficient data for a risk assessment. Members of TCNES were also very unimpressed by industries who over-interpreted available data to the benefit of their own substances.

One of the main differences between TCNES and ECHA is that while industry groups could meet regulatory members of TCNES face to face to discuss outstanding issues, this is not a process that is planned to take place under REACH. It is also unlikely that industry groups will have much, if any, influence over the choice of competent authority to whom ECHA may send substance dossiers and Chemical Safety Reports for assessment. The competent authority could therefore be highly skilled and experienced in assessing chemical risk assessments (e.g., Germany, the Netherlands, Denmark or the UK), or relatively inexperienced.

It is therefore important that:

1. Dossiers and reports submitted to ECHA are transparent, and written very clearly and simply (although not in a manner that might appear to be patronising to an experienced assessor).

2. All requirements, or apparent requirements, under REACH are dealt with in submitted dossiers and reports, even if they do not apply to metals or organometals. In other words any derogations must be adequately justified. This is so that

inexperienced assessors are provided with sufficient information to make sound scientific decisions.

3. All arguments for read-across and data waivers are clearly evidence-based and, where possible, cite precedents from other regulatory areas that have been accepted by the European Commission (e.g., Existing Substances Regulations and OECD HPV programme).

REACH Annex III Assessment methodology

Article 12 of REACH stipulates the minimum level of information required depending on the tonnage to be registered. For substances registered in quantities between 1 and 10 tonnes Article 12 states that we must regard the criteria listed in Annex III of the legislation. REACH Annex III states the criteria for substances registered in quantities between 1 and 10 tonnes with reference to Article 12 (1)(a) and (b). Taken together Article 12 and Annex III indicate that for substances registered between 1 and 10 tonnes only the physicochemical data requirements must be met if:

1. The substance is unlikely to meet the criteria for category 1 or 2 classification for carcinogenicity, mutagenicity or reproductive toxicity or the criteria in REACH Annex VIII (PBT, vPvB)
2. The substance does not have dispersive or diffuse uses, particularly where such substances are used in consumer preparations and
3. The substance is unlikely to meet the classification criteria for any human health or environmental effects endpoints under Directive 67/548/EEC.

Note also that Article 12 states that all available physicochemical, toxicological and ecotoxicological information must also be supplied. So although additional aquatic ecotoxicity and biodegradation testing may not be required for substances fulfilling these criteria all existing data must be included.

Substances registered between 1 and 10 tonnes and not meeting these criteria must fulfil all Annex VII data requirements. For substances manufactured or imported in the tonnage band of 10 to 100 tonnes all the information requirements in Annexes VII and VIII apply.

Data on individual compounds will not be gathered and assessed until Phase II of this project, and so at this stage we are only able to identify compounds which may fulfil these criteria based on tonnage and which are not included in Annex I of Directive 67/548/EEC. These are shown in Table 3. Based on the present information the only rhenium compound that definitely will not meet these criteria is ammonium perrhenate as this is registered in the 10-100 tonne band.

Table 3. Rhenium substances which may meet the criteria for an Annex III exemption.

Tonnage band	Name of the substance	CAS number
1-10	Rhenium	7440-15-5
1-10	Perrhenic acid	13768-11-1
1-10	Dirhenium heptaoxide	1314-68-7
1-10	Sodium rhenate	13472-33-8
unknown	Calcium perrhenate	13768-54-2
unknown	Dirhenium heptasulphide	12038-67-4
unknown	Rhenium-containing scrap	
unknown	Ion-exchanger polymer	

PMC members should note that all parties to the registration must agree the classification of each substance based on all the available data. Therefore, if a member of the SIEF has data which indicate that a classification under Directive 67/548/EEC is required or that the CMR, PBT or vPvB criteria are met then this may increase data requirements or bring forward the registration date significantly.

Results of REACH Annex III Assessment

The results of the REACH Annex III assessment fulfil the fourth and final objective of Phase I of the project to perform a REACH Annex III assessment to identify substances for which it is predicted that establishing only a physico-chemical dataset will be required.

These results will be refined in Phase II of the project where we will gather specific information on the toxicology and ecotoxicology of each substance to allow us to confirm whether an Annex III exemption will apply to any of the rhenium compounds included in this project. Data on use patterns will also be important to demonstrate non-dispersive uses of each substance for which an exemption is sought.

Conclusions

Phase I is now complete and has resulted in several outputs:

- The results of literature searches conducted by wca have been combined with non-proprietary and proprietary data. The references have been reviewed and those considered relevant to a REACH endpoint have been reported on a per substance basis as 'CAS number_PMC list.xls'.
- Preliminary categories have been identified on the basis of oxidation state and the potential toxicity of the counter ion. These categories will be reviewed in Phase II once data on each substance have been assessed.
- A data matrix has been constructed to identify data gaps. Where possible we have given an indication of the potential for read-across or derogation. This matrix is supplied as 'Data analysis matrix rhenium 181108.xls'.

- An initial assessment has been made to identify rhenium substances that may fulfil the criteria for an Annex III exemption. This will be reconsidered in Phase II once we have reviewed the available information so that we can make an informed judgement.

The project now moves into Phase II: Test derogation assessments and the design and progression of any enabling tests relevant to Intelligent Testing Strategies and test waiving.

The main tasks to be completed in this phase of the project are:

- Final review of reference lists following comments on Phase I outputs.
- Review each reference, assign a Klimisch code and complete a robust summary where appropriate.
- Finalise substance categories and justifications and agree these with the PMC.
- Create category data matrices to identify data gaps.
- For data gaps, either justify data waiving (including Annex III exemptions), justify read across, or identify as a 'true' data gap.

The output of Phase II will be a short report, and for each substance or category a set of fully quality assured data, carefully argued cases for any test waivers on the basis of their likely importance in either an environmental or human health risk assessment, fully justified arguments for read-across, and the final identification of data gaps (which will be addressed in Phase III).

To allow the PMC to budget more accurately, Phase II of the project will begin with a trial of two PGM categories so that the length of time required to complete this phase is based on evidence. At the project meeting of the 14th November 2008 the PMC proposed to use the categories that include Hexachloroplatinic acid and either Palladium or Palladium oxide as these will represent substances with a high and low hazard profile. The results of this trial will be used to improve the estimate of the potential costs of Phase II of the Rhenium REACH Registration project.