



# Pd RAAF – Face-to-Face meeting with Bibra

*Final minutes, London, 02 November 2016 (11-16)*

**Participants:** Richard Young and Chris Waine (Bibra), Mark Raffray (PMC Consultant), Dave Boyd (PMC Consultant), Jelle Mertens (PMC)

**Agenda** – cfr appendix I

Action		Who
<b>GENERIC</b>	Redraft reports for use of category approach (not analogue)	Bibra
	Replace any RAAF/read-across reference to Pd <sup>2+</sup> by Pd(II)	Bibra
	Remove any RAAF/read-across reference to (NH <sub>3</sub> ) <sub>2</sub> Pd <sup>2+</sup>	Bibra
	Replace 'biotransformation' by 'transformation'	Bibra
	Expand grouping justification with mammalian routes	Bibra
	Acute tox (dermal) – test waiver for all Pd compounds	Bibra
<b>Pd metal</b>	Check TK assessment - too conservative	Bibra
	Take Pd metal out of group – use waivers for datagaps + include Pd(II) data as supportive evidence	Bibra
<b>Hexachloro Pd cmpds</b>	<i>Check validity of last sentence on p 1 and last sentence on p 3</i>	<i>Bibra</i>
	water solubility Pd dichloride is ~4 g/l rather than 60 g/l – check dossier (and update if required), and ensure RAAF report uses the ~4 g/L value throughout	Bibra
<b>Chloro Pd cmpds</b>	take Pd dichloride and DDP out of the group to form internally consistent tetrachloropalladate new grouping; place Pd dichloride into realigned Pd(II) group (see overpage)	Bibra (&WCA?)
	Tetrachloropalladate group: For RDT endpoint leverage use of low KL rank Moore et al (1975) RDT study for potassium salt with supporting data/WoE from DDP & Pd(OH) <sub>2</sub> as Pd(II) other reference substances (including coverage of reprotox)	Bibra



<b>Pd(II) cmpds</b>	Rename group as 'uncomplexed and partially complexed Pd(II) substances' - Group members are Pd monoxide, dihydroxide and dichloride	Bibra
	Use Pd(OH) <sub>2</sub> as source substance for RDT and Reprotox rather than reliance on DDP	Bibra
	Genetox: use WoE approach combining data from PdCl <sub>2</sub> and tetraammine Pd cmpds	Bibra
	Pd dichloride mammalian gene mutation : check if Comet study might fill endpoint with substance specific data, both from a scientific standpoint, and with regard to a IUCLID "technical completeness" perspective.	Bibra
	Pd dichloride skin sensitization: classify based on WoE (include published Klimisch 3-4 studies together with supporting statement related to Pd(II) common property of skin sensitization potential	Bibra
	Pd dihydroxide skin sensitization: classify based on WoE (statement on skin sensitization potential Pd(II))	Bibra
	Pd(OH) <sub>2</sub> acute tox (oral), skin irrit/corr and eye irrit/corr: use Pd dichloride as source substance rather than Pd(acac)/Pd nitrate	Bibra
<b>Pd nitrate</b>	UVCB, take out of group	Bibra
	RDT and reprotox: As primary argument include waiver (low pH/corrosivity – testing not scientifically justified); secondary argument of Pd(II) relevant reference of Pd dihydroxide data	Bibra
<b>Pd(acac)</b>	Pd(acac) – check tonnage with registrants to ensure still Annex VIII	PMC
	Pd(acac) – check presence in DNEL reports of previous group members and remove	Bibra
	Acac-toxicity (RDT,oral): Look for availability additional evidence (registration dossiers Ca(acac), Zn(acac) and acac-ligand)	PMC
	RDT and reprotox: RA from Pd dihydroxide	Bibra
	Given this is not an ideal solution, relay to WG members that some risk exists	PMC



**Generic comments:**

- °Analogue vs category:
  - °ITS originally set-up as grouping
  - °category used by other metal consortia
  - °agreement to use category approach
- °Refer to Pd(II) instead of Pd<sup>2+</sup>
- °use 'transformation' rather than 'biotransformation'
- °justification for grouping: should be applicable to all mammalian receptor compartments (gastric/lung/dermal etc.)
- °Acute tox dermal endpoint: waive for all Pd dossiers (following updated ECHA direction/ (EU) 2016/863)
- °expectation: Pd metal and Pd dichloride dossiers have highest risk to be checked by ECHA

**Groups in revised approach:**

- 3 tetraammine Pd cmpds (2 in scope, 1 out of scope source substance)
- 2 hexachloropalladates
- 3 Tetrachloropalladates (2 in scope, 1 out of scope source substance)
- Pd monoxide, dihydroxide and dichloride

**Substances no longer part of any group:**

- DDP (substance specific full dataset available)
- Pd metal (essentially addressed via waiving and WoE approaches)
- Pd nitrate
- Pd(acac)

**Tetraammine Pd compounds**

- °reports are OK as is – no major updating required
- °RA of harmonized STOT-RE2 classification hydrogen carbonate salt (out of scope substance!) to other tetrammine Pd cmpds scientifically not justified (considered an overclassification – cfr available test data) – not appropriate to RA this classification

*[Post meeting note and not discussed during meeting: hexachloropalladate salts*

- °grouping and report considered OK
- °suggestion to check validity of last sentence on p 1 and last sentence on p 3]

**Tetrachloropalladates (TCPd)**

- ° decision to take Pd dichloride out of this group - Primary reason for relocation is chemistry/speciation differences (cfr further)
- °Potassium TCPd: Moore et al study available for Repeated Dose Tox (RDT) – include in dossier/RA reports (despite poor Klimish score) supported by other Pd(II) compound data.
- °RA from DDP not considered scientifically valid for chemistry and speciation reasons, plus anticipated TK differences (- remove DDP as group member
- °Note that DDP is to be clearly defined as being outside the group (so as not to risk setting a precedent of analogue vs. category approach). Note applies to other substances intended for



use in the read-across justification reports as supporting/reference/WoE and not as members of the respective groups.

°conclusion to use WoE argumentation

-for RDT: leverage use of low KL rank Moore et al (1975) RDT study for potassium salt with supporting data/WoE from DDP & Pd(OH)<sub>2</sub> as Pd(II) other reference substances

-for reprotox: use of data from DDP & Pd(OH)<sub>2</sub>

°acute tox (dermal): waive as for all Pd substances

### **Pd(II) compounds**

°rename as 'uncomplexed and partially complexed Pd(II) substances'

°group contains Pd oxide, dihydroxide and dichloride

°Use Pd(OH)<sub>2</sub> as source substance for RDT & reprotox

°genetox:

-PdO: read-across from Ames PdCl<sub>2</sub> (PdO is Annex VII).

-Pd(OH)<sub>2</sub>: use WoE approach (concluding on 'no genetox expected) combining

-primarily data Pd dichloride (included in IUCLID and RA justification report)

-with supporting Pd(II) group evidence (eg Tetraammine Pd cmpds - included in RA justification report)

°Genetox: potential weakness identified and suggestion to test OECD471 and 476 with Pd dichloride to have high quality data for this group (as source)

°skin sensitization Pd dichloride: include evidence from (poor quality (Klimisch 3-4)) studies & statement on skin sensitization potential from Pd(II) compounds in WoE approach

°skin sensitization Pd dihydroxide: classification agreed by PMC members – fill endpoint by statement on skin sensitization potential from Pd(II) compounds in WoE approach

°acute tox (oral), skin irrit/corr and eye irrit/corr of Pd dihydroxide: use Pd dichloride as source substance

°acute tox (dermal) Pd dihydroxide: waive as for all Pd substances

### **Pd metal:**

°keep out of any RA strategy/RAAF reports (not used as source substance anyway)

°use waivers to fill data gaps ('study scientifically not justified' or exposure based waiver):

-reference to substance inertness (cfr water solubility, bioelution data/(updated) & TK assessment)

-reference to other Pd compounds being negative for RDT, reprotox & genetox (as supporting evidence

-also consider use of industrial experience statements, e.g. for lack of chemical irritancy to eye/only mechanical irritant; absence of skin sensitisation case reports in workers; absence of respiratory irritation reports etc.

### **Pd nitrate:**

°not a stoichiometric compound, UVCB



- °for this reason a poor choice as source substance for monoconstituent substances – decision to separate from group containing (dihydr)oxide and dichloride
- °RDT and reprotox: include waiver (low pH – testing not scientifically justified) + reference to other Pd(II) data – primarily Pd dihydroxide.
- °At this time, no alterations will be made to the Pd nitrate DNELs (derived from Pd dihydroxide data). This minimises the knock-on effect and reduces the workload. Further, suitable and sufficient RMMs are already in place (considering pH, etc.)

#### **Pd(acac)**

- °Atypical Pd compound: acac-ligand can be metabolized, e.g. to 2-oxopropanal with potential for metabolite specific toxicity
- °RDT and reprotox: OK to keep RA from Pd dihydroxide if bioaccessibility Pd dihydroxide >> Pd(acac), and if acac-ligand does not contribute to RDT & reprotox (and thus Pd responsible for effects)
- °suggestion to verify tonnage band with registrants, and registration dossiers for Ca(acac), Zn(acac) and acac-ligand – check with Ca(acac) registrants/consortium (only inhalation data on ECHA dissem WS, oral data needed)
- °conclusion to stick to RA from Pd dihydroxide for RDT and reprotox, with no mention of acac chemistry/toxicology/metabolism, and see if this is challenged by ECHA (WG should be notified of the potential risk). Read-across justification report will only discuss expected similarity in behaviour of Pd(II) from Pd dihydroxide and Pd acac in gastric fluid.
- °Pd(acac)<sub>2</sub> as source compound:
  - skin sensit: not required anymore (Pd[II] class approach)
  - skin irrit: not required anymore (RA from Pd dichloride)
  - eye irrit: not required anymore (in vivo data available/classified as Eye dam 1 agreed by PMC members)

#### **AOB:**

- °Env assessment: RA from Pd HCO<sub>3</sub> to Pd(acac) – check
- °Pd acetate not classified as skin sensit – reason?
- °Pt RA: 3 groups identified:
  - 3 tetraammine Pt cmpds (2+1 out of scope)
  - 3 hexachloro Pt cmpds
  - RA HHPA to Pt nitrate for RDT & reprotox not justified – cfr approach Pd nitrate (waiver + WoE from eg HHPA (supporting studies)

#### **Identified weaknesses/supplemental testing needs:**

- TK assessments conservative: re-assess
- Pd ecotox assessment: further studies have already been identified as a need; these should seek to also reduce reliance on DDP as a general read-across and differentiate toxicity in a more rigorous grouping (expected to result in improved PNEC situation)
- Tetraammine Pd diacetate: no read-across of STOT-RE2 classification– ECHA might request confirming study



-TCPd group, Pd(acac), Pd dichloride: limited RDT / no Reprotox data available – for referral to WG as to whether an OECD 422 should be pre-emptively conducted or whether to await potential ECHA follow up instead. Moore et al is poor quality study to fill endpoint.

-PdO: bioelution data was not generated in the initial set of enabling studies; this data would be valuable for validating waiving and non-classification and would significantly strengthen the PdO dossier (sensitization, acute tox, irritancy endpoints etc.)

-Pd dichloride genetox (and other group members) – suggestion to test OECD 471 and 476 due to an imperfect existing dataset and increased reliance on this compound as a source substance

-Pd dihydroxide: classified as Eye Dam 1 (RA from Pd dichloride) – test required if classification needs to be removed [post meeting note Mark R: „...based on what is known about Pd(II) and the bioelution nature of the compound, I consider it likely that it would test positive in the necessary in vivo assay. Hence a conservative approach is supported.“]



## Appendix I: Meeting Agenda

# bibra/EPMF/PMC Face-to-Face Meeting

*bibra offices, Wallington, 11:00 Wednesday 2<sup>nd</sup> November 2016*

**Present:**

*Pete Watts, Richard Young, Chris Waine (bibra)*

*Jelle Mertens, France Capon (EPMF)*

*David Boyd (PMC Expert Consultant)*

*Mark Raffray (PMC Expert Consultant)*

**Introductions**

**General Comments**

Analogue vs. Category Approach

Grouping of Reports

**Discussion of Group 1**

Palladium metal: remove from RA strategy?

Palladium dihydroxide: registration stopped/postponed?

Palladium dinitrate: UVCB character.

Palladium acac: general discussion on applicability, especially in light of known toxicity (skin sensitisation) of acac moiety.

**Discussion of Group 2**

Tetrachloropalladates

Palladium dichloride: Group 2 or Group 1?

DDP: suitability for inclusion in RA strategy? Chemical vs. toxicological suitability?

**Discussion of Group 3**

General

Tetraammine dichloride/hydrogen carbonate: harmonised classification of hydrogen carbonate not being read-across to dichloride.

**Discussion of Group 4**

General

**Future Work**

Approach (and tentative timeline) for future PGM read-across (starting with Pt)

**Any Other Business**