Precious Metals Consortium

Precious Metals & Rhenium Consortium

Karstedt Concentrate - meeting Reconsile-PMC

15 February 2017 | MCC, Brussels

Welcome and introduction

Confidentiality and Competition law

Tour-de-table

DO	DON'T
Application of competition law	
Art. 101 and 102 TFEU may be applicable to the conclusion of any preliminary agreement and activities of any preliminary phase.	Don't assume that conflicts with competition law are excluded simply by the fact that the Agreement complies with the provisions of the REACH Regulation.
Consultation in Matters of Competition Law	
Consult an in-house legal expert or the compliance officer of your company or an external lawyer whenever there are uncertainties respecting compliance with competition law. Stop all meetings/discussions which are not in compliance with these Compliance Guidelines until a legal expert has been involved.	Don't assume that these Compliance Guidelines deal with all competition law issues exhaustively. Basically, compliance with Art. 101 and 102 TFEU can be determined only on the basis of market impact in each individual case. These Compliance Guidelines may therefore be regarded only as a means of providing general conduct recommendations.
Activities in any preliminary phase and at any other stage of operation of the Consortium	
Restrict cooperation within the scope of the preliminary phase to the initially defined goals and purposes of the cooperation.	Pursuant to Art. 101 and 102 TFEU, activities which have the object of the effect of preventing, restricting and/or distorting competition are prohibited within the scope of this Agreement, including: - Coming to agreement, including arrangements or collusions, about prices, markets and customers (see Art. 101 paragraph 1 a)-e) TFEU); - Joint boycotting of other companies; - The unjustified unequal treatment of trade partners; - The abusive exploitation of a dominating market position.
Exchange of Confidential Information	
Involve a Trustee for the exchange of Confidential Information.	The exchange of Information concerning market behaviour and having the object or the effect of preventing, restricting and/or distorting competition is inadmissible; in particular, this relates to : - Production capacities; - Productions or sales volumes; - Import volumes; - Market shares; - Price policy; - Distribution and marketing terms; - Marketing strategies; - Information regarding the relationship with suppliers.
Documentation on Cooperation	
Keep minutes of all meetings which detail the subject of the meeting. In case of uncertainty, have the contents of the minutes reviewed by an external legal expert prior to sending them to all parties of the Agreement. Stop all meetings which are not in compliance with these Guidelines until a legal expert has been involved.	

Agenda points

- Content of the REACH dossier
  - Substance ID
  - Use information
  - hazard data as included: phys-chem, environmental fate and toxicity, mammalian toxicity
  - ongoing testing: OECD422
- Dossier status + further steps/timing
- Comments on LoA agreement

Precious Metals Consortium

Content of the REACH dossier

Substance ID

- Draft substance ID card available 3 March 2016, sent to PFA&Reconsile 4 March 2016
  - Modified wording on Silicone content

The·total·silicon·content·of·the·Karstedt·concentrate·is·~~in·principle·also·~~around·20%·and·ranging·from·15%·to·30%.· The· proportion· of· the· silicon· content· bounded· in· the· Platinum,· 1,3-diethenyl-1,1,3,3-tetramethylsiloxane·complexes·(Constituents·A,·B,·and·C)·is·approximately·15%.¶

- Request to update water content to max. 7%

4	Water·¤	·¤	231-791-2·¤	H_2O·¤	0·-·~~5~~7·¤	ca.·2,0¤

- Final version available 15 March 2016

Use information

- Email sent to Reconsile secretariat 15 March 2016
  - Use questionnaire
  - Occupational exposure questionnaire
  - Environmental exposure questionnaire
- 9 May 2016
  - 3 use questionnaires
  - 1 occupational exposure questionnaire
- 31 May 2016
  - 1 environmental exposure questionnaire
- 27 June, 1 July, 29 Sept 2016
  - Further clarifications received on KC use
- All uses collated and included in dossier (cfr next slide)

Use information

Life Cycle Step	Use name	ERC	PROCs	PC	SU	TF	AC
Manufacture	Manufacture of Karstedt concentrate	1	1, 4, 8a, 8b, 9, 15	-	-	-	-
Formulation	Formulation of preparations	2	1, 2, 3, 4, 5, 8a, 8b, 9, 15	1, 9a, 9b, 14, 15, 20, 32, 0: mould material	-	catalyst, process regulator	-
	Formulation in materials	3	1, 2, 3, 4, 5, 8a, 8b, 9, 15	1, 9a, 9b, 14, 15, 20, 23, 26, 31, 32, 34	-	catalyst, process regulator	-
Use at industrial site	Use in silicone elastomer and silicone article production	5, 6d	1, 2, 3, 4, 5, 8a, 8b, 9, 13, 14, 15	1, 9a, 9b, 14, 15, 20, 23, 26, 31, 32, 34, 0: Mouldable rubber compound	5, 6a, 6b, 9, 11, 12, 13, 16, 17, 18, 19, 20, 24	process regulator	-
	Use in polymer functionalisation	6b	3, 8a, 8b, 15	9a, 17, 23, 24, 25, 26, 27, 31, 32, 34, 35, 39, 40	9	catalyst	-
	Use in polymer preparation	5	1, 8b, 9	32		cross-linking agent	-
	Use in paper coatings	5	1, 2, 3, 4, 5, 8a, 8b, 9, 15	9a, 26, 32	6b, 7	process regulator, cross-linking agent	-

Use information

Life Cycle Step	Use name	ERC	PROCs	PC	SU	TF	AC
Widespread uses by professional workers	Use in silicone production	8c	4, 5, 8a, 8b, 9, 13, 14, 15, 21	1, 9a, 9b, 14, 15, 20, 23, 26, 31, 32, 34	5, 11, 12, 13, 17, 18, 19, 20	process regulator	-
Consumer uses	Use of silicones	8c, 8f		1, 9a, 9b, 14, 15, 23, 26, 31, 32, 34, 39		process regulator	-
Service life	Processing of silicones in industrial settings	12a	21	-	-	process regulator	-
	Handling of silicones in professional settings	10a, 11a	21	-	-	process regulator	-
	Handling of silicones by consumers	10a, 11a	-	-	-	process regulator	0: Silicone articles

Hazard data as included – Phys-Chem

- Approach:
  - Include substance specific data where available
  - Include standard waivers where required
  - Include read-across data or QSAR from e.g. ligand if no standard waiver applicable

!! ECHA manual check during registration !!

Hazard data as included – Phys-Chem

Appearance/Physical State/Colour	Substance specific study data (yellow liquid)
Melting / Freezing point	Read-across data solvent + data SDS (melting point <20°C)
Boiling point	Substance specific study data (>35°C, endotherm reaction between 180-200°C suggests boiling point, residue of black stain suggests decomposition)
Density	Standard waiver + supporting data via read-across from solvent
PSD	Standard waiver
Vapour Pressure	Read-across data solvent + data SDS (17 hPa at 25 °C)
Partition coefficient	QSAR organic compound (log Kow 5.96)
Water solub	Substance specific study data (0.035 g/L)
Surface Tension	Standard waiver
Flash Point	Substance specific study data (17 °C -> **Flamm Liquid Cat 2**)
Autoflammability	Substance specific study data (auto-ignition temperature 254 °C)
Flammability	Standard waiver
Explosiveness	Standard waiver
Oxidizing properties	Standard waiver

Hazard data as included – ENV fate

- Hydrolysis:

  Pre-test: assess water accommodated fraction ('WAF') & hydrolysis

  WAF:

  - Determine Pt and organic ligand (KC could not be analysed) via ICP-MS and GC-MS
  - 2L P-buffer (pH7) + 1 mL KC, 24h stirring
    - Pt: acidification of sample
    - Ligand: extraction using BME solvent (9:1 buffer:solvent), 30 min shaking, centrifuged. Internal standard added

  Hydrolysis:

  - 4.3 mg KC in 100 mL P-buffer (pH7)
  - Sampling after 1, 5, 48, 96 h

Hazard data as included – ENV fate

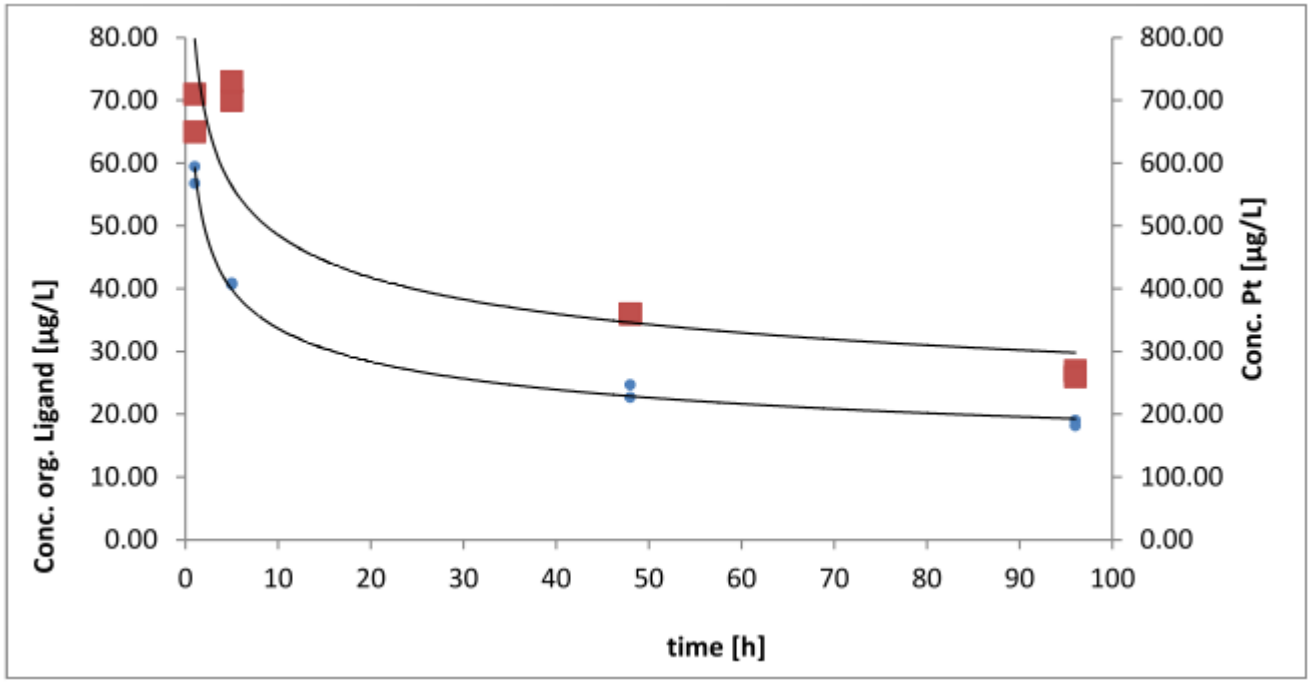
Sample	Conc. DVTMDS [µg/L]	Conc. Pt [µg/L]
March 3, 2016 WAF-Sample 1	22.70	788.87
March 3, 2016 WAF-Sample 2	50.93	816.22
March 3, 2016 WAF-Sample 3	65.09	803.74
March 3, 2016 WAF Sample 4	38.57	814.09
Sample*	**Concentration DVTMDS [µg/L]**	**Conc. Pt [µg/L]**
March 4, 2016 WAF-Sample 1	12.63	872.56
March 4, 2016 WAF-Sample 2	11.94	891.52
March 4, 2016 WAF-Sample 3	11.76	871.47
March 4, 2016 WAF-Sample 4	12.46	909.44
Sample**	**Concentration DVTMDS [µg/L]**	**Conc. Pt [µg/L]**
March 5, 2016 WAF-Sample 1	16.26	
March 5, 2016 WAF-Sample 2	14.79	
March 5, 2016 WAF-Sample 3	15.36	
March 5, 2016 WAF-Sample 4	15.10	

24h: high variability -> no equilibrium?

24h settling + resampling

48h settling + resampling

Hazard data as included – ENV fate



≥ 50% reduction of Pt and ligand concentration after 48 h

Hazard data as included – ENV fate

- Hydrolysis:
  - Decision PMC members to **waive** full hydrolysis test (OECD111)
  - Considered technically not feasible: not possible to analyse parent substance

Waiving argumentation:

A preliminary hydrolysis study was conducted with the test item and based on the results of this study conducting a full hydrolysis study is considered to be technically not feasible. In order to conduct a full hydrolysis test, analysis of the parent substance is required. In the preliminary test, LC and GC-based methods were used to analyse the organic ligand, and ICP-MS was used to analyse for platinum. It appears from the preliminary results that platinum and the organic ligand dissociate and over time concentrations of the organic ligand decrease, potentially due to further hydrolysis. A full hydrolysis study assesses hydrolysis of the parent substance initially, at a range of pH values. As no analytical method is available for analysing the parent substance as a whole, in this case it would not be possible to determine hydrolysis of the parent and conducting the full study is considered to be technically not feasible. Results from the preliminary hydrolysis study analysing separately for platinum and the organic ligand are reported as supporting information.

Hazard data as included – ENV fate

- Biodegradation:

  Standard waiver: *the study does not need to be conducted because the substance is inorganic*

  - Pt = not biodegradable (inorganic)
  - Supporting data from ligand: QSAR data show not readily biodegradable

- Adsorption/desorption:

  Data taken from peer reviewed publications

  - logKd(water) = 3.27
  - logKd(soil) = 1.57

Hazard data as included – Ecotox

- Acute toxicity testing to algae, daphnia, fish, micro-organisms
- Range finding studies algae/daphnia/fish:
  - Toxicity tested at 0.1 – 1 – 10 mg/L
  - No effects observed at any concentration
  - Soluble Pt only detected at higher dose, organic ligand not detected at all
  - Potentially related to separation technique (filtration rather than settlement)

- Additional experimentation:
  - Single concentration (4.2 mg/L) filtration vs centrifugation vs settling, reduced pH value of 6 to improve solubility
  - 96 h incubation, sampling with 24 h intervals

Hazard data as included – Ecotox

Incubation time (h)	Decanted	Filtered	Centrifuged	Stock solution, shaken up
	µg/L	µg/L	µg/L	µg/L
0	48,76	< LOQ	2,25	-
24	2,41	< LOQ	< LOQ	7,13
48	< LOQ	< LOQ	< LOQ	6,12
72	< LOQ	< LOQ	< LOQ	4,13
96	< LOQ	< LOQ	< LOQ	2,74

Ligand:

- Rarely detected >LOQ (2.16 µg/L)
- Not detectable ≥48h

Incubation time (h)	decanted Pt conc.	filtered Pt conc.	centrifuged Pt conc.
	µg/L	µg/L	µg/L
0	45.164	3.901	6.474
24	7.466	4.480	5.173
48	6.554	5.377	9.432
72	9.208	6.988	8.123
96	7.025	5.561	6.188

Platinum (2.2 **m**g/L added!):

- Rapid decrease first 24 h
- Stable, but low concentrations ≥24 h

Hazard data as included – Ecotox

- Decision PMC members:
  - **Waive full acute tox tests** algae/daphnids/fish:
    - *test substance is highly insoluble in water* (standard waiver)
    - solubility trials and the non-GLP DRF tests included as supporting evidence
  - Provided evidence:
    - Pt:
      - Acute ERVs other Pt substances (20.5 - 9750 µg/L) >> measured Pt concentrations released from KC => aquatic toxicity is not expected
      - Hexachloroplatinates are most toxic Pt compounds, likely related to presence as chloroplatinate anion. Although exact speciation Pt from KC unknown, not expected to be chloroplatinate.
    - Organic ligand:
      - present close to or below the LOQ (solubility lower than for ligand alone)
      - adsorption to test vessels or filters unlikely (cfr solubility trials), hydrolysis to breakdown products not contributing to tox (cfr range-finders)
  - ENV classification:
    - standard approach = test up to 100 mg/L.
    - Considered unnecessary: limit of solubility reached at 10 mg/L, testing at higher concentrations would not lead to additional test item in solution. No effects observed so no classification

Hazard data as included – Ecotox

- Toxicity to micro-organisms:
  - Inhibition of respiration of activated sludge (OECD 209 and EU-Method C.11) (Muckle 2016).
  - Three hours test, activated sludge collected from predominantly domestic STP
  - Range-finding test:
    - 4 nominal concentrations (1-10-100-1000 mg/L), + and - nitrification inhibitor N-allylthiourea
    - Inhibition in 3 highest doses - strong scattering caused by poor solubility?
  - Full test:
    - Control and1, 3.2, 10, 32, 100 mg/L
    - 3h-NOEC = 3.2 mg/L, 3h-EC10 = 31 mg/L, 3h-EC50 f>100 mg/L based on inhibition of total respiration
    - 3h-NOEC = 1 mg/L, 3h-EC10 = 20 mg/L, 3h-EC50 >100 mg/L based on inhibition of heterotrophic respiration
- Toxic thresholds:
  - PNEC STP = 0.1 mg/L
  - No other PNECs (cfr above)

Hazard data as included – Mammalian tox

- Acute toxicity
  - Oral:
    - Female rats, OECD425 (up-and-down procedure)
    - Limit dose (5000 mg/kg bw) – no pathological changes / mortality following 14-d observation period
    - LD50 >5000 mg/kg bw
    - No classification
  - Inhalation:
    - Waiver (exposure based considerations)
  - Dermal:
    - Waiver (limited absorption via skin, not acutely toxic via oral administration, limited dermal exposure)

Hazard data as included – Mammalian tox

- Irritation:
  - Skin:
    - In vitro testing (OECD439 (EpiDerm), EU Method B.46) – reconstructed human epidermis
    - 30 µL undiluted test material, 60 minutes exposure + 42 h post-treatment incubation
    - Cell viability measurement via MTT assay, OD determined spectrophotometrically

	Optical density (n=3 tissues)	SD	% OD540 compared to the control
Negative control (D-PBS)	1.773	0.0907	-
"Karstedt concentrate"	1.607	0.091	90.6
Positive control (5% SDS)	0.106	0.012	6.0

→ mean cell viability >>50%

- KC not cytotoxic and predicted non-irritant to skin
- No classification as skin irritant (acc to EU CLP)

Hazard data as included – Mammalian tox

- Irritation:
  - Eye:
    - In vitro testing (OECD437, EU Method B.47) – Bovine Corneal Opacity and Permeability
    - 0,75 mL undiluted test material, 10 minutes exposure + 2 h post-treatment incubation
    - Corneal opacity via light transmission, corneal permeability with sodium fluorescein solution (90 min exposure) & spectrophotometry

	Mean opacity (n=3)	Mean permeability (n=3)	IVIS (In Vitro Irritancy Score)
Negative control (0,9% NaCl)	0,36	0,015	0,579
Karstedt Concentrate	-0,41	-0,005	-0,492
Positive control (1% NaOH)	72,6	1,65	97,4

→ IVIS << 3 (UN GHS 'no category')

- No classification as irritating or corrosive to the eye

  - Respiratory tract:
    - No resp tract irritation (data) identified – no study conducted as no standard REACH requirement

Hazard data as included – Mammalian tox

- Skin sensitization:
  - Mixed results existing study, new study performed with ‘low-chlorine’ test material
  - OECD442B – Local Lymph Node Assay BrdU-ELISA (mice, n = 5/group))
  - Vehicle = acetone/olive oil (4:1), concentration main study 0-10-25-50%, topical application, administration on 3 consecutive days
  - Ear thickness measurements: day 1 (pre-dose) – day 3 (48 h after 1st dose) – day 6, systemic toxicity and irritation: daily checks, cell proliferation via BrdU-ELISA (spectrophotometry)

Hazard data as included – Mammalian tox

- Skin sensitization:

	Negative control (vehicle)	10%	25%	50%	Positive control (25% alpha-hexyl cinnamic aldehyde)
BrdU Labelling index (SI)	1	1,236	**1,503***	**1,588***	**1,794***
Ear punch weight	1	1,006	1,188	1,263	**1,363***
Ear thickness increase (%, TD3)	1	1,4	0	7,3	9,6
Ear thickness increase (%, TD6)	1,9	3,7	3,3	15,7	13,4

*Signif increase at p<0,01

  - No mortality / clinical signs / effects on body weight
  - No signs of erythrema at any concentration
  - Dose-related increase ear weight & thickness at 50%: caused by local irritation at high concentrations
  - BrdU Labelling index: dose-related increase of stimulation index, **SI not exceeding threshold of 1,6**
- Not classified as skin sensitizer (according to EU CLP)
- Waiver included for in vitro study, as in vivo data available

- Respiratory tract sensitization:
  - No data identified – no study conducted as no standard REACH requirement

Hazard data as included – Mammalian tox

- Genetic toxicity:
  - In vitro – AMES (OECD471)
    - S typhimurium TA1535, 1537, 98, 100; E coli WP2 uvrA; +/- S-9
    - pre-incubation method (test1) and plate incorporation method (test2)
    - Vehicle = aceton, doses up to 5000 µg/plate in both experiments
    - No evidence of mutagenic activity detected

Hazard data as included – Mammalian tox

- Genetic toxicity:
  - In vitro – Micronucleus test in human lymphocytes (OECD487)
    - Pooled blood female donors
    - Vehicle = DMF, 3h +/- S-9 (+21h recovery) and 24h -S-9 (no recovery)

	Conc. (µg/mL)	% MN	Cytotoxicity (% reduction in RI)
3/21 –S-9	0	0.68	-
	0.5	**1.03**	5
	0.9	0.68	24
	1.2	0.65	46
3/21 +S-9	0	0.80	-
	22.5	0.90	5
	32.5	0.35	38
	35.0	0.20	45
	37.5	0.18	68
24/0 –S-9	0	0.65	-
	0.3	0.75	0
	0.5	**1.35**	32
	0.7	**1.30**	55

Bold = significantly different from vehicle control, shaded = MN frequencies exceeding historical control range

24h treatment: statistically significant increase, dose-response, outside historical control range (also at 32% cytotoxicity)

All criteria for positive outcome satisfied → induction of MN

Hazard data as included – Mammalian tox

- Genetic toxicity:
  - *In vitro*: MN induced in absence of metabolic activation → agreement to perform *in vivo* MN test
  - Integrated in repeated-dose toxicity assay with repro/dev tox screening (OECD422):
    - Measure MN in young reticulocytes using flow cytometry
    - Acceptable as alternative to bone marrow MN test
    - If *in vivo* = negative → evidence that *in vitro* genotoxic potential is not manifest *in vivo*
    - Robust assay = dosing to MTD, sufficient cells scored, verification exposure
  - In vivo MN assay (OECD474)
    - Rats (♀ and ♂) , 28-day test, via gavage (vehicle = corn oil), vehicle control and high dose (0 and 500 mg/kg)
    - Blood samples taken 24h after final dose
    - Positive controls: Mitomycin C (0.75-1 mg/kg) and Vincristin sulphate (0.04 and 0.05 mg/kg), *ip* injection, once daily for 2 consecutive days
    - Peripheral blood samples taken and analysed via cytometry, 20000 RET evaluated per sample

Hazard data as included – Mammalian tox

- Genetic toxicity:
  - *In vivo* MN assay (OECD474)
    - % RET = indication of bone marrow toxicity, %MN-RETs = indication of genotoxic potential

Group	Concentration (mg/kg/day)	Average % RET (females)	Average % MN-RET (females)	Average % RET (males)	Average % MN-RET (males)
1	0 (control)	0.91	0.11	1.11	0.13
4	500 (500 high dose)	1.60	0.10	1.12	0.12
6	0.75 (Mitomycin-C)	1.69	0.23	1.90	0.21
8	0.04 (Vincristin sulphate)	1.03	0.57	0.72	0.95

      - positive control treatments significantly different from control treatment
      - data from control and high dose do not differ

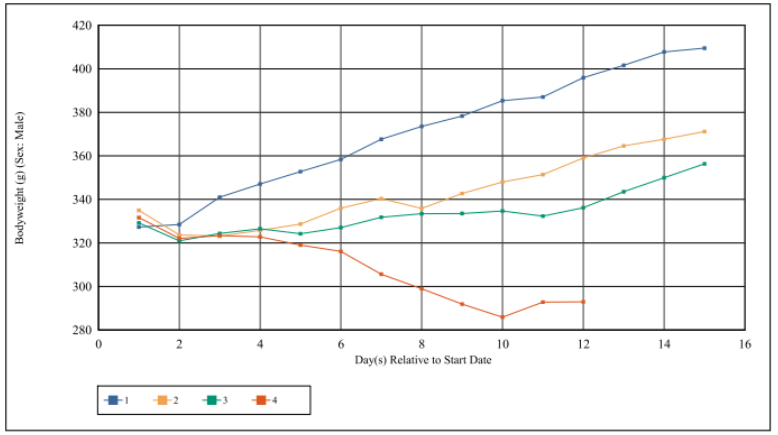
=> Valid study confirmed, clear negative outcome for *in vivo* genetox

- Open point: analysis of rat blood samples for Pt to confirm exposure (suggestion for exposure: parental males were significantly affected at the high dose (tested at MTD))

Ongoing testing – OECD422

- OECD422 - 14-d dose range finding study
  - Setup:
    - 0 - 500 - 750 - 1000 mg/kg/d, 5♂ and 5♀ per dose
    - Gavaging (5 mL/kg bw/d), vehicle = corn oil
    - 27 June – 11 July 2016, final report 17 October 2016
  - Findings:
    - 1000 mg/kg/day:
      - **terminated on d12 due to 1 mortality**
      - adverse clinical signs and effects on body weight
        - ♂: no body weight gain to day 7 and body weight loss to day 12.
        - lower food consumption in both sexes
        - evidence of GI tract irritation at necropsy in both sexes (more severe in males).
    - 750 mg/kg/day:
      - adverse clinical signs in both sexes
      - lower body weight in males (-13% day 15),
      - lower food consumption in both sexes (more pronounced in week 1)

Ongoing testing – OECD422

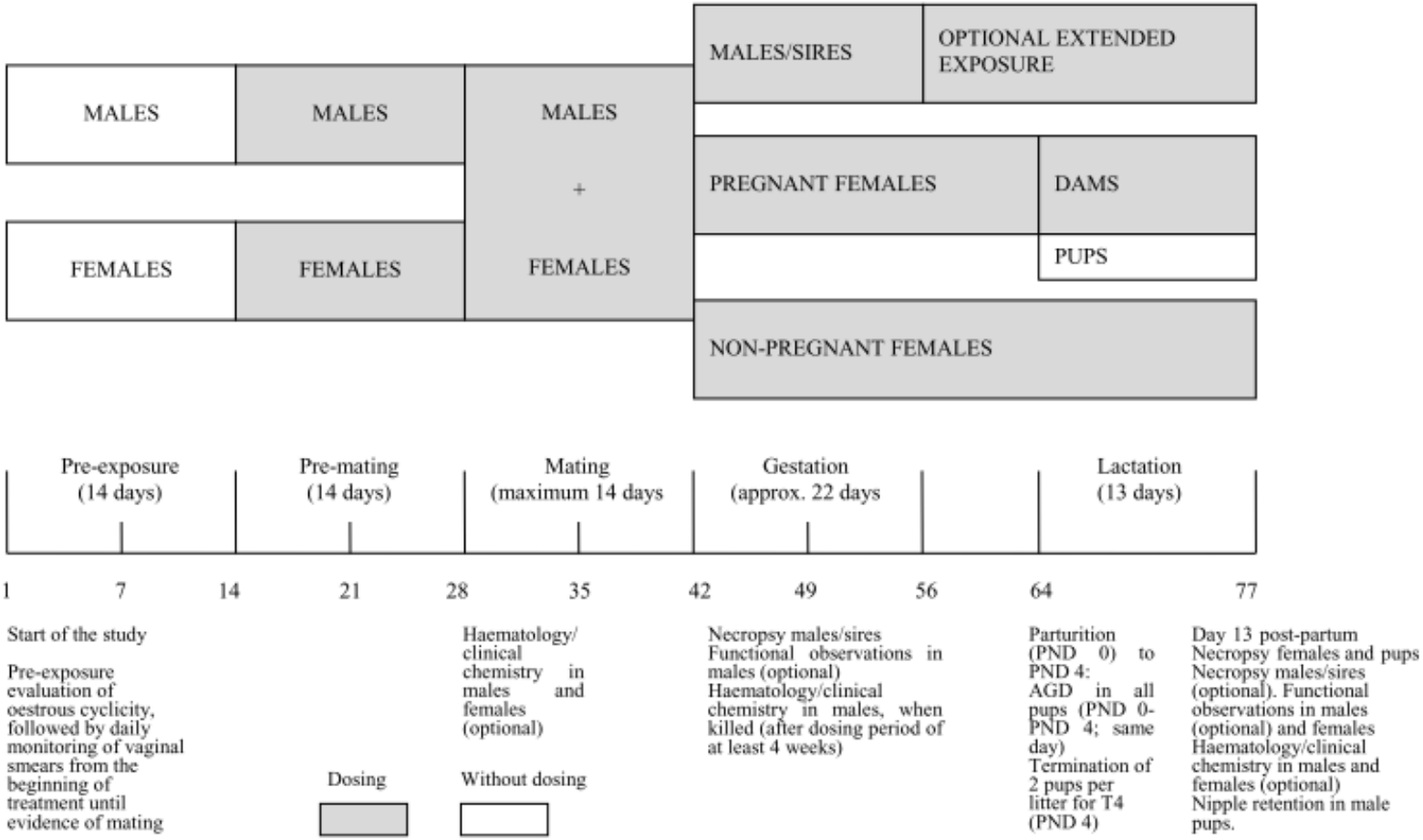


- OECD422 - 14-d dose range finding study
  - Findings (continued):
    - 500 mg/kg/d:
      - minor adverse clinical signs (2M, 1F)
      - lower body weight in males (-9.8% day 15, not significant)
      - lower food consumption in both sexes (more pronounced in week 1)
  - Actual concentrations of test item within the formulations: 88.8% to 109.8% of nominal platinum concentrations

  - **<u>Conclusion:</u>**
    - 1000 mg/kg bw/d in excess of a maximum tolerated dose
    - 750 mg/kg bw/d marked effects on body weight in males after 14 days
    - **500 mg/kg bw/d selected as maximum dose for full study**

Ongoing testing – OECD422

- OECD422 – Full study



Ongoing testing – OECD422

- OECD422 – Full study (*combined with in vivo MN assay*!)
  - Dose selection: 0 – 30 – 125 – 500 mg/kg/d
  - In-life phase started 1 Aug 2016, and was completed in Oct 2016. Draft report excluding formulation analysis received 3 Jan 2017. Draft pathology report received 7 Feb 2017.
  - Findings (**TENTATIVE** !):
    - 500 mg/kg/d:

    PARENTAL MALES:
      - significantly lower BW than control from d4, lower food consumption week 1
      - Effects on clinical chemistry and haematology parameters. Increases in relative organ weights (testes, kidneys, liver and epididymides). Decrease in absolute weight of spleen, thymus and prostate with seminal vesicles. Decrease in T4 measurements.
      - Pathology: Treatment-related microscopic findings in the lungs generally in combination with slight pigment deposition. Possible treatment related changes in stomach.

    → **Clear evidence of toxicity in males**

Ongoing testing – OECD422

- OECD422 – Full study (*combined with in vivo MN assay*!)
  - Findings:
    - 500 mg/kg/d: (continued)

    PARENTAL FEMALES:

    - One premature death (no 77 during lactation). Pathology for this female not conclusive. No effects on BW pre-mating or during lactation. Gestation weight gain slightly lower than control but consistent with reduced pup weight and numbers.
    - No effects on haematology or clinical pathology.
    - Increase in absolute and relative adrenal weight [see pathology].
    - Pathology: Treatment-related changes in the lungs as described for males and hypertrophy of the adrenal gland in females. Possible treatment related changes in stomach.

    REPRODUCTIVE ENDPOINTS:

    - Increase in post implantation loss.

Ongoing testing – OECD422

- OECD422 – Full study (*combined with in vivo MN assay*!)
  - Findings:
    - 500 mg/kg/d: (continued)

    F1 OFFSPRING:

      - Slightly lower Live Birth Index 94.77% (control 100%), accompanied by lower pup weights. Significantly lower body weights at all time points. Decrease in mean pup survival (no clear effect as difference is due to only 2 litters). Survival in the remaining 7 litters was good and similar to that of the control group.
      - No effects on endocrine/developmental parameters
      - No difference for the weights of the thyroid glands and for thyroid hormone T4 levels in pups on LD 4. On LD 13 lower levels of the thyroid hormone T4 were noted for the male and female pups of the dams treated with 500 mg /kg b.w./day compared to control group. NOTE marked effect on body weight at this dose level and no pathology findings in thyroid.

Ongoing testing – OECD422

- OECD422 – Full study (*combined with in vivo MN assay*!)
  - Findings:
    - 125 mg/kg/d:
      - In parental males lower food consumption week 1 of study, approximately 15% below control value and minimal effects on clinical pathology. No treatment-related effects identified in parental females.
      - Higher mean post implantation loss but only 2 values outside concurrent control.
      - Pathologist conclusion: in selected animals of 30 and 125 mg/kg bw/day, no test item-related effects observed in the stomach (both sexes) and adrenals (females only).

  ***(PRELIMINARY** conclusions:*
    - *NOAEL = 125 mg/kg bw/day ?*
    - *lung findings = local effect of small amounts of test material in the lung*
    - *findings in animal 77: non specific and no target organ toxicity. Some the tissues were autolysed and no conclusions can be drawn about cause of death)*

  - Formulation analysis: pending

Classification

- Phys-chem: Flam. Liquid 2 (H225)
- Human health: Not Classified
  …mutagenicity? (likely not)
  …STOT-RE? (likely not)
  …Reproductive toxicity?
- Environment: Not Classified

Hazard data as included – PBT assessment

- PBT assessment:
  - Not relevant for inorganic substances
  - Performed for organic component
    - Persistent:
      - QSAR: not readily biodegradable
      - Karstedt hydrolysis pre-test: concentrations ligand decrease over time (96h test)

      → ***not persistent/very persistent***
    - Bioaccumulative:
      - QSAR: logKow = 5.96
      - Potentially bioaccumulative, but unable to perform definitive assessment as only screening data is available

      → ***No conclusion can be reached based on available information***
    - Toxicity:
      - ENV: no toxicity in acute range-finder studies (10 mg/L)
      - Mamm tox: no Carcin cat1A/B, Germ cell mutagen cat1A/B, Reproductive toxicant cat1A/B/2 or STOT-RE cat1/2 (according to EU CLP)

      → ***not toxic***

  → **Karstedt Concentrate not considered PBT/vPvB**

Precious Metals Consortium

Dossier status + further steps/timing

Status

- All available data included in dossier
- No further testing scheduled before registration
- No Reconsile owned data included in dossier
- No HH/ENV classification required (based on currently available data), so no exposure/risk assessment required
- Dossier has been approved by PGM Management Committee and Karstedt Concentrate registrants, and submitted to/accepted by ECHA (Feb 2017)

- **HOWEVER:**
  - OECD422 study report not yet available, so dossier update required
  - Discussion and decision on need to classify (for HH endpoints) required
    - Not classified – resubmit with OECD422 included
    - Classified – do additional exposure and risk assessment, and resubmit

  !! **Review & approval** of updated dossier by PMC registrants / LoA buyers before resubmission !!

Timeline

- Decide on OECD422 (effects and need to classify) – end Feb 2017

- If classification required:
  - finalise exposure and risk assessment <31 May 2017
  - resubmit dossier <30 June 2017

- If no classification required:
  - update dossier and resubmit (to be confirmed)

!! Registration = first step, afterwards dossier maintenance / regulatory actions … !!

Precious Metals Consortium

Comments on LoA agreement

Precious Metals Consortium

THANK YOU

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