

# Rodent Toxicology Studies Silver Acetate:

**PREPARED FOR:**

**European Precious Metals Federation**

**ENVIGO PROPOSAL NO:**

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## 1. Executive summary

Envigo are delighted to provide European Precious Metals Federation with a proposal for a Rodent Toxicology package on Silver Acetate:

Included within this proposal you will find:

- A pricing summary and suggested project timings for you to discuss with your colleagues
- Details of how Envigo's experience can help you reach your research goals
- Next steps including implementation of services
- Outline study plans
- An introduction to Envigo so you can get to know us or if you simply want a reminder

We look forward to receiving your feedback on this proposal and if you have any further questions or comments please feel free to contact Hannah Izod or Andrea Macquarrie whose details are on the contact information page of this proposal.

“The Envigo team is professional, open to communication and sharing of data. They overcome challenges by taking an open and scientific approach.” - Customer feedback, 2018

## 2. Pricing Summary

Envigo ref no.	Study	Price (GBP)
NR98KN	Development of ICP-MS methods to measure silver, selenium and copper in rat plasma, so the methods can be validated to regulatory standard <i>Price is based on 12 days' work. If additional experimental work is required beyond the highlighted days this will be charged pro rata at £1,300 daily rate</i>	15,600
BB55LW	Validation of an ICP-MS method to measure silver, selenium and copper in rat plasma	16,400
GH28GX	2 week preliminary dietary study in the rat	11,684
YC23RN	OECD 443 Dietary preliminary study in the rat Includes analysis of As, Se and Cu	128,481
YQ21BX	OECD 443 Dietary in the rat	
	<b>Option 1</b> 10 weeks pre-pairing treatment, Cohort 1A and 1B only & NO F1 breeding	651,032
	<b>Option 2</b> 2 weeks pre-pairing treatment, Cohort 1A and 1B only & NO F1 breeding	622,278
	<b>Option 3</b> 10 weeks pre-pairing treatment, Cohorts 1A and 1B only PLUS F1 breeding	733,696
	<b>Option 5</b> 10 weeks pre-pairing treatment, Cohorts 1A, 1B, 2A, 2B & 3	834,152
	<b>Option 5</b> 10 weeks pre-pairing treatment, Cohorts 1A, 1B, 2A, 2B & 3 PLUS F1 breeding	916,816
CC71MP	<b>Option 1</b> OECD 417: Comparative in vivo toxicokinetics (TK) study in the Rat n=3	133,322
CC71MP	<b>Option 2</b> OECD 417: Comparative in vivo toxicokinetics (TK) study in the Rat n=5	192,250

### Price assumptions

- + The purchase of specialized reagents, kits and consumables will be charged as pass-through costs
- + The customer shall be responsible for all out-of-pocket costs associated with the services, including but not limited to transportation and shipping costs related to samples and reports
- + **Not included any possible tissues analyses or ceruloplasmin analysis**
- + Additional sample price would be £100 per sample for any extra samples .
- + For analysis on separate days, we charge an additional £1300 per day.
- + Cost for a Phase report is an additional £1950
- + If it is not possible to develop a suitable method to eliminate interference, then testing/sample analysis may not be possible
- + Analytical costs;
  - Non GLP - for the TK study
  - 3 analytes are £43 per sample (minimum batch 50 samples)
  - excel report £3,000
  
  - GLP - for the OECD 443 studies
  - 3 analytes are £48 per samples (minimum batch 50 samples)
  - GLP summary word report QA audited £6,200

The prices provided in the table above are based upon the scope of work outlined in this document and the associated outline study plans. They are intended as a guide and final prices may differ depending on the final study designs.

**The provision of services herein is subject to contract between the parties. The prices given in this proposal are valid for a period of 30 days from the date of issue.**

## 3. Study Design and Considerations

We have experience of adjusting dietary inclusion levels as the growth rate of the rat changes throughout the study

## 4. Timings

Study	Compliance/ Regulatory	Start	Draft report
<b>Rodent Toxicity Studies</b>			
Pre-study chemistry	GLP	July 2019	August 2019
14 day rat study	Non-GLP	September 2019	November 2019
Prelim to the OECD 443	Non-GLP	November 2019	May 2020
OECD 443	GLP	May 2020	May 2021
TK study	Non-GLP	October 2019	February 2020

This proposal is for information purposes and therefore no start dates have been formally identified or allocated to any of the studies. However, we would recommend that, should you wish to place one or more studies at Envigo, the appropriate contractual agreements are put in place at the earliest opportunity. This will allow us to ensure resource and timings are secured and we can finalize a schedule, which fully satisfies the required timescales.

**Please note that no resources are held until a signed agreement is in place. Therefore, the dates provided in this proposal are only valid at the time of issue and are subject to change over time.**



## 5. Our experience, your goals

Envigo provides essential research services, models and products for pharmaceutical, crop protection, and chemical companies as well as universities, governments, and other research organizations. Our business is founded on a dedication to customer service and the expertise and experience of our 3,300+ people.

At Envigo, we've been helping our customers make effective safety assessment decisions for decades. We can support your research programs in the following areas:

- Mammalian toxicology
- Animal metabolism and toxicokinetics
- Genetic and *in vitro* toxicology
- Product chemistry
- Residue chemistry
- Environmental fate
- Ecotoxicology
- *In silico* (Q)SAR assessments

Our services are designed to meet the regulatory requirements of global governments and are an essential part of safety assessment of new and existing plant protection products.

Our Regulatory Consulting team is also industry recognised as 'best in class' and we work with many satisfied customers to offer bespoke consulting packages, specific regulatory project work and program management services.

Work with us and you'll have access to our industry-leading senior scientists and experts. Our registration services satisfy regulations worldwide so we can register your product wherever you need. We have consultants globally that can speak the language, have a network of contacts in the authorities and understand the relevant legislative frameworks.

### Leading the way in animal welfare

Envigo is a global company that is committed to helping customers realize the full potential of their products and research which contribute to enhancing the lives of people and animals, as well as protecting the environment. The use of animals in this research remains essential for advancing our understanding of the body in health and disease and for developing new medicines and other compounds.

In carrying out animal research for our customers at Envigo we follow the principles of the 3Rs - replacement, reduction and refinement, and we ensure they are considered at all levels of the company. This means we use alternatives to animals whenever we can, we aim to carry out studies with the fewest number of animals possible, and we take measures to minimise any pain or distress before, during, and after experimental procedures. To read more about our animal welfare policy please click [here](#).





## Envigo Blog

We know it's important for you to be aware of the latest industry news and updates so here's a round-up of our most popular chemical posts from the Envigo blog.



### **Brexit and REACH: what will the future hold?**

It's hard to avoid the topic of Brexit. It pervades almost everything we do both professionally and personally. We explore the uncertainties Brexit presents and how much energy is being spent in speculation about, as well as planning for, multiple possible outcomes where REACH is concerned.

### **Understanding EOGRTS – 3 key factors when conducting OECD 443 studies**

After successfully completing some of our first studies relating to the extended one generation reproductive toxicity study (EOGRTS) OECD test guideline (TG) 443 we felt it appropriate to share some key findings. Learn more about the three vitally important factors; experience, communication and planning.

### **Life beyond 2018 – navigate through the hurdles**

In a turbulent world, where the geopolitical order is in transition, the one thing you can rely on is the constancy of the May 2018 REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) deadline. Although this marks the formal finish of dossier generation for existing substances, it is by no means the end of the process. Explore the hurdles you'll meet on the road post-REACH submission.

### **Visit our blog and sign up for updates**

Join our community of scientific experts and receive the latest industry insights straight to your inbox. [Sign up here.](#)



## 6. Implementation of services

If you decide to place this work with Envigo, we can issue a contract based on this proposal. Once this has been signed and authorized, the work will be formally scheduled and we will assign Study Directors to work with you on study plans.

A study plan must be in place before study start and if applicable, any analytical methods should also be in place and validated.



“Envigo has always been a great experience. Timely, friendly, helpful.” - Customer feedback, 2018



## 7. Outline study plans

### 7.1 Palatability/ Preliminary Toxicity Study By Dietary Administration To Sprague Dawley Rats For 14 Days

#### Non-GLP Compliant

<b>Envigo Reference Number:</b>	GH28GX			
<b>Test item:</b>	Silver acetate			
<b>Groups:</b>	1	2	3	4
<b>Treatment:</b>	Control	Low	Intermediate	High
<b>Number of animals:</b>	3M + 3F	3M + 3F	3M + 3F	3M + 3F
<b>Route:</b>	Dietary			
<b>Room occupancy:</b>	Approximately 3 weeks Acclimatization and 2 week in life			
<b>Treatment regime:</b>	Treatment daily for 14 days (Envigo recommend 14 days for test materials with limited repeat dose toxicity data)			
<b>Species (strain):</b>	Rat (Charles River - Sprague Dawley)			
<b>Age at start of treatment:</b>	Ca 7-8 weeks of age			



	<b>Occasions (Week)</b>	<b>Details</b>
<b>Clinical observations:</b>	Day -3, once during each treatment week and on Day 15 prior to dispatch to necropsy.	
<b>Bodyweights:</b>	Day -3, Daily from Day 1 of treatment up to termination	
<b>Food consumption:</b>	From Day -3 to Day -1 and daily from Day 1 of treatment up to termination	
<b>Water consumption:</b>	By visual assessment	
<b>Necropsy and organ weights:</b>	Macroscopic examination. Organ weights – liver, spleen, kidneys Tissue retention – abnormalities only	
<b>Histopathology:</b>	n/a	
<b>Formulation:</b>	Weekly (if appropriate)	By Envigo

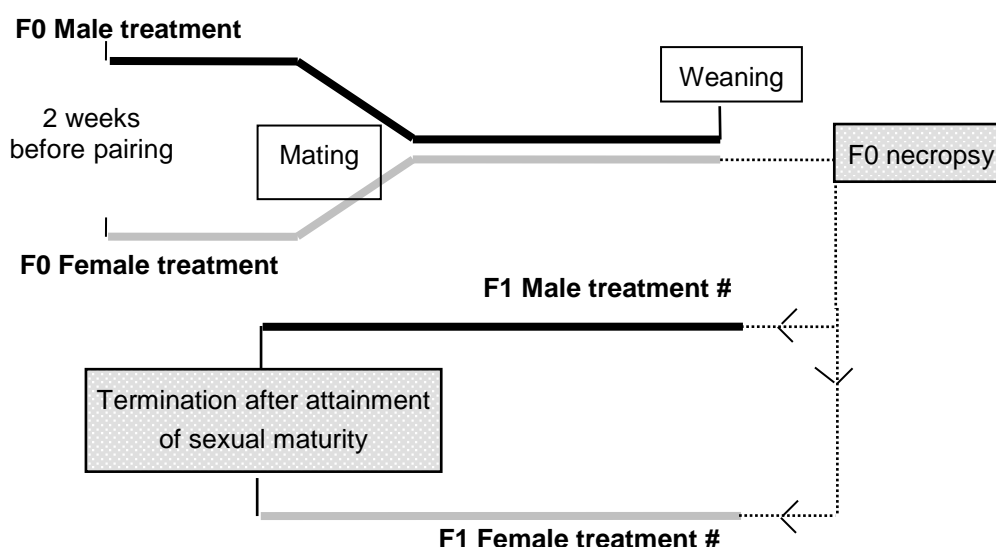
<b>Formulation analysis by Envigo:</b>	Stability and homogeneity	Data within a GLP compliant study will be required as part of the programme for GLP compliance  Assessment within this study may be performed if suitable GLP-compliant data are not already available. In which case this study should be performed as fully GLP compliant
	Achieved concentration	No formal analysis required

<b>Data:</b>	
<b>Archives:</b>	1 year

## 7.2 Preliminary Reproductive Performance Study In The Rat By Dietary Administration

This study design is intended to assist in dose selection for an Extended One Generation Reproductive Toxicity Study (EOGRTS) i.e. OECD Test Guideline 443, **Non-GLP**

Envigo Reference Number	YC23RN				
Test substance:	Silver Acetate				
Groups:	1	2	3	4	5
Treatment:	Control	Low	Low Intermediate	High Intermediate	High
Number of F0 animals: (M-Male, F-Female)	8M + 8F	8M + 8F	8M + 8F	8M + 8F	8M + 8F
Number of F1 animals: (M-Male, F-Female)	10M + 10F	10M + 10F	10M + 10F	10M + 10F	10M + 10F
Route:	Dietary				
Room occupancy:	Approximately 16 weeks Acclimatisation. Approximately 15 weeks in life				
Treatment regime:	F0 males - 2 weeks pre-pairing up to weaning of F1 F0 females - 2 weeks pre-pairing up to weaning of F1 Dietary: F1 offspring – no direct treatment up to approximately mid-lactation when offspring start to consume treated diet. Selected F1 offspring – direct treatment from approximately mid-lactation up to termination F1 animals terminated after attainment of sexual maturation				
Species (strain):	Rat (Sprague Dawley)				
Age at start of treatment:	CD rats : males and females approx. 11 weeks				
Age at pairing:	CD rats : males and females approx. 13 weeks				



Dietary: # Formal F1 generation commences on approximately Day 28 of age (offspring start to consume treated diet from mid-lactation)

Clinical observations	Routine physical examination - weekly	
Bodyweights:	F0 males	Weekly
	F0 females	Weekly until pairing Days 0, 7, 14 and 20 after mating Days 1 7, 14 and 21 of lactation
	F1 animals	Twice weekly from 4 weeks of age
Food consumption:	F0 males	Weekly until pairing
	F0 females	Weekly until pairing, Then approximately twice weekly after mating until Day 21 of lactation (to coincide with bodyweight recording occasions)
	F1 animals	Twice weekly from 4 weeks of age
Oestrus cycle monitoring (F0 only):	Dry smears for 15 days before pairing for females of the F0 generation only	
Exposure assessment blood sampling:	<p>F0 animals: Three males and three females per group bled at 0900 on Days 2 (both sexes), 12 (both sexes), 56 (males only), Day 17 of gestation and Day 21 of lactation (total of 105 samples for analysis of each of Ag, Cu and Se in plasma). Analysis at Envigo Shardlow</p> <p>F1 culled offspring: up to six pups per group bled on Day 4 of age; up to two for Ag analysis, up to 2 for Cu analysis and up to 2 for Se analysis (NB if insufficient culled pups are available within a litter for all analyses, analyses will be counterbalanced between litters to ensure all 3 analytes can be analysed in each group) - up to 240 pups bled and up to 40 pooled plasma samples for analysis of each of Ag, Cu and Se in plasma. Analysis at Envigo Shardlow</p> <p>F1 selected offspring at termination: Three males and three females per group bled at 0900 on last day of study (total of 30 samples for analysis of each of Ag, Cu and Se in plasma). Analysis at Envigo Shardlow</p>	
Pairing:	For up to 2 weeks	Daily vaginal smears (by pipette lavage) until positive indication of mating
Littering observations:	Duration of gestation/parturition	
In-life observations – F1 offspring:		
Littering observations:	Litter size	Recorded daily
	Litter standardisation	Cull on Day 4 of age Sprague Dawley - Cull to 10 per litter (5 males + 5 females, where possible)
	Sex ratio	Recorded Days 1, 4 of lactation and at weaning on Day 21 of lactation
	Offspring bodyweights	Days 1, 4, 7, 14, 17, 21, 25 & 28 of age.
Sexual maturation:	Females assessed for vaginal opening; males assessed for balano-preputial separation. Bodyweight and age at completion recorded.	
Necropsy timing:	F0 males	After litters established - generally after at least 8 weeks of treatment
	F0 females	On Day 21 of lactation
	Culled F1 offspring	On Day 4 of age

	F1 unselected offspring	Day 21 of age
	F1 selected offspring	At approximately 7 weeks (50 days) of age, after attainment of sexual maturation.
<b>Macroscopic examination:</b>	F0 males	All animals – macroscopic examination Gut (small intestine) samples retained for possible future biome analysis
	F0 females	All animals – macroscopic examination Including count of implantation sites Gut (small intestine) samples retained for possible future biome analysis
	Culled F1 offspring	Grossly normal offspring discarded without internal examination.
	Unselected offspring (Day 21 of age)	Macroscopic examination
	F1 animals (7 Weeks of age)	Macroscopic examination Gut (small intestine) samples retained for possible future biome analysis
<b>Organ weights and tissue prevention:</b>	No organ weights scheduled. Abnormal tissues retained	
<b>Histopathology:</b>	None scheduled	
<b>Data treatment:</b>	Statistical evaluation as appropriate	





<b>Formulation:</b>	Weekly (if appropriate)	By Envigo
<b>Formulation analysis by Envigo:</b>	Stability and homogeneity	Data within a GLP compliant study will be required as part of the programme for GLP compliance  Assessment within this study may be performed if suitable GLP-compliant data are not already available. In which case this study should be performed as fully GLP compliant
	Achieved concentration	No formal analysis required If GLP compliance required, formulation analysis must be included
<b>Data:</b>		
<b>Archives:</b>	1 year	

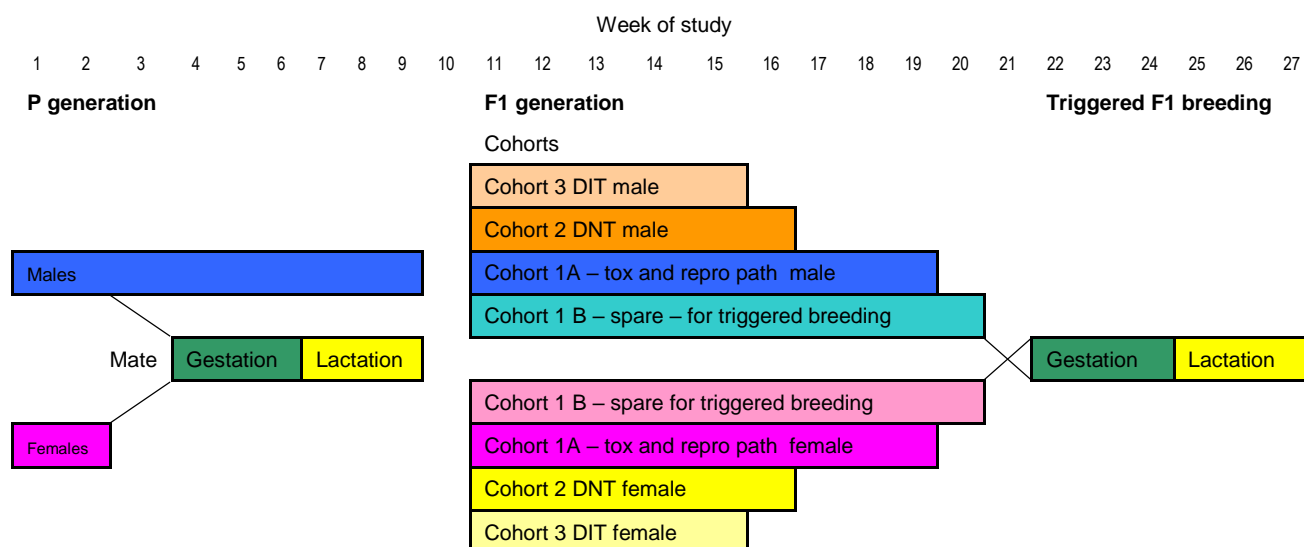
### 7.3 OECD 443: Extended One Generation Reproductive Toxicity Study In The Rat, GLP Compliant

<b>Envigo Reference number</b>	YK21BX			
<b>Test item:</b>	Silver acetate			
<b>Route:</b>	Dietary			
<b>Room occupancy:</b>	<p>Option1: 10 weeks F0 pre pairing treatment: approximately 30 weeks (no triggered F1 mating phase)</p> <p>Option 2: 2 weeks F0 pre pairing treatment: approximately 22 weeks (no triggered F1 mating phase)</p> <p>Option 3: 10 weeks F0 pre pairing treatment and Cohort F1 1B breeding : approximately 38 weeks ( triggered F1 mating phase)</p>			
<b>F0 Treatment regime:</b>	<p>Option 1</p> <p>Males: 10 weeks pre-pairing to necropsy after selection of the F1 generation (approximately 18 weeks)</p> <p>Females: 10 weeks pre-pairing to necropsy on or soon after Day 28 of lactation following selection of the F1 generation</p> <p>Option 2</p> <p>Males: 2 weeks pre-pairing to necropsy after selection of the F1 generation (approximately 10 weeks)</p> <p>Females: 2 weeks pre-pairing to necropsy on or soon after Day 28 of lactation following selection of the F1 generation</p>			
<b>F1 Treatment regime:</b>	<p>Cohort 1A: treated from weaning to 13 weeks of age (Day 90)</p> <p>Cohort 1B: treated from weaning to 14 weeks of age or Option 3: for a further 8 weeks if F1 breeding triggered</p> <p>Option 4: Cohort 2: treated from weaning to Day 75 of age</p> <p>Cohort 3: treated from weaning to 8 weeks of age</p>			
<b>Species (strain):</b>	<p>Rat (Sprague Dawley or Han Wistar)</p> <p><b>Animal order must specify males NOT related to females</b></p>			
<b>Age at start of treatment:</b>	<p>F0 generation – Approximately 5 weeks</p> <p>F1 generation – Approximately 3 weeks</p>			
<b>Age at pairing:</b>	<p>F0 generation – Approximately 15 weeks</p> <p>F1 generation – Approximately 13 to 14 weeks</p>			
Generation	Designation	Animals per group per cohort *	Sexual maturation	Approx age (wks) at necropsy
F0 generation	Reproductive	24M + 24F	-	20
F1 generation Cohort 1A	Reproductive & general toxicity	20M +20F	Yes	13
F1 generation Cohort 1B	For follow up assessment of equivocal findings in Cohort 1A#	20M +20F	Yes	14 or 20#
F1 generation Cohort 2A Option 4	Neurotoxicity	10M +10F@	No	11-12
F1 generation Cohort 2B Option 4	Neurotoxicity	10M +10F@	Yes	3
F1 generation Cohort 3	Immunotoxicity	10M +10F@	No	8


# If breeding triggered



@ Representatives of 20 litters, one offspring per sex per litter where possible

\* Assumes one Control group and three treated dose groups



<b>Preliminary work and selection of dose levels:</b>	Preliminary work will be required to establish suitable dose levels in littering females. Collection of toxicokinetic data is recommended to assess potential exposure in fetuses and of offspring during lactation and at puberty. The highest dose level will normally be expected to induce some systemic toxicity or be at the level at which toxicokinetic exposure becomes non-linear, with two or more lower doses selected at intervals of less than x 10 to determine NOAEL values	
<b>Trigger criteria for second generation (ref OECD guideline document 117)</b>		
<b>ADULT END POINTS</b>		
<b>F0 fertility: Pregnancy rate/gestation length/implantations</b>	Mate F1 cohort 1B in absence of corresponding biologically relevant and dose-related changes in reproductive histopathology	Compromised F0 fertility may mean inadequate numbers of F1 within group
<b>F1 oestrous cycle</b>	Mate F1 cohort 1B if biologically relevant and dose-related changes in estrous cycle length without severe toxicity in the dams	Early warning data may be available from F0 generation
<b>OFFSPRING ENDPOINTS</b>		
<b>F1 malformations</b>	Mate F1 cohort 1B in absence of severe maternal toxicity	Effects may be better resolved in OECD 414 study or termination at D20 pc
<b>F1 litter size</b>	Mate F1 cohort 1B if biologically relevant and dose-related changes in litter size without severe toxicity in the dams	Implies effects at more than one dose level
<b>Reduced F1 live birth index</b>	Mate F1 cohort 1B in absence of severe maternal toxicity	Tests parturition and peri-natal survival
<b>Reduced F1 survival</b>	Mate F1 cohort 1B in absence of severe maternal toxicity	Tests juvenile exposure effects
<b>Reduced F1 pup bodyweight</b>	Mate F1 cohort 1B if pup body weight decrease is biologically relevant and in the absence of maternal body weight decrements	Effects on pup weight may be due to effects on lactation or of direct effects of toxicity due to exposure via the milk or high exposure when direct consumption of treated diet
<b>Altered F1 AGD, nipple retention and/or puberty onset</b>	Mate F1 cohort 1B if biologically relevant and dose-related effects in the absence of body weight-mediated changes	Implies effects at more than one dose level

F0 Parental (P) generation	
<b>Clinical observations:</b>	Weekly Physical examination and arena observation
<b>Bodyweights:</b>	F0 males: Weekly until termination F0 females: Weekly until pairing, GD 0, 6, 13 and 20, LD 1, 4, 7, 14, and 21
<b>Food consumption:</b>	F0 males: Weekly until termination except for pairing period F0 females: Weekly until pairing. Approximately weekly after mating, matching bodyweight, during pregnancy and lactation.
<b>Oestrous cycle monitoring:</b>	For 15 days prior to pairing (dry smears) Days 25 to 28 post-partum (wet smears, to assess stage at necropsy)
<b>Clinical biochemistry and haematology:</b>	10 randomly selected M+F per group before termination (80 samples)
<b>T4 + TSH measurements</b> 	10 randomly selected M+F per group before termination (80 samples for T4 and a further 80 samples for TSH – total 160 samples)
<b>Urinalysis (OPTIONAL - ADDITIONAL COST IF INCLUDED)</b>	Unless existing data from repeated-dose studies indicate that it is not affected, Urinalysis should be included for 10 randomly selected M+F per group before termination (80 samples)
<b>Pairing:</b>	Up to 2 weeks. Vaginal smears (pipette lavage) daily until evidence of mating. No mating changeovers
<b>Littering observations:</b>	Duration of gestation/parturition.

F1 offspring	
<b>Litter observations:</b>	Daily assessment of offspring clinical condition (special attention paid to body temperature, state of activity and reaction to handling)
	Litter size      Daily
	Sex ratio      Days 1, 4 and 21 of lactation
	Litter standardisation      Cull on Day 4 of age. Sprague-Dawley: to 10 per litter (5m+ 5f where possible) Han Wistar: to 8 per litter (4m+ 4f where possible)
	Offspring bodyweights      All: Days 1, 4, 7, 14 and 21 of age. Unselected F1: Day 22 of age  Selected F1: Days 25 and 28 of age
	Pre-weaning assessments      Day 1: measurement of anogenital distance Day 13: male nipple count
<b>Thyroid hormone analysis</b> 	Unselected offspring: samples from 10M/10F per group at necropsy on D22 pp for T4 and TSH measurement (80 samples for T4 and a further 80 samples for TSH – total 160 samples). OPTIONAL @ ADDITIONAL COST: Day 4 culls T4 analysis – 10 samples per group, blood pooled per litter (max. 40 samples)

<b>F1 generation: Cohort 1A (General &amp; Reproductive systems)</b>	
<b>Clinical observations:</b>	Weekly Physical examination and arena observation
<b>Bodyweights:</b>	Weekly until termination
<b>Food consumption:</b>	Weekly until termination
<b>Sexual maturation:</b>	Vaginal opening and balano-preputial separation: time of completion and bodyweight
<b>Oestrous cycle monitoring:</b>	Wet smears: Following onset of vaginal patency until the first cornified (estrus) smear is recorded.  For at least three days prior to the start of the necropsy phase and on the day of termination.  Dry smears: For 14 days from approximately Day 75 of age.
<b>Clinical biochemistry and haematology:</b>	10 randomly selected M+F per group before termination (80 samples)
<b>T4 + TSH measurements</b>	10 randomly selected M+F per group before termination (80 samples for T4 and a further 80 samples for TSH – total 160 samples).
<b>Urinalysis</b>	10 randomly selected M+F per group before termination (80 samples)
<b>Spleen cell immunophotyping</b>	10 randomly selected M+F per group before termination (80 samples)
<b>F1 generation: Cohort 1B (spare reproductive cohort, if triggered)</b>	
<b>Clinical observations:</b>	Weekly Physical examination and arena observation
<b>Bodyweights:</b>	Weekly until termination
<b>Food consumption:</b>	Weekly until termination
<b>Sexual maturation:</b>	Vaginal opening and balano-preputial separation: time of completion and bodyweight
<b>Triggered breeding: initiated after 14 weeks of treatment <i>if required</i></b>	Paired 1:1 within groups and allowed to litter: records to follow F0 generation breeding up to weaning <b><u>Additional cost (reservation fee for 8 extra weeks animal room usage)</u></b>
<b>Oestrus cycle monitoring</b>	Wet smears: For at least three days prior to the start of the necropsy phase and on the day of termination.
<b>Cohort 2A: DNT in vivo testing - Option 4</b>	
<b>Clinical observations:</b>	Weekly Physical examination and arena observation
<b>Bodyweights:</b>	Weekly until termination
<b>Food consumption:</b>	Weekly until termination
<b>Sexual maturation:</b>	Vaginal opening / balano-preputial separation: time & bodyweight at completion
<b>Auditory startle habituation:</b>	Day 24 of age ( $\pm 1$ day) 10 male and 10 female per group
<b>Functional observation battery:</b>	Functional observation battery between D63-75 (nominally Day 70 $\pm 1$ ), 10 M + 10 F per group.
<b>Motor activity:</b>	Motor activity between D63-75 (nominally D65 $\pm 1$ ), 10 M + 10 F per group

**Cohort 2B: DNT pathology at D21-22 of age – Option 4**

No in-life observations


**Cohort 3: DIT in vivo testing**

<b>Clinical observations:</b>	Weekly Physical examination and arena observation
<b>Bodyweights:</b>	Weekly until termination
<b>Food consumption:</b>	Weekly until termination
<b>Sexual maturation:</b>	Vaginal opening and balano-preputial separation: time of completion and bodyweight
<b>Immunology testing:</b>	10 males and 10 females per group – KLH method. Animals dosed Day 47 and Day 54 of age. Blood samples taken on Days 46, 53 and 60 of age for assessment of IgM (240 samples for analysis) . Necropsy on Day 60 of age.

**Terminal examinations**

<b>Necropsy timings</b>	<b>F0 adults</b>	Males after at least 10 weeks of treatment Females Day 28 post-partum
	<b>F1 unselected</b>	Day 4 and 22 of age
	<b>F1 Cohort 1A</b>	Approximately 13 weeks of age (~Week 9 of F1 generation)
	<b>F1 Cohort 1B</b>	Approximately 14 weeks of age (if breeding isn't triggered) (~Week 10 of F1 generation)
	<b>F1 Cohort 2A</b>	Approximately 11-12 weeks of age (~Week 7-8 of F1 generation)
	<b>F1 Cohort 2B</b>	Day 21/22 of age
	<b>F1 Cohort 3</b>	Approximately 8 weeks of age (~Week 4 of F1 generation)
<b>Necropsy and histology:</b>	<b>F0 and F1 Cohort 1A</b>	Full necropsy, retention of tissues and microscopic examination - see table of procedures. CASA for males, Quantitative ovarian corpora lutea and ovarian follicle assessment for females
	<b>F1 Cohort 1A</b>	Spleen cell types characterised for 10 males +10 females per group (ALL groups). 1 male or 1 female per litter; all litters represented by at least 1 pup; randomly selected.
	<b>F1 Cohort 1B</b>	Full necropsy, limited retention of tissues - see table of procedures.
	<b>F1 Cohort 2A</b>	Perfusion fixation: retention of brain, eyes (retina and optic nerve), muscle, spinal cord and peripheral nerve samples. Special histology according to OECD TG 426.
	<b>F1 Cohort 2B</b>	Perfusion fixation : retention of brain



	<b>F1 Cohort 3</b>	10 males and 10 females per group – KLH method. Animals dosed Day 47 and Day 54 of age. Blood samples taken on Days 46, 53 and 60 of age for assessment of IgM (240 samples for analysis) Necropsy on Day 60 of age.
	<b>F1 unselected</b>	Day 22 of age 1M+1F per litter: full necropsy – weigh and retain brain, spleen and thymus - see table of procedures Day 4 of age: all offspring examined
<b>Seminology:</b> 	can be waived for F0 males if there is existing data from a 90 day study to show that sperm parameters are unaffected	
<b>F0 &amp; Cohort 1A males</b>	<u>Vas deferens (left side)</u> : Sperm from all males for motility assessment (CASA) #. Sperm sample fixed from all males for visual morphology analysis <u>Cauda epididymis (left side)</u> : Weighed for all males and retained. Homogenised and number of sperm counted for cauda sperm reserves (by CASA) <u>Testis (left side)</u> : Weighed for all males and retained. Homogenised and number of homogenised-resistant spermatids counted (by CASA)	
	# Sperm motility is assessed from all animals as a fresh sample and all groups are reported. All other examinations are initially confined to High dose and Control groups only plus any other males with suspected reduced fertility, at the discretion of the Study Director	



**TABLE 1 Procedure table for organ weight/retention/histopathology**

Tissue and regions to be examined	Generation						
	F0	F1 Offspring	F1 - Cohort				
			1A	1B	2A	2B	3
Abnormalities	WRHP	WR*	WRHP	WRHP			WR
Target organs, if possible ^	WRHP	WR*	WRHP	WRHP			WR
Adrenals	WRHP		WRHP	R			
Brain	WRHP	WR	WRHP	R	WRHP	WRH P	
Caecum	RHP		RHP	R			
Colon	RHP		RHP	R			
Duodenum	RHP		RHP	R			
Epididymides (caput, corpus & cauda)	WRHP ##	R	WRHP ##	WRH			
Eyes	RHP		RHP	R	RHP		
Femur (longitudinal section through joint)	RHP		RHP				
Heart (including auricular and ventricular regions)	WRHP		WRHP	R			
Ileum	RHP		RHP	R			
Jejunum	RHP		RHP	R			
Kidneys	WRHP		WRHP	R			
Liver (section from two lobes)	WRHP		WRHP	R			
Lungs (section from two major lobes including bronchi)	RHP		RHP	R			
Lymph nodes – proximal and distal			WRHP				
Oesophagus	RHP		RHP	R			
Optic nerves	RHP		RHP	R	RHP		
Ovaries	WRHP	R	WRHP	WRH			
Pancreas	RHP		RHP				
Pituitary	WRHP	R	WRHP	WRH			
Prostate dorsolateral and ventral combined	WRHPD	R	WRHPD	WRHD			
Rectum	RHP		RHP	R			
Sciatic nerves	RHP		RHP	R	RHP		
Seminal vesicles (with coagulation gland)	WRHP	R	WRHP	WRH			
Skeletal muscle	RHP		RHP	R	RHP		
Skin with mammary glands (inguinal area)	RHP	R	RHP	R			
Spinal cord (transverse and longitudinal sections at the cervical, thoracic and lumbar levels)	RHP		RHP	R	RHP		
Spleen	WRHP	WR	WRHPC	R			WR
Sternum - bone marrow	RHP		RHP	R			
Stomach	RHP		RHP	R			
Testes	WRHP##	R	WRHP##	WRH			
Thymus	WRHP	WR	WRHP	R			
Thyroid with parathyroids (post fixation)	WRHP		WRHP	R			
Trachea	RHP		RHP	R			
Urinary bladder	RHP		RHP	R			
Uterus with cervix and oviducts	WRHP	R	WRHP	WRH			
Vagina	RHP	R	RHP	RH			
Vas deferens	RHP ##		RHP ##	R			

W - tissue weighed

## CASA

R - tissue retained

\* Processed and examined if considered necessary  
**additional cost**

H - tissue processed to block stage

P - tissue examined microscopically

C - counts of cell types

D - if effects on prostate wt, segments should be dissected and weighed separately

Light Microscopy			
Category	Generation/ Cohort	Animals	Tissues
Premature deaths	F0/F1 adult	All animals from all groups.	All specified in Table 1
	F1 offspring	All from all groups	Abnormalities (only those deemed appropriate will be examined)
Terminal sacrifice	F0 adult	All animals of Groups 1 and 4.	All specified in Table 1
		All animals of Groups 2 and 3.	Abnormalities only.
		All animals of Groups 2 and 3 with suspect fertility*	Reproductive organs only
	F1 Cohort 1A	All animals of Groups 1 and 4.	All specified in Table 1
		All animals of Groups 2 and 3.	Abnormalities only.
		Groups 1 and 4 10 males/10 females per group	Lymph nodes and, splenic lymphocyte subpopulation analysis (all groups)
	F1 Cohort 1B **	All animals	Abnormalities only.
	F1 Cohort 2A≠	All animals of Groups 1 and 4.	All specified in Table 1
	F1 Cohort 2B≠	All animals of Groups 1 and 4.	All specified in Table 1
	F1 Cohort 3	-	-
	F1 offspring	All from all groups	Abnormalities (only those deemed appropriate will be examined)

\* Includes animals not pregnant, failed to mate, failed to sire a pregnancy, sired 2 or less live young, failed to litter, females with litter death, females with abnormal oestrous cycles or males with abnormal seminology.

\*\* Reproductive and endocrine tissues processed to block stage; examined in cases of suspected reproductive or endocrine toxicants (**additional cost**)

≠ Tissues for Groups 2 and 3 processed to block stage

Cohort 1A	
Ovaries	Qualitative evaluation of 5 sections from each ovary with quantitative assessment of primordial and small growing follicle population as well as corpora lutea.  Initially restricted to 10 females from Control and High dose
Testes	Detailed qualitative examination will be made, taking into account the tubular stages of the spermatogenic cycle. The examination will be conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings will be noted.
Vagina	Stage of vaginal oestrus evaluated based on vaginal epithelial morphology (and appearance of the uterus and endometrial glands).

Cohort 2A and 2B	
Brain	Sections to include: olfactory bulbs, cerebral cortex, hippocampus, basal ganglia olfactory bulbs, cerebral cortex, hippocampus, basal ganglia thalamus, hypothalamus, mid brain (tectum, tegmentum cerebral peduncles), brain stem and cerebellum.  Morphometric (quantitative) evaluations should be performed on representative areas of the brain (homologous sections carefully selected based on reliable microscopic landmarks) and may include linear and/or areal measurements of specific brain regions

<b>Formulation</b>	Weekly
<b>Formulation analysis</b>	<p>By Envigo</p> <p>Stability and homogeneity data for the test material in the diet will be required as part of the programme.</p> <p>Achieved concentration on 3 suitable occasions</p> <p>For example: First week of treatment (P generation); First week of treatment (F1 generation); Last week of F1 generation</p>
<b>Data Treatment</b>	Statistical evaluation as appropriate
<b>Archives</b>	1 Year

## 7.4 Toxicokinetic Study in Rats

## Non-GLP Compliant

<b>Envigo Ref. Number:</b>	CC71MP												
<b>Test Item:</b>	Vehicle Control; AgAc; AgNO <sub>3</sub> ; bulk Ag; Ag NP												
<b>Duration:</b>	Repeated PO dose 28 days Groups 1 – 13; Single dose PO Groups 14 – 26 0 – 72 h and single dose IV Groups 27 – 39 0-72 h												
<b>Route:</b>	Intravenous and oral gavage												
<b>Species:</b>	Rat (Wistar Han)												
<b>Groups:</b>	1	2	3	4	5	6	7	8	9	10	11	12	13
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO
<b>Groups:</b>	14	15	16	17	18	19	20	21	22	23	24	25	26
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO
<b>Groups:</b>	27	28	29	30	31	32	33	34	35	36	37	38	39
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F	3M+3F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
<b>Serial Observations</b>													
<b>Bodyweights</b>	On arrival and day of dosing												
<b>Clinical observations</b>	Mortality check Post-dose observations												
<b>Toxicokinetics blood sampling:</b>	<p>Samples taken from 6 animals (3M and 3F) in each group at each of the following time points:</p> <p>Repeated Dosing PO Groups 1 - 13: Day 14: 3 hours post-dose; Day 28: 3, 6, 12, 24, 72 hours post-dose</p> <p>Single Dose PO Groups 14 - 26: 1, 3, 6, 12, 24, 72 hours post-dose</p> <p>Single Dose IV Groups 27 - 39: 0.25, 1, 3, 6, 12, 24, 72 hours post-dose</p> <p>Actual sample times to be confirmed.</p> <p>Total number of samples: 468 (repeat PO dosing), 468 (single PO dosing) and 546 (single IV dosing) = 1,482</p>												

Pharmacy/Analytical Chemistry	
<b>Formulation:</b>	By Envigo
<b>Formulation analysis by Envigo:</b>	Not required
<b>Bioanalysis</b>	Samples as indicated under “Toxicokinetics” Assumes assessment for 1 analyte per sample using ICP-MS
<b>Toxicokinetic evaluation by Envigo:</b>	Parameters appropriate to data and may include: $C_{max}$ , $T_{max}$ , $AUC_{last}$ , $AUC_{inf}$ , $k$ , $t_{1/2}$ , $CL$ , $V_{dss}$ and $F$ (relevant to route of administration) Assessment: dose proportionality, bioavailability
Data	
<b>CTD tables:</b>	Not required
<b>Archives:</b>	1 year

7.5 Toxicokinetic Study in Rats, **Non GLP Compliant**

<b>Envigo Ref. Number:</b>	CC71MP												
<b>Test Item:</b>	Vehicle Control; AgAc; AgNO <sub>3</sub> ; bulk Ag; Ag NP												
<b>Duration:</b>	Repeated PO dose 28 days Groups 1 – 13; Single dose PO Groups 14 – 26 0 – 72 h and single dose IV Groups 27 – 39 0-72 h												
<b>Route:</b>	Intravenous and oral gavage												
<b>Species:</b>	Rat (Wistar Han)												
<b>Groups:</b>	1	2	3	4	5	6	7	8	9	10	11	12	13
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO
<b>Groups:</b>	14	15	16	17	18	19	20	21	22	23	24	25	26
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO
<b>Groups:</b>	27	28	29	30	31	32	33	34	35	36	37	38	39
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
<b>Serial Observations</b>													
<b>Bodyweights</b>	On arrival and day of dosing												
<b>Clinical observations</b>	Mortality check Post-dose observations												
<b>Toxicokinetics blood sampling:</b>	<p>Samples taken from 6 animals (3M and 3F) in each group at each of the following time points:</p> <p>Repeated Dosing PO Groups 1 - 13: Day 14: 3 hours post-dose; Day 28: 3, 6, 12, 24, 72 hours post-dose</p> <p>Single Dose PO Groups 14 - 26: 1, 3, 6, 12, 24, 72 hours post-dose</p> <p>Single Dose IV Groups 27 - 39: 0.25, 1, 3, 6, 12, 24, 72 hours post-dose</p> <p>Actual sample times to be confirmed.</p> <p>Total number of samples: 780 (repeat PO dosing), 780 (single PO dosing) and 910 (single IV dosing) = 2,470</p>												

Pharmacy/Analytical Chemistry	
<b>Formulation:</b>	By Envigo
<b>Formulation analysis by Envigo:</b>	Not required
<b>Bioanalysis</b>	Samples as indicated under “Toxicokinetics” Assumes assessment for 1 analyte per sample using ICP-MS
<b>Toxicokinetic evaluation by Envigo:</b>	Parameters appropriate to data and may include: $C_{max}$ , $T_{max}$ , $AUC_{last}$ , $AUC_{inf}$ , $k$ , $t_{1/2}$ , $CL$ , $V_{dss}$ and $F$ (relevant to route of administration) Assessment: dose proportionality, bioavailability
Data	
<b>CTD tables:</b>	Not required
<b>Archives:</b>	1 year



## 7.6 Toxicokinetic Study in Rats, Non-GLP Compliant

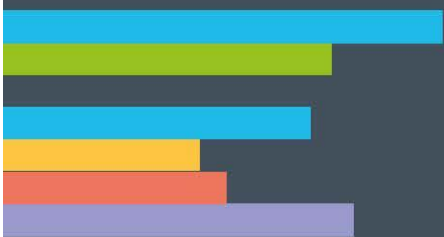
<b>Envigo Ref. Number:</b>	CC71MP												
<b>Test Item:</b>	Vehicle Control; AgAc; AgNO <sub>3</sub> ; bulk Ag; Ag NP												
<b>Duration:</b>	Single dose 0-72 h												
<b>Route:</b>	Intravenous and oral gavage												
<b>Species:</b>	Rat (Hann Wistar)												
<b>Groups:</b>	1	2	3	4	5	6	7	8	9	10	11	12	13
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO	PO
<b>Groups:</b>	14	15	16	17	18	19	20	21	22	23	24	25	26
<b>Test Item:</b>	Vehicle Control	AgAc	AgAc	AgAc	AgN O <sub>3</sub>	AgN O <sub>3</sub>	AgN O <sub>3</sub>	bulk Ag	bulk Ag	bulk Ag	Ag NP	Ag NP	Ag NP
<b>Animals:</b>	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F	5M+5F
<b>Dose:</b>		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Route:</b>	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
<b>Serial Observations</b>													
<b>Bodyweights</b>	On arrival and day of dosing												
<b>Clinical observations</b>	Mortality check Post-dose observations												
<b>Toxicokinetics blood sampling:</b>	<p>Samples taken from 10 animals (5M and 5F) in each group at each of the following time points:</p> <p>IV: 0.033, 0.133, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 hours post-dose</p> <p>PO: Day 1: 0.5, 1, 2, 4, 8, 12, 24, 48, 72 hours post-dose; Day 14: Pre-dose; Day 29: Pre-dose, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 hours post-dose</p> <p>Actual sample times to be confirmed.</p> <p>Total number of samples: 1,170 for PO and 1,560 for IV = 2,730</p>												
<b>Pharmacy/Analytical Chemistry</b>													
<b>Formulation:</b>	By Envigo												
<b>Formulation analysis by Envigo:</b>	Not required												
<b>Bioanalysis</b>	<p>Samples as indicated under "Toxicokinetics"</p> <p>Assumes assessment for 1 analyte per sample using ICP-MS</p>												
<b>Toxicokinetic evaluation by Envigo:</b>	<p>Parameters appropriate to data and may include: C<sub>max</sub>, T<sub>max</sub>, AUC<sub>last</sub>, AUC<sub>inf</sub>, k, t<sub>1/2</sub>, CL, V<sub>dss</sub> and F (relevant to route of administration)</p> <p>Assessment: dose proportionality, bioavailability</p>												
<b>Data</b>													
<b>CTD tables:</b>	Not required												
<b>Archives:</b>	1 year												

# Who we are



Envigo is a global contract research products and services company serving pharmaceutical, chemical, crop protection, academic and government markets

## Our people



600+ Technicians  
100+ Analysts  
70+ PhDs  
40+ Surgeons  
20+ Pathologists

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Virtual companies to multinationals



Academic and government biomedical researchers

