Petitioner AMVAC Exhibit 29

EPA OALJ Docket No. FIFRA-HQ-2022-0002

Plan for completion of DCPA developmental thyroid studies:

1) **DCPA (Chlorthal Dimethyl): Dose Range Finding Pre and Post Natal Developmental Thyroid Study in Sprague Dawley Rats by Oral Administration (Envigo Study: BDG0204).**

We need to rerun Phase I of this study because the rat Luminex immunofluorescence assay which was used at the time the study was performed was not able to detect quantifiable levels of T4 and T3 in plasma from rat fetuses: and these are critical endpoints on the study. The assays were validated to the lowest possible limits of detection taking into account the limited available scientific literature on this subject.

As Phases II and III of the study were scheduled to start after Phase I, we acted quickly and those phases were not performed and will be performed once the rerun of Phase I has been completed. Detection of T4 and T3 and TSH in the dams and TSH in the fetuses was successful using the Luminex assay.

In order to overcome this challenge Envigo has now developed an LC-MS MS assay with much lower detection limits (pg/ml) which has been proven to detect T4 and T3 in Control fetuses. The assay, which detects T4 and T3 simultaneously, has been satisfactorily validated for accuracy and precision and we also have 1 month frozen stability data and are currently investigating stability for longer periods of storage. The Luminex assay is also currently being validated for detection of TSH in serum so that all 3 hormones are assayed in the same medium, serum.

The rerun of Phase I was authorised by UK Home Office and the in life phase and thyroid hormone assays have been successfully completed as follows:

Animal arrival 22 February 2017.

Start of dosing on Day 6 after mating: 6 March 2017

Completion of in life phase: 26 March 2017

Thyroid hormone assay results issued: 19 May 2017

The results from Phase I have been reviewed by US EPA.

As per the results/discussion/conclusions of the US EPA HED Review dated November 16, 2017 of the comparative thyroid assay range-finding study and thyroid hormone methods data, the plan moving forwards is as follows:

Submission to EPA of the outline of the proposed design of the new range-finding pre- and post-natal developmental thyroid study (Envigo Study No. JV36WK) which will incorporate all aspects (data originally planned to be provided on Phases II and II of BDG0204) as requested by the HED review – May 2018

Submission to EPA of a summary table of validated thyroid hormone analysis methods and measured levels using these methods at different developmental stages – July 2018.

Submission to EPA of the QA audited final report for validation of method of analysis and stability of TSH in rat serum – July 2018.

Submission to EPA of the QA audited final report for validation of methods of analysis and stability of T4 and T3 in rat serum –July 2018.

Submission of the full draft study plan for the range-finding pre- and post-natal developmental thyroid study (Envigo Study No. JV36WK) to EPA – November 2018

Submission of validation report for the DCPA assay in rat plasma (Envigo Study No. DC87NT) to EPA – March 2019

Submission of validation data for the DCPA assay in rat milk (Envigo Study No.CH09GN) to EPA – April 2019

Submission of the revised full draft study plan for the Dose Range Finding Comparative Thyroid Assay Investigating Milk Transfer and Thyroid Hormone Levels in Dams and Pups Including a PTU Positive Control Group in Sprague-Dawley Rats by Oral Administration (Covance Study No. PM86YP; now redesignated as Covance Study No. 8441728) as requested by EPA and the AMVAC response to DCPA CTA Memorandum dated 17-Sep-2019 from EPA – both submitted in December 2019.

Formulation chemistry study GQ12XG to assess stability/homogeneity of 0.002 mg/mL formulations, worked completed and has been reported.

April 2020: US EPA review (TXR No: 0057999 dated 19 March 2020) of draft study protocol received Comments have been addressed:

- The air supply has a minimum of 10 air changes per hour
- In the UK, the HO guidance is to group house rats, were possible. The test facility has a policy of improvement of animal welfare which includes permitting social interaction through multiple housing of rats whenever possible. Therefore, in this study, animals will be housed up to 4/cage.
- Method validation for DCPA concentration in milk analysis, will be included in the submitted study results data package. Calibration curves will also be provided, along with data on the sensitivity of the assay (Lower Limit of Quantification or LLOQ).

- Blood sampling will be controlled to minimize any potential confounding effect of the time of day and to allow satisfactory inter group comparison.
- Animals will be held in a separate area prior to sampling to reduce stress-induced hormonal fluctuations.
- The most appropriate method of sacrifice will be used considering the animal age and parameters being evaluated. The same method will be used across groups of animals at the same life stage and across studies.
- Method validation for TSH, T3 and T4 analysis will be included in the submitted study results data package.
- T3 and T4 are analysed from the same plasma sample, therefore the same priority is given to both thyroid hormones. TSH is analysed from a different plasma sample. In this study, the sample for T3/T4 analysis will be collected first, followed by TSH, at the same sampling occasion.

Following confirmation that the Agency had reviewed the study plan and the protocol is considered adequate for a range-finding study (TXR No: 0057999 dated 19 March 2020) Covance Study No. 8441728 has been scheduled.

The confirmed study schedule is:

Animal arrival: 16 September 2020

Treatment commenced: 28 September 2020
In life phase successfully completed: 7 November 2020
In life phase terminal summary available: 30 November 2020

QA Audited Draft Report (including QC checked and QA audited thyroid hormone data) to be issued: 27 January 2021

The results are awaited and will determine the doses for the definitive main pre and post natal developmental thyroid study (BDG0202) and, the precise design and size of the study (i.e. if direct dosing of pups is required should transfer of DCPA to milk be poor and/or thyroid hormone levels are affected in the dams but unaffected in the offspring) and if it is how many groups of pups will need to be dosed. All this information, will be shared with EPA, as soon as it becomes available.

1) DCPA (Chlorthal Dimethyl): Definitive Main Pre and Post Natal Developmental Thyroid Study in CD Rats by Oral Administration (Envigo Study:BDG0202)

Testing will proceed as soon as possible once the Dose Range-Finding Comparative Thyroid Assay (Covance Study No. PM86YP now redesignated as Covance Study No. 8441728) has been completed and all of the results from that study have been reviewed by US EPA and authorisation to proceed is received.

D. P. Myers 12 November 2020

Signed: David P Myers, BSc, PhD, IDT, Senior Toxicologist, Department of Toxicology

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