

**SYNGENTA HUMAN SAFETY
POTENTIALLY REFERABLE FINDINGS APPROACH COMMITTEE**

**MINUTES OF A MEETING HELD ON 19th May 2009
CONFIDENTIAL**

Present:

P Botham	(Chairman, Human Safety, EAME)
P Hertl	(Product Safety, Americas)
J Akins	(Human Safety, Americas)
R Lewis	(Human Safety, EAME)
E Puri	(Global Product Registration)
B Parr-Dobrzanski	(Technical Secretary)
C Davies	(Item 2)
A Cook	(Item 3)
N Sturgess	(Item 3)

Apologies: T Pastoor, J Wright,

1. Minutes of the last meeting (5th May) and Matters Arising

SYN545813 (CARMA) : 20d Rat (IIS0909). The following action is carried forward to the next HS PRF meeting;

“The committee requested further analysis of historical control data for bilirubin are provided to assist with the interpretation of study data on this endpoint”.

Action : RG/RC to complete and update the PRF committee when available

There were no other matters arising, therefore the draft minutes for 11th Mar were approved by the Committee.

2. EMAMECTIN BENZOATE : 5-Day PGP Deficient (-/-) Mouse Inhalation Prelim Study (HS0913)

Results from the above study were presented to and discussed by the committee. The committee concluded that this study meets the technical criteria for referral based on lethality seen at exposure concentrations less than 2mg/L in a different strain of mouse. The committee noted the degree of variability in achieved exposure concentrations in the study (due to the preliminary nature of the study and the low target concentration) and recommended that these should not be quoted as definitive values.

Action : BPD to notify EP.

3. Review of verbal presentation by Dino Di Monte regarding preliminary findings from experimental studies with paraquat (PQ) and MPTP in non-human primates (Squirrel monkeys).

NS gave an overview of the preliminary data verbally presented by Dr Di Monte to the paraquat health science team and summarised in the notes made by NCS and KZT (See Attached).

Botham, Philip
Exhibit_75
6/17/2020



The brain findings in the non-human primate were unanimously agreed as constituting new data. The participants noted that the study had not yet been completed, peer reviewed or published and that the data, by Dr Di Monte's own admission, required further verification. The participants also noted that the toxicological significance of the apparent phenotypic changes is unclear. On the basis of the preliminary nature of the findings and the lack of obvious adverse consequence of the findings in the brain the data do not meet the necessary technical criteria for referral.

The meeting noted that data on doses causing lethality in squirrel monkeys had also been verbally reported. There is therefore a need to establish whether or not the lethality data constitute a new finding taking into account the species, route (sub-cutaneous injection), dose regimen and dose stated to result in lethality.

Action: ARC & NCS to follow-up as a matter of priority to establish what data already exists on the toxicity of paraquat to the squirrel monkey.

Subsequent to the meeting it was identified that there is a report in the literature originating from the Di Monte lab [O'Leary et al., (2008) JPET 327:124-129]. This describes toxicity in the Squirrel monkey (*Saimiri sciureus*) via the s.c. route with the same dosing regimen of once per week:

"The paraquat group received one s.c. injection of 2.5 mg/kg paraquat dichloride hydrate (Sigma-Aldrich, St. Louis, MO) per week for 6 weeks and were euthanized 2 or 4 weeks after the final injection. This treatment paradigm was chosen for several reasons. We used a dose of 2.5 mg/kg paraquat because higher doses induced lung toxicity, as previously reported in other species including humans and mice"

Therefore the dosing of 5 mg/kg once per week through the s.c. route and the toxicity observed as reported by Di Monte verbally has been reported before in the publically available literature.

Based on the above, the committee concluded that this information does not meet the technical criteria for referral.

4. No other business items were identified.

Date of next meeting: TBA