

PQ & PD Experimental Studies team

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It was agreed to use a shared site for lodging minutes and supporting documents. CBB has actioned the site. BME to file minutes there.

A key consideration for future work is which species to use to generate data to further understand the effects of PQ on the neuronal processes, eg:

- non human primate (more relevance to humans)
- mouse (current sensitive animal model)

**Product Safety to review and propose position at next meeting
(interim meeting required to discuss further)**

Current literature uses the mouse model at high dose levels and generally the ip route of administration. Options for refining such data include:

- (i) A mouse study by a relevant route and range of doses would allow a better definition of the NOEL for neuronal events and provide better data for risk assessment from the mouse (eg see A experiment below)
- (ii) A NHP study could be conducted at a more relevant dose eg a fold over the current AOEL, eg max of 20x, and provide a better extrapolation platform for humans (eg see Experiment M below)

Considerations for doing these and other studies include

- supporting the human safety considerations and position
- supporting the case against any possible future legal actions

These are separate, but impinge on each other.

There are existing data in the mouse and will likely always be more data from this simple rodent model. The mouse is recognised as being a sensitive model. There are limited data on the mechanism of PQ induced changes in the mouse model, and therefore limited data to extrapolate to humans and to consider possible thresholds. Gaining mechanistic data on the action of PQ in the mouse model (1) would inform further on the value of the mouse data. This would likely involve both in vitro and in vivo studies (eg see H and I experiments below.)

The mouse model (or in vitro work) will also be more amenable to investigating a number of compounds to determine the range of structures that can cause the changes seen in this model

(2). Such studies would primarily be for supporting the case against any possible future legal actions against PQ.

Feed back to the Steering team on proposals in these areas 1 and 2 above, to address specific questions.

The MRC Leicester group (P Nicotera) is expert in the area of neuronal toxicity and would be well placed to contribute to these mechanistic studies.

NS to lead on dialogue with PN once NS/CBB/KT have consolidated question.

It is recognised that PN will require freedom in the design of experiments.

The route of exposure of animal models is important since the first data from Exponent (DEFRA study), indicate that the nasal route of administration (in rodents) gives a significant exposure to the brain. It would be helpful to gain more detailed insight into the data emerging from the Exponent group, however it is important that this study remains an independent study and one not perceived as influenced by Syngenta.

Consider approaching DEFRA for access to the Exponent data.

If this is not considered appropriate consider waiting for the work to be published before conducting any mouse NOEL studies.

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