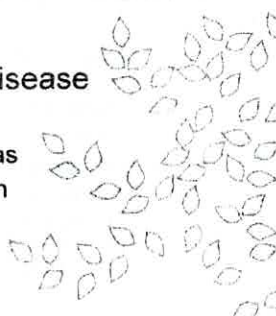




**Paraquat and Parkinson's Disease**  
 Update on activities to manage the potential impact of PQ being used as an academic model for PD research



Botham, Phillip  
 Exhibit\_56  
 6/17/2020

SYNG-PQ-00476926



**Paraquat and Parkinson's Disease**  
 Update on activities to manage the potential impact of PQ being used as an academic model for PD research



Health Assessment status

SYNG-PQ-00476930

**Health Assessment Status**

Consider:

- Mechanistic work
- Epidemiology

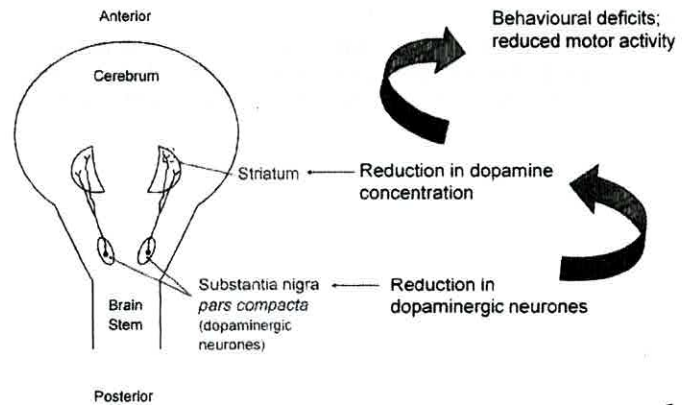
For both External and Syngenta inputs:

- 2004 position
- Current position
- Syngenta future plans
- Major threats



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**Nigrostriatal dopaminergic system**



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## Mechanistic work: Summary of status at end 2004

### External

- Evidence for reduction in neuronal cell count in mouse model from two main labs (Cory-Slechta, Di Monte)
- Limited and inconsistent reports of dopamine reduction
- Limited reports of behavioural effects
- One report of effects in the rat
- Consistent message that PQ, alone or in combination with maneb, can cause effects in the mouse model

### Syngenta

- Initial evidence of reduction in neuronal cell count in mouse model
- No evidence for dopamine reduction or behavioural effects
- No evidence of being a substrate for the dopamine transporter
- No evidence of binding to post-synaptic dopamine receptors

## Mechanistic work: Summary of status at end 2004

### External - IEH review

- IEH review of mechanistic work concludes
  - "...there are sufficient data to suggest that with certain routes of administration rotenone and paraquat may have neurotoxic actions that could potentially play a role in the development of Parkinson's"
  - "...while there is some indication of a potential role for some pesticides in the aetiology of PD, there are insufficient data from relevant studies using routes of administration and doses to conclude that exposure to these pesticides at occupational or environmental levels would lead to the neurotoxicity observed"

## Epidemiology: Summary of status at end 2004

### External

- IEH review of epidemiology concludes "...extended exposure to classes of pesticides, such as herbicides and insecticides, especially possibly paraquat, appear to be risk factors in the development of PD"

## Mechanistic work: Summary of current status

### External

- Di Monte publishes paper supporting oxidative stress as the mechanism behind PQ induced loss of neurones in the mouse model
- Cory-Slechta publishes on atrazine-induced changes in a rat model
- Two more reports of PQ induced changes in the rat (*Kuter et al.*, - *Krakow, Cicchetti et al.*, - *Emory*)
- UK DEFRA invites for bids to conduct mechanistic work on the mode of action of pesticides with respect to Parkinson's

### Syngenta

- Loss of neuronal cells in the mouse model confirmed
- Artefact due to stereology technique ruled out following consultation with experts
- Reversibility study to assess robustness of cell loss underway (7, 28 & 90 days)
- Assessment of selectivity of cell loss to dopaminergic neurones underway
- Acute and sub-chronic rat neurotoxicity studies in-life phase complete

## Epidemiology: Summary of current status

### External

- UK ACP ratify IEH review conclusions
  - Press report on ACP conclusion
- Geoparkinson study interim statement made indicating correlation between pesticide use and risk of Parkinson's
  - Press reports on Geoparkinson statement
- Ag Health study announces plan for first report on correlation of pesticide use and Parkinson's incidence in 2006
- UK DEFRA invites for bids to conduct an epidemiology study into pesticide use and Parkinson's
- ECPA proposes an epidemiology study to evaluate agricultural uses and cancer (will Parkinson's be included?)

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## Mechanistic work: Future plans 2005/6

### Syngenta *\*challenge the model \*\*move to risk assessment*

- Examine for non-specific effect of chemicals at toxic doses\*
  - Use a number of well-known chemicals (e.g. paracetamol)
- Examine for evidence of the mouse model (C<sub>57</sub>Bl<sub>6</sub>) being isolated in its response\*
  - Examine PQ in the rat (also to repeat the literature claim)
- Conduct a detailed examination for evidence of neurotoxicity in the mouse model\*
  - Examine for morphological and histochemical changes
- Examine to confirm no subsequent effects of neuronal cell loss\*
  - Examine dopamine concentrations and look for behavioural changes after longer periods of dosing and at later time-points
- Place exposure from the mouse model into context with relevant route\*\*
  - Determine exposure following intraperitoneal and oral administration

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## Epidemiology: Future plans 2005/6

### Syngenta

Important driver is the planned Ag Health study publication in 2006

- Gain external expert input into general study design/interpretation
  - Identify a panel of expert epidemiologist, clinician, neurobiologist
  - Gain review of risk and confounding factors in epidemiology studies looking at Parkinson's. Publish
- Refine exposure estimates for occupational use
  - Identify use patterns in Ag Health study
  - Determine potential exposure scenarios
  - Estimate actual exposure from received dose

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## Possible threats

### Mechanistic

- Neuronal cell loss and/or sequelae in the mouse model following relevant route of administration of PQ
- Robust publication of effects from PQ in another rodent species
- Effects of PQ in a non-human primate (*Di Monte already active*)

### Epidemiology

- Association of herbicide use with Parkinson's cases
- Association of paraquat use/exposure with Parkinson's cases

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## Influencing

- Identify key individuals and organisations in the scientific field
- Identify key non-scientific groups/people to influence
- Generate data
  - Allow vehicle for entering the debate through presentation and discussion
- Attend scientific conferences
  - Present data; challenge others
  - Network
- Make personal contact with individuals where appropriate
  - Identify who is awarded the DEFRA mechanistic and epidemiology work
  - Influence the ECPA study through committee membership

## Influencing

Names of key individuals in the area

### *Mechanistic*

- Di Monte (Parkinson's Inst. CA)
  - also Langston, McCormack, Manning-Bog & Tanner.
- Cory-Slechta (Rutgers)
  - also Thiruchelvam, Richfield & Barlow
- Miller (Emory, Atlanta)
  - also Richardson & Greenamyre
- Ray (Nottingham)
  - links with Chanyachukul group in Thailand (no direct contact)
- Andersen (Buck Institute for Aging, Novato, CA)
- Shimizu (Asahikawa, Japan) (no contact made)

## Influencing

Names of key individuals in the area

### *Epidemiology*

- Tanner (Parkinson's Inst. CA) & Kamel (NIEHS, RTP) - *Farming & Movement Evaluation Study: Pesticides & PD risk in the agricultural health study.*
- Chesselet (UCLA) - *Gene environment studies in PD.*
- Chan (Sydney, Australia) - *Study of PD in Australia.*
- Ritz (UCLA) - *PD susceptibility genes & pesticides.*
- Firestone & Checkoway (Washington) - *Environment & biochemical risk factors for PD.*
- Nelson (Stanford) - *Environmental & genetic risks for PD.*
- Seaton (Aberdeen) - *Genetic, environmental & occupational risk factors for PD.*
- Greenlee (Marshfield Medical Research Foundation, Wisconsin) - *Pesticides, genetics and risk of PD.*
- Elbaz (ISERM, France) - *Case control study of PD among subjects characterised by a high prevalence of professional exposure to pesticides.*
- Louis (Columbia) - *Environmental epidemiology of essential tremor.*

## Influencing

Names of key individuals in the area

### *Mechanistic & Epidemiology*

- Abi Li (Exponent, San Francisco)
- Ian Dewhurst (PSD, York; rapporteur for EU review)
- Paul Rumsby (MRC IEH, Leicester) - Pesticides & PD review.
- Jim O'Callaghan (CDC, WV) - MPTP expert

## Influencing

### Fora for presentation

#### *Scientific meetings*

- Society for Neuroscience (USA)
- International Neurotoxicology Meeting (USA)
- Society of Toxicology (USA)
- Neurotox (UK)
- British Toxicology Society (UK)
- International Neuroscience Association (Europe)
- International Congress of Toxicology (Europe)

## Influencing

### Milestones for triggering publication / presentation

- Market basket survey completion
- Drinking water survey completion
- Cell loss is reversible
- Other well-known chemicals at peri-lethal doses cause a similar effect
- Mouse model is isolated in its response
- Intraperitoneal versus oral route exposure comparison in mouse model
  
- "Paraquat In Perspective" publication or presentation in 2005 or early 2006 to put mechanistic and epidemiology publications to date in context?