syngenta

Paraquat Update

Jonathan Sullivan
Lewis Smith
Gerardo Ramos

Syngenta Executive Committee Meeting
9 November 2009

CONFIDENTIAL

Agenda

- **Progress and Initial Conclusions of Research Program**
- **Dialogue with Australian Regulators**
- **Programme of Communication with Regulatory Authorities**
- **Communications Strategy**
- **EU PIC-listing**

Progress and Initial Conclusions of Research Program

Lewis Smith

Paraquat and Health

- Our aim
  - To protect people and our reputation
- Scope
  - To understand the significance of laboratory data and epidemiology data related to parkinsonism and to take appropriate action
- Modus operandi
  - Use our legacy of expertise in paraquat toxicology to bring together scientific expertise inside and outside of Syngenta and integrate it with our expertise in business, regulations, communication and legal

We are working on 4 questions

- Are the effects reported in the literature of paraquat in mice ***real*** (actually caused by treatment or an artifact)?
- If they are real, are the effects in mice ***relevant*** to humans?
- If they are relevant, would the effects in mice ***impact*** the current recommended safety levels?
- Will the scientific community conclude from the laboratory and epidemiology data that paraquat exposure is a ***causal factor*** in Parkinson's Disease or parkinsonism?

Initial Conclusions from Investigative Studies

- **Pathology showed PQ did not cause loss or damage to cells in substantia nigra in mice**
- **Cell counts by steriology or Unbiased Digital Image Quantification (QUID) showed no loss of dopamine-containing cells**
- **Since both measures are independent we can conclude that although the positive control (MPTP) showed a loss of cells, PQ did not harm cells in the substantia nigra**

  Hypotheses:
  - Problem with dosing
  - Not enough PQ given
  - Staining for loss of cells was inadequate
  - Steriology and QUID is not sensitive enough
  - Other technical reasons not identified
  - The result is real and previous results are false
- **Studies are being repeated with higher doses of PQ and using verified staining techniques**

Human Investigations- summary

- **the Widnes mortality study is under way; on the advice of epidemiological experts we will not investigate survivors in the Widnes cohort**
- **a review by Berry/Nicotera/La Vecchia of the external literature including epidemiological studies is being updated and will be finalised shortly**
- **an expert review of all risk factors for PD is near completion**
- **an expert review of the clinical features of PQ poisoning and their relationship to PD is near completion. Preliminary data has shown no evidence of clinical features of PD**
- **an assessment of the need for , and technical and ethical issues involved in, a PQ case control study is on-going**
- **the kinetic data together with an understanding of the pathology and neuronal cell loss (if any) in the brain of mice will allow the design of a safety assessment protocol by Product Safety in order to refine the risk assessment of PQ for safety and regulatory purposes**

Conclusions

- **we have developed a deeper understanding of Parkinsonism and Parkinson's Disease**
- **we have a comprehensive overview of the PQ/literature**
- **we have completed a series of kinetic studies that allows us to predict the level of PQ in the brain of experimental animals**
- **we have demonstrated that PQ will cross the blood brain barrier**
- **using an established protocol for the effect of PQ on mouse brain, we have failed to find evidence of cellular damage of dopamine cell loss.**
- **Human investigations are under way and further consideration of additional studies is being evaluated. It is premature to state whether additional studies will be required.**

Future Studies

- To explain the absence of effect of PQ on mouse brain cells seen in our recent studies in comparison with the published data
- Continue with mode of action studies
  - Uptake of PQ into brain cell
  - Molecular effects of PQ on brain cells
  - Species and strain variation of effect
  - Investigate the effect of other 'brain toxicants' to put PQ into perspective
  - Complete human investigative studies
  - Develop a scientifically based risk assessment narrative for the relationship (if any) of PQ to Parkinsonism in humans.

Dialogue with Australian Regulators

Gerardo Ramos

Background

- Office of Chemical Safety and Health (OCSEH) and Australian Pesticides and Veterinary Medicines Authority (APVMA) at meeting with Syngenta representatives on 17 July 2009 raised concerns arising from published data which had appeared since last toxicology review in April 2004
- OCSEH signalled that continued support for paraquat would be contingent upon determination of a NOEL for dopaminergic neuron loss; requested generation by Syngenta of guideline neurotoxicity and developmental neurotoxicity studies
- We instead volunteered to undertake 90-day mouse study using dietary exposure, preferably preceded by kinetic study, reporting in October 2010
- At October 2 2009 meeting OCSEH and APVMA agreed to this, with inclusion of recovery group requiring extended observation period
- NOEL study has inherent risk of setting lower value for inclusion in risk assessment with potential impact on product use profile

Key Outputs from October 2 Meeting

AU regulators

1. understand that Syngenta is taking the issue seriously
2. understand that even in the absence of an effect specific NOEL study the available information suggests an acceptable margin of safety for consumers and operators
3. Accepted the two guideline neurotoxicity studies (acute and subchronic) that we already conducted in rats which did not show any neurotoxic effects of paraquat
4. understand and support Syngenta's approach to determine an appropriate endpoint for operator safety evaluation
5. no longer ask Syngenta to perform the 3 neurotoxicity studies they initially suggested, particularly the developmental neurotoxicity study
6. understand that the CFI concern over PQ and PD during the EU review was procedural

Programme of Communication with Regulatory Authorities

Gerardo Ramos

Communication Objectives

- Regulatory communication
  - Objectives
    1. Aligned and timely communication with key regulatory authorities worldwide
    2. Regulators will understand that Syngenta is taking the issue seriously
    3. Regulators will understand that there is no reason to regulate based on the alleged but unconfirmed effect at this stage as there is a sufficient margin of safety for consumers and operators
    4. Regulators remain confident in Syngenta's approach to the issue: Syngenta is committed to study the alleged effect

Proposal on aligned communication with key regulatory authorities worldwide

Communication timing
- Communication with AU regulators took place on October 2nd. The meeting was considered business confidential.
- However, it is prudent to assume that information on our research program will become more available to others in the near future

Communication approach
- Proposal is to inform the following countries proactively: LATAM (Brazil); APAC (AU (done), NZ, Japan, S. Korea); NAFTA (US, Canada); EAME (none).
- Proposed process: Use the Inteon communication strategy: one communication plan; one globally aligned message; one global PowerPoint presentation; all discussions within a relatively short period of time delivered by defined Syngenta regulatory colleagues (light touch).
- The same communication to be used in future for reactive responses.

Communications Strategy

Jonathan Sullivan

New standby language

Last year,Syngenta consulted with several independent senior medical and epidemiological scientists under the guidance of Professor Sir Colin Berry (Emeritus Professor at Queen Mary, University of London, and former member of the UK Medical Research Council) and Professor Pierluigi Nicotera (Founding Director of the German Center for Neurodegenerative Diseases, Bonn) to learn their views on the hypothesis that there might be a causal link between exposure to paraquat and PD. Their conclusion was that no such link existed and a publication summarizing these conclusions will be issued in 2010.

Nevertheless we understand that this is a developing area of study, so we are examining whether there are any additional areas of research where we can offer to contribute substantively to the literature, for example to the output from large scale studies already being undertaken by respected organisations, such as the study by Exponent for the UK Government Department for Environment, Food and Rural Affairs, and the Agricultural Health Study in the U.S.

Syngenta has also commissioned additional external and internal studies to examine different aspects of this question in order to ensure that we possess the most robust and accurate scientific and technical evidence available.

Communications approach

- Reactive until we have new information; however aggressively correct misinformation
  - SWAT Team: Sullivan, Brown, Hull, Stanbrook
  - External support for in-depth reviews of other reports: Nadel/Breckenridge
  - Media (including social) monitoring/posting: Stanbrook, Brown
  - Regulatory communications: Brady
- Strategically proactive when new research available
  - Paraquat.com posting: Scott
  - Scientific forums program: Doe, Botham
  - Regulatory community strategy: Brady

EU PIC-listing

Jonathan Sullivan

Status update

<u>News since briefing of 8 September 2009</u>

- Meeting with Cabinet of DG Environment (Mr Giotakos) took place on 16 September 2009 – although Commission appeared uncomfortable with the basis of the listing proposal, listing process continues
- The expected entry into force of the amending Regulation is at earliest at the beginning of December 2009
- Preparation work for procedural/compliance aspects and by Business/Supply Chain is on track
  - Action plans of importing countries established (communication, requirements from EU etc.)
  - Supply chain planning and supply of certain stocks
  - Preparation work for PIC notification procedure
- To date, there is no new notification of a regulatory action against paraquat to the Rotterdam Convention, and a notification from the EU alone would not trigger the first step of the PIC listing process .