

Zumbiehl Janine CHBS

From: Atkin John CHBS
Sent: Freitag, 13. Juli 2007 22:14
To: Sullivan Jonathan Dale CHBS
Subject: Fw: Priveleged and Confidential

Attachments: PQ PD document J Atkin.doc

Jonathan, have you reviewed this? - John

----- Original Message -----

From: Burton Judith GBAP
To: Atkin John CHBS
Cc: Lawrence David CHBS
Sent: Fri Jul 13 19:33:30 2007
Subject: FW: Priveleged and Confidential

Dear John

Please find attached a short paper to clarify the discussion we had last week on the relationship between paraquat and Parkinson's disease. Also, an organisational chart of the critical elements of managing ourselves when dealing with paraquat issues and the paraquat and Parkinson's issue in particular.

The organisational chart breaks the issue management into five segments as follows:

1. The technical review of the scientific evidence of the relationship of paraquat to Parkinson's disease and the risk assessment that is necessary to establish the safety of those exposed to paraquat in the course of their work or through adventitious exposure.
2. Regulatory assessment is handled by the registration leads, globally and in the regions. This involves the use of the science and knowledge of the registration standards applicable on a case-by-case basis.
3. Reputation management, which is led by Public Affairs in order to present Syngenta's assessment of the issues surrounding paraquat and Parkinson's disease, both internally and externally.
4. Litigation is handled by Legal Affairs, both globally and in the regions. This is the case-by-case process using the science and regulatory positioning in the context of individual legal challenges.
5. Business decision, which is essentially a review of all the components which impact on the making, marketing and selling of paraquat, by paying specific regard to the regulatory, legal and reputational impacts on our business.

The critical questions we need to ask are, Should we sell it?, Can we sell it?, and Will we sell it? The should we, is the safety assessment, the can we, is the regulatory assessment and the dare we, is the business assessment. You may want to consider actually nominating individuals who would be responsible for the activities within each of the boxes. By bringing these together under your (?) leadership, you will have a holistic view of all aspects of the paraquat issue. My suggestion for those who would lead each segment are as follows:

Technical: me

Regulatory: Angela Brady and/or Janis McFarland (for NAFTA issues)
Reputation: Caspar Ridley
Legal: Jonathan Sullivan and/or Alan Nadel (for NAFTA issues)
Business: Andre Dias

No doubt for major business strategic issues, you might want to drop some of this team and/or include regional heads or marketing heads.

I hope this and the attached documents are helpful.

Lewis



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Paraquat/Parkinson's Disease

Following our recent conversation on the relationship between paraquat (PQ) and Parkinson's disease (PD), I wanted to put down on paper the position as I see it:

1. I believe there are at least five issues to be considered when assessing the allegation that there is a causal relationship between the exposure to paraquat and the development of Parkinson's disease.

- (i) What does the science say and how best can it be interpreted?
- (ii) The regulatory implication of the science base.
- (iii) Potential Litigation
- (iv) Reputation Management
- (v) The Business options

(i) The science base.

The evidence from the scientific literature and some of Syngenta's own studies show that paraquat is able to cause neuronal cell loss in the mouse brain. This effect is dose dependent and current data indicate that the maximum neuronal cell loss that can be achieved may be approximately 30-35%. The acute dose of paraquat required to cause this loss is large, although we do not know the NOEL of this effect. Because these data were generated in mice, there is no certainty that the human brain will respond in the same way, that is, more or less sensitively. Recent data suggested that following paraquat administration to mice at weaning (5-19 days of age) there is a loss of neurones and reduction in striatal dopamine in the brain which eventually (18-22 months later) causes a loss of mobility. The interpretation of these data is difficult. Paraquat appears to be able to cause brain neuronal cell loss, but the dose and the route of dosing may not be relevant to humans. Also, the most effective way of getting paraquat into the brain of mice appears to be dosing paraquat to pups (young mice) before their blood brain barrier has fully developed. The blood brain barrier significantly reduces the movement of paraquat into the brain, but does not provide an absolute barrier for access.

There is a continuing increase in the number of scientific papers describing the potential of paraquat to cause neuronal cell loss. However, at the time of writing there is no clear causal relationship which can be established to show that paraquat contributes to the development, and/or, severity of Parkinson's disease in humans.

The epidemiological data which describes the effect of pesticides and in particular, paraquat, on the incidence of Parkinson's disease are difficult to interpret. Some studies have found no effect, whereas others have shown a clear association between the incidence of Parkinson's disease and reported exposure to pesticides. In a few of these studies, paraquat in particular has been identified a pesticide which is associated with the development of Parkinson's disease. This association does not mean there is a causal relationship between exposure to paraquat and Parkinson's disease. However, the combination of the experimental evidence with the conflicting results from epidemiological studies has lead some scientists to conclude that the association of paraquat with Parkinson's symptoms is so strong as to mean that paraquat is at least contributing to an earlier onset of Parkinson's symptoms, particularly for individuals who would naturally develop the disease.

At present because of the considerable uncertainty of the relevance of results from the experimental studies to humans, combined with conflicting data from the epidemiological studies, we remain highly sceptical as to whether there is a causal association between paraquat and Parkinson's. However, not all scientists will agree with this view and will argue that the potential to cause neuronal cell loss in mice, together with the association of reported paraquat use and Parkinson's disease, makes a compelling argument.

(ii) Regulatory Impact

The Regulatory impact on the more recent data describing the effect of paraquat on the brains of mice is unclear. Although various authorities are aware of these data, they have not been comprehensively reviewed from a regulatory standpoint. It seems probable that when these data are reviewed, at least some Regulatory Authorities will ask Syngenta to comment on the data and may well request that we carry out studies to further characterise the effect of paraquat on neuronal cell loss. This will be part of the risk assessment process to allow Regulators to decide whether or not there is an acceptable safety margin for humans exposed to paraquat.

We are currently gathering the most recent experimental data that are available on this issue and will work with our Risk Analysis group in Product Safety to determine the margin of safety. It is to be hoped and intended that this approach will be consistent with that of Regulatory Authorities.

(iii) Litigation

We are aware that in the USA some lawyers are already interested in identifying individuals who have worked with paraquat and maneb with a view to establishing whether or not they are suffering from Parkinson's disease (or symptoms) as part of a possible class action suit. There has been considerable publicity associated with the effect of paraquat on neuronal cell loss and recent epidemiological studies have also raised the profile of this issue with some NGO's who have a long standing bias against paraquat. These NGO's interpret the data as indicating an unacceptable risk of Parkinson's disease for those involved in spraying the pesticide. The recent decision on the annulment of paraquat Annex I decision will not help. These developments may stimulate litigation and it seems possible that clever trial lawyers may be able to persuade the jury that the association between paraquat and Parkinson's disease is causal. This, of course, does not mean that it is causal, just that juries may be persuaded that paraquat does cause Parkinson's disease. No doubt Jonathan and/or Alan Nadel will be able to provide a greater insight on this aspect of the problem.

(iv) Reputation Management

We already know that paraquat has a negative reputation in the minds of some NGO's and also for significant segment of the population largely because some NGO's are determined to undermine the reputation of paraquat.

The apparent association of paraquat with Parkinson's disease provides them with an opportunity to maintain their attack. This will undoubtedly influence third parties and more worryingly Regulators who might tire of relying on purely scientific arguments on what is becoming a more politicised issue. The only way we will be able to undermine the influence of the NGO's is to have high quality scientific evidence that the allegations they make about paraquat are not true.

(v) Business situation

The business situation will need to take account of the science, regulatory, litigant and reputation issues. My view is that the major risk to Syngenta is from litigation because we cannot be categorical that the hazard that paraquat poses to the neurones in experimental animals will never express itself in humans. This problem is no different to many other compounds where risk assessments are required to demonstrate the acceptability of exposing humans to small quantities of specific compounds. However, given the reputation of paraquat and the determination of NGO's to spread a negative image of the product, we may find it difficult to persuade a jury of our viewpoint. However, we have not yet undertaken additional scientific studies that may show paraquat is not responsible for neuronal cell loss. Our best judgement suggests that paraquat should not increase an incidence of Parkinson's disease in humans. However, confirming a negative in epidemiology studies is difficult, and we may not be able to provide sufficiently persuasive evidence to show that paraquat does not cause an increase in Parkinson's disease in humans.

The business decision on paraquat will most likely involve a comprehensive review of the technical, regulatory, reputational and legal aspects of the allegation that paraquat causes Parkinson's disease as well as commercial realities.

Lewis Smith/July 2007

PARAQUAT TECHNICAL MANAGEMENT

WHO	WHAT	ACCOUNTABILITY
- Product Safety - Global Regulatory (+ Regions) - Stewardship - Business practice	TECHNICAL ASSESSMENT ↓ RISK ASSESSMENT ↓ then “SHOULD WE?” ↓	Product Safety Product Safety Consensus or go to SEC
- Global Regulatory (+ regions) - Product Safety - Stewardship - Marketing - Legal Affairs	REGULATORY ASSESSMENT ↓ then “CAN WE?” ↓	- Global Regulatory - Legal Affairs - Global Regulatory - Legal Affairs
- Public Affairs - Global Regulatory (+ regions) - Product Safety - Product Stewardship - Marketing - Legal Affairs	REPUTATION MANAGEMENT ↓	Public Affairs Consensus or go to SEC
Legal Affairs Plus appropriate Syngenta functional groups	LITIGATION ASSESSMENT ↓	Legal Affairs
	BUSINESS RISK “WILL WE?”	Legal Affairs John Atkin and/or SEC