Message

From: French Dave CHBS [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1CBCECED6AD94B52A994EEA61B019EB7-FRENCH DAVI]
Sent: 5/1/2019 5:01:37 PM
To: Cook Andy GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b012593ccd764559b2f9986da61a2e8f-Cook Andy A]
Subject: RE: Syngenta Paraquat Emetic Notes

Thanks Andy for taking care of this on a holiday. Make sure you take the time in lieu and use when things are less hectic. Talk tomorrow.
Regards Dave

From: Cook Andy GBJH
Sent: 01 May 2019 18:58
To: Fournier Jean Marc CHBS <jean_marc.fournier@syngenta.com>; Smith Mark USGR <mark.smith-1@syngenta.com>; Mazzotta Roman CHBS <roman.mazzotta@syngenta.com>
Cc: French Dave CHBS <dave.french@syngenta.com>; Botham Phil GBJH <phil.botham@syngenta.com>; Travis Kim GBJH <kim.travis@syngenta.com>
Subject: FW: Syngenta Paraquat Emetic Notes

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Dear all,

As discussed I have prepared (for internal reference use only at this point) some statements regarding the allegations made by Jon Heylings in his most comprehensive e-mail to date (i.e. the one sent on 17th April 2019 following his meeting with Dave and Jean Marc). I think this addresses most of the key points ahead of the planned teleconference on Friday.

Regards.

Andy

Correction of factual inaccuracies

From: Jon Heylings [mailto:j.heylings@dermaltechnology.com]
Sent: Wednesday, 17 April, 2019 04:30 PM
To: French Dave CHBS <dave.french@syngenta.com>
Cc: Fournier Jean Marc CHBS <jean_marc.fournier@syngenta.com>
Subject: Syngenta Paraquat Emetic Notes

Dear Dave,
Following our call yesterday I am happy to have another face-to-face meeting with you and any other Syngenta staff you wish to involve. When you mentioned you had a list of factual points that we can use as a basis for agreement or disagreement, I thought I would formulate a few points of my own to capture what I see as the key issues with the paraquat emetic. As I mentioned in our call, Friday May 3rd works for me. I really need to get this off my back to the Regulators very soon after that, since I am giving a presentation on paraquat safety at the CBRNE Conference in Nantes on May 22nd and have arranged to meet up with Allistair Vale (Meredith and Vale 1987 Paraquat survey) for discussions

on the emetic. I am having dinner with my confidante, Professor Garner on Good Friday evening, who is interested to hear how our April 12th meeting went.

Jon Heylings Notes on the Key Points relating to the Paraquat Emetic PP796 Issue (April 2019)

1. Data Fabrication: It is pretty clear cut that the Rose report CTL/R/390 contains a fabricated human dose response for the paraquat emetic, PP796. This was detailed in my signed letter to Lewis Smith in Sept 1990, comparing the Bayliss Pharms data with the data in the Rose report on the same human volunteer study. The fabrication was detailed in my own signed follow up letters to the CTL Executive in 1990 and to Bob Scott (CTL), Andy Cook (RAD) and Martin Wilks at Fernhurst in the following years. The fact that I was never challenged on this serious allegation lends credence to my observation being correct. Every enquiry that I was promised to review the human data on PP796 was either disbanded or never reported.

We have independently located copies of the memos from Jon Heylings to Dr Jaggers dated 31st January 1990 and from Dr Smith to Dr Heylings dated 6th November 1990 in Mr Willis' hard copy files indicating that the CTL recommendation was raised by Dr Smith with ICI Plant Protection Division in 1990 and, in all probability, discussion took place prior to the 'Safer Paraquat formulations' TRC of 5th March 1990 (Reported in ICI report number TMY 387C) issued by Dr Swaine. Consistent with Dr Lewis' recollection of events as shared with Dr Heylings in January 2019 there is no record of Jon Heylings detailed memo to Lewis dated 5th September 1990 having been shared with anyone outside of CTL but this may have been unnecessary given the TRC discussion earlier in the year. The contributors to the March 1990 TRC included Jon Heylings and Dr Smith from CTL. The pre-read which Jon Heylings jointly authored simply stated that the original decision was probably an underestimate of the effective emetic dose in man and went on to suggest that based on dog studies conducted some 5 years earlier (in 1985 / 1986) the minimum concentration be raised 5-fold. A meeting of the Toxicology sub-committee of the PSAC (Paraquat Strategic Action Committee) subsequently took place on 30th March 1990, at which CTL was represented by Dr Lewis, Product Safety and Stewardship by Mr Willis and Dr Sabapathy and Regulatory by Jee-Mok Fua. There was no suggestion in any of these communications or the other internal CTL memos at that time that the extremely limited human clinical data available to Dr Rose in 1976 had been deliberately 'falsified' or 'fabricated'. Indeed at no time that we are aware prior to 2018 did Jon Heylings or anyone else, ever make such a serious allegation.

The appropriate emetic concentration was extensively discussed internally and externally since the formation of Syngenta in 2000 in the context of the development of 'Inteon', as part of the current investigation we have identified multiple internal communications and powerpoint presentations within CTL, the stewardship and safety and regulatory functions in which Jon Heylings states that he considers the PP796 ED50 (50% vomiting response) across higher mammals to be very similar at around 0.5 mg/kg. There is clear documentary evidence that Jon Heylings' personal views on the effective emetic concentration were known to those involved in the development of 'Inteon' in the period 2000 to 2007.

2. Clear proof of fabrication is the hand drawn dose response curve on the emetic in man that I have the original of. This sigmoidal curve was constructed by Mike Rose between and parallel to the sigmoidal animal dose response

curves. He then added the points to the curve as detailed in the crossings out in his lab note book using his own % vomiting responses to fit on the line and to make it appear that there was a very good relationship between emetic dose in man and % vomiting response at the dose levels of ICI 63197 (PP796) used by Bayliss in 1973. Syngenta now agree with me following a more recent review of the emetic data in man (and presented on Jan 15th 2019) that there is no dose of emetic that reliably causes vomiting in man in the original ICI Pharms reports. This in itself contradicts the Rose conclusions in CTL/R/390 that 0.5g/L emetic was very effective in man and was the basis for the FAO specification still used today. At least we are all in agreement on this one!

Dr Rose clearly stated that his analysis represented only an estimation of the effective emetic dose given the limited clinical data available in man. Dr Rose estimated that the majority of those ingesting 10 mL of a formulation containing 0.05% w/v PP796 would vomit within an hour.

3. In the 1990s, a total of 11 Company staff were made aware that the human dose response in CTL/R/390 was fabricated: Mike Rose, Lewis Smith, Stuart Jaggers, Rod Morrod, Iain Purchase, Gerry Oliver, Bob Scott, Martin Wilks, Andy Cook, John Ishmael and Keith Atherton. I was told to focus on the development of a high emetic Magnoxone formulation as the best way of dealing with this issue and also told that the original decision for the 0.5g/L concentration of emetic being effective as reported by Rose would not be investigated. As a company employee I was not in a position to challenge this without major repercussions for my own career.

In the 1990s there was no claim that the data had been fabricated, simply that the data on PP796 alone was not sufficient to reliably establish the effective emetic dose in man when in used in paraquat-containing formulations. At that time the Company position was based on the 1987 Meredith and Vale publication. A listing of the senior Company personnel present at the March 1990 is not available but certainly included Dr Smith and Dr Swaine. Those present at the subsequent meeting of the Toxicology sub-committee of the PSAC (Paraquat Strategic Action Committee) which took place on 30th March 1990, at which CTL was represented by Dr Lewis, Product Safety and Stewardship by Mr Willis and Dr Sabapathy and Regulatory by Jee-Mok Fua also included Nick Geach (Public Affairs), Rob Morrison (Herbicides asset management) and Alan Calderbank (consultant). The recipients of Rob Morrison's 22nd October 1990 memo included Bernard Graciet and Jeremy Batch (Development Department), Tony Stapleton and David Walker (),

4. Moving on to the present day and in a completely different position as a Professor of Toxicology and out of the company for 12 years I am now much more confident to take on the Establishment. Having begun a research project on paraquat on behalf of the UK Department of Health in 2018, I naturally looked at the current Syngenta strategy with their formulations. Firstly, I noted that the costly higher emetic Inteon product had been dropped by Syngenta and very worryingly that the FAO spec for paraquat products is still to this day incorrect. I therefore made a further 7 Syngenta staff aware of the data fabrication issue, since the recent "One Sip can Kill" EPA publication showed that children are still being accidentally poisoned by paraquat products that the Regulators approved on the basis of Syngenta's information that all their products contain an effective emetic concentration at a minimally lethal dose. The new Syngenta staff who are aware of this over the last 6 months or so now include: Phil Botham, Mathew Bayliss, Kim Travis, Dave French, Janis McFarland, Jean-Marc Fournier and Jonathan Parr (plus the main Syngenta Board).

5. FAO Spec: Whichever way you look at it the 0.5g/L (0.05%), 1:400 PP796 : PQ ion for Gramoxone or for the USA G max/Australian 360g/L product at 0.8g/L (0.08%), 1:450 or as a ratio 0.23% PP796 : PQ ion, comes directly from the Rose report on Gramoxone, pro rata adjusted for Gramoxone Max etc. Where else would an actual number have come

from to use for emetic addition, since there were no other human studies on PP796? The text about the "majority of patients", "within 30 minutes", "minimally lethal dose" and "0.5g/L" in the FAO spec comes straight from the text in the Rose report and as presented to the ICI Agrochemicals Board by Peter Slade with the Rose report as evidence for the concentration of emetic.

The 0.5 g PP796/litre in 'standard' Gramoxone (containing 200 g paraquat ion/litre) is established at 1 : 400 (0.05%). The FAO Specification for the TK (paraquat dichloride technical) sets the minimum concentration as 0.8 g/litre, this is the manufacturing concentrate not a formulation and there would be no expectation of any end user exposure to the TK. SL (liquid) formulations must contain > / = 0.23% of the paraquat ion content, i.e.

= 0.83 g PP796 for 360 g/litre
= 0.58 g PP796 for 250 g/litre
= 0.46 g PP796 for 200 g/litre (1:435, @ 0.5 g/litre this would be 1:400)
= 0.31 g PP796 for 133 g/litre
= 0.28 g PP796 for 120 g/litre
= 0.23 g PP796 for 100 g/litre
= 0.12 g PP796/litre for 50 g/litre
= 0.09 g PP796/litre for 40 g/litre

In the case of the current Australian 360 g/litre formulation (approved by Global DeCo RTFS for use exclusively in closed transfer systems) the emetic concentration is 1.5 g PP796/litre (1:240), the future US Gramoxone 360 g paraquat ion/litre formulation (approved by Global DeCo RTFS exclusively for use in closed transfer systems) also contains 1.5 g PP796/litre (1:240). Syngenta and predecessor companies have for many years routinely included 0.5 g PP796/litre in liquid paraquat formulations, including those containing less than 200 g paraquat ion/litre. This is clearly not consistent with cost (of the emetic) being the primary driver.

The FAO also established that water soluble granular formulations must contain > / = 0.23% of the paraquat ion content, i.e.

= 0.18 g PP796 for 80 g/kg
= 0.06 g PP796 for 25 g/kg

Incidents involving a granular formulation are more likely to have occurred as a result of deliberate consumption of the product than incidents involving liquid formulations. If 10 mL (2 g) represents a minimally lethal dose of paraquat from a 200 g paraquat ion/litre formulation then this would equate to 16 g of a granular formulation containing 25 g paraquat ion/kg.

The FAO text does not refer to "*majority of patients*" but to "*at least 50% of cases*". The FAO text refers to "*within 30 minutes*", Rose refers to "*within an hour*". The FAO makes no reference to a "*minimally lethal dose*".

6. Zeneca even used the Paraquat: emetic ratio approach in the FAO Spec rather than a fixed minimum concentration or % emetic in the product, to reduce the emetic even further in Preeglox (45g/L PQ). This made the Japanese product more profitable since it contained much less of the costly emetic. Unsurprisingly, Preeglox was just as lethal in humans as the previously registered Gramoxone.

Untrue, the FAO Specification of a minimum PP796 concentration was not established until 2003. Syngenta and predecessor companies use a global minimum emetic concentration of 0.5 g PP796/litre for formulations containing less than 200 g paraquat ion/litre. So far as we have been able to ascertain, the Japanese 'Preeglox' formulation has always contained 0.5 g PP796/litre, certainly it currently (and in the recent past) contains 0.5 g PP796/litre and approximately 40 g paraquat ion/litre (emetic : paraquat ratio 1:80 – coincidentally the ratio 'recommended' by Jon Heylings in 1990). The current independently published (2007-2011, published 2013) Japanese fatality rate from paraquat ingestions (as a result of incidents of deliberate self-harm) is 80%.

7. Other documents I still have include the EU 91/414 Paraquat Dichloride MII submission in 1995. This states that PP796 is 10 times more potent in man compared with other vomiting animal species. This is incorrect since the statement is based on the fabricated emetic dose response data in man reported by Rose. The effective dose of PP796 to meet the FAO requirements is certainly not 0.5g/L. There is no human data to support this but a wealth of animal data in 3 vomiting species suggesting the effective PP796 concentration should be 10 times higher. I provided Andy Cook, Martin Wilks and Bob Scott with a written response criticising this regulatory document that Zeneca were submitting to the EU Authorities. Naturally, I retained the original documents on this from 1995, recognising the importance of my correspondence, plus the way that the company had mishandled my earlier statements on this matter.

Untrue, the first draft EU regulatory submission document was provided to Dr Heylings, Dr Scott and Dr Wilks for technical review and comment from a toxicology and clinical medical perspective. The emetic (PP796) document was a voluntary submission of the reports available to the company in 1995 and was not a regulatory requirement under EU Directive 91/414. As a result of comments received from those reviewers and incorporated in the document the final version was extensively revised prior to submission in April 1995. The document provided short summaries of the available study reports and does not make any claim regarding the relative sensitivities of man and other vomiting species. The final agreed document was shared with CTL and was retrieved from the CTL electronic archive in March 2019. The 1995 e-mail correspondence from Dr Heylings indicates his personal disagreement with the conclusions of Rose but does not claim fabrication or falsification. The 1987 Meredith and Vale publication provided the basis of the Zeneca Agrochemicals Medical Doctors recommendations on the concentration of PP796 in Zeneca paraquat products as had previously been discussed following a February 1994 meeting which included CTL, represented by Dr Scott as paraquat product toxicologist, the two Zeneca Agrochemicals Divisional medical doctors (Drs Sabapathy

and Wilks), Dr Johnen as head of the Safety and Stewardship Department, Mr Willis as head of Regulatory Affairs Department and Mr Cook as EU paraquat regulatory lead.

8. Paraquat registrations granted from 1977 were based on an ineffective emetic concentration in Gramoxone, detailing the Rose report in the Appendix of the Agrochemicals Board Paper. The Rose report is also cited in the open literature as proof of the effective emetic dose in man. No improvement in survival following introduction of the emetic was demonstrated by Ohno et al, Japan or by Meredith and Vale. The latter paper noted more emesis but not the prompt centrally-acting emesis you get with an effective emetic dose.

Untrue, since the initial introduction of the emetic PP796 in paraquat-containing formulations in the UK in 1977 the initial recommendations on the emetic concentration were kept under review by the ICI, Zeneca and Syngenta. Following the commercial introduction of emeticized paraquat-containing formulations in the UK in 1977, ICI Plant Protection Division, working with the National Poisons Information Service (NPIS), set up a toxico-vigilance program to monitor the impact of the introduction of the emeticized formulation. This was, in fact, one of the stipulated regulatory requirements of the commercial authorization. ICI also recognized the importance of that monitoring since a thorough human evaluation needed to be made in view of the limited data for PP796 alone and, more importantly, on the basis of the inclusion of PP796 in liquid paraquat formulations also containing surfactant blends and the olfactory alerting agent (thus assessing both the impact of the dispersion of PP796 and the human emetic response) and the professional and low-strength amateur granular formulations without the olfactory alerting agent. The Rose report was cited in a January 1987 publication by the UK National Poisons Information Service, NPIS (Onyon L J and Volans G N, The Epidemiology and Prevention of Paraquat Poisoning, Human Toxicology, volume 6, pp 19-29). The Meredith and Vale 1987 publication provides empirical support for the occurrence of rapid emesis following ingestion of emeticized paraquat formulations.

9. Gramoxone Inteon (which I developed at CTL and am the patent holder) demonstrated that even a small increase in emetic (X3) improved survival following paraquat poisoning (Wilks et al). Diluting the product and increasing the emetic to an effective PQ : emetic ratio is likely to be much more effective and save many lives. The high cost of this manoeuvre was overturned by the TRC at Jealotts Hill. I have the memo on this from the Non-Selective Herbicides lead, Rob Morrison detailing this as a fact. It required a new emetic plant to be built in Huddersfield and circa. £30m recurrent cost per annum to move from standard Gramoxone with 0.5g/L emetic to Magnoxone with 2.4g/L emetic.

The global business decision to terminate the 'Inteon' project in 1Q2008 was taken after commercial launch in multiple countries since it had become clear that the improvement in safety was considerably less than the anticipated (and repeatedly claimed) 10-fold. In addition there were significant formulation production problems, formulation separation under field conditions and a high volume of end user complaints of clogging and gelling in bulk tanks requiring manual clean-up. The Company's development of 'Inteon' cost more than US$50 million on the basis of the technical specification for emetic concentration recommended by the CTL technical team (1.5g PP796/litre) which Jon Heylings now claims to have been inappropriate. As late as 1999 Jon Heylings was proposing a new project with conventional 'Gramoxone' formulations with greater dispersion of the existing (0.5 g PP796/litre) emetic

concentration (e.g. through use of the solvent NMP – now prohibited in many countries) in liquid paraquat formulations.

10. Inteon has now been dropped by Syngenta and the company continues to endorse an ineffective concentration of PP796 emetic in all its paraquat products, deliberately flouting the FAO spec requirements. People are still dying from paraquat poisoning round the globe and Syngenta have not acted on information provided to senior staff in the Company nor made any attempt to investigate the rationale for introducing the ineffective 0.5g/L emetic in Gramoxone in 1977.

The company decision to terminate the 'Inteon' project in 1Q2008 was taken after commercial launch in several countries since while both of the Sri Lankan studies and the South Korean investigations provided some limited evidence for improvements in survival it had become clear that the improvement in safety was considerably less than the anticipated (and repeatedly claimed) 10-fold and no longer met the company's objectives established for the project. The PP796 concentration in Syngenta paraquat formulations complies with the FAO specification requirements (note the FAO specification requires the emetic to induce vomiting in about 30 minutes in at least 50% of cases without reference to the formulation volume consumed). The rationale for the initial emetic concentration introduced in Gramoxone in 1977 has been thoroughly investigated since Jon Heylings raised this issue with us in 2018.

11. A comprehensive letter detailing the history and dialogue between myself and company management together with my own version of events has been prepared and will be sent initially to OPPTS Re-registration Branch at US EPA in May 2019. This includes the scientific rationale behind my findings and references to original documents and reports including CTL/R/390 by Mike Rose. Syngenta has always advocated "Science led Regulation "for many challenging regulatory issues over the years, I foresee "Science led Litigation" may well result from this. I am sure we all agree that falsified data should not be used on matters of human safety with Syngenta's products. At the end of the day it will be for the Regulators to decide on the next course of action once they become aware that there is a problem.

Naturally, I would be more than happy to discuss or debate any of the points above. If there is any disagreement with any of the facts I have presented here do let me know so I can make sure my dialogue, initially with US EPA is factually correct.

Best regards

Jon Heylings

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