Message

From: McFarland Janis USGR [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=A33943217CE44D2EB4FF015CD4B0B9BC-MCFARLAND J]
Sent: 4/26/2019 2:11:25 PM
To: Smith Mark USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdf4206be37c47a6ae76849cd206596c-Smith Mark]; Nadel Alan USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=234c0a8065d94bf8ac515c24f1c2274c-Nadel Alan]; Reeve Brian USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=39cb6c5f61324eefbd92bac808646d70-Reeve Brian]
CC: Dixon Monty USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a7fd9c5f9c4f453e8a32e6e5b80e6636-Dixon Monty]; Abbott John USGR [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d2d9589574a0445bb5a93bcda08044de-Abbott John]
Subject: FW: Syngenta Paraquat Emetic Notes
Attachments: EPA-HQ-OPP-2011-0855-0020.pdf

Importance: High

From: Jon Heylings [mailto:j[redacted]
Sent: Friday, April 26, 2019 9:51 AM
To: McFarland Janis USGR <janis.mcfarland@syngenta.com>
Cc: French Dave CHBS <dave.french@syngenta.com>; Fournier Jean Marc CHBS <jean_marc.fournier@syngenta.com>; Botham Phil GBJH <phil.botham@syngenta.com>
Subject: Fw: Syngenta Paraquat Emetic Notes
Importance: High

Dear Janis,
I assume that Dave French is keeping you on board with the developments on the emetic issue following our face-to-face meeting on April 12th. My latest email to him is below this email.
Since Dave explained that he is on holiday this week I have a question for you relating to the US registration and dialogue with EPA on paraquat human poisoning that was published in the Federal Register in 2014. In the attached PDF, it has a statement that Gramoxone Inteon containing a gelling agent (with no reference that it also contained a higher emetic concentration) "did not prove successful in saving lives". Did this statement originate from Syngenta, and, if so, on what is it based? Surely, the most important scientific data on the ability of the Inteon technology to improve safety is the extensive human investigation that was published by Syngenta by Wilks et al in PLoS Med in 2008. As I am sure you are aware, the Inteon technology demonstrated a significant improvement in survival in actual human poisoning and this was further supported by the Time Trends paper in 2011, as Martin Wilks pointed out to me just last week. I am fully aware that the MPI dog studies showed that the Inteon technology was more effective with the US built-in surfactant system, but if you read the Fed Reg document, if you combine a dilution of the Gramoxone Max (as suggested by Dr Richard Geller of the California CPCS) with with the Inteon technology you would improve the safety of the product.

I do feel that Syngenta have continued to mislead the Agency on factual information on paraquat safety and have continued to defend the high strength Gramoxone Max product that is still responsible for many deaths in the USA and thousands more with standard Gramoxone in developing countries. Inteon was a costly technology for Syngenta to roll out globally. Likewise, dilution, as stipulated by Japan in the 1980s took a lot of profit out of the market. The Syngenta strategy to keep the paraquat concentration as high as possible and the emetic concentration as low a possible will become clear when they receive my detailed document in May. I am addressing my report to Marianne Mannix at OPP, who looked after the most recent deliberations on

Paraquat safety and is familiar with the product and human paraquat poisoning in North America. As I explained to Dave French, the Agency will see that the 0.23% emetic by ratio and not less than 0.8g/L in the FAO Specification was based on fabricated human data reported by Rose in CTL/R/390. The Regulators with see that both Gramoxone Max and the global Gramoxone 200 products contain an ineffective emetic concentration and the currently registered paraquat products do not meet the criteria for the emetic in the FAO Specification. Perhaps more worryingly for Syngenta is that this error was not rectified by the senior Toxicology, Regulatory and Product Stewardship staff made aware of this data fabrication several times in the 1990s.
I explained to Dave French and Jean-Marc Fournier from Syngenta legal, who also attended our April meeting, that I will wait until Monday May 6th before sending my report to EPA, since Dave wanted to have another meeting with me on Friday May 3rd. This allows Syngenta to raise any final challenge to my scientific position on this matter before we let the Regulatory Authorities decide what to do.

Yours faithfully,

Jon Heylings

Professor Jon Heylings
Chairman and Chief Scientific Officer, DTL Ltd

From: Jon Heylings
Sent: 17 April 2019 15:29
To: French Dave CHBS
Cc: 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.

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!

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.

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.

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.

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.

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.

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.

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.

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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