Message

From: Jon Heylings [redacted]
Sent: [redacted]2018 4:18:49 PM
To: Botham Phil GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=675e0b3a54374a76b913a2fb682de1b2-Botham Phil]
CC: Cook Andy GBJH [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b012593ccd764559b2f9986da61a2e8f-Cook Andy A]
Subject: RE: FAO Specification for Paraquat Products

Dear Phil,
Thanks for your email. I figured there would be some internal discussion on the emetic before you got back to me. Sorry, you have actually picked a bad week for me for a telecon. As I mentioned during our chat at EFSA in Parma, we had planned quite a long time ago to move back to the Macclesfield area, since our 3 grown up children all live there. The week you have proposed is actually when Debra and I are moving house to Prestbury. Our completion date is Sept 27th so I will be on leave from Sept 25th until the middle of the following week. It's an extra 20 min commute to Keele but at least we can see more of the family.

Due to the importance of this FAO spec matter on the effective PP796 concentration to cause vomiting in man, I am happy to have a call ahead of your proposed dates, or from Oct 8th onwards. In fact, wouldn't it be better for all concerned if we sat round the table to go through this face to face. I could then show you all the original documents between myself and the CTL Executive at the time and the original report copies I have comparing the human data on PP796 in Mike Rose's report with the ICI Pharms report on the same human volunteer study. I don't want to send out PDF copies of some of the more sensitive information.

There were (and probably still are) considerable sensitivities surrounding this matter of the effective dose of PP796 in man. Everyone that was party to this in the early 1990s left CTL. Therefore, it was never satisfactorily resolved, despite the internal reviews that were set up but never reported. I think it warrants more than a telecon don't you think? I would be happy to host such a meeting here at DTL at your convenience, or pay you a visit at Jealotts Hill if you wish to involve others.

Best regards

Jon Heylings

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From: Botham Phil GBJH [mailto:phil.botham@syngenta.com]
Sent: 14 September 2018 10:45
To: Jon Heylings [redacted]
Cc: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Subject: RE: FAO Specification for Paraquat Products

Dear Jon

First of all, sincere apologies for the significant delay in responding to your e-mail. Andy and I wanted to discuss this before getting back to you, but a combination of business commitments and vacations meant that we couldn't do so until this week.

As a consequence of our discussion we would like to propose a phone call with you to follow up on some of the points you make. Could you let us know if you would be available at any of these times:-

Thu Sep 27th 1000 – 1100
Fri Sep 28th 1200 – 1300
Tue Oct 2nd 1100 – 1200

Kind regards

Phil

From: Jon Heylings [redacted]
Sent: 16 August 2018 11:51
To: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Cc: Botham Phil GBJH <phil.botham@syngenta.com>
Subject: FAO Specification for Paraquat Products

Hi Andy,
I wasn't sure if you were still in the old company, but great to hear from you again! Amazingly, we are now in our 12th year operating as a private company. We still have quite a few former Syngenta CTL staff on the DTL books and more recent recruits from AstraZeneca. Our main activity is still providing our Crop Protection customers worldwide with regulatory dermal absorption studies for the human risk assessment part of their registrations. I am currently assisting EFSA as their nominated expert, tasked with re-writing the test guidelines for Dermal Absorption, OECD 427 and OECD 428, over the next year or so, so I am kept very busy.

Many thanks for answering my question on the paraquat colourant/dye. The project I am involved with, funded by the Department of Health, is looking at the human safety and treatment of specific toxic chemicals of public interest. One of these is my old friend paraquat (or "Turnips" as Geoff Willis used to call her when we were in the pub!) - hence my renewed acquaintance with the herbicide. We are also involved with new studies here at DTL using radiolabelled paraquat and various decontamination and treatment strategies with other organisations.

Although, sadly, paraquat products are banned in Europe, it is still a great example of how we maintained its registration for many years by various "safening" strategies introduced as long ago as the 1970s. The colourant/dye was an important move, alerting children, in particular, that any decanted liquid from the labelled container was not, in fact, Coca Cola! We also did a lot of work at CTL on the stenching agent with our "sniffing" trials to see if we could reduce the pyridine bases that were proving to be a nuisance to farmers. However, the addition of a stench as an alerting agent was actually another smart move by ICI and probably prevented a number of accidental human poisonings.

Another area of considerable interest to me with paraquat is the emetic PP796 or ICI 63197, as it was known, when I first worked with the compound at ICI Pharms in the late 1970s. As I am sure you will know, ICI started adding the

triazolopyrimidine emetic, PP796, to its paraquat products as long ago as 1977, anticipating an improvement in survival, particularly in the accidental and para-suicide (low volume) ingestion cases. Unfortunately, there was no proven improvement in survival rates, as published by Bramley and Hart in 1987. There was a higher incidence of vomiting in paraquat poisoning cases with the emetic, but the emesis reflex was too slow and occurred after a lethal dose of paraquat had already been absorbed into the bloodstream. Time from ingestion to productive emesis was not understood to be critical in relation to paraquat absorption kinetics at the time, as we showed later in our extensive CTL studies in the 1990s.

Armed with the knowledge of what is an effective emetic dose of PP796 in man from studies at ICI Pharmaceuticals, reported by Bayliss PFC in PH20992C in 1973, my own research at CTL used a much higher level of PP796 in the concentrated Gramoxone product than recommended by Rose in his infamous 1976 report (CTL/R/390R). The ICI Pharms data on the human volunteer study at different doses of emetic presented by Mike Rose concluded that PP796 was ten times more potent in man than the other three vomiting species that had been investigated during the drug development stage of the compound. This internal CTL report is even cited in the open literature (e.g. Onyon, LJ and Volans GN, in Human and Experimental Toxicology Vol 6, 19-29, 1987). However, the actual ED50 to cause emesis in man (circa. 0.5mg/kg) is very close to the ED50 in pig, dog and primate. Rose had stated in CTL/R/390R that the ED50 in man was ten-fold lower at 0.05mg/kg.

The original Magnoxone 20% paraquat formulation that we developed in the early 1990s at CTL in order to maintain the Company's worldwide registrations of the product, in response to severe regulatory pressure, had 5 times the standard PP796 concentration that was in Gramoxone, in addition to a high level of an acid-triggered gelling agent and a purgative agent, magnesium sulphate to remove any remaining product from the gut. We had demonstrated across many in vivo studies that we could manoeuvre the 10 X emetic uplift back down to 5 X, by delaying the absorption of paraquat from the gastrointestinal tract. The final composition of this new Magnoxone formulation was based on our extensive and promising in vivo studies that resulted in very rapid onset of emesis of the gelled product and consequently very low and survivable plasma levels of paraquat. Emesis following Magnoxone was much earlier than occurred with standard emeticised Gramoxone and the gelling kept it in the stomach longer and away from the site of active paraquat absorption in the jejunum. In fact, the original Magnoxone formulation was shown to be 20 X less toxic by mg/kg paraquat ion dose, compared with standard emeticised Gramoxone in our CTL studies. We claimed that this was likely to reduce oral toxicity in man in our ICI Agrochemicals patent. Magnoxone went into full development as a replacement for Gramoxone to not only maintain key territorial registrations, but also as a mechanism for increasing the emetic in our main product with the new gelling technology.

However, due to various cost and some manufacturing issues, Zeneca Agrochemicals decided firstly to substantially reduce the acid-triggered gelling capacity using a much lower alginate level and reduced the emetic to just a 3-fold increase over current levels. This was shown to be much less effective in our CTL studies than the original Magnoxone. When this new product, now called Gramoxone Inteon, was evaluated in the Sri Lanka trial, it was unsurprisingly far from ideal, safety wise. I still maintain that there was considerable reluctance by the Agrochemicals business to use a higher, and more effective emetic concentration, in combination with the Inteon technology. This was likely to have produced a much less toxic product in man, particularly with a higher amount of gelling agent to slow down gastric emptying. More of the ingested product would be removed by earlier and more productive emesis. The additional emetic I proposed to John Finney and his TRC colleagues was documented as too much of a cost penalty to the business at the time.

Unfortunately, and to my surprise, when I recently reviewed the current FAO specification for paraquat as part of this new DoH project, I noted that the specification for the PP796 : paraquat mass ratio is still set at a minimum of 0.23% for all paraquat concentrates. This 0.23% ratio remains to this day an ineffective emetic concentration, if a minimally-lethal dose of paraquat ion (circa. 20mg/kg) is ingested in man. For the reasons I have described above, this should be ten-fold higher at a ratio of 2.3% PP796 : paraquat ion dose in order to cause prompt emesis in man. The FAO spec goes on to describe how "emesis must occur within 30 min in at least 50% of poisoning cases". Since the PP796 dose would be below threshold for causing vomiting in a minimally-lethal paraquat dose, this 0.23% PP796 would be completely ineffective. You would come to the same conclusion if you reviewed the correct emetic dose response data from ICI

Pharmaceuticals. This is, of course, independent of any of the Inteon type gelling technology and just based on the FAO specifications for the emetic alone in the Syngenta or generic's paraquat products.

I am not sure how much of this background on the addition of the emetic PP796 to paraquat products you are aware of, in your capacity as Bipyridyl lead for Syngenta, but if you look into the evidence as to what is an effective dose of PP796 in man you will probably come to the same conclusion as I did back in 1990.

I am happy to discuss these issues with a view to updating the FAO specification for paraquat products including the TK concentrate used in the USA which has the same PP796 : paraquat ratio. Due to the importance surrounding this matter I have all the original reports referred to above and all the correspondence on this matter if you want to investigate this further or challenge the scientific facts I have presented on this.

You (and others) may, of course, see this as "sour grapes" since my own research leading to Inteon didn't lead to a major improvement in survival in paraquat poisoning cases, or an improvement in the registerability of the product. It is, after all, 28 years since I first raised this emetic matter with senior management. However, having recently noted the FAO Specification for the concentration of the emetic PP796, I feel obliged to ensure that human safety overrides politics and commercial sensitivities that have always been associated with paraquat products.

Best regards

Jon Heylings

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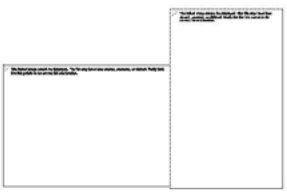

From: Cook Andy GBJH [mailto:Andy.Cook@SYNGENTA.COM]
Sent: 13 August 2018 10:10
To: Botham Phil GBJH < >
Cc: Jon Heylings [redacted]
Subject: RE: Paraquat

Hi Jon,

The specific choice of colourant /dye depends on the market and formulation. The US requires an FDA-approved 'food grade' colourant. The matter is further complicated by the terminology for commercial dyestuffs being rather inconsistent.

The dye normally used in Syngenta paraquat formulations is "Sulfacide brilliant blue 5 J" (**CAS Number 3844-45-9**), other include: "Green Carbolan G", "Triphenylmethane brilliant blue FCF" and "C.I. Acid blue 9, disodium salt" (**CAS No. 3844-45-9**).

Regards.

Andy Cook

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From: Botham Phil GBJH
Sent: 12 August 2018 21:22
To: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Cc: Jon Heylings [redacted]
Subject: FW: Paraquat

Andy

Can you help with Jon's enquiry?

Phil

From: Jon Heylings [redacted]
Sent: 10 August 2018 13:42
To: Botham Phil GBJH <phil.botham@syngenta.com>
Subject: Paraquat

Hi Phil,
Greetings from DTL. I am working on a project for the Department of Health related to the treatment of paraquat poisoning, and have a question for Syngenta on a component added as an alerting agent to the original Gramoxone product.
I still have a lot of my old personal files with details on the PP796 emetic and stenching agent that were added to the product in the 1970s to prevent human poisoning. However, I cannot find much about the nature of the blue/green dye that ICI added to the product. I seem to recall it was Alcian Blue, originally made by ICI and still used as a histological stain for mucins. It just states blue/green "colorant" in the FAO specification and US EPA R.E.D. documents in the sections on the composition of paraquat products.
I vaguely recall, you mentioning that it was Dan Ashdown who was looking after paraquat or there may be someone else in the Stewardship area at Guildford or Greensboro that would be able to help. If you can point me in the right direction that would be great.

Many thanks

Jon Heylings

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