From: Jon Heylings
Sent: Thursday, June 6, 2019 8:24 AM
To: French Dave CHBS <dave.french@syngenta.com>
Cc: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>; Fournier Jean Marc CHBS <jean_marc.fournier@syngenta.com>; Botham Phil GBJH <phil.botham@syngenta.com>; Travis Kim GBJH <kim.travis@syngenta.com>; McFarland Janis USGR <janis.mcfarland@syngenta.com>
Subject: RE: Response on behalf of Syngenta

Dear Dave,

Thank you for sending me the formal response on behalf of Syngenta on my claims relating to the concentration of the emetic agent, PP796, that was first added to paraquat products back in 1977. First of all, thank you for listening to my views and the various in depth meetings I have had with Syngenta, and in particular senior members of Product Safety and Lewis Smith on the various technical points I have challenged. Syngenta obviously take this matter very seriously which I really do appreciate and the time that you and your colleagues have devoted to this. Hopefully, by involving your legal representatives, they also understand what is a complex issue and the basis for my challenge. With the benefit of hindsight, if your predecessor organisation had done as thorough a job as Product Safety have done in 2019, when I first raised my concerns back in the early 1990s, then a lot of the mysteries surrounding the emetic would have been addressed at the time. I admire the more open approach you have taken on this which is very much in contrast to the situation I experienced in the 1990s.

It would be really good for both parties if there had been a breakthrough piece of new evidence in either Kim Travis' new analysis of the ICI Pharms data or this May 2019 Syngenta position document that would have made me retract from my mission. However, my position on the emetic concentration that was added to Gramoxone in 1977 and how this was handled through to the 1990s and beyond remains largely unchanged. In fact, the new Syngenta analysis of the ICI Pharms human data (independent of the Rose report) actually reinforces my hypothesis that the 0.5g/L concentration that was added to Gramoxone was based on (for want of a better word) a "fabricated" human dose response curve to the emetic. Angela Brady told me to focus on the single hypothesis and that is the 1977 decision and not the Inteon story or what Syngenta are doing now with regard to emetic levels in paraquat products or other methods Syngenta are doing to address the poisoning problem such as closed transfer systems. We must not forget that it was ICI Agrochemicals Division that endorsed the 0.5g/L emetic concentration in the Board Paper entitled: **Emetic Formulation of Paraquat: Proposed Strategy for Introduction Worldwide (EDC No. 729, 1976. Author: Peter Slade)**. This had the Rose report CTL/R/390 in the Appendix of the Board Paper with the original text: "*induce vomiting in approximately 70%" of those ingesting it*". The 0.5g/L concentration and these reports were used alongside other measures to protect the global registrations of paraquat products that were under threat following numerous fatal poisonings with the herbicide.

The CTL/R/390 research report dated October 1976 by Rose became a revised report with the R suffix in February 1977 with the "toned" down term "*majority of those ingesting it "* replacing 70% (that was the exact intersect between the 5 and 70% on the Y axis on Mike Rose's hand drawn line and even marked on it in his lab book). This CTL report was used by ICI Agrochemicals extensively as the basis for supporting the concentration of 0.5g/L emetic to be added to Gramoxone with the text that it was estimated that this concentration would be "effective at producing vomiting in the majority of individuals ingesting a minimal lethal volume of Gramoxone". The Rose research report with the Revised "R" tag is even cited in the open literature. One example of its appearance in the literature is in the

same 1987 volume of Human Toxicology as the Meredith and Vale publication in 1987, as being the evidence for an effective concentration of emetic in man and that it was 10 X more potent in man compared to the pig, dog and monkey. **Onyon, L. J. and Volans, G.N., The epidemiology and prevention of paraquat poisoning. Human Toxicology 6, pp 19-29, 1987.** Single author research reports are not subject to QA audit or peer review and this one did the rounds of the Poisons experts at the time. The report was cited at the same Paraquat Symposium at Guy's hospital in 1986 that Meredith and Vale showed data on ICIs poisons survey in the UK and Ireland. Interestingly, the information on vomiting within 30 min with emeticised product came directly from ICI as unpublished observations in Table 2 in this paper and the same table is in the Bismuth and Hall book, entitled Paraquat Poisoning in 1995. Surely, if this was so important and featured eventually in the FAO, it would have been written up by ICI and published in a peer reviewed journal. Syngenta keep citing this Meredith and Vale 1987 paper as the key publication supporting the "within 30 min" in the FAO spec. Well do you not realise that this is "unpublished data" originated from ICI itself? Perhaps the rationale for not publishing this at the time was because the emeticised product did not improve the survival figures in the same survey.

You must all realise that it is not easy for me to take on a corporate giant such as Syngenta single handed on such a serious matter where human deaths from poisoning with a Syngenta registered product are concerned. You probably all think that I have a touch or paranoia over this by continuing to argue that there were errors of judgement in 1977. Alas no, I just want to present a clear case to Poisons Centres and the Regulators to look into this matter again. Even the comment of why now? after all these years am I doing this I hope is clear to you all with our new work for the UK government on paraquat decontamination. It would be quite easy for me to say that your new investigations have satisfied me that the "estimation" of the concentration was not a bad call back in 1977. However, that is not the point, it is the fact that I informed senior management on several occasions in the 1990s that this "estimation" was based on a human dose response curve to the emetic that was constructed or fabricated to make it appear that there was a clear dose related effect in man. This misled a number of Stakeholders including various National Regulatory Authorities who continued to permit the sale of paraquat products on the basis that it was now less likely to cause death via oral ingestion, particularly in accidental low volume exposures.

There was no feedback to me in the early 1990s that I was correct or not on my accusations with abandoned enquiries on the matter and I was told to forget the past and focus on high emetic Magnoxone. You state that this was thoroughly investigated in 1990. Well considering I was not reprimanded because I was wrong, this is rather odd. At the very least as head of the team working on this at CTL, surely if there had been an internal enquiry I would have been involved with it. Perhaps you can see where the "collusion" terminology comes in. None of the senior staff at CTL wanted to deal with this in the early 1990s. In fact all 4 seniors that I sent confidential memos to detailing the Rose fabrication all left CTL in the months following my revelations. This included Lewis Smith (Paraquat Product Manager, Section Head Biochemical Toxicology and my own line Manager), Rod Morrod (CTL Executive - Research and Industrial Toxicology), Stuart Jaggers (CTL Executive - Regulatory Toxicology) and Gerry Oliver (Section Head - Metabolism and Pharmacokinetics, Chair of the Emetic enquiry team in 1991). Mike Rose had already moved from Alderley Park to ICI Specialties. It was almost as though the" kiss of death" came with my September 1990 memo to Lewis Smith. You can imagine how I felt about all these departures at the time. I didn't want to go above my station and discuss the matter directly with Geoff Willis and Bernie Hart at Fernhurst and had been advised not to. The only remaining person that was aware of this was Iain Purchase himself, the CTL Director.

Back in 1990, I was reassured by Lewis Smith that he would inform Agrochemicals. This was in a signed memo I have in my files. However, Lewis told us at our Jealotts Hill meeting on January 15th this year that he had not passed my September 1990 memo on to Agrochemicals. Lewis and I never had a crossed word on this emetic matter over many years. It was always a bit difficult since Mike Rose was Lewis' PhD supervisor, Line Manager at the time and Mentor. Lewis has always backed me on the development of Magnoxone with 5 X emetic which he fully supported when he returned to CTL a few years later and later on the development of Inteon when he was Head of Development in Basel. I met up with Lewis after our last meeting at Jealotts Hill in January this year and he promised to come to see me at DTL on several occasions to go through all this. However, he has chosen not to do this despite being just 12 miles up the road and invited on more than one occasion.

As you all know, this new 2018/19 mission I have on the emetic began last year following DTL winning a 3 year contract with Public Health England to look at paraquat decontamination. This led me to review the current FAO spec for paraquat which I noted still contained the Rose 1977 ineffective concentration of emetic. My deliberations with Phil Botham and his colleagues was further spurred on by hearing that Syngenta had dropped Inteon (and not even bothered to inform me as the Patent Holder) and also the "One Sip Can Kill" article by Cal EPA on accidental paraquat poisonings in children.

My confidante, our Dean of Health, Professor Garner has encouraged me to pursue this, hence my renewed confidence during our conference call with you on May 3rd. He has reassured me that since I have probably more knowledge of the technical, pharmacological and political aspects surrounding the emetic than anyone else, that I would almost certainly be listened to by the Poisons Centre Experts and the Regulators. He also said he would happily get involved but, of course, could not be able to claim complete impartiality in a legal case, since he knew Mike Rose and was my own mentor at ICI Pharms, in the same way that Mike Rose was Lewis Smith's mentor at ICI CTL. When I showed Andy Garner your recent note about Syngenta endorsing Rose only using the "even dosings" of emetic so the 3mg could be conveniently be left out because it spoiled the dose response curve, he used words a lot stronger than "fabrication".

Anyway Dave, it is really useful to have your formal Syngenta position challenging my "assertions" on the emetic that I suspect will be used by Syngenta to defend the emetic concentration that was added to Gramoxone back in 1977. I would like to provide you with my own response to your position document and explain what I intend to do (and have done already).

As I documented to you on May 16th 2019, I am concerned about 3 important areas that you have ignored in your position document. I have raised these on each occasion at my meetings with Syngenta during the last 6 months, but either you and your colleagues feel they are not important to comment on in relation to the emetic added to Gramoxone, or perhaps you all believe they are not relevant to the case. These are as follows:

1. **Pharmacology of PP796 and ED50 values in pig, dog and monkey compared with man**

2. **The origin of the actual minimum level of PP796 in grams/L, as stated in the FAO specification**

3. **Registration of Gramoxone Plus in France in the 1980s with an equivalent 6 X increase in PP796**

For the first point, it is quite odd that the comparative pharmacology has not been referred to in the Syngenta position document. There is a wealth of information on the emetic dose response to PP796 in pigs, dogs and monkeys with good group sizes and good estimates of ED50 values. There are no physiological grounds to say that human would respond differently with a centrally acting emetic and certainly no evidence that humans are 10 X more sensitive to the drug, compared with the 3 other vomiting species, as used in later Company external documents used for EU re-registration purposes. The data speaks for itself. I have proposed all along that the predicted or estimated ED50 in man would probably be similar to that obtained in the animal studies. The 2mg dose given to human volunteers was used in the disease trials because this dose did not cause vomiting in the normal volunteers, neither did the higher dose of 3mg. Even the comment by Rose that tablet or diet administration would be "more slowly absorbed" than liquid in Gramoxone is overturned by the fact that the dogs and monkeys were gavage dosed. You cannot derive even an approximate ED50 in man from the human data summarised by Bayliss, even by mixing and matching various clinical trials, ignoring the time to emesis and using a single person that vomited at 4mg as the basis for a curve fit. Therefore, why not at least begin with the animal data as a reasonable position on what a predicted ED50 in man might actually be? At least Rose was confident to do this and used the dose response curves in animals in CTL/R/390 to position the human data in parallel to it, albeit by constructing his own human dose response curve and then his "estimate" an ED50 being 10 X lower in man than 3 other vomiting species. He may have falsely claimed the emetic was 10 X more potent in man, but at least he didn't ignore the animal data which is conspicuously absent from the Syngenta position document.

2. **Point 2 The origin of the actual minimum level of PP796 in grams/L, as stated in the FAO specification**

Throughout our discussions and Kim Travis' report there was no mention of the actual concentration of emetic that is required by the FAO spec. It was mentioned in our telecon that this varies between territories. Yes it does. The Australian and Japanese registration documents show this. The end user product with surfactants has a concentration of emetic relating to the paraquat ion, often quoted as a % of the paraquat concentration or a g/L value. The main FAO spec has a value for the TK and this is a minimum of 0.8g/L. No-one in Syngenta has explained to me where this value has come from or the other values for the SL, WG etc. My view is that they all line up to the ineffective 400 paraquat : 1 emetic ratio. I claimed that the 0.8g/L for G Max (or 0.5g/L for G 200) was based on the Rose CTL/R/390 report. Am I correct or not? Do you have an alternative explanation as to where the values in the FAO spec come from? The other mystery is the text in the FAO spec not actually mentioning anything to do with the "minimal lethal dose". This is why there is a subtle difference between the Rose text and the FAO text. Rose came up with a concentration that he "estimated" would be effective in the "majority" of people ingesting a "minimal lethal dose" i.e. 10ml Gramoxone. The lethal dose of paraquat in man, of course, is widely known and not an estimate. Ohno and others have the LD50 very close to 3 grams of paraquat ion to an adult human. The other wording in the FAO spec such as "in at least 50% of cases" I presume originated from Rose where he changed the term 70% of cases in the original report to "the majority" of cases i.e. at least 50%. The issue of a minimal lethal dose is absent from the FAO since the Rose concentration was not supported by the data in CTL/R/390. The ICI unpublished data in the Meredith and Vale paper fits with the percentage vomiting in the cases that were estimated to be ingestions within 30 min. This data came from the unpublished UK monitoring exercise on Weedol poisoning, sponsored by ICI. This is all very concerning as we discussed in January, that 0.5g/L had been added to Gramoxone for 10 years before the Meredith and Vale publication. Many years later, the company were surprise, surprise, meeting the FAO spec and still using the very low concentration of emetic estimated by Rose. You can really see why no one wanted to look too hard at all this.

This is almost as misleading as the SDS information on paraquat where the GHS hazard classification for Gramoxone liquid herbicide is only Category 4 for oral toxicity i.e. LD50 above 300 mg/kg, Category II in the US EPA RED and an oral LD50 of 1098 mg/kg. I realise that this relates to volume of product and rat which is a much less sensitive species to paraquat. Considering the safety relates to the human use of paraquat where the LD50 is considerably lower, by at least an order of magnitude, this is again another example of misleading public information from Syngenta on the acute toxicity of paraquat.

3. **Registration of Gramoxone Plus in France in the 1980s with an equivalent 6 X increase in PP796**

My French paraquat file is almost as large as my Japanese one for the Preglox introduction. I have lots of memos between Fernhurst, CTL, ICI SOPRA in France, Chantel Bismuth , Prof Rico etc in the 1980s. The bottom line here is the registration of 2 high emetic level French formulations that were introduced in the mid-1980s. This followed a similar strategy in Japan with one a paraquat solo at a more dilute 100 g/L and the other had a diluted paraquat and diquat in the product. The major difference is the French formulations had a high emetic loading whereas the early Preglox products had a pro-rata lower level of emetic in line with the paraquat content. The French paraquat solo product (AV 8700169) was tested at CTL by my team. This had 1.5g/L emetic and performed very well in the dog at 2 high doses, with prompt emesis events within 20 mins of dosing, no vomiting thereafter and an estimated 10 X safety factor in dogs, compared with Gramoxone with 0.5g/L emetic where emesis was beyond 1 hour or not at all with 100% mortality. Obviously, decisions had been made between CTL and Fernhurst to make this uplift to the emetic concentration with minimal publicity. Why would ICI Agrochemicals do this? Are we suggesting that such a manoeuvre would improve the safening of the product? After all, there was a real problem with paraquat deaths in the French colonies in the 1980s and Prof Rico was going to ban it in France (which he ultimately did). Why have Syngenta continually ignored this with me? Perhaps it is because it overturns the issue of prolonged vomiting in poisoning cases with very high emetic levels which doesn't occur with prompt effective vomiting ahead of any gastric irritation caused by the paraquat surfactants. I have memos on this but surely you have an archive with records of exactly why ICI did this at the time and what the outcome was with an improvement in survival following the introduction of Gramoxone Plus? Of course, the cost of this manoeuvre globally would have been enormous. This is central to the issue of what is an effective emetic concentration in man and also supports the introduction of high emetic to improve survival rather than causing this uncontrollable vomiting that keeps getting mentioned to keep high emetic products off the market. I have always maintained that dilution combined with 3 X emetic would be a much more registerable product if Syngenta were not going to develop Magnoxone with 5 X emetic. It just needs that xanthan thickener (AV 8700169) or acid-triggered gelling agent (YF8004A) to go with the emetic uplift in a 100g/L formulation.

In addition to these 3 areas that do not form part of your position document, I have some new information following discussions with colleagues in Pharmacy here at Keele University. This was following our telecon on May 3rd.

Adaptive effect of the 2mg dose of PP796 in patient trials

We have several clinical pharmacologists in our School of Pharmacy here, where I am based. They organise patient trials on Campus and at the University Hospital of North Staffordshire. Without discussing the background or paraquat itself with my colleagues, I raised the issue of a potential

“adaptive response” with a drug and whether it is correct to use an individual patient effect only on first dosing (as per the Rose 4/37 or the Kim Travis 3/19) or to consider all the doses over a period of time in the same patients. I also posed the question on the impact of taking a new drug that causes nausea or vomiting when administered for the first time and then the patient being somehow de-sensitised to emesis following further dosing. I am afraid to inform you that the consensus was that each event (taking 2mg of drug) addresses the hypothesis as to whether a 2mg emetic dose causes vomiting, as opposed to restricting it to the first event only. They therefore agree with me that there is much more evidence as to whether 2mg causes vomiting by adding up all the events across all the patients. You can obviously analyse it by individual patient but there are over 1300 dosings of 2mg across all the human trials and this dose does not cause vomiting in man.

Here is the Pharmacy rationale. Firstly, unlike Ipecac which primarily causes vomiting via irritating the nerve endings in the gastric mucosa, PP796 is a centrally-acting phosphodiesterase emetic (as required by the FAO spec). It is very lipophilic and absorbed from the GI tract very rapidly. Once in the bloodstream, it can easily cross the blood-brain barrier and its phosphodiesterase mechanism of action elevates cAMP in the vomit centre of the brain. If the drug is given at a sufficiently high dose it will trigger vomiting as soon as the local drug concentration in the vomit centre has reached the trigger point for emesis. It will do this every time it is administered. It is extremely unlikely that there would be some sort of adaptive response in man. If the drug is at its therapeutic concentration in plasma it will trigger vomiting each time it is administered…..unless, of course, the dose given does not cause vomiting and 2mg did not cause vomiting in the volunteer trials and was a very rare occurrence in more than 1,300 dosings. One colleague went on to mention that patient trials are much more challenging than the student volunteer trials. Patients with various diseases are often already on medication and when faced with a new therapy and unsure of what is likely to happen they will often initially record symptoms such as nausea. Clearly the 2mg of PP796 does not cause vomiting at the frequency you claim with your new analysis or Rose claimed at 2mg in 1976. This was the largest group size in the volunteer study and yet it was replaced by Rose with his 4/37 value. In fact, why would ICI Pharms have tested this dose in the patient trials if nausea and vomiting was such a prevalent effect or indeed not stopped the trials if this was a significant side effect at 2mg?

With regard to “adaptive” effects, there are certain drugs that clearly do this, often over a period of days or even weeks. These include liver enzyme inducing drugs. Alcohol Dehydrogenase, for example, can be induced by repeated alcohol intake and an adaptive response can occur. The triazolopyrimidine emetic is an enzyme inhibitor not an enzyme inducer. If the incidence of vomiting on first dose at 2mg was real then this would have occurred following subsequent dosing at 2mg. If anything, any residual drug not metabolised after each dose would only make it more likely that the patient would vomit at the next dose, since they would be adding to any effect with the next dose. Furthermore, if the patient had nausea and perhaps even vomiting the first time they had the drug they could be sensitised to this and have the same symptoms again when they took the next dose rather than what you propose as some kind of adaptive response that would make them less likely to vomit. I therefore do not agree with the “adaptive response” theory. A pharmacologist’s input to this would have been prudent before dismissing the hundreds of dosings at 2mg as irrelevant. I am sticking to my opinion on this that the 4/37 or 3/19 which creates this nice threshold part of the human dose response curve between zero and 50% is not scientifically valid for the 2mg dose of PP796. Rose was quite smart on this and he simply drew a line after the first 37 individuals then ignored everything after that including all the multiple dosings. His parallel sigmoidal curve right between pig and monkey could be drawn through 11% for the 2mg dose and exactly through 70% for the 5mg dose, so 4/37 did nicely.

Do you not understand why I have used the term “fabrication” rather than say “grossly misleading”? I stand by my position that the sigmoidal curve of 11%, 50%, 100% in man was constructed or fabricated to make it appear as a classic dose response. Your comment about only using the even doses and leaving out the zero vomiting at 3mg, in addition to zero vomiting at 2mg in the volunteer trial that the other data is based on, is really going too far. After the cherry picking at the 2mg dose, the basket is already full of cherries with the replacement of other doses and ignoring the time to emesis of 2h at 8mg. You are getting as bad as Rose with omission of unwanted information at 3mg that would spoil any relationship between dose and response! This really worries me as a Toxicologist that Syngenta would condone what Rose did on this.

I take it that your colleagues in Product Safety are also happy with this deletion of the zero incidence of vomiting at the 3mg dose and the other manoeuvres to make the dose response look palatable, since I assume you have had your position document reviewed internally before you sent it to me?

With regard to motivation to make it appear that the emetic was 10 X more potent in man compared with dog, pig and monkey, I have already given my personal opinion on this backed up by Rob Morrison’s challenges at John Finney’s TRC meeting on the cost of the emetic in the 1990s. I agree with you that Syngenta has always had a high regard for safety of its products. The new moves for closed systems may help reduce human poisoning in the developed territories but I cannot see this being widely rolled out in the smallholder farming communities in the developing countries (as per The Guardian Newspaper reports on paraquat in the 3rd world and those of the Pesticide Action Network).

You must focus on the challenge I made in 1990 on the Rose report and the original decision back in 1977 when the emetic was first added to Gramoxone. This may have been an “estimate” but it was based on a fabricated human dose response curve to make it appear that humans were 10 X more sensitive to the emetic than 3 other vomiting species. The proof is there for everyone to see, it did not improve survival since any earlier vomiting was either too late or ineffective. Kim Travis’ report does nothing to sway my views on this. You may have done a more thorough evaluation of the 1970s ICI Pharms human data in 2019 and presented it in a slightly different way to Rose in 1976 but there is still no dose response and you cannot derive any dose that would cause emesis in man. Obviously, Syngenta have got to find a way of supporting the Rose position due to the seriousness of the situation and any legal challenges that may arise going forward. Otherwise, as the CTL Executive Team told me this is not only a serious reputation issue for CTL but for the Company as a whole, if the Poisons Experts and Regulators agreed that the human dose response was fabricated and this was used to gain or preserve registrations.

I realise that I have provided quite a detailed response in this cover note. Just when you thought the bugger had written enough about this I have also inserted a considerable number of comments into the Syngenta position document so they are below each topic you have mentioned. Apologies again for the detail and in some case repetition of what is in this cover note. However, when you have over 25 years working in this area and the considerable politics surrounding the emetic there is a lot to consider. Again if there is anything here you wish to challenge me on either in this cover email or within the document itself (as attached) do let me know. As I have opened a dialogue with California Poisons Center and this will be referred on the Federal EPA Office of Pesticides. Please understand that I am not trying to have paraquat banned globally I just want to see poisoned victims, particularly children, survive if they inadvertently swallow a mouthful of paraquat concentrate.

Yours faithfully

Jon Heylings

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Subject: Response on behalf of Syngenta

Dear Jon,

Thanks once again for our additional discussions on Friday last week. As agreed, please find attached my response on behalf of Syngenta in relation to the matters you have raised.

We remain open to dialogue should you have further questions or new information to discuss.

Kind regards

Dave French
Global Head Regulatory, CP
Ad-interim Head Product Safety

PARAQUAT AND PP796 – Received from Dave French Head of Global Regulatory and interim Head of Product Safety on May 10th 2019

Response from Professor Jon Heylings, Chairman and Chief Scientific Officer, DTL Ltd on June 6th 2019 in red text

As you will already appreciate we take your current perspectives and the extensive inputs you have made about the level of emetic (PP796) in Syngenta's paraquat products very seriously. Safety is paramount to Syngenta. In the intervening months since we began this dialogue last year, we have had multiple discussions and face-to-face meetings with you involving both current and predecessor company employees, and have thoroughly investigated your concerns. Syngenta continues to take an industry-leading approach to the stewardship of paraquat.

Syngenta and many others have extensively evaluated and tested various ratios of emetic in paraquat over many years. At times, this approach was combined with the use of solid (granular) formulations and thickening agents.

Yes, including Preglox in Japan in the 1980s, where the emetic concentration was initially lowered from the 0.5g/L. to the pro-rata % concentration now 4.5% paraquat ion. This offset the high cost of the new diluted product in the 1980s. I went through the ICI Japan poisoning statistics with Lewis Smith in August 2006. There was a measurable improvement in survival from 25.4% (n=67) to 41.7% n=24) simply by the dilution effect. I have the full report that Robin Birtley sent me at the time since we had an issue with the Korean RDA on the management of this issue and we used the Japanese survey with them. I went over to South Korea myself and we kept the product on the books by informing of what we were doing with Inteon to further improve safening. Reducing the ratio of paraquat to emetic improves survival. In response to many deaths in Ireland, ICI introduced Weedol and Pathclear as a granular formulation in the UK and Ireland with higher ratio of emetic to paraquat. The poisoning statistics fell accordingly. Why did ICI Agrochemicals (via ICI Sopra France) increase the emetic 6 X equivalent to standard Gramoxone SL 200 in the newly registered Gramoxone Plus product in the 1980s? This improved survival and was used to try to maintain the registration with the Commission des Toxiques. (I was given the Emetic Correspondence File when Lewis Smith left CTL, as the Research Lead Scientist developing Magnoxone. This file contains many memos between Professor Rico, Chantal Bismuth, Bernie Hart, Lewis Smith, Geoff Willis etc. on the French strategy to increase the emetic in a bid to save this registration that was about to be lost).

The formulations sold by Syngenta are based on this extensive body of research (some of which is discussed below), and these formulations contain the ratio of emetic most appropriate in addressing the risk of ingestions, particularly when combined with dyes and odours. We do not agree with your suggestion that an elevated ratio of emetic would be

more appropriate in these circumstances, and, indeed, believe that your suggestion would result in a product which is likely to create more risk and injury in the event of an ingestion.

Perhaps you can share with me any evidence that increasing the emetic from 0.5g/L to a higher level has resulted in "more risk and injury in the event of an ingestion"? Do access the Gramoxone Plus poisons survey data. Also don't forget the title of the Wilks *et al* publication "Improvement in Survival…." This whole argument about treating uncontrollable vomiting is completely irrelevant when it comes to a child taking one sip of Gramoxone. Who are we trying to save the suicide victim who drinks a pint of product or the unsuspecting child taking a sip of Gramoxone?

Do you not realise that the "extensive body of research" on the ratio of emetic was largely conducted at CTL by my own group. You seem to ignore my experience of more than 20 years where I not only tested multiple concentrations of emetic in Gramoxone, but led projects on multiple emulsions, granule forms, microemulsions, microcapsules, SDS gel forms, Gramoxone Max, Gramoxone Plus, Magnoxone, several versions of YF8004 which led to Inteon etc. There is a lot on this I have yet to share with you. One example, is my first encounter with paraquat back in the mid-1980s. I attended a TRC meeting at Jealotts Hill, chaired by John Finney. It was agreed that CTL should test the acute toxicity of the new Multiple Emulsion technology developed by Tharawat Tadros at Jealotts Hill and that all the candidate formulations should contain an equivalent 6 X level of emetic to Gramoxone (equivalent to the French "safer" product). This would be a 100g/l PQ ion with 3X emetic. Over the next few years until I tracked down the rationale of why Agchem were doing this all the paraquat products tested at CTL (and there were many) contained this emetic uplift including the 200g/l development candidate that contained twice this new emetic level. Please tell me why ICI and then Zeneca would want to develop a new high emetic product when this is "likely to create more risk than injury" and add a significant amount to the cost? Bit odd unless they knew there was a problem with the 1977 decision! My inquisitive mind led me to trawl through the old files and that's where I found Mike Rose's lab book with his crossings out and hand drawn dose fabricated response curve. I was intrigued as to why standard Gramoxone contained 0.5g/L emetic and wanted to know where this loading had originated from. It was pretty obvious when we ran studies with standard Gramoxone at 0.5, 1.0, 1.5, 2.0 and 2.5g/L emetic in dogs. It was only when you got to 2.5g/L did you produce prompt emesis that was early enough to prevent lung toxicity and death. Doses below this were ineffective at causing emesis and preventing death as had occurred in man over the previous decade. Of course Rose clearly thought that the emetic was 10 times more potent in man so he could advise only putting one tenth the effective amount in Gramoxone!

We also flatly disagree with any suggestion that in developing this product that Syngenta and its predecessors would have had any motive other than to find the most appropriate level of emetic in paraquat to best address the ingestion risk; Syngenta's primary focus is always to create products which are the most safe and effective.

Paraquat has brought in millions of dollars over many years and I hopefully, have played a key role in the product's success by assisting with the influencing strategy and helping to

maintain the registrations of the product myself in my numerous meetings in the UK with visitors to CTL and my meetings overseas over 20 years, defending the product with Regulators and other Influencers. Despite this, I really feel that my views on the emetic are being treated with disdain, not just back in the 1990s but now by Product Safety. Over recent years, Syngenta have really pulled away from involving me in any capacity and not even bothering to inform me as patent holder for Inteon that Syngenta were withdrawing its registration. I can clearly see the rationale now. CTL has closed and the Inventor of the Inteon technology long gone. Rather than try to improve the safety of its products in the developing world where there won't be able to afford closed transfer systems, Syngenta have returned to registering its highly toxic product with as much paraquat in it and as little emetic in it. The FAO spec even allows the emetic level to be as a % of the paraquat ion, that is to say "ineffective" at both low and high paraquat loadings. The actual concentration of emetic in the FAO specification is based on the original Rose report. A point you won't confirm with me.

This cost-saving approach to the Agrochemicals business has not altered from the days that CTL tried to develop a much safer product than Inteon (3 X emetic) or with the Magnoxone technology (5 X emetic). It all boils down to cost and profitability. If you had been at the TRC meetings chaired by David Evans in the 1990s there was considerable reluctance from folks like Rob Morrison to add anything to the VPC of paraquat products with the higher emetic or dilution from 200g/L. Lewis Smith was a great advocate for increasing the emetic and between us we managed to get agreement from David Evans to develop the technology with higher emetic but only up to 3X. Of course, in later times with Lewis as Head of Development Syngenta were not going to drop this strategy in the 2000s. Now that we are both ex-employees of Syngenta you can do what you want on this without challenge from either of us.

I am sure the same cost sensitivities applied in 1977 as they do now. Addition of an emetic was a great idea, but the cost of what would have been an effective concentration to produce vomiting in a child drinking 10 ml of Gramoxone would have been very high to use in all the company's worldwide paraquat products. The cost of an effective dose of emetic as demonstrated in the vomiting species, pig, dog and primate was probably just too much for ICI Agrochemicals to bear. As Rob Morrison's calculations showed in later years, an effective level of emetic equivalent to an ED50 in the animal studies would have cost £30m per annum for the volumes ICI were selling, plus investment in new plant. I cannot prove the cost factor but let's see if others follow the logic of minimizing the emetic loading due to its cost.

Syngenta further believes that safety would be enhanced if there is an increased use of closed transfer engineering technology that seeks to prevent direct human contact with the product, an approach which also offers significant additional benefits for the user. Syngenta considers this to be an appropriate and targeted strategy to reduce incidences of paraquat ingestion. The engineering solutions for large scale tractor-based systems and for backpack/knapsack systems are being progressively introduced subject to external regulatory approvals.

The closed transfer engineering technology is “a step forward…but in the wrong direction” as one of my Poisons Experts explained. You keep going off track with the main hypothesis. Stick to the 1977 decision as Angela Brady would recommend. The issue is the decision in 1977 not what Syngenta are doing in 2019. Do you know how many deaths there have been from paraquat poisoning since 1977? Do you really expect the small-holder farmers in the developing world not to share Gramoxone concentrate and the product to still appear in unlabelled containers? The new technology may help the poisonings in the USA but the engineering solutions will not be affordable universally. This is another good one for The Guardian.

To systematically address what we understand to be your current claims:

You claim that the data in the Rose 1976 report were fabricated

You have raised concerns about the data from an analysis of clinical trials reported in an ICI 1976 research report, which you are concerned cannot properly be used to support the level of emetic in Syngenta’s paraquat products because it was fabricated. There is no evidence of fabrication associated with the 1976 research report and simply no basis to believe the author would have reason to fabricate results. In any event, this 43 year old study has long since been superseded by later studies of human ingestion incidents reviewed by global regulators.

I can’t think of a more appropriate word than “fabricate”. I guess you could use terms like “grossly misleading” but when something is constructed to make it appear plausible what is the best term to use? I think “fabricated” is quite appropriate here for the sigmoidal dose response curve that Rose drew through the points of 11%, 50% and 100% and exactly through 70% for the 5mg dose. The question is what is the basis for this being fabricated? To a pharmacologist it is not just the points on a curve it is the shape of the curve. A typical drug dose response is “sigmoidal” in shape. It has a threshold area where there is a significant effect that cannot be considered as “no effect”. An ideal sigmoidal dose response has some form of “maximal” response where all the replicates (or humans in this case) respond with the effect that the drug was designed to do. The ED50 or point at which it is predicted that half the population will respond is usually where the sigmoidal curve passes through 50%.

Conveniently, the Rose report has a table with 0, 11, 50, 100%. To the non-scientific members of the ICI Agrochemicals Board, Rose managed to convince them that the human dose response was sound and parallel to the animal dose response curves and indeed right between them. What Rose failed to mention was he had cherry picked the human data to construct the curve. Mixing and matching data from normal volunteers with patient data, omitting results that don’t fit, replacing results from one study with another, not mentioning the time to emesis, because it didn’t meet his own criteria, and ignoring the repeated use of 2mg (the largest group size in the volunteer study on which the rest of the data is based) that showed that 2mg was ineffective. This is by my reckoning a falsification of the true picture on the effectiveness of the emetic in man. As you know this was the focus of my letter to Lewis Smith in 1990. I stand by this signed memo and the signed reply

to me saying he did not intend to look into the dose response that Rose had presented to Agrochemicals.

You try to deflect this serious accusation I have made on the emetic. You keep missing the point, it is the 1977 decision that was based on fabricated data. It may have been "superseded by later studies of human ingestion" but the dose response was fabricated at the time and a lot of people have died from paraquat poisoning since. Mike Rose was a maverick and ran his own show as Section Head of Biochemical Toxicology. It is a single Author report and being a Research report was not subject to peer review or Quality Assurance audit. Lewis Smith sent me a signed letter saying he would "ensure the Agrochemicals Business were informed". Well we found out in January this year that he did not send my letter on to Geoff Willis et al. Lewis also informed me in a separate signed memo that he did not intend to look into the origin of the Rose human dose response in CTL/R/390 and the original decision to only add 0.5g/L emetic to Gramoxone. I have sent you all these signed memos over the last 6 months, but let me know if you need them once more. The originals I have could be important pieces of evidence. There are lots more signed memos in my files including a key one I have not shared with you from Geoff Willis to me preventing any communications on the topic with any staff both inside and outside the Company without his personal approval. I guess this does not apply to former employees of Syngenta, but he was never a man to cross was Geoff!

Although the basis for our conclusions do not depend upon this old study, we nonetheless disagree with your challenges to it. The report you highlighted, CTL/R/390 [subsequently revised as CTL/R/390(R), 1977] summarised existing data from clinical trials with PP796 alone. The report presented an analysis of the data originally reported by ICI Pharmaceuticals (Bayliss PFC, Report no. PH20992C, 23rd July 1973) rather than the brief selected extracts which were provided to you by the ICI Pharmaceuticals library on 25th January 1990. 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.

The CTL/R/390 report was amended in February 1977, since Rose got carried away and the original version issued in October 1976 that said "70%" would vomit with his 0.5g/L emetic addition. He toned this down, perhaps asking a bit too much of his fabricated curve to "the majority" in the (R) version of CTL/R/390. This was circulated to many seniors in the ICI Business so it would have been mighty embarrassing if it had been re-issued again. I take the point that this was an "estimated" dose, However, Peter Slade turned this into this being "crucial" to getting the correct dose in his EDC Board paper of 1976 on the introduction of the emetic into global paraquat products. As you all know the infamous Rose report is even cited in the open literature as the key piece of evidence for an effective dose of emetic in man. Note this has moved up a gear from an "estimation" to being "crucial" in other documents. Internal reports should not appear in the literature, but of course Rose wasn't going to attempt to publish this since it was based on just a couple of people

vomiting and a fabricated dose response curve. He would have been shot down in a peer review, a bit like the position you guys are in now trying to defend the indefensible!

I do not accept that I had only brief selected extracts of the clinical data. I send Kim the selected extracts since it summarised the picture as I had this bound by ICI Pharms Reports Centre in 1990, when we were still all part of ICI. I wanted the Bayliss extracts in an "official" Category C Report cover, due to the seriousness of my allegations in 1990. I have other background clinical data on the emetic in animals and man, including the repeat dose in patients with various diseases which I will come to later. In fact, I cannot see any additional clinical data in either volunteers or patients that adds to the Bayliss Summary I sent Kim Travis. As far as I am aware, there is no other human data on the emetic since it was dropped as an ICI Pharms development candidate drug.

While it is not possible to confirm with 100% certainty the way in which Dr Rose considered the limited data set partly because Dr. Rose is deceased, our recent internal review of the complete clinical data suggest that another plausible interpretation of his approach was only to use doses which represented approximately 2-fold increases between doses in order to derive an estimated dose response (hence the omission of the data at 0.04 mg/kg and the use of the data for the 0.03 mg/kg dose extracted from one of the other clinical studies).

I do find this a bit of an insult to one's scientific integrity. You are really standing on thin ice now with this assertion that the ineffective 0.04 mg/kg can be disregarded on the basis of only using 2-fold dose intervals (as Rose did) when it forms part of the data set from the same volunteer study that the rest of the dose response is based on. I cannot believe you would contemplate this as a "get out of jail" ploy in 2019. Your cherry picking basket is already full of cherries. This is almost as bad as Rose, by defending him on this and not mentioning the missing doses that don't fit the sigmoidal curve. "Unbelievable", was a comment made by Professor Garner when I showed him this paragraph.

In addition, our review has concluded that incidence should not be based on multiple dosing of the same patient (your contention to support an incidence rate of only 0.3% at 0.03 mg/kg) but only on the <u>first</u> dose of PP796. The reason for not considering the results for a single patient dosed on multiple occasions with 2 mg (0.03 mg/kg), and incorporating all dosing events into the overall dose-response assessment as independent observations, is that these observations are not independent because they are for the same patient. In addition, in the trial by Eccleston at Edinburgh it was noted that patients receiving 2 mg of PP796 three times a day for 21 days experienced nausea for the first 3-5 days, which subsequently "*wore off with no intervention*". This is suggestive of an adaptive response which, if it occurred, would further invalidate the consideration of emesis after multiple doses when estimating the dose-response of a single dose of PP796.

I do not agree with you. Rose not only replaced a perfectly good "no response" in the normal volunteer study for 2mg (which was the largest group size in the volunteer trial) but replaced it with responses on patients with various diseases basing it only on the first dose. Your argument about "adapting" to the 2mg according to my Pharmacy colleagues is complete nonsense. If a patient takes a drug at an effective dose, why would the

pharmacological effect wear off when the drug is cleared from the blood and they take the same dose the next day? The mechanism of PP796 is not like Ipecac which irritates the nerve endings in the stomach lining. It is a centrally-acting emetic (as specified in the FAO). Once absorbed into the blood, and being lipophilic, this occurs very rapidly (we measured it at 5 mins post dose) it crosses the blood brain barrier and once in the vomit centre in the brain the phosphodiesterase inhibitor elevates cAMP to a threshold point where it triggers vomiting. Each time a dose of PP796 is given there is no reason at all why a subsequent dose would not do the same. The emetic is an enzyme inhibitor not an enzyme inducer. I am sorry but I do not concur with your "adaptive response" argument. The 2mg dose of emetic in over 1300 dosings does not cause emesis in man, as demonstrated in the much more relevant normal human volunteer study. My Pharmacy colleagues explained that a new tablet to a patient already on medication and in an experimental trial is more likely to record symptoms such as nausea during the first few days. Once this has settled you observe the effect new drug is doing. In the trials with multiple dosings, the 2mg certainly doesn't even cause nausea never mind vomiting. Sorry, but you can't wriggle out of that one either. They may be independent observations by patient (and not even correctly collated by Rose) but on the hypothesis based on whether 2mg does or does not cause emesis in man the answer is "no". Funnily enough that agrees with the original volunteer study too!

Regarding the omission of the data for 8 mg/kg, our review has concluded that this may reflect Dr Rose's focus on the one hour time period. Contrary to your assertion, there is in fact no reference in Dr Rose's report to the significance of emesis within 30 minutes.

The single volunteer that was given 8mg did not vomit until 2 hours and it is stated in the Rose report that his "estimation" is based on vomiting within 1 hour. By my reckoning 2 hours is later than both 30 mins and 1 hour. Rose cleverly kept this 100% (or 1/1) as the top point on his fabricated curve. It would like mighty thin without it. He does not discuss this late vomiter in fact ignores the fact that it was 2 hours in his report. Conveniently it pops up in Kim Travis' report, although Kim did qualify that his curve relates to any vomiting time and that a meaningful ED50 cannot be ascertained, even with all the mixing and matching of data. Not much use if a child swallows a mouthful of Gramoxone and the peak plasma paraquat level occurs prior to vomiting! This leads me on to another key piece of evidence I presented in 1990 on this timing of vomiting. Our extensive dog studies showed that the peak plasma paraquat levels (independent of dose are around 1 hour after oral dosing (capsule or gavage). This CMax is very consistent up the doses with Gramoxone. Once this has happened you either die rapidly or more slowly with pulmonary failure depending on volume of Gramoxone ingested. Both Lewis and I realised that the emetic must not only be rapidly absorbed orally but reach a plasma (and brain) concentration that will trigger the vomit centre before the peak paraquat blood level. In simple terms the critical factor is the ratio of paraquat : emetic in the dose that is ingested. If this ratio is too big as judged in 1977 at 400 :1, the vomiting may occur relatively early, but paraquat will have already reached a level in the blood that will ultimately be fatal, depending of course on the volume and concentration of the paraquat that has been consumed. In the Rose era there was too much influence on the rat plasma paraquat profile. This is completely different to higher

mammals including man. After an oral dose of Gramoxone in rats the plasma level rises over 24-48 hours. It was thought that emetic in the product and even emetic intervention would help. Alas, no. The CMax for paraquat occurs very rapidly in higher mammals so the only way the emetic going to benefit is to ensure it reaches effective concentrations in the blood as quickly as possible. This is very different to the use of emetics several hours after a poisoning where the paraquat and surfactants have severely irritated the gastric mucosa and you get the classical uncontrollable vomiting that the clinicians have observed, particularly in high ingestion suicides.

Rose may not have been aware of the difference in plasma paraquat kinetics back in the 1970s when all the acute toxicity work was done in rodents. Therefore the late vomiter at 2 hours perhaps did not concern him too much. However, Lewis and I agreed that the new data from my group showed that the emetic has to work within 30 minutes and be at the correct ratio with paraquat. Of course my invention with acid triggered gels allowed more time for the emetic to work and kept paraquat (but not the lipophilic and rapidly absorbed emetic) in the stomach longer so you end up with more time for effective and productive vomiting of a semi-solid. Same applies to the French thickened system. Effective ratio (67 not 400) and product remaining in the stomach longer = better chance of survival.

Magnoxone with the higher emetic to paraquat ratio would have worked much better than Inteon that had less gel and only 3 X emetic. However, if you look at the Wilks investigation you will see that there was a statistically significant improvement in survival across each band of ingestion volumes. What we will never know from the Sri Lanka exercise is just how many poisoned victims didn't actually make it to hospital, not because they died, but because their symptoms were mild and they survived without treatment. The same applies to the "Time Trends" exercise where even Martin Wilks agrees that there was still an improvement in survival with Inteon, just it wasn't statistically significant due to the smaller numbers…very convenient for Syngenta to drop Inteon! Interestingly, Janice McFarland did not reply to me on the evidence for the statement saying that Inteon did not work.

ICI and Dr Rose had no conceivable motivation to falsify or fabricate this 1976 analysis, the voluntary actions of the company were clearly directed to improving survival. As you already know there was no suggestion in any of the 1990 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'.

If you had ever met Mike Rose (as I have) you may have reached a different conclusion. I agree we shouldn't pass judgement on the deceased. However, he did his own thing, was highly outspoken and of course, was Lewis Smith's PhD supervisor, line manager and Mentor. What would Lewis do when faced with a memo from one of his staff, Jon Heylings making very serious allegations about Rose? Lewis' memo back to me not only falsely informed me that he would pass this information on to the Agrochemicals Business, but also that he would not be taking any action on my allegation of fabrication or how the human data in the Rose report had been arrived at. What does this tell you? Lewis chose to support me and the Magnoxone development but not to do what we are all doing in 2019 and looking at the human data again and the decision to add only 0.5g/L emetic to Gramoxone.

Because nothing was done to address the situation in 1990, including a severe reprimand for my accusations, I began to realise that there had been serious errors of judgement. Lewis decided to leave CTL in the following months so I took the unresolved issue to the CTL Executive. They were quite shocked at my findings and I was promised an internal and confidential enquiry. Stuart Jaggers (Head of Regulatory Toxicology) appointed Gerry Oliver (Section Head of Metabolism) to chair the enquiry with Bob Scott (paraquat product manager) and myself. Following some quite heated discussions within the CTL Bipyridyl project team, Gerry Oliver failed to report on the Enquiry and left CTL. I then had further discussions on the matter with Stuart Jaggers and Rod Morrod on how to deal with this. Again, I was never accused of any wrong-doing. The problem was no one could handle the situation and within a short time both Stuart and Rod left CTL. I was left with just the CTL Director, Iain Purchase as the only member of the company who was aware of the matter. We were now in 1991/2. Since this was a CTL issue, I did not want to expose CTL as covering this up by discussing it with Geoff Willis or Bernie Hart etc at Fernhurst. Iain also agreed with me that mistakes had been made but the advice was to keep Magnoxone moving through development since it had 5X emetic and everything would hopefully be OK. The strategy was to develop a high emetic formulation as opposed to raking over the old coals and, of course, making CTL look rather incompetent to the Agrochemicals Business. This is where the term “collusion“ rears its ugly head.

Having gone through quite a stressful period as a relatively junior Work Group leader criticising senior ICI management of fabricating data my career actually advanced quite rapidly in the next 12 months. I was not only promoted twice but took over Bob Scott’s area with 7 more direct reports in addition to my paraquat research group, appointed Deputy Section Head and things look quite good as we moved into the Zeneca era. Iain Purchase and I had a number of discussions on paraquat up to his retirement. The most memorable in 1993 was an all-expenses paid trip with wives to Bermuda where I was educated on “risk” by Iain.

I have very fond memories of ICI, Zeneca and Syngenta and in particular the support from Agrochemicals to develop and launch a safer paraquat product incorporating higher emetic. Despite all these new deliberations that we disagree on I still treasure my Syngenta Award I received in Basel from Rolf Furter for my work on safer paraquat formulations. It is somewhat of a shame that you guys are wrecking it all after all these years by defending the Rose position and his level of emetic in the FAO spec and getting rid of Inteon without considering how a new version could be developed and not trying to use all the knowledge we have on safening the formulation to prevent particularly the accidental poisoning that still occurs throughout the world.

Indeed at no time that we are aware prior to 2018 did you, or anyone else, ever make such a serious allegation. The original research report was never re-issued, revised, retracted or withdrawn by CTL prior to the laboratory closure in 2007.

Of course the report wasn’t re-issued after its first amendment in 1977 (see above) and every enquiry set up was disbanded or failed to report. The Rose report was even in the citations of publications. How could it be re-issued? It was all carefully covered up instead.

Even Phil Botham admitted that the matter had not been handed down through successive Senior CTL management. It only reared its ugly head when the EU Re-registration came up in 1995 when I was asked to comment on the ED50 of the emetic in man by Andy Cook's in his draft EU document on the emetic which contained the same fabricated data (as I have already explained in earlier emails) and the statement that the emetic was 10 x more potent in man compared to 3 vomiting species. I just had to speak out then for my own scientific integrity. However, as you have seen in my emails earlier this year, I received no response from Andy Cook or martin Wilks etc on my accusations about the Rose fabrication in 1995. I would not be party to a cover up that was obviously going on within CTL. In fact, the EU registration Annex with the fabricated Rose data on the emetic in 1995 clearly demonstrates that Agrochemicals Regulatory staff were still unaware of the true facts.

On the basis of the new statistical analysis which we discussed with you in January 2019, it is completely understandable why, on the basis of a limited data set, Dr Rose and Dr Nicolls jointly reached the judgement that they did.

You may think so. My reading of the situation is the new analysis reaffirms that there is a problem and no effective dose of the emetic in man can be derived from the Pharms data. Dr Nicholls is not a co-author on the report and was probably never aware of its final content or implications for paraquat safety. As far as the new statistical analysis is concerned there is still no scientific evidence as to what an effective dose of emetic is in man, despite the way the modern analysis and this position document has tried to defend the inclusion of data that fits a sigmoidal dose response curve and exclusion of data that does not.

In the interests of transparency Syngenta has also provided you with a copy of the report of the new (2019) statistical analysis of the limited human clinical data from ICI Pharmaceuticals. In summary we do not concur with your assertion that the data were fabricated or falsified.

It is probably better to let the California Poison Control System (CPCS), US EPA and other Regulatory Authorities make the call on this when they review my report and ask Syngenta questions on the content of the September 1990 memo I sent to Lewis Smith on my allegation that the decision to add only 0.5g/L emetic to Gramoxone was based on a fabricated human dose response in a report authored by Dr Mike Rose at ICI Central Toxicology Laboratory.

You assert that the Rose data forms the basis of all subsequent decisions on the level of emetic in paraquat-containing formulations worldwide, as well as the current FAO recommendation

We disagree. There have been extensive reviews and evaluation of emetic concentrations since 1976 which create a substantial independent record for the conclusions on paraquat.

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 granular formulations without the olfactory alerting agent.

The resulting UK human monitoring data were subsequently published (**Meredith, T.J., and Vale, J.A., 1987, Treatment of paraquat poisoning in man: methods to prevent absorption. Human Toxicology 6, pp 49-55**) and later by Bismuth and Hall. It is this published human poisoning data which supports the current (2008) FAO 'emetic clause', i.e. "*Emesis must occur in about half an hour in at least 50% of cases*". The Meredith and Vale publication reports that, overall, 65% of those drinking a paraquat formulation containing the emetic vomited within 30 minutes and, with respect to accidental poisoning where lower volumes were ingested, 55% of those consuming < 2 g paraquat ion vomited within 30 minutes.

I do not concur with this. The data on a limited number of cases of Weedol poisoning and the "within about half an hour" is not published data. The Meredith and Vale 1987 paper is from a Paraquat Symposium at Guys Hospital, sponsored by ICI and each paper in the symposium is not externally peer reviewed. However, more importantly, the part of the Meredith and Vale paper that mentions the 30 min vomiting is labelled in Table 2 as "unpublished data", if you read the paper. The Meredith and Vale 1987 paper and the book on Paraquat Poisoning by Bismuth and Hall shows the same table on this early vomiting and from guess who… ICI Agrochemicals. If this was so important for the Syngenta FAO, surely it would have been written up and published as a peer reviewed journal article. However, since the same survey showed that the emetic concentration used did not improve survival I can see why Bernie Hart didn't publish it!

More recent human data is available from the Sri Lanka studies. In the first Sri Lanka 'Inteon' study, 38% of the patients drinking the standard 'Gramoxone' formulation vomited within 15 minutes (**Wilks, M.F., et al., 2008, Improvement in survival following paraquat ingestion after introduction of a new formulation in Sri Lanka. PLoS Medicine 5(2), e49**). Although the proportion of patients vomiting within 15 minutes after ingestion of confirmed, probable or possible 'Inteon' formulation was higher (54.7%), this difference could not be substantiated in later studies. In the second Sri Lanka 'Inteon' study (in which only confirmed standard formulation and confirmed 'Inteon' formulation exposures were analyzed) the figure for standard 'Gramoxone' was 49.2% and for 'Inteon' 42.5% (**Wilks, M.F., et al., 2011, Formulation changes and time trends in outcome following paraquat ingestion in Sri Lanka. Clin Toxicol 49, pp 21-28**). Although these two later studies did not include a specific assessment of the outcome at 30 minutes, the results of both studies demonstrate that Syngenta paraquat products continue to satisfy the current FAO specification.

Another point on this is the timing of the FAO text and the unpublished observations on 30 min vomiting. Conveniently, the FAO spec came after the observations but the most concerning issue is the early vomiting was not shown to improve survival. If a suicide case drinks a large quantity of Gramoxone even the Rose level of 0.5g/L will cause vomiting. However, there will have been far too much paraquat at this ratio to prevent death. Again it is all about the ratio of paraquat to emetic in the product. The 1977 400 : 1 (PQ : E) just doesn't work. You need prompt effective vomiting in a minimally lethal dose of Gramoxone.

Inteon was shown to improve survival even at the smaller 3 X increase with earlier vomiting and more survivors. I have always maintained that the 5 X increase (similar to Gramoxone Plus) or better still the Magnoxone L which had dilution to 100g/L paraquat and 5 X emetic would save many lives. Here the ratio for PQ to emetic is 80 in Magnoxone L not the 400 in the Rose 1977 Gramoxone. An expensive solution but since Syngenta is keen on its Stewardship and Safety of its products, a natural step forward in the right direction.

I can understand the reluctance for Syngenta to deal with this in an open forum since if Syngenta did do this and there was evidence of wrongdoing there may be hundreds of law suit cases against Syngenta not just from poisoned victim's families but also from the generic paraquat producers who have also been incorporating an ineffective level of emetic in their own products. I always knew this was important hence my careful management of the signed memos and original reports on the lack of attention to dealing with this in the early 1990s.

The basis for what later became the FAO criteria were established using the available human poisoning data by the Zeneca Agrochemicals Medical Advisor, in July 1994, following a February 1994 meeting which included the CTL paraquat product toxicologist. The current specific PP796 minimum concentration clauses for technical material and formulations were not submitted to FAO until September 2002 (granted 2003), and the documentary record indicates that you were consulted during the FAO process. Specifically your 1st May 2002 memo set out your personal views on "*Potential Areas of Toxicology that could be utilised in a new Syngenta FAO Specification*". In that memo you made no recommendation with respect to any proposal for change to either the pre-existing or newly proposed emetic specification.

In May 2002 it was full steam ahead for a new higher emetic formulation. You are wondering why I was more reluctant than I am now with my new concerns or the concerns I had in 1995. Well my boss now was a certain Lewis Smith who had now returned as CTL Director. Lewis had made it clear to me that he did not want to re-visit the Rose matter.

Although I was now a Senior Scientist in Syngenta and still managing the paraquat area the focus in 2002 was on the paraquat antidotes area and reducing skin irritation potential - two paraquat projects that I presented to Michael Voerman and David Vitolo in May 2002, when they visited CTL. I have just been through the memos on the FAO spec between Rupert and myself in May 2002. The emails in relation to the FAO spec were not to do with the emetic they were on the other paraquat topics (skin irritation and antidotes). If I had been

specifically asked about the FAO spec in relation to the emetic level in Gramoxone I would have had to have spilled the beans so to speak.

You claim that senior management of CTL, Safety & Stewardship, Regulatory Affairs and commercial functions repeatedly ignored concerns, and colluded to keep emetic levels low for cost reasons

We deny that there is any support for these accusations. To the contrary, there is an extensive record of review on this issue in 1990 and on multiple subsequent occasions during the development of 'Inteon' both internally (within CTL and with the safety and stewardship functions) and externally (with medical doctors and regulators) during the period of your employment with the Company (ICI, Zeneca and Syngenta).

This is an interesting comment. So there is an extensive record of review of this issue in 1990. Well this must have followed my accusations in September 1990 to Lewis Smith and the CTL executive that Rose had fabricated the human dose response to the emetic. Very odd that the CTL Exec never involved me in these reviews nor put me on a disciplinary for accusing senior CTL staff of fabrication and collusion if this was not true. It was Stuart Jaggers himself who asked me to participate in the review that never reported. Of course if this was all done behind my back then what does this say? Very odd that either CTL Management or Agrochemicals didn't inform me that I was wrong! It was obviously a time to bury bad news not surface it for all to see. Of course Mike Rose was still alive then so I wonder if they ever locked him in a room to discuss his actions. As Professor Garner told me earlier this year it was a case of finding a new job for Rose at the time. They moved him to Pharms for a while and then to ICI Specialties.

The key issue was the need to take the appropriate clinical medical judgements and decisions based on all of the available information in circumstances in which, since the 1980s, the majority of global paraquat ingestions occur through deliberate acts of self-harm. Clinical management of paraquat poisoning through the use of emetics needs to consider a very broad range of factors, including orders of magnitude differences in ingestion volumes, significant variation in patient bodyweights, co-ingestion of other substances including alcohol, presence / absence of food in the stomach and access to primary and secondary medical care facilities. Since at least the mid-1980s the prevailing view of the medical community for the treatment of general chemical poisoning incidents has cautioned against the use of emetics. Indeed, such doubts were already voiced in the Meredith and Vale, 1987, publication. Since then, a consensus among the scientific bodies representing clinical toxicologists both in Europe and the USA has emerged arguing that the routine administration of emetics (using ipecac syrup as the case in point) should definitively be avoided (**Höjer, J. et al., 2013, Position paper update: ipecac syrup for gastrointestinal decontamination, Clin Toxicol 51, pp 134-139**).

At last I agree with something in your document. Ipecac syrup unlike a centrally-acting emetic works by irritating the nerve endings in the stomach causing retching and vomiting. A centrally acting emetic given simultaneously with the poison will (if given at the correct

dose) cause a rapid vomiting response. Once the CAMP levels in the vomit centre fall below threshold the vomiting stops. Ipecac goes on irritating the mucosa and coupled with the topical irritancy of paraquat and surfactants leads to the classical uncontrollable vomiting in paraquat poisoning.

The position paper also clearly states that emesis should not be induced if the product swallowed is corrosive to the digestive tract. This creates another significant dilemma at least for the standard built-in surfactant formulations (which are severely irritating / corrosive to the GI tract resulting in oesophageal ulceration with risk of oesophageal rupture).

An additional medical concern is the likelihood of lung aspiration, critical for a substance such as paraquat which has a toxic mode of action on the lung combined with the surfactant systems present in the vast majority of paraquat-containing formulations. The 'Inteon' technology was considered to overcome this issue since the presence of the sodium alginate, intended to form a gel on contact with the low stomach pH, should have significantly reduced the risk of aspiration of the vomitus into the lungs.

There is clear published evidence of rapid and repeated emesis from published paraquat ingestion cases. In some circumstances this occurs to such an extent that an anti-emetic has to be administered for the protection of the patient and the medical staff treating them. In the two Sri Lanka investigations approximately 10 to 13% of patients ingesting 'standard' formulation required administration of an anti-emetic. This indicates at least the possibility that profuse emesis may delay the administration or reduce the effectiveness of the standard paraquat treatment which is based on giving adsorbents such as activated charcoal. The risks of emetic over-dosing can be severe.

What its need to improve survival in poisoning cases is the prompt effective emesis at a minimally lethal dose of paraquat. This is what PP796 emetic will do and if it is in the correct ratio you are very likely have an improvement in survival. Another point relates to the paraquat kinetics. The peak plasma level of paraquat occurs within one hour in all higher mammals (not rodents as I have outlined earlier). If a child accidently drinks Gramoxone how long do you think it takes for any intervention to take place? I think one hour is very optimistic and considering this may be in a farming area a long way from a hospital or in a developing country with no emergency care then the only way you are going to save lives is to build in this prompt emetic effect into the product. Back in 1977, ICI got this wrong due to Rose and his fabrication and his influencing with Agrochemicals. They believed him without proper due diligence and peer review of his report. With Inteon we had brought the paraquat : emetic ratio closer from the ineffective 400 : 1, but it was quite clear from the Wilks publication that it needed to go further. Dilution and 3 X emetic is one strategy I have suggested this to the California Poison Centre Director. The proof that it isn't a medical problem but saves lives is Gramoxone Plus in France.

A critical issue that has often been highlighted is the productivity of emesis in reducing the volume of paraquat retained so as to change the human clinical outcome. Your conclusion was that only with the acid-triggered gelling property of the 'Inteon' formulation would the

formulation be retained in the stomach resulting in productive emesis. This was also a critical element of your synergistic patent for 'Inteon'.

You are probably thinking of the part of my patent that covered the slower gastric emptying you get with a triggered gel. This is using physiology to close the pylorus at the exit of the stomach which is a reflex based on stomach stretching after a meal. My idea was to keep the formulation in the stomach longer than a run through liquid so when the first bout of vomiting occurs it would remove more of the ingested product. Once the liquid Gramoxone runs through the pylorus and into the absorptive small intestine it is almost impossible to remove it. This allowed us to reduce the costly emetic down a notch. Agrochemicals went even further and reduced the gel from 400g/L in Magnoxone to 100g/L in Inteon as well as lowering the emetic from 2.5g/L to 1.5g/L.

Many of the human clinical concerns were communicated to us by the Australian regulators in 2006 when, following the October 2004 'Inteon' submission, the regulatory authorities commissioned an independent human clinical assessment of all of the relevant CTL and published data.

I will check this with Utz Meuller from the Australian OCS when I next see him. I will also ask the Japanese Pesticide Regulators who are here at DTL on Jun 25th The Australians and Japanese have voiced their opinions on the high acute toxicity of paraquat and will be interested to hear my views on the emetic.

The PP796 capacity expansion cost which you consider to have been a driver for the decisions taken in 1990 could no longer have been a relevant factor for the 'Inteon' development since the substantive Zeneca PP796 manufacturing capacity expansion had already taken place in the mid-1990s, coincident with the move of paraquat production from Widnes to Huddersfield, and PP796 was already commercially available from alternative Chinese suppliers prior to the commercialization of 'Inteon'.

The PP796 expansion costs were tabled at the 1991 TRC at Jealotts Hill. I have the minutes but I am sure you can source them yourselves. To develop a high emetic product then they needed to sanction a major capital investment to increase the emetic capacity at Huddersfield. The emetic production capacity to uplift the Rose concentration of 0.5g/L for Magnoxone with 5 X emetic required a new plant in 1990. These capital one-off costs never went down well with the TRC.

The global business decision to terminate the 'Inteon' project was taken following commercial launch in multiple countries due to 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. In addition, it had become clear that the improvement in safety was considerably less than the anticipated 10-fold in the dog and 5-fold in man.

This is quite convenient for Syngenta. Again rather odd since there were several years of carefully controlled field use trials before the YF8004A Inteon formulation was approved as being suitable in all climates, water hardness and all the mixing and spray application types

used. Syngenta do not register a new product unless they are sure of the manufacture and the farmer acceptability and all the other product specs are right. Yalding signed this off after a lot of work with Rupert Sohm's team.

With regard to the 5X target for safety. Of course this was never written down. If it was my child who had inadvertently drunk Gramoxone I would accept any safening if they did not die. If 2 X saved lives and most of them were suicides is this not a good thing? If you add up all the additional survivors with Inteon in Sri Lanka (even in the misleading Time Trends publication) you get quite a lot of people who are still alive than with the Gramoxone SL with 0.5g/L emetic. Never mind the accidentals who probably never needed to go to hospital. This survival group is overlooked in both surveys. Syngenta seem to focus on overall mortality statistics rather than a minimally lethal dose in children.

You claim that more lives could have been saved had levels of emetic been higher

There is universal consensus that the primary approach should always be one of prevention of drinking accidents. Starting in the 1970s, ICI progressively and voluntarily adopted multiple measures to reduce the frequency of incidents of accidental drinking of paraquat-containing products (as detailed in the next section). It is only in the broader context of these prevention strategies that the potential incremental value of the addition of the emetic to paraquat formulations can be judged.

Yes, I have always advocated that the Magnoxone level of emetic (2.5g/L) would have been much less toxic than Inteon. As I mentioned earlier, the core issue I have a problem with relates to the original decision in 1977 not what Syngenta are doing now and that an ineffective ratio of paraquat: emetic is still quoted in the FAO spec.

You specifically referred to six drinking incidents highlighted by US EPA as having occurred following illegal decanting of paraquat products over a 13 year time period. Any accidental drinking incident is highly regrettable and clearly tragic for those involved. The oldest three incidents were prior to the introduction of 'Inteon', the latter three post-date Syngenta's commercial introduction of 'Inteon' in the USA.

Are you saying that any accidental poisoning incident after a particular date shows that Inteon doesn't work? People often store product for months or even years particularly if it has been decanted into another container. According to Andy Cook only one of the many accidental poisonings in the "One Sip can Kill" article was thought to be Inteon. If you recall, Inteon is unlikely to eliminate <u>all</u> incidences of poisoning. There is even a counter argument that the number of reported incidences of accidental poisonings has fallen because people vomited the Inteon product out promptly and don't get to hospital and therefore never appear as a "survivor" in the statistical analyses. I can check this with the CPCS. On the USA poisonings. Since this is USA issue perhaps Janis McFarland can answer my question I put to her a while ago on what was the evidence that Inteon did not work? In fact, what constitutes success here with a new product such as Inteon? Is it 10 lives saved per annum, 100 saved?

Importantly, from a medical perspective, there was a significant concern that a small reduction in toxicity (for example, that associated with the same 2 or 3-fold toxicity reduction achievable through product dilution) would, in the absence of a breakthrough in the development of an effective antidote, result in an increase in time to death without meaningful improvement in overall survival. This would clearly be an unacceptable outcome.

I do not understand your logic here Unacceptable to whom? Is it the press and increased notoriety or the poisons agencies? Surely any life saved is a good thing or would Syngenta prefer paraquat poisoned victims to die quickly?

You assert that Syngenta is not taking the issue of accidental poisoning seriously enough, and should consider actions such as diluting the formulation or raising emetic levels

Syngenta and its predecessor companies have consistently maintained a long-term commitment to other measures aimed at reducing the frequency and improving the treatment of incidents of accidental oral ingestion of paraquat-containing products. These include:

- use of a dye and odour in liquid paraquat products to distinguish them from beverages,
- training of users on safe storage, handling and use,
- supply of market appropriate user pack sizes to reduce the likelihood of needing to pour the product into another container,
- improvements in labelling emphasizing the importance of not removing paraquat from the original sales container into drink or other containers,
- free production and distribution of paraquat analytical test kits and a paraquat treatment booklet in many parts of the world.

After more than 30 years of formulation research and development, Syngenta has, over recent years, focused on taking prevention to the next level with the development of innovative closed transfer systems for backpack / knapsack and tractor-based systems with the first planned commercial introduction scheduled for 2019. These effectively preclude exposure to accidental ingestion of the formulation concentrate, e.g. resulting from irresponsible practices such as decanting from the original storage container.

This is the second point where we have agreement. Any manoeuvre that saves lives or reduces the incidence of paraquat deaths has got to be a good thing. As I mentioned earlier, the majority of paraquat deaths are in the developing countries. These new measures with closed transfer systems are not going to be used in the poorer parts of India for example where a farmer may have a small plot of land and only need a few bottles of Gramoxone.

Experience in other countries introducing low strength products, e.g. Japan (4%), UK (2.5%) Sri Lanka (6.5%), is that reduced concentration did not eliminate fatalities. CTL's detailed analysis of volumes ingested in paraquat poisoning cases demonstrated that a small (2-3x)

reduction in toxicity would continue to result in a high overall fatality rate. The most recent Japanese published statistics for the dilute (c.40 g paraquat ion/litre) formulation in Japan (reported mortality rate 80%) clearly demonstrate the challenge in reaching a significant reduction in mortality rate even with the current significantly elevated Japanese emetic : paraquat ratio.

Dilution will do nothing to further reduce the practice of decanting to inappropriate containers. If all other factors remain unchanged then the potential for an accidental oral ingestion to occur (frequency) will largely be a function of the number of containers in the market place / at the end user level. A more dilute product will inevitably result in the transport, storage and handling of many more product containers and a probable increase in the number of partially used (unsealed) product containers on farm. In the case of end users there would also be a significant increase in the number of mixing/loading operations

involving the concentrate. There is a low potential for each individual operation involving the product concentrate to result in incremental exposure, including accidental splashes to the skin or eyes. These negative factors for legitimate users of the product and potential impact on incident frequency need to be weighed when considering any potential for reduction in oral toxicity which may result from the introduction of a more dilute product. Dilution may change the clinical progression for an individual but there is also the potential that this does not result in survival.

This is another example of where Syngenta are trying to defend the position of not diluting the product. I have the Ohno Japan human poisoning statistics from the time we introduced Preeglox as a Paraquat solo and with a 4.5% paraquat 4.5% diquat mix. Yes, there are cases where the Japanese ingest quite heroic volumes in suicides and no maneouvre will prevent them from dying. However, on the graphs I have showing the LD50 quite close to 4 grams of paraquat ion the survival statistics are improved with Preglox over Gramoxone. Therefore, dilution does improve survival. I went through this with Lewis Smith in August 2006. There was a measurable improvement in survival up from 25.4% (n=67) to 41.7% n=24) simply by the dilution effect. I have the full report that Robin Birtley sent me at the time. If this was coupled with higher emetic and triggered gel technology Syngenta may be able to bear the cost rather than lose even more registrations.

Rick Geller the Director of CPCS in the USA has pointed out that dilution of paraquat products as occurred in Japan is a good thing. He wants to do this in the USA. When coupled with high emetic you may even regain registrations rather than have a total global ban of paraquat products.

While we respect your opinion, we believe we have thoroughly investigated and addressed your concerns. If you have any new information to provide, we are willing to review and further discuss with you.

D A French

Head of Global Regulatory and interim Head of Product Safety