Dear Professor Heylings,

PARAQUAT AND PP796

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. 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. Although Syngenta now has a considerably smaller geographic footprint and a low molecular share of the paraquat market the company continues to take an industry-leading approach to potentially effective measures to address these issues.

We agree that the current consensus of the medical and regulatory community is that the various PP796 : paraquat ratios employed in paraquat-containing formulations of different concentrations from a range of companies over the years (ranging from between approximately 1:720 to 1:40, i.e. more than an order of magnitude) have not resulted in a meaningful improvement in overall survival of paraquat drinking incidents. As you recall this approach was also at times combined with the use of solid (granular) formulations and thickening agents. A number of elevated emetic : paraquat ratios have been evaluated over the years but have not proved to be effective in eliminating human fatalities. If, as you have suggested, one simply ignores the fact that the great majority of cases involve deliberate drinking of the formulation concentrate and focus solely on the relatively low frequency of accidental drinking incidents then, with the benefit of all of the information available today, there could be merit in once again engaging with the medical profession and regulators on alternative proposals. Medical advice is that even if the sole focus was on accidental ingestion incidents it is unlikely that the conclusion would be to recommend a significant elevation in the existing approved emetic concentrations.

The reality of the position in 2019 is that in countries where there is a cultural prevalence of deliberate self-harm the external medical community (and hence also the regulatory authorities) has a strong focus on reduction or elimination of deliberate drinking incidents and improved survival outcomes. As we explained at our meetings in 2018 and 2019 Syngenta's agreed approach is to use modern closed transfer engineering technology to effectively address this, an approach which also offers significant additional benefits for the user. Syngenta consider this to be a much more appropriate and targeted strategy to reduction of the incidence of paraquat poisoning than any possible combination of dilution or elevated emetic concentration. The engineering solutions for large scale tractor-based systems and for backpack/knapsack systems are being progressively introduced subject to external regulatory approvals.

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

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. There is no evidence of fabrication associated with the 1976 research report which, as indicated in the next section of this letter, has long since been superseded by later studies of human poisoning incidents reviewed by global regulators.

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.

While it is not possible to confirm with 100% certainty the way in which Dr Rose considered the limited data set, 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). 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 first 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. 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.

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'. 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. On the basis of the new statistical analysis which we shared 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. In the interests of transparency Syngenta has 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. We agree that the limited data set was not sufficient for a statistically robust assessment.

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

Following the commercial introduction of emeticized paraquat-containing formulations in the UK in 1977, ICI Plant Protection Division, working with the National Poisons Information Service (NPIS), set up a toxico-vigilance program to monitor the impact of the introduction of the emeticized formulation. This was, in fact, one of the stipulated regulatory requirements of the commercial authorization. ICI also recognized the importance of that monitoring since a thorough human evaluation needed to be made in view of the limited data for PP796 alone and, more importantly, on the basis of the inclusion of PP796 in liquid paraquat formulations also containing surfactant blends and the olfactory alerting agent (thus assessing both the impact of the dispersion of PP796 and the human emetic response) and the professional and low-strength amateur granular formulations without the olfactory alerting agent.

The 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 (approximately 10 mL of formulation) vomited within 30 minutes.

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.

The basis for what later became the FAO criteria were established using the available human poisoning data by the Zeneca Agrochemicals Medical Advisor, Dr Sabapathy, in July 1994, following a February 1994 meeting which included CTL, represented by Dr Scott as paraquat product toxicologist. The 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 to Mr Wheals copied to Dr Clapp, Dr Wilks and Mr Sohm 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.

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

The documentary record clearly indicates that the issues you now raise were extensively discussed at a senior level 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) and that at the heart of the 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 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 has shifted against the use of emetics in the treatment of general chemical poisoning incidents. 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**).

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 irritant / corrosive to the GI tract resulting in oesophageal ulceration with risk of oesophageal rupture) since unreported

accidents do not involve consumption of a toxic dose. This concern, you will recall, was somewhat lessened with the development of 'Inteon' which was considered to be significantly less irritant.

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 poisoning 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.

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 last (May 2006, subsequently revised by you in October 2006) CTL report jointly authored with Dr Swain states that solely increasing the emetic content of 'Gramoxone' by 5-fold resulted in a toxicity reduction in dogs of only approximately 3-fold in this animal model. It is unclear whether that modest reduction would translate in the human clinical context. 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 claim for 'Inteon'.

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.

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 global business decision to terminate the 'Inteon' project in 1Q2008 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 (and repeatedly claimed) 10-fold in the dog and 5-fold in man. The Company's development of 'Inteon' cost more than US$50 million on the basis of the technical specification for emetic concentration recommended by the CTL technical team which you now claim to be inappropriate.

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.

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. At least one of the 'Inteon' fatalities was subsequently reported in the published literature.

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.

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 global distribution of paraquat analytical test kits and a paraquat treatment booklet

Syngenta has, over recent years, focused on taking prevention to the next level with the development of innovative closed transfer systems for both backpack / knapsack and tractor-based systems with the first planned commercial introduction scheduled for 2019. These effectively preclude any possibility of exposure to the formulation concentrate and can therefore confidently be anticipated to remove any possibility of accidental drinking incidents involving the undiluted formulation, e.g. resulting from irresponsible practices such as decanting from the original storage container. Therefore after more than 30 years and US$100 millions of research and development we are no longer actively pursuing innovative approaches to intrinsic improvements in formulations or research on antidotes, though we have continued to monitor the literature in case of a genuine breakthrough. The failure of 'Inteon' to deliver the anticipated and repeatedly claimed safety improvement resulted in de-registrations in the majority of our former major markets (including China, Malaysia, Philippines, South Korea, Sri Lanka, Taiwan and Vietnam).

Experience in other countries introducing low strength products, e.g. Japan (4%), UK (2.5%) Sri Lanka (6.5%), is that reduced concentration cannot eliminate fatalities. Dr Pate'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 also 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 (but non-negligible) 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 and potential impact on incident frequency need to be weighed up 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.

The level of emetic in Syngenta paraquat formulations meets or exceeds global standards and, for the reasons already detailed in this letter, we have no plans to increase the emetic :

paraquat ratio in current Syngenta formulations. It is possible, once the closed transfer systems are widely adopted, that we will seek to remove the emetic and / or other formulation additives from Syngenta formulations if there is good evidence that they no longer serve a useful purpose. Clearly, as for any other development, this would require independent decisions by the medical community, regulators and FAO.

D A French

Head of Global Regulatory and interim Head of Product Safety