Dear Professor Heylings,

PARAQUAT AND PP796

As you will already appreciate we take your current perspectives on the 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 spent dozens of hours investigating your claims and reviewing correspondence and studies from decades ago.

Our extensive investigation has revealed that your claims are largely unsupported. You have raised concerns about the data from an analysis of clinical trial data reported in an ICI 1976 research report, which you claim cannot properly be used to support the level of emetic in Syngenta's paraquat products. There is no evidence of any fabrication associated with the 1976 research report which has in any case now been superseded by later studies of human poisoning incidents. The appropriate level of the emetic in Syngenta's paraquat products has been discussed extensively internally and externally on multiple occasions during the period of your employment with Syngenta and its predecessors.

The 1976 report was not used as the basis of the emetic clause in the current FAO Specification even if it formed the original basis for the initial recommended concentration of emetic in 200 g paraquat ion/litre formulations. The human poisoning data which underpin the current FAO Specification, that an effective emetic must induce emesis (vomiting) within half an hour in 50% of cases, are taken from a later publication assessing the emetic response in individuals drinking commercial paraquat formulations containing emetic at the concentration originally recommended by Syngenta predecessor companies. The human data were published in 1987 (Meredith, T.J., and Vale, J.A., 1987, Treatment of paraquat poisoning in man: methods to prevent absorption. Human Toxicology 6, pp 49-55). The 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.

As evidence of how seriously Syngenta has taken your allegations, Syngenta re-assessed in January 2019 the limited human pharmaceutical clinical data from ICI Pharmaceuticals Report PH20992C (23rd July 1973) for dosing of PP796 alone considered in the 1976 research report. The best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg bodyweight (i.e. 3.5 mg). This result is consistent with the original interpretation of this very limited human dataset. Data subsequently obtained from monitoring of human paraquat poisoning cases were used to establish the current FAO PP796 concentration specification in 2002. You were specifically consulted as part of that process.

You asked what Syngenta is now doing following the failure of 'Inteon' to deliver the anticipated safety improvement and the resultant de-registrations in the majority of our

former major markets in Asia Pacific (including China, Malaysia, Philippines, South Korea, Sri Lanka, Taiwan and Vietnam). ~~After more than 30 years and US$100 millions of research and development directed towards the successful commercialization of 'safer' formulations we are no longer actively pursuing this approach.~~

Syngenta and its predecessor companies have invested more than $100 million USD over ~~many~~ 30 years to study paraquat and develop means of protecting human health. Prevention of accidental drinking incidents remains the cornerstone of our approach. The emetic contained in Syngenta's paraquat products is only one example of Syngenta's stewardship efforts. Over the years, working with regulators, Syngenta and predecessor companies have progressively and voluntarily adopted multiple measures to reduce the frequency of incidents of accidental drinking 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,
- supplied market appropriate user pack sizes to reduce the likelihood of needing to pour the product into another container,
- improved labelling emphasizing the importance of not removing paraquat from the original sales container into drink or other containers.

It is only in this broader context of prevention strategies that the potential incremental value of the addition of the emetic to paraquat formulations can be judged.

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 in the USA scheduled for 2019.

J Parr R Mazzotta