JON HEYLINGS

Background

Professor Jon Heylings is a former employee of Syngenta and its predecessor Companies, ICI and Zeneca. He was employed by the Central Toxicology Laboratory (CTL) at Alderley Park in 1986 and was later appointed as a Senior Toxicologist and Section Head at CTL. Jon left the Company with a full redundancy package in 2007 following the announcement of the closure of CTL in September 2006.

After leaving Syngenta Jon Heylings set up his own business, Dermal Technology Laboratory Ltd (Keele University Science and Business Park); Jon is the Chairman and Chief Scientific Officer of this Company. Jon is also an honorary Professor of Toxicology at the School of Pharmacy at Keele University. Jon has worked with the OECD, WHO and several UK and European Industry and Government bodies to develop and advocate *in vitro* (non-animal) methods and test guidelines to evaluate the dermal absorption of chemicals.

Jon Heylings was employed by ICI specifically to work on the 'safening' of paraquat formulations and spent much of his 20-year career working on the various formulation technology innovations intended to reduce fatalities following drinking of undiluted paraquat formulations. Jon was the registered patent holder for some of these innovations, most recently for the 'Inteon' technology.

What is Jon's allegation?

Jon claims that ~~T~~the data from an analysis of clinical trial data reported in a 1976 research report, on which the current 'emetic clause' in the paraquat FAO Specification is set is 'fabricated' and the level of emetic in paraquat formulations should be significantly higher. Jon also claims that although he highlighted this to the Company in 1990, no action was taken simply for commercial reasons.

What is Syngenta's position?

(i) There is ~~insufficient~~ no evidence of any fabrication associated with the 1976 research report which has in any case now been superseded by later studies of human poisoning incidents.

(ii) ~~-~~Moreover, this report does not form the basis of the support for the 'emetic clause' in the FAO Specification.

(i) The level of the emetic (PP796) in Syngenta's paraquat products meets the FAO Specification criteria (in effect since 2003) that an effective emetic must induce emesis (vomiting) within half an hour in 50% of cases. The 1976 review by the ICI Central Toxicology Laboratory (CTL) of earlier pharmaceutical clinical trial data that Jon Heylings has questioned formed the original basis for the inclusion concentration of emetic in paraquat formulations.

(ii) ~~-~~ However, it does not ~~the~~ form the basis of the support for the 'emetic clause' in the ~~current (2008)~~ FAO Specification. The human poisoning data which underpin the FAO Specification are taken from a later publication assessing the emetic response in individuals drinking paraquat formulations containing emetic at the concentration originally recommended by CTL. 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**). It is this published human poisoning data which supports the FAO 'emetic clause', i.e. "*Emesis must occur in about half an hour in at least 50% of cases*". 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.

The inclusion of the emetic was one of several measures which ICI, one of Syngenta's predecessor companies, voluntarily adopted from 1977 onwards to reduce the frequency and severity of incidents of accidental drinking of paraquat-containing products. These measures amount in total to more than 100M USD and include use of a dye and odour in paraquat products to distinguish them from beverages, increased training for applicators, labelling emphasizing the importance of not placing paraquat into drink or other containers, and later the introduction of closed application systems.

A 20 year survey from the United Kingdom National Poisons Information Centre (London) noted in 2001 that most of the cases of poisonings from mistaken ingestion occurred in the early 1980s, with the last one recorded in 1992, confirming the virtual disappearance of fatalities in the UK due to accidental ingestion since their peak in the early 1970s (**Northall F S, Wilks M F, 2001, Two Decades of Paraquat Surveillance in the UK. J Tox Clin Tox 39: 283 - 284**).

Q & A

What are Jon's ~~stated motivations~~claims for his current actions?

- Jon stated that he has recently been reviewing the toxicology of paraquat for a project on behalf of the UK Department of Health. As part of that process Jon's attention has focused on a US EPA document "*Paraquat Dichloride Ingestion Risk Message for Pesticide Applicators*" and the 'emetic clause' in the (2008) FAO Specification for paraquat technical and paraquat formulations. Jon considers the FAO Specification to be incorrect (specifically that the minimum emetic concentration is too low to ensure that "*emesis must occur in about half an hour in at least 50% of cases*").

Why is Jon bringing that topic now? What are his motivations?

- It is not easy to really understand what his motivations are while he left the company 12 years ago, in 2007, and spent more than 20 years at Syngenta where he was specifically working on the 'safening' of paraquat formulations? He left 17 years after he raised the topic of the level of emetic in the formulations, topic which was extensively discussed both internally and externally.
  During the meetings held the last few months in 2018 and early 2019, we heard him talking about Inteon, the patent he's one of the holders, a project which the company decided to discontinue.

What is PP796?

- PP796 (or ICI 63,197) is a phosphodiesterase inhibitor. The compound was originally discovered by ICI Pharmaceuticals and was extensively studied as a potential drug for the relief of asthma. Mammalian toxicology studies were completed to the satisfaction of the UK Committee for the Safety of Medicines, which granted a Clinical Trials Certificate, enabling clinical trials to take place. During the clinical trials, it became apparent that PP796 had an unexpectedly high emetic effect in humans. It was therefore withdrawn from further development as a drug. Its emetic properties did however indicate considerable potential for use with pesticide formulations or other products with high acute toxicity.

What prompted publication of the US EPA document that Jon referenced?

- The California Poison Control System and the American Association of Poison Control Centers (AAPCC) sent letters of concern to EPA regarding a series of deaths from accidental ingestion of paraquat in the San Joaquin Valley of California. AAPCC cited 50 deaths from paraquat; at least 12 were from accidental ingestion of paraquat from a beverage container. Paraquat is a "Restricted Use Pesticide" that should not be accessible to the general public and, as with all pesticides, should never be placed into a beverage container. Paraquat is highly toxic to humans; one small accidental sip can be fatal and there is no antidote. The product labels clearly prohibit pouring paraquat into food or beverage containers with the prominently-placed statements "*NEVER PUT INTO FOOD, DRINK OR OTHER CONTAINERS*" and "*DO NOT REMOVE CONTENTS EXCEPT FOR IMMEDIATE USE.*"

Comment [FJMC1]: When did that happe

What actions does Jon expect Syngenta to take?

- He has stated that he would like to force the Company to act through notifying regulatory authorities of the alleged error in the FAO Specification and either removing the emetic entirely or increasing the emetic concentration. For us, there is no error. As for removing the emetic, that would be unacceptable and there is insufficient evidence of the clinical benefits of increasing its concentration with potential downsides such as uncontrolled vomiting and angina.

What actions have Syngenta taken to date following receipt of Jon Heylings' initial allegations?

- Syngenta has taken Jon's allegations extremely seriously.
- Jon first raised his current concerns with the Company in August 2018. The Company has sought an open and transparent dialogue to further the scientific understanding of the issues. The Company met with Jon in October 2018 then, at Jon's request, with one of Jon's former Managers, Professor Lewis

Smith in December 2018. As a result of these two discussions a further meeting took place with both Jon and Lewis in January 2019 and another one on April 12, 2019 with the Head of Crop Protection Regulatory Affairs and the Lead Counsel Weed Control.

- Simultaneously, Syngenta has also undertaken a significant internal review of available documents and data and convened a group of Product Safety experts to thoroughly investigate and assess the allegations.

What is the current global situation regarding accidental drinking accidents involving undiluted paraquat formulations?

- Syngenta has over many years taken a series of measures to reduce the incidence of accidental drinking of the undiluted formulation. These include:
    - supplying market-appropriate pack sizes to reduce the likelihood of decanting
    - label warnings not to remove the formulation concentrate from the original container
    - addition of two 'alerting agents' (a coloured dye and an odour) to differentiate the appearance of the product from beverages such as soda or coffee
    - addition of a potent emetic, the phosphodiesterase inhibitor PP796, into paraquat formulations to induce vomiting to reduce the volume of product in the GI tract and to alert the user of the need to seek urgent medical treatment

What is the Companies current position on the voluntary measures taken to date?

- As part of a series of stewardship measures to address accidental ingestion of paraquat, mainly as a result of grossly negligent practices such as decanting into drink bottles, in 1977 ICI (now Syngenta) progressively introduced a potent emetic, the phosphodiesterase inhibitor PP796, into all its soluble liquid (SL) paraquat formulations globally, along with a dye (blue green colour) and olfactory alert.
- Syngenta has also made labelling changes, instituted additional training programs for applicators, and is introducing closed system paraquat products to prevent accidental ingestion.

What is Syngenta currently doing to address the issue of accidental drinking accidents involving undiluted paraquat formulations?

- Syngenta is launching new closed mixing / loading systems for tractor application equipment in major paraquat markets (e.g. USA, Canada, Brazil) which will make it impossible to access or decant the formulation concentrate to another (inappropriate) container. Syngenta is also developing a novel closed mixing / loading system for backpack / knapsack applications which will also preclude access to the formulation concentrate. This technology also offers additional user benefits.
- By the fall of 2020, Syngenta will introduce closed systems for all package sizes less than 120 gallons in accordance with the EPA's paraquat Human Health Mitigation Decision.

What is the evolution of the 'emetic clause' in the FAO Specification for paraquat and on what data is it based?

- The 'emetic clause' ("*Emesis must occur in about half an hour in at least 50% of cases*") first appeared in the 1994 specification for paraquat. The critical data included the human poisoning data 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) supporting the FAO 'emetic clause'. 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. In 2003 the FAO Specification was amended to state that where PP796 is the effective emetic employed, it must be present at a minimum level of 0.23% by weight of the paraquat ion content.
- In the US, PP796 is approved for use in paraquat products up to a nominal content of 0.3% concentration of a formulation.

Does Syngenta agree with the conclusions presented in the 1976 CTL research report?

- In January 2019, Syngenta re-assessed the human pharmaceutical clinical data considered in the 1976 research report and there is. no evidenceThe available data were, and still are, very limited a of any data fabricationnd it is not possible to calculate statistically-robust effective levels of emetic in humans based on these data. Nevertheless, our reassessment concluded that the best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg bodyweight (i.e. 3.5mg), which is consistent with the original study interpretation of this limited human dataset.
- In spite of the uncertainties in interpreting the human clinical trial data, eExperience with cases involving drinking of paraquat formulations have shown that the levels of emetic in the FAO Specification have continued to meet the requirements of the Specification (*"Emesis must occur in about half an hour in at least 50% of cases)*

Does Syngenta agree that the conclusions presented in the 1976 CTL research report are 'fabricated' or 'flawed'?

On the basis of our detailed re-analysis of the data, we do not considerthere is no evidence that the report was deliberately fabricated to support some pre-determined emetic dose or concentration in paraquat-containing formulations. It is certainly feasible Rose's laboratory notebook annotations were simply part of an exploration of the data and its analysis. The 1976 research report based on this analysis is a single author Research report and was not subject to internal scientific peer review.

More importantly, the later human poisoning data 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**) supports the FAO 'emetic clause', i.e. *"Emesis must occur in about half an hour in at least 50% of cases*". 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.

What is Syngenta's current interpretation of the human pharmaceutical clinical data available for PP796 alone?

- In January 2019, Syngenta re-assessed the limited human pharmaceutical clinical data 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 is consistent with the original, 1976 study interpretation of this limited human dataset.

What actions did the Company take in 1990 / 1991?

- The Syngenta predecessor Company, ICI, increased its on-going development of alternative formulation technologies with the objective of reducing human fatalities resulting from drinking incidents. Syngenta has continued to seek to prevent accidental ingestions through a number of stewardship efforts, labelling, use of a dye and odor in paraquat products, and enhanced packaging that makes it more unlikely that accidental ingestions will occur.
- Jon has stated that at no time during the development of 'Intoxn' did he ever share the results of his 1990 analysis (and resultant discussions with the CTL Executive) with the paraquat product managers or his line managers at CTL following the formation of Syngenta.

Will Syngenta now increase the PP796 concentration in all Syngenta paraquat formulations or recommend a change in the FAO Specification for paraquat?

- Syngenta currently has no plans to increase the PP796 concentration in paraquat formulations or request a change in the FAO Specification because tThere is insufficient evidence of the clinical benefits of such a move and potential downsides with increasing the emetic level, such as uncontrolled vomiting and angina.

- Syngenta also continues its efforts to reduce the likelihood of accidental ingestion through the use of closed paraquat application systems, training programs, continued use of a dye and odor to distinguish paraquat from beverages, and other stewardship efforts.

What is the 'correct' level of the emetic in paraquat-containing formulations?

- On the basis of human clinical data the minimum concentration currently required by the FAO is sufficient to satisfy the criterion ***"Emesis must occur in about half an hour in at least 50% of cases"***. The 'correct' level depends on the balance of deliberate and accidental drinking incidents, the bodyweight of the patient and the volume of product consumed.

- Emetic was increased as part of a safening strategy during the development of Inteon. Following the decision to discontinue Inteon, the higher level of emetic was maintained in the current US formulation.

Was ICI's decision motivated primarily by considerations of cost rather than human safety?

- There is ~~insufficient~~ no evidence that considerations of cost were paramount. At the time Jon raised his concerns while still employed at CTL, there was sufficient scientific evidence from sources apart from the 1976 study to support the emetic level in Syngenta's paraquat products. Second, the final decision regarding whether to increase the emetic level would have been based on the recommendations of Medical Doctors. Moreover, Jon's allegation is not consistent with the fact that Syngenta and its predecessor companies have invested many US $100 million over many years to study paraquat and develop means of protecting human health, including the development and proof of concept of innovative formulations, label warnings, and other technologies intended to address accidental ingestions.

Who in Syngenta and its predecessor companies was actually accountable for determining the 'correct' level of the emetic from a human Medical perspective?

- CTL was a corporate toxicology laboratory acting in an advisory capacity; business decisions were taken by the individual Divisions of ICI. In the case of the Agrochemicals business, the final decision by the Division was based on the specific recommendations of the qualified Medical Doctors employed at the time. The human clinical datasets considered by these Doctors were for individuals ingesting paraquat formulations both with and without PP796. The much more limited human data which forms the basis of Jon's assessment involved direct administration of PP796 alone as part of pharmaceutical clinical evaluation or studies in dogs.

Have Syngenta or legacy Companies ever been asked by a regulator to increase the concentration of PP796 in paraquat-containing formulations?

- No, to the best of our current knowledge Syngenta and its predecessor companies have not been asked to increase the concentration of the emetic PP796 in paraquat-containing formulations.

What ~~is~~are the current paraquat : PP796 ratio in Syngenta paraquat-containing formulations?

- Syngenta commercializes a broad range of paraquat-containing liquid formulations; in all cases the concentration of PP796 meets or exceeds the minimum concentration specified in the global FAO Specification. Typically 200 g paraquat formulations contain a minimum of 0.5 g PP796/litre.

What is the current paraquat : PP796 ratio in Syngenta paraquat-containing formulations sold in the USA?

- Syngenta currently commercializes a single paraquat-containing product, the ratio of PP796 to paraquat ion is significantly in excess of the minimum concentration specified in the global FAO Specification. The formulation, containing 240 g paraquat ion/litre contains 1.5 g PP796/litre equivalent to paraquat to emetic ratio of 0.0063. The emetic content of this product is approximately

2.7 x the minimum FAO standard of 0.552 g PP796/litre. Syngenta will maintain the current (1.5 g PP796 /240 g paraquat cation) its US paraquat formulations.